JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW™
eViralHepatitis Review

Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

Supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, Inc., and Merck & Co, Inc.

eViralHepatitis Review
VOLUME 4, ISSUE 6

THE HCV VIRAL LIFE CYCLE AND TREATMENT IN HIV COINFECTION AND DIALYSIS POPULATIONS

In this Issue...

The ongoing revolution in HCV treatment has been powered by researchers' increased knowledge of the life cycle of the hepatitis C virus and where DAA agents can disrupt the infection process. Despite the outstanding results achieved in the general population, certain patient groups could be challenging like those with HIV/HCV coinfection or "hard to treat" like those with severe renal dysfunction.

In this issue, Drs. Paul Martin and Kalyan Ram Bhamidimarri from the University of Miami School of Medicine review the recent literature describing:

- the HCV life cycle and the antiviral drug targets
- options for treating HCV/HIV coinfected patients
- potential DAA options for treating patients with severe renal disease

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the HCV life cycle, drug targets, and interactions between HIV-HCV viruses in coinfection.
- Evaluate the data on sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, paritaprevir/ritonavir/ombitasvir and dasabuvir (3D) and grazoprevir/elbasvir for the treatment of HCV in patients with HIV-HCV coinfection.
- Summarize the current evidence providing guidance on HCV treatment options in ESRD patients who need to be treated urgently.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

IN THIS ISSUE

Program Directors

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Program Information
CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Planners Disclosures
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 contact hour Nurses

Launch Date
March 17, 2016

Expiration Date
March 16, 2018

COMPLETE THE POST-TEST

PHYSICIAN POST-TEST

NURSE POST-TEST

Raymond T. Chung, MD
Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research Scholar
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Julie McArthur, MS, CRNP
Adult Nurse Practitioner
Division of Infectious Disease
Johns Hopkins University School of Medicine
Baltimore, Maryland

GUEST AUTHORS OF THE MONTH

Commentary:

Paul Martin, MD, FRCP, FRCPI
Professor of Medicine, Chief
Division of Hepatology
University of Miami School of Medicine
Miami, Florida

Kalyan Ram Bhamidimarri, MD, MPH
Assistant Professor of Clinical Medicine
Medical Director for Small Bowel & Multi-Visceral Transplantation
University of Miami School of Medicine
Miami Transplant Institute
Miami, Florida

Guest Faculty Disclosures

Dr. Martin has indicated that he has received grant support from Gilead Sciences, Inc. and Merck.

Dr. Bhamidimarri has indicated that he has served as an advisor for and received research grant support from Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen, and AbbVie. He has also received research grant funding from Biotest.

Unlabeled/Unapproved Uses

Dr. Martin and Dr. Bhamidimarri have indicated that there will be reference to the off-label use of DAAs in patients with severe renal impairment or end stage renal disease on hemodialysis in urgent need HCV treatment.

Program Directors' Disclosures

COMMENTARY

HCV is still a major public health burden affecting 170 million individuals worldwide. It remains the leading indication for liver transplantation in North America and western Europe. Direct-acting antiviral (DAA) agents have revolutionized HCV treatment. The HCV treatment field has been rapidly evolving with the approval of newer DAAs, and clinicians need to update themselves on the topic, to understand the rationale for evolving treatment recommendations.

Dubuisson et al describe the HCV life cycle and the antiviral drugs targets and their article (reviewed herein) puts the topic in perspective by elucidating the mechanisms of action and pros and cons of both the available DAAs (NS3 PI, NS5A, and NS5B inhibitors) and the newer DAAs in the investigational phase.[1] Similar to HIV treatment, the treatment of HCV clearly should involve more than one DAA with complementary mechanism of actions to improve efficacy and minimize resistance. The virologic mechanisms in HIV-HCV coinfection are complex, and there is clear evidence that HIV enhances the replication of HCV and stimulates stellate cells, leading to accelerated fibrosis in coinfected patients.[2] HIV-HCV coinfection, which was historically considered a special population, should now no longer be considered such because of similar treatment outcomes compared to HCV monoinfection. The following papers summarize the recently published data on the HIV-HCV coinfection cohort.

Prior studies of sofosbuvir (SOF) plus ribavirin (RBV) in PHOTON-1 and PHOTON-2 resulted in SVR rates between 75% to 92%.[3,4] ION-4 is a large, multicenter, phase III study that explored the efficacy of two DAAs, sofosbuvir plus ledipasvir (LED), in treating HCV genotype (GT) 1 or 4 for 12 weeks. The SVR 12 rate with the combination was 98% with only one relapse. In ALLY-2, coinfected patients with HCV GT 1, 2, 3, or 4 were treated with two DAAs, SOF plus daclatasvir (DCV), for eight or 12 weeks. Although the shorter eight-week trial resulted in a compromised SVR12 of 75%, the longer duration arm of 12 weeks achieved an SVR 12 greater than 96%. In the TURQUOISE-I study 3D or PrOD regimen (paritaprevir/ritonavir/ombitasvir, and dasabuvir) for 12 or 24 weeks resulted in SVR 12 of 94% and 91%, respectively.

