JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eHIV Review

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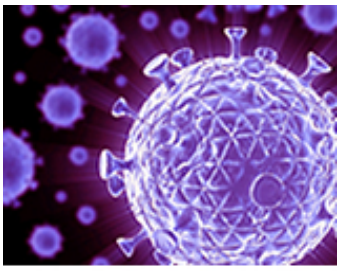

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CURRENT ISSUES IN HIV/HCV COINFECTION

In this Issue...

Current treatment guidelines from the American Association for the Study for Liver Diseases and the Infectious Diseases Society of America recommend the use of interferon and ribavirin-based treatment options in combination with sofosbuvir for genotypes other than 2 and 3. However, the standard of care for HCV infection is rapidly changing with the availability of newer direct acting agents (DAAs) and all-oral treatment regimens — some of which are ribavirin free and short-course (12 weeks or less) and are effective across all HCV genotypes. There is accumulating evidence that HIV/HCV coinfected patients have equally high response rates as those that are monoinfected.

In this issue we review the relevant data supporting the efficacy and safety of DAAs for the treatment of patients with HIV/HCV coinfection.

LEARNING OBJECTIVES

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

- Identify the use of newer HCV direct-acting agents for the treatments of HIV/HCV infection.
- Compare the efficacy results of the HCV direct-acting agents between HCV monoinfected and HIV/HCV coinfected patients.
- Discuss the limitations of the currently available treatment options for HIV/HCV coinfected patients.

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Guest Faculty Disclosure

Shobha Swaminathan, MD and **Lisa L. Dever, MD** have indicated that they no financial interests or relationships with a commercial entity whose products or services are relevant to the content of their presentation.

Unlabeled/Unapproved Uses

Dr. Swaminathan and Dr. Dever have indicated that there will be references to the following products for the treatment of HCV infection: MK-5172, MK-8742, paritaprevir, ombitasvir, dasabuvir, daclatasvir, and vaniprevir.

Program Directors' Disclosures

IN THIS ISSUE

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COMMENTARY

Worldwide, currently 35 million people are infected with HIV[1] and 130 million are infected with HCV.[2] HIV/HCV coinfected persons are known to have accelerated liver disease progression, cirrhosis, and decompensation, compared to HCV monoinfected persons.[3] In addition, HIV/HCV patients are frequently diagnosed with hepatocellular carcinoma and are more likely to have multifocal disease.[4] There has been a recent explosion of direct acting agents (DAAs) for the treatment of HCV infection. The focus of this discussion is to review emerging treatment options and their practical applications.

Newer therapies appear to be equally efficacious in HIV/HCV coinfected and HCV monoinfected patients. This is a critically important difference because previously, HIV/HCV coinfected patients had poorer response rates.[5,6] Current guidelines recommend different medication combinations for different durations, based HCV genotype and HCV treatment history.[7] The COSMOS trial showed that the combination of sofosbuvir and simeprevir with or without ribavirin (RBV) for 12 or 24 weeks resulted in sustained virologic response (SVR12) rates from 67%-100% for patients with genotype 1 HCV monoinfection.[8] For patients with HIV/HCV, genotype 1 coinfection, sofosbuvir with pegylated interferon (IFN) and RBV for 12 weeks, sofosbuvir and weight-based RBV for 24 weeks, or sofosbuvir with simeprevir with or without RBV for 12 weeks, are all guidelines-recommended treatment options. These guidelines continue to recommend IFN-based treatment as the standard of care; however data from multiple clinical trials of DAAs support the use of IFN-free, all-oral HCV treatment regimens. As more medications receive approval from the United States Federal Drug Administration, these guidelines will most likely be revised to reflect an increased emphasis on all-oral HCV therapy with interferon containing regimens playing a limited role.

In the PHOTON-1 trial, as reported by Sulkowski and colleagues and reviewed in this issue, patients with HIV/HCV co-infection (182 treatment-naïve and 41 treatment-experienced) with genotypes 1, 2, or 3 given an all-oral regimen of sofosbuvir and RBV for 12 or 24 weeks had SVR12 rates ranging from 67%- 94% with few adverse events. These results are exciting because they are similar to the 68% SVR 24 results in the SPARE trial that looked at 60 genotype 1 HCV monoinfected patients with difficult to treat characteristics (black race, higher fibrosis scores, early to moderate liver cirrhosis) using sofosbuvir with weight based ribavirin for 24 weeks (SVR 24 for the arm with low dose ribavirin was only 48%).[9]