Finally, in the C-EDGE trial, grazoprevir plus elbasvir (GZP/EBR), which were recently approved, were studied in HCV GT 1, 4, or 6 and 12-week therapy, with the combination resulting in SVR 12 of 96%.

HCV-infected patients with ESRD are still considered a special population because of limited options for HCV treatment in this cohort. Although all approved DAAs are safe in varying stages of renal insufficiency, an optimal or safe SOF dose has not been established for those with ESRD or those on hemodialysis (HD). GZP/EBR which were recently approved were used in the C-SURFER trial which resulted in an SVR 12 rate of 99% in per-protocol analysis.[5] However, patients currently in clinical practices who need urgent treatment of HCV could be treated with other alternate options.

We reviewed our own paper, which looked at HCV treatment in ESRD with reduced dose SOF plus full dose simeprevir (SIM). Although the sample size was small, in our experience the SVR12 was 87%. The only relapsers in our cohort were those with cirrhosis and those who failed prior NS3 PI therapy. The PrOD regimen, which does not need renal dose adjustment when combined with RBV in GT1a and without RBV in GT1b, has resulted in SVR12 of 90%.[6]

The current review summarizes the published data on HCV treatment in HIV coinfection and in dialysis populations. Ongoing clinical trials using other DAAs target HCV not only at the polymerase but also at other sites in the HCV life cycle. The DAAs which are currently under investigation have pan-genotypic activity and high barrier to resistance and could potentially lead to shorter duration of therapy. The results of these trials are eagerly awaited which could transform the field in the future.

References

1. Rupp D, Bartenschlager R. Targets for antiviral therapy of hepatitis C. *Semin Liver Dis*. 2014 Feb;34(1):9-21.
2. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: *Clin Infect Dis*. 2001;33(4):562-569
3. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA*. 2014; 312: 353-361.
4. Molina JM, Orkin C, Iser DM, et al; for the PHOTON-2 study team. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *Lancet*. 2015 Mar 21;385(9973):1098-1106.

COMPLETE THE POST-TEST

PHYSICIAN POST-TEST

NURSE POST-TEST

5. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 2015 Oct 17;386(10003):1537-1545.
6. Pockros PJ, Reddy KR, Mantry PS, et al. Safety of ombitasvir/paritaprevir/ritonavir plus dasabuvir for treating HCV GT1 infection in patients with severe renal impairment or end-stage renal disease: The RU BY-I study. *J Hepatol*. 2015 Apr;62(Suppl 2):S257.

back to top

HCV LIFE CYCLE, INTERACTIONS BETWEEN HIV-HCV VIRUSES AND DRUG TARGETS

Dubuisson J, Cosset FL. Virology and cell biology of the hepatitis C virus life cycle: an update. *J Hepatol*. 2014 Nov;61(1 Suppl):S3-S13.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View full article

HCV was identified in 1989 as a positive sense, single stranded RNA virus of *Flaviviridae* family.[1] HCV virions are pleomorphic, measuring 50-80 nm consisting of SS-RNA genome, core, and envelope glycoproteins (E1, E2). Several phases of the HCV life cycle are closely linked to lipid metabolism in the human hepatocyte. HCV virus has high tropism/affinity for the hepatocytes as the virus particles are transported via the portal venous blood stream during the primary infection.

Life cycle stages and antiviral targets include:
• *HCV entry*: The virus particle enters the hepatocyte by a fusion process between the viral envelope proteins and the host lipoprotein receptors (ApoE, LDLR, SRB1, etc) present on hepatocyte membranes. Inhibition of HCV entry into the hepatocyte is thus a potential antiviral target. Neutralizing antibodies against viral E1/ E2 complex, or even those that specifically target E2, have in vitro efficacy but have limited antiviral efficacy due to high variability of HCV envelope proteins and inability to block cell to cell transmission of HCV.[2,3] Other drugs targeting host cell entry such as CD81, SCARB1, EGFR, or NPC1L1 are currently under investigation in animal models.

• *HCV Replication*: The HCV RNA consists of a single open reading frame (ORF) flanked by 5' and 3' nontranslated regions (NTRs). The 5' NTR enters the ribosome and initiates the translation of the HCV genome into a single polyprotein which is then processed into 10 mature proteins (core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) by host/viral proteases. HCV induces major alterations in the cytoplasmic milieu to form a membranous web consisting of double membrane vesicles (DMVs) to facilitate HCV replication. The structural proteins (core, E1, E2, p7) form the virus particle, whereas the non-structural proteins NS2, NS3 mediate protein cleavage for viral assembly; NS4A activates NS3; NS4B induces membrane alterations; NS5A assists in replication/ assembly; and NS5B is the actual RNA dependent RNA polymerase (RdRp) that is essential for amplification of the RNA template. Newly formed nucleocapsids assemble with the structural proteins close to the lipid droplets and acquire ER membrane using the host VLDL secretory pathway to form the lipoviroparticle. Large amounts of such virus particles are now ready to infect new host cells.[4] Antiviral agents targeting the HCV replication cycle include:
a) *NS3 Protease*: NS3 has two functions: a protease that's responsible for cleavage at NS3-4A, NS4A4B, NS4B-NS5A, and NS5A-NS5B; and a helicase that's responsible for unwinding HCV RNA. NS3 is also responsible for inactivating or down-regulating the host innate immune response and thus perpetuating viral replication. The protease inhibitors were the first DAAs introduced in the field. They interfere with HCV viral replication by causing a conformational change in the substrate and blocking their cleavage.

There are three different classes of NS3 PIs: 1) covalent and reversible binders (telaprevir, boceprevir); 2) noncovalent binding inhibitors (asunaprevir, faldaprevir); and 3) macrocyclic inhibitors (simeprevir, vaniprevir, danoprevir, grazoprevir). Although these drugs are highly potent, a single nucleotide substitution can induce antiviral drug resistance without diminishing viral fitness. The presence of baseline mutations and limited activity against multiple genotypes are some of the disadvantages seen with first-generation NS3 PIs, but newer PIs like grazoprevir have no such limitations.
b) *NS5B*: NS5B RdRp is an enzyme essential for HCV replication. It has the configuration of a right hand with palm, thumb, and fingers and can occur in a closed state seen during RNA synthesis, or an open state seen during RNA elongation. New RNA synthesized by NS5B is stabilized by host liver-specific microRNA (miR-122) before packaging as new virion particles. There are two subclasses of NS5B inhibitors 1) nucleos(t)ide inhibitors (NIs, eg, sofosbuvir), which mimic natural substrate and become incorporated into the new RNA, resulting in chair termination, or 2) nonnucleoside inhibitors (NNIs, eg, dasabuvir, beclabuvir), which bind to the enzyme and impair its function as RdRp.

The delivery of NIs into the hepatocyte is complex and involves several steps. NIs are administered as prodrug in monophosphate form to increase cellular permeability/uptake and are then converted to a triphosphate by host kinases, becoming a substrate for viral RdRp. NIs are pangenotypic and highly potent, and have a high genetic barrier to resistance. A single nucleotide polymorphism S282T confers resistance to NIs, but the variant occurs rarely, and its replication fitness is dramatically reduced.

On the other hand, NNIs can be chemically different based on their allosteric binding sites on NS5B (palm-1, palm-2, thumb-1, thumb-2) and thus are highly specific to certain genotypes. NNI mutations are typically nonoverlapping except for palm-1 and 2; thus more than one NNI can be used in a combination regimen if needed.
c) NS5A: Unlike NS3 and NS5B, NS5A has no enzymatic property but is essential for RNA replication due to its role in formation of the membranous web and viral assembly. It also exerts other functions by interacting with viral proteins (NS4B, NS5B, RNA) and host cell proteins (cyclophilin A, kinases, etc). It is thought that NS5A inhibitors can disrupt or fragment the NS5A multimers and the membranous web, resulting in marked inhibition of RNA replication. De novo formation of DMVs is also blocked by cyclophilin A inhibitor, which is a partner of NS5A.

d) *New targets*: As discussed above, microRNAs like miR-122 and cyclophilin A inhibitors are also crucial in HCV replication. Miravirsen is a modified antisense oligonucleotide (antagomirs) that can deplete miR-122 and block HCV replication. Preliminary results confirm no development of resistance, but animal studies detected development of steatohepatitis, fibrosis, and even tumors.[5] Cyclophilin A inhibitors like alisporivir can induce conformational changes in NS5A and block HCV replication directly or indirectly through stimulation of NS5B activity.

• *HCV assembly and release*: The newly formed nucleocapsids interact with the core protein and are assembled into cytosolic lipid droplets. NS2 interacts with E1/E2 and p7 close to the lipid droplets during the assembly. It's interesting to note that HCV virion biogenesis closely resembles VLDL biogenesis and involves recruitment of several common factors in the VLDL secretory pathway. Assembled virus particles separate from ER via budding and exit the cell through a p7-dependent secretory pathway.