In addition, sofosbuvir does not have significant drug interactions with the cytochrome P450 system, making it an attractive option for HIV patients on antiretrovirals metabolized through the cytochrome P450 system. In PHOTON-1, HIV/HCV patients with genotype 1 HCV infection who received 24 weeks of sofosbuvir and RBV had SVR12 rates of 76%. Preliminary data from the ERADICATE trial were presented at the European Association for the Study of the Liver (EASL) 2014. This study assessed the efficacy of the recently FDA-approved single pill, fixed-dose combination of ledipasvir (NS5A inhibitor) and sofosbuvir in 50 HIV/HCV coinfected patients with genotype 1a and found an SVR12 rate of 100% in patients not on antiretroviral therapy (ART).[10] These data are comparable to the 94%-100% SVR 12 rate observed with ledipasvir/sofosbuvir when given for 8, 12, or 24 weeks among treatment-naïve and treatment-experienced patients with HCV monoinfection, with or without ribavirin.[11-13]

At EASL 2014, Sulkowski et al presented data on the C-WORTHY study, an all oral regimen combining MK5172 (HCV NS3/4A protease inhibitor) with MK 8742 (NS5A replication complex inhibitor) with or without RBV for 12 weeks among 59 non-cirrhotic patients with HIV/HCV genotype 1 co-infection and for 8 or 12 weeks among 94 treatment-naïve, non-cirrhotic patients with HCV monoinfection. The C-WORTHY study, included in this review, showed an SVR4 rate of 97% with and 90% without RBV, with 29 and 30 subjects included in the two arms of the study. However, it was observed that the shorter-duration treatment group (8 weeks) among HCV monoinfected patients had a higher relapse rate of 17%. It is also important to note that MK 5172 affects the CYP3A4 enzyme system, which may pose a challenge for HIV/HCV patients on ART.

The TURQUOISE-1 trial presented by Sulkowski and co-workers (reviewed in this issue) showed that an all-oral regimen of paritaprevir (formerly ABT-450)/ritonavir/ombitasvir with dasabuvir and RBV in HIV/HCV coinfected genotype 1 patients had SVR12 rates of 94% with 12 weeks of therapy (N = 31) and SVR 4 rate of 97% with 24 weeks of therapy (N = 3 2, SVR 12 results pending). These data were similar to those reported among 380 treatment naïve and experienced HCV monoinfected genotype 1 patients with compensated cirrhosis in the TURQUOISE-II trial, which assessed the same treatment regimen. SVR12 rates were 92% for patients treated for 12 weeks and 96% for those treated for 24 weeks.[14] In the SAPPHIRE-1 trial, 631 HCV genotype 1 monoinfected treatment-naïve, non-cirrhotic patients were treated with the regimen and had SVR12 rates of 95-98%.[15] This multidrug oral regimen is unique in incorporating ritonavir as a booster agent for the HCV DAAs. Its use in HIV/HCV coinfected patients may require adjustment of ART regimens to avoid ritonavir-related drug-drug interactions.

As reviewed in this issue, Sulkowski and others studied an oral combination of daclatasvir and sofosbuvir among 211 patients with HCV monoinfection. The trial included treatment-naïve patients and those that had previously been treated with telaprevir or boceprevir and pegylated interferon and ribavirin. The study authors reported SVR12 rates of 89-100% across HCV genotypes 1-3, including patients with genotype 1 infection who had previously failed treatment with boceprevir and telaprevir-containing regimens. Ribavirin use and the presence of IL28B variants had no effect on SVR rates. A notable feature of daclatasvir is that it has activity across all genotypes. There is an ongoing study to assess this combination in HIV/HCV co-infection (ALLY-2: Daclatasvir and Sofosbuvir for HIV/HCV Co-Infection)

Vaniprevir, a next-generation HCV protease inhibitor, was evaluated as an add-on to IFN and RBV in 211 non-cirrhotic HCV-monoinfected genotype 1 patients that had previously failed IFN-based therapy. This study by Lawitz et al, reviewed in this issue, had multiple treatment arms, including a control group that received IFN and RBV. Patients in the treatment arms achieved SVR24 rates of 67% to 84%, compared with 19% in the control arm. The regimen still requires a backbone of IFN and RBV, as well as twice daily dosing of vaniprevir. Further investigations are needed in the coinfected patient population – and in a regimen free of IFN

With the advent of all-oral DAAs regimens, justifiable concerns have arisen about HCV resistance and its impact on treatment outcomes.[16] The COSMOS study showed that the presence of the Q80K polymorphism at baseline in HCV genotype 1a was associated with numerically inferior SVR12 results when monoinfected patients were treated with sofosbuvir and simeprevir with or without ribavirin.8 HCV variants with pre-existing polymorphisms associated with drug resistance variants have been detected , although their clinical significance is unclear. In general, HCV protease inhibitors have a low barrier to the development of resistance, whereas polymerase inhibitors (nucleos(t)ide and non-nucleoside) have a higher resistance barrier. In the ION-1 and ION-2 studies, the presence of baseline variants associated with resistance did not have an impact on SVR12 results.[12,13] The S282T variant, associated with reduced susceptibility to sofosbuvir, was not detected when used in combination with ledipasvir, suggesting that combination therapy with the newer HCV direct-acting agents may help protect against emergence of resistance.[12,13,17] While NS3 variants generally decayed over time, the NS5A variants persisted – the clinical implications of these variants are still not clear.[18,19]