• *HIV-HCV coinfection*: HIV and HCV have shared modes of transmission, thus coinfection with HCV is prevalent in up to a third of patients infected with HIV globally. In the US, 1.2 million HIV patients (25%) are coinfected with HCV. Due to the profound immune dysregulation that induces HIV, coinfected patients with HCV have lower rates of spontaneous virologic control of HCV, accelerated fibrosis, and higher rates of hepatocellular cancer.[6] HIV and HCV proteins interact with host immune responses and can evade the innate defense mechanisms. Specific mechanisms involved in coinfection include:
a) Effect of HIV on HCV: HIV proteins gp120, Rev, Tat, Nef, and Vpr play an important role in enhancing HCV replication, and gp120 is associated with increased levels of proinflammatory cytokines (IL8), hepatocyte apoptosis, and stimulation of fibrogenesis via stellate cells.

b) Effect of HCV on HIV: The effect of HCV on HIV replication is not well understood. The NS3/ NS4A proteins of HCV interact with the Vpu protein of HIV-1 genome and stimulate the transcription of HIV. HCV core protein also modulates cellular transduction, gene expression and leads to enhanced HIV replication in the macrophages.[6]

These interactions translate clinically into coinfected patients being at three-fold greater risk of progression to liver cirrhosis or decompensation and ten-fold greater risk for liver-related mortality compared to HCV monoinfected patients.[7,8]

References

1. Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989;244:359–362.
2. Zeisel MB, Felmlee DJ, Baumert TF. Hepatitis C virus entry. *Curr Top Microbiol Immunol*. 2013;369:87–112.
3. Zeisel MB, Fofana I, Fafi-Kremer S, Baumert TF. Hepatitis C virus entry into hepatocytes: molecular mechanisms and targets for antiviral therapies. *J Hepatol*. 2011;54(3):566–576.
4) Rupp D, Bartenschlager R. Targets for antiviral therapy of hepatitis C. *Semin Liver Dis*. 2014 Feb;34(1):9-21.
5) Hsu SH, Wang B, Kota J, et al. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver.*J Clin Invest*. 2012;122(8):2871–2883.
6. Liberto MC, Zicca E. Virological Mechanisms in the Coinfection between HIV and HCV. *Mediators Inflamm*. 2015;2015:320532.
7. Lo Re V III, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. *Ann Intern Med*. 2014;160 (6):369-379.
8. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: *Clin Infect Dis*. 2001;33(4):562-569.

back to top

ION-4: SOFOSBUVIR PLUS LEDIPASVIR IN HIV-HCV COINFECTED PATIENTS (GENOTYPE 1 OR 4)

Naggie S, Cooper C, Saag M, et al; for the ION-4 Investigators. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med*. 2015 Aug 20;373(8):705-13

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract

Prior to the DAA era, HIV-HCV coinfected patients represented one of the difficult-to-treat cohorts with interferon (IFN) containing regimens. Pegylated interferon and ribavirin therapy (PR) was associated with low SVR rates, poor tolerability due to AEs resulting from treatment-induced cytopenias.[1,2] Addition of a protease inhibitor (PI), i.e. telaprevir or boceprevir, to PR improved SVR 12 rates compared to PR therapy alone, although such regimens were initially not approved.[3,4] Furthermore many coinfected patients were ineligible to receive interferon and the first generation NS3/4A protease inhibitors due to concerns about side effects with several drug-drug interactions with anti-retroviral therapy (ART) complicating treatment.[3,4]

Sofosbuvir (SOF) is a potent pan-genotypic NS5B nucleotide inhibitor; in the early DAA era, SOF plus ribavirin (RBV) established the concept that all-oral, IFN-free regimens are feasible to treat HCV in HCV-HIV coinfected patients. Initial experience with the IFN-free regimen (SOF plus RBV) was confirmed in the PHOTON-1 and PHOTON-2 trials.[5,6] In PHOTON-1, SOF plus RBV for 12 or 24 weeks in genotype (GT) 1, 2, or 3 resulted in high SVR rates of 75-92%.[5] PHOTON-2 explored the results of same treatment agents as in PHOTON-1, but also in GT4 and for an extended duration of 24 weeks in GT3 coinfected patients.[6] SVR rates > 85% were observed in all the arms of the study across all genotypes.

RECOMMEND TO A COLLEAGUE
NEWSLETTER ARCHIVE
COMPLETE THE POST-TEST
PHYSICIAN POST-TEST
NURSE POST-TEST

Ledipasvir (LED) an NS5A inhibitor, in combination with SOF, was reported in the treatment of HIV-HCV coinfected patients in a phase II pilot study by Osinusi et al.[7] Twelve week therapy in a noncirrhotic, HCV GT1 treatment naïve cohort resulted in an SVR 12 rate of 98% with only one relapse.

ION-4 is a large multicenter phase III study that explored SOF/LED as a fixed-dose combination for 12 weeks in HIV-HCV coinfected patients with GT 1 or 4; the study also included those with prior treatment experience (55%) and compensated cirrhosis (20%). Patients were required to have stable HIV (CD4+ count> 100 and HIV RNA < 50 copies/ml), and to have been on antiretroviral therapy (ART) for at least eight weeks prior to treatment. Several ART agents – emtricitabine, tenofovir, efavirenz, raltegravir, or rilpivirine — were allowed in the study, but not those that included ritonavir or cobicistat-boosted ART. SVR 12 was 96%. Neither the presence of cirrhosis nor prior HCV treatment negatively affected the SVR. Pharmacokinetic profile and SVR rates were identical in all patients, regardless of the ART regimen. Two patients had HCV virologic breakthrough during treatment, which was attributable to noncompliance.

Baseline NS5A RAVs were noted in 18% of the study subjects with GT 1; SVR12 rates were 93% and 97% in those with and without RAVs, respectively. The two patients with on-treatment virologic failure did not have baseline NS5A RAVs but did develop treatment-emergent NS5A RAVs and no NS5B RAVs at the time of breakthrough. CD4+ counts and HIV RNA levels were stable in all patients.

The majority of the patients (77%) had mild to moderate adverse effects (AEs). Serious AEs were noted only in cirrhotic patients, which included development of hepatocellular carcinoma (HCC), spontaneous bacterial peritonitis (SBP), or portal vein thrombosis. One patient died post-treatment from septic endocarditis in the setting of intravenous drug use.

Based on these results, all-oral therapy with SOF/LED —one pill once daily for 12 weeks — appears to be an effective and attractive option in HIV-HCV coinfection. The SVR rates in HIV-HCV coinfected patients are similar to those observed in phase III SOF/LED trials for HCV monoinfected patients (ION-1, 2, 3).[8-10]

References

1. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;351:438-450.
2. Chung RT, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med*. 2004;351:451-459.
3. Sulkowski MS, Sherman KE, Dieterich DT, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. *Ann Intern Med*. 2013;159:86-96.
4. Sulkowski M, Pol S, Mallolas J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, doubleblind, controlled phase 2 trial. *Lancet Infect Dis*. 2013;13:597-605.
5. Sulkowski MS, Naggie S, Lalezari J, et al; for the PHOTON-1 Investigators. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA*. 2014;312:353-361.
6. Molina JM, Orkin C, Iser DM, et al; for the PHOTON-2 study team. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *Lancet*. 2015 Mar 21;385(9973):1098-1106.
7. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA*. 2015;313:1232-1239.
8. Afdhal N, Zeuzem S, Kwo P, et al; for the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection (ION-1). *N Engl J Med*. 2014 May 15;370(20):1889-1898.
9. Afdhal N, Reddy KR. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection (ION-2). *N Engl J Med*. 2014 Apr 17;370(16):1483-1493.
10. Kowdley KV, Gordon SC, Nelson DR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis (ION-3). *N Engl J Med*. 2014 May 15;370(20):1879-1888.

back to top

ALLY-2: SOFOSBUVIR PLUS DACLATASVIR IN HIV-HCV COINFECTED PATIENTS (GENOTYPE 1, 2, 3, OR 4)

Wyles DL, Ruane PJ, Sulkowski MS et al; for the ALLY-2 Investigators. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med*. 2015 Aug 20;373(8):714-725.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View Full Text

Sofosbuvir (SOF), an NS5B nucleotide inhibitor, and daclatasvir (DCV), an NS5A inhibitor, have pangenotypic activity effective in the treatment of HCV genotypes 1 to 6.[1,2] SOF and DCV have good pharmacokinetic profiles and lower potential for drug-drug interactions with most agents used in antiretroviral therapy (ART).[3] The QUADRIH study with DCV, asunaprevir, pegylated interferon, and ribavirin in HIV-HCV coinfected patients resulted in SVR12 of 96%.[4] Results from the ION-3 study[5] showed high SVR rates in HCV GT1 monoinfected patients who were treated with SOF (NS5B) plus ledipasvir (NS5A). ALLY-2 explored whether treatment duration could be truncated to eight weeks in the coinfected population.

ALLY-2 is an open label study in 203 coinfected patients: 151 treatment naïve patients were randomized assigned in 2:1 fashion to receive SOF + DCV for eight weeks or 12 weeks, and 52 treatment-experienced patients (any prior DAA except NS5A) received the therapy for 12 weeks. The study included patients with genotypes 1, 2, 3, or 4 and up to 14% with compensated cirrhosis. The majority of the patients (98%) were on ART and had good HIV virologic control (CD4 > 100, HIV RNA < 200 copies/ml). Several ART agents were allowed in the study, including darunavir–ritonavir, atazanavir– ritonavir, lopinavir–ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc, tenofovir, emtricitabine, abacavir, lamivudine, and zidovudine.

There was a striking difference in the SVR12 rates between the eight-week and 12 week duration arms. Therapy duration of 12 weeks in treatment naïve and treatment experienced HCV GT 1 coinfected patients resulted in high SVR rates of 96% and 97% respectively, whereas those who received only eight weeks of therapy had lower SVR12 of 75%. Among GT 2, 3, and 4 patients, those who received the 12 week course had 100% SVR12, but those who received the eight week course had 78% SVR12. SVR rates were 92% in the patients who had cirrhosis. ALLY-2 results did not mirror ION-3 results because the study subjects were quite different between the two studies (treatment naïve noncirrhotics in ION-3). Therefore, 12 week therapy has been found to be the best approach for patients similar to those in the ALLY-2 cohort (coinfected, multigenotypic, with or without treatment experience, with or without cirrhosis).