Some areas still need further investigation. This is especially true for patients with HCV genotype 3 infections (both HCV mono- and HIV-HCV coinfection), for which limited data are available on the use of DAAs. Additional studies should also be performed in underrepresented populations — including blacks, Hispanics, women, and non-genotype 1 patients—to ensure applicability of study results across patient groups.

In summary, the treatment of HCV infection with regimens containing newer DAAs has been shown to be highly effective and safe. There is accumulating evidence that HIV-infected patients respond equally well to these regimens. Multiple new DAAs are likely to be approved in the near future, giving patients and providers additional treatment options.

Factors driving optimal HCV treatment regimens include efficacy and tolerability of the drugs, fixed-dose combinations such as ledipasvir-sofosbuvir, consideration of drug

interactions, concern for emergence of HCV resistant mutants, and cost. Treatment decisions, including whether to begin HCV therapy with the currently available DAAs or to wait for approval of drugs currently under investigation will have to be individualized and made in discussion with the patient.

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PHOTON-1: SOFOSBUVIR PLUS RIBAVIRIN FOR HIV/HCV CO-INFECTION

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for Hepatitis C in patients with HIV coinfection. *JAMA*. 2014(4);312:353.

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Sulkowski and coinvestigators report the results of the PHOTON-1 trial, an open-label, nonrandomized, multicenter, uncontrolled phase 3 trial of an all-oral regimen of sofosbuvir and an NS5B polymerase inhibitor, plus ribavirin for coinfected patients with HCV genotypes 1, 2, or 3. Treatment-naïve patients with HCV genotypes 2 or 3 received 400 mg of sofosbuvir and weight-based ribavirin for 12 weeks. All patients with genotype 1 infection and treatment-experienced patients with HCV genotypes 2 or 3 received the same treatment for 24 weeks. All patients were receiving antiretroviral therapy (ART) with HIV RNA viral loads of 50 copies/ml or less and CD4 counts greater than 200 cells/μl or had untreated infection with CD4 cell counts greater than 500 cells/μl. The primary study outcome was the proportion of patients with sustained HCV virologic response (< 25 copies of HCV/ml) 12 weeks after completion of therapy (SVR12).

The study enrolled 224 coinfected patients. Included were 115 treatment-naïve subjects with HCV genotype 1, 68 treatment-naïve subjects with genotype 2 or 3, and 41 patients with genotype 2 or 3 that had been previously treated with peginterferon and ribavirin. Across all treatment arms the majority of patients were men (~85%) and the mean age was ~50 years. Of the HCV genotype 1 patients, 61% were white and 33% black. HCV genotype 1a, a more difficult to treat subtype, was the most common HCV 1 genotype subtype (79%). The IL28B CC gene variant, associated with better interferon treatment responses, was present in ~30% of treatment-naïve patients and in 49% of treatment-experienced patients. Cirrhosis was more common in treatment-experienced patients (24%) vs. treatment-naïve patients (10% or less). In each treatment group, 90-98% of patients were taking ART. Median CD4 counts for the groups ranged from 562 to 581.

The investigators found:

- 92% of patients completed treatment.
- Rapid virologic response rates at week 4 of treatment were high: 96% for HCV genotype 1 and 2 and 100% for HCV genotype 3.
- 76% of treatment-naïve patients with HCV genotype 1 and 88% with HCV genotype 2 achieved SVR12.
- Only 67% of treatment-naïve patients with HCV genotype 3 achieved SVR12.
- 92% of treatment-experienced patients with HCV genotype 2 and 94% with HCV genotype 3 achieved SVR12.
- No mutations were detected by HCV viral sequencing in patients with virologic failure.
- The two patients with viral breakthrough during treatment had undetectable levels of sofosbuvir, suggesting nonadherence.
- The factor most strongly associated with successful outcome (SVR12) was completion of treatment.
- 14 patients (6%) experienced serious adverse effects; only 7 (3%) required discontinuation of therapy.
- Fatigue, insomnia, headache, and nausea were the most frequent adverse effects
- The most common laboratory abnormalities were anemia (15% of patients) and elevated indirect bilirubin (32 of 34 of these patients were taking ritonavir-boosted atazanavir).
- There were no