No virologic breakthroughs occurred. Baseline NS5A mutation testing was performed in 98% of the patients, 17% of whom harbored RAVs against DCV, although their presence did not significantly effect SVR 12 rates. Among the 12 patients who relapsed, three patients (25%) each with GT 1a, GT 2, GT 3, had baseline RAVs against DCV. Treatment emergent RAVs were found in three other patients.

The treatment was well tolerated, with no drug discontinuation because of AEs. The most common AEs were fatigue, nausea, and headache. Two deaths occurred from cardiac causes after treatment completion but were unrelated to the therapy. Laboratory abnormalities included grade 3-4 hyperbilirubinemia in 4% (among patients taking atazanavir-ritonavir) and lipase elevation in 3% without pancreatitis. CD4 counts remained unchanged, and HIV RNA levels also remained stable, except in one patient who was incarcerated and discontinued the study.

References
1. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al; for the AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014;370:211-221.
2. Nelson DR, Cooper JN, Lalezari JP, et al; ALLY-3 Study Team. All-oral 12-week treatment with Daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*. 2015;61:1127-1135.
3. Eley T, You X, Wang R, et al. Daclatasvir: overview of drug-drug interactions with antiretroviral agents and other common concomitant drugs. *Global Antiviral Journal*. 2014;10:Suppl 1:54-55.
4. Piroth L, Paniez H, Taburet AM, et al; ANRS HC30 QUADRIH Study Group. High Cure Rate With 24 Weeks of Daclatasvir-Based Quadruple Therapy in Treatment-Experienced, Null-Responder Patients With HIV/Hepatitis C Virus Genotype 1/4 Coinfection: The ANRS HC30 QUADRIH Study. *Clin Infect Dis*. 2015 Sep 1;61(5):817-825.
5. Kowdley KV, Gordon SC, Reddy KR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014; 370: 1879-1888.

back to top

TURQUOISE-I: ABBVIE 3D IN HIV-HCV COINFECTED PATIENTS (GENOTYPE 1)

Sulkowski M, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. 2015 Mar 24-31;313(12):1223-1231.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View Full Text

TURQUOISE-I is a randomized, multicenter, open-label study that addressed the safety, efficacy, and tolerability of ombitasvir, paritaprevir plus ritonavir, dasabuvir (3D/PrOD), and ribavirin in HIV-HCV coinfected patients with genotype 1. Ombitasvir is a potent HCV NS5A inhibitor, dasabuvir is a nonnucleoside NS5B polymerase inhibitor, and paritaprevir is a potent NS3/4A protease inhibitor which is boosted with ritonavir. Paritaprevir/ritonavir and ombitasvir are coformulated in a single pill, enabling once daily administration, and along with dasabuvir twice daily with or without ribavirin (RBV), have shown good efficacy in HCV genotype 1 treatment naïve or experienced patients.[1,2] Even with the inclusion of ritonavir in the 3D regimen, no clinically significant drug-drug interactions (DDI) occurred with ART containing any of the following agents: tenofovir, emtricitabine, atazanavir, and raltegravir.[3]

The TURQUOISE-I study included 63 coinfected patients (19% cirrhotics) with HCV GT1 who were randomized to receive 3D plus RBV for 12 or 24 weeks. All patients were on stable antiretroviral therapy with undetectable HIV RNA and CD4 > 200 for at least 24 weeks prior to enrollment. The ART regimen consisted of atazanavir or raltegravir plus two nucleos(t)ide analogue reverse transcriptase inhibitors for at least eight weeks prior to enrollment. SVR 12 rates in the 12 and 24 week arms were 94% and 91%, respectively. Two patients each in the 12 week and 24 week arms relapsed, and one patient in the 24 week arm experienced a virologic breakthrough. Among the patients who relapsed, those who were previously treatment experienced had treatment emergent RAVs against all three viral targets, namely NS3/4A, NS5A, and NS5B.

There was a mild decline in CD4 count (although only during treatment duration in both arms), and three patients had an elevation in HIV RNA > 40 copies/ml but < 200 copies/ml. However, none of the patients required modification of ART regimen during the study period. Up to 90% of the patients reported AEs, but most were mild to moderate. No treatment related SAEs and no drug discontinuations were reported. Severe (grade 3 or 4) laboratory abnormalities were infrequent. Most patients (up to 32%) taking atazanavir inclusive ART experienced indirect hyperbilirubinemia, and up to 19% of patients had RBV induced anemia, which was managed solely by RBV dose adjustment.

References
1. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet*. 2015 Jun 20;385(9986):2502-2509.
2. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med*. 2014 May 22;370(21):1983-1992.
3. Eron JJ, Lalezari J, Slim J, et al. Safety and efficacy of ombitasvir - 450/r and dasabuvir and ribavirin in HCV/HIV-1 co-infected patients receiving atazanavir or raltegravir ART regimens. *J Int AIDS Soc*. 2014 Nov 2;17(4 Suppl 3):19500.

back to top

C-EDGE CO-INFECTION: GRAZOPREVIR/ELBASVIR IN HIV-HCV COINFECTED PATIENTS (GENOTYPE 1, 4 OR 6)

Rockstroh JK, Nelson M, Katlama C, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV*. 2015 Aug;2(8):e319-327.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View journal abstract View Full Text

Grazoprevir (GZP), a next-generation NS3/4A protease inhibitor (MK-5172) and elbasvir (EBR), an NS5A inhibitor (MK-8742) have activity against multiple HCV genotypes (1, 4, 6) and are coformulated in a single pill as a fixed dose combination taken once daily. GZP/EBR has been tested successfully in HCV monoinfection, C-EDGE treatment naïve/treatment experienced trials[1,2] and also in a previously published open label phase II trial in HIV-HCV coinfected patients.[3] In the C-WORTHY trial, 59 HIV-HCV coinfected patients who had good HIV virologic control (undetectable HIV for at least 24 weeks, CD4 count > 300, on antiretroviral therapy for at least eight weeks) were randomized to 12 weeks of GZP/EBR with or without ribavirin (RBV). SVR12 rates for GZP/EBR with and without RBV was 97% and 87%, respectively. The treatment was reportedly well tolerated in this study, which did not include any cirrhotic patients.

The C-EDGE CO-INFECTION study is a phase III, multicenter, international trial that included HIV-HCV coinfected patients with multiple genotypes (1, 4, and 6) and also included patients with compensated cirrhosis (16%). The study included 218 patients who were on stable antiretroviral therapy (ART) and also those who were ART naïve but had favorable characteristics (baseline CD4 > 300, HIV RNA < 50,000 copies/ml). In this open label, single arm trial, all patients received the GZP/EBR fixed dose combination pill once daily (without RBV) for 12 weeks. SVR 12 was reported to be 96% with no virologic breakthrough during treatment. Interestingly, all coinfected patients with cirrhosis (100%) achieved SVR 12. There were no virologic breakthroughs; however, five patients relapsed, two patients reinfected, and one was lost to follow up.

Baseline NS3 resistance was found in 41% of patients, of whom only one had > five-fold resistance to GZP (D168E). All genotype 1b with NS3 resistance associated variants (RAVs) achieved SVR12, and 96% of genotype 1a patients achieved SVR12 — comparable to those who did not have NS3 RAVs. Baseline NS5A RAVs were found in 8% of the total study subjects with genotype 1, with resultant SVR12 of 87%. Only four patients had baseline NS5A RAVs > five-fold against EBR, and three achieved SVR12 (75%). Treatment emergent NS3 and NS5A RAVs were noted in three of four relapsed genotype 1 patients, and only one NS5A RAV was noted in the relapsed genotype 4 patient.

The treatment was generally well tolerated; although a majority of subjects reported at least one mild AE, none led to drug discontinuation. Six SAEs were noted post treatment completion, none of which were drug related. Of note, four patients had increased liver enzymes (ALT/AST > 5x ULN) during and even after treatment completion, which resolved spontaneously and did not affect SVR12. There were no clinically significant changes in CD4 counts or HIV RNA levels during the study period.

References

1. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med*. 2015 Jul 7;163(1):1-13.
2. Kwo P, Gane E, Peng C-Y, et al. P0886 : Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-edge treatment-experienced trial. *J Hepatol*. 2015 Apr;62, Supplement 2:S674–675.
3. Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015 Mar 21;385(9973):1087-1097.

back to top

SOFOSBUVIR PLUS SIMEPREVIR IN HCV PATIENTS WITH SEVERE RENAL IMPAIRMENT OR DIALYSIS

Bhamidimarri KR, Czul F, Adam P, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of Hepatitis C in patients with end stage renal disease. *J Hepatol*. 2015 Sep;63(3):763-765.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)

View Full Text

All the DAAs approved thus far can be safely used without any dose adjustments in patients with glomerular filtration rate (GFR) more than 30 ml/min/1.73 m2. However, no DAAs have been approved for patients with severe renal impairment or end stage renal disease (ESRD) patients on hemodialysis (HD). The C-SURFER study using grazoprevir/elbasvir (GZP/EBR) in severe renal impairment or HD patients demonstrated excellent SVR rates of 99% per protocol analysis and is currently pending approval.[1] HCV treatment in this difficult to treat cohort is feasible with the currently available DAAs, although they are not approved for the indication. This commentary therefore should be considered for off-label use of DAAs in the ESRD cohort and is intended solely to summarize the currently available data so clinicians can consider their use only in patients in urgent need HCV treatment.

Among currently approved drugs to treat HCV, interferon (IFN), ribavirin (RBV) and sofosbuvir (SOF) are eliminated renally. Although IFN is now no longer required in the DAA era, RBV still remains an important component of certain drug regimens. RBV causes hemolytic anemia, which can exacerbate the anemia typically seen in ESRD patients. Thus, RBV dose reduction to approximately 20% of the total dose used in patients with normal renal function is recommended.

The paritaprevir/ritonavir/ombitasvir and dasabuvir (3D/PrOD) regimen requires no dose adjustment in ESRD or HD patients. In the RUBY-1 trial, 20 noncirrhotic ESRD patients, 13 with GT1a received 3D plus RBV 200 mg daily, and seven with GT1b received 3D alone for 12 weeks. Their primary end point was SVR 12, which was achieved in 90% of the patients.[2]

Reduced dose SOF (200mg daily) plus RBV was used in noncirrhotic, non-HD patients with severe renal impairment, but the results showed SVR of only 40%.[3] SOF 200 mg daily had

equivalent drug levels compared to SOF 400 mg daily and significantly reduced GS-331007 metabolite level (300% vs 2070%).[3] This report describes a series of 15 HCV GT 1, ESRD patients (60% cirrhotic) on the transplant waiting list (kidney or liver plus kidney). Treatment in this series included a RBV-free regimen with reduced dose SOF plus full dose simeprevir (SIM) for 12 or 24 weeks. SVR12 was 87%. Two patients, both of whom were cirrhotic, relapsed post treatment completion, had failed prior HCV treatment with protease inhibitor (PI), and were on HD. The treatment was well tolerated and there were no SAEs or treatment discontinuations.

Real world observational data collected by the HCV TARGET group showed that full dose SOF in combination with PR or RBV or SIM (with or without RBV) was well tolerated by the patients, and an overall SVR 12 of 88% was observed.[4] Another small case series of 17 patients by Nazario et al reported SVR12 of 100% with full dose SOF plus SIM for 12 weeks; the regimen was well tolerated in their cohort.[5] Their cohort included 24% cirrhotics, 82% treatment naïve patients, and no PI failures, which could explain the higher SVR12 observed in their study.

Ledipasvir (LED) and daclatasvir (DCV) are NS5A inhibitors that do not need renal dose adjustment and could be combined with another DAAs to treat HCV in ESRD patients. Currently there is no strong safety data in humans with the use of full dose SOF in the ESRD setting, except those reported in small case series. The optimal dose of SOF needs to be formally studied not only in severe renal insufficiency (GFR < 30 ml/min) but also in the HD setting. The PrOD regimen, although unapproved, is a reasonable option to treat HCV patients with ESRD, but it is to be noted that RBV is recommended in those with GT1a. HCV treatment strategies for wait-listed patients for kidney transplant have also been evolving and the transplant team (hepatologist and nephrologist) should be involved in deciding the timing of HCV treatment.

In summary, there are current options to treat HCV in ESRD patients who need to be treated urgently. We recommend individualizing such off-label use to every patient and managed preferably by an HCV expert.

References

1. Roth D, Nelson DR, Bruchfeld A, et al. LP02 : C-surfer: Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 2015 Oct 17;386(10003):1537-1545.
2. Pockros PJ, Reddy KR, Mantry PS, et al. Safety of ombitasvir/paritaprevir/ritonavir plus dasabuvir for treating HCV GT1 infection in patients with severe renal impairment or end-stage renal disease: The RUBY-I study. *J Hepatol*. 2015 Apr;62, Supplement 2:S257.
3. Gane EJ, Robson RA, Bonacini M, et al. Anti-viral efficacy and pharmacokinetics (PK) of Sofosbuvir (SOF) in patients with severe renal impairment. *Hepatology*. 2014;60:667A.
4. Saxena V, Koraishy FM, Sise M, et al. Safety and efficacy of Sofosbuvir-containing regimens in Hepatitis C infected patients with reduced renal function: real-world experience from HCV-target. *J Hepatol*. 2015;62:S267.
5. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and Simeprevir in Hepatitis C genotype 1-patients with End-Stage Renal Disease on hemodialysis or GFR < 30mL/min. *Liver Int*. 2015 Nov 19

back to top

KEY TAKEAWAYS

- The review summarizes the current knowledge of HCV life cycle and possible drug targets of approved and investigational DAAs.
- Current treatment strategies for HIV-HCV coinfection include a variety of DAA combinations (with or without ribavirin), with research showing efficacy differences determined by both HCV genotype and length of therapy.
- There is some case-report guidance on the use of currently available DAAs for HCV treatment in ESRD patients, although no particular combinations or dosing schedules are as yet approved.

back to top

IMPORTANT CME/CE INFORMATION

Program Begins Below

ACCREDITATION STATEMENTS

Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATIONS

Physicians
eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of *1.0 AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
eNewsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hour, or a total of 8 contact hours for the 8 newsletters in this program.

back to top

This activity was developed in collaboration with DKBmed.

PHYSICIAN POST-TEST

NURSE POST-TEST

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

COMPLETE THE POST-TEST

PHYSICIAN POST-TEST

NURSE POST-TEST

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

COMPLETE THE POST-TEST

Step 1.
Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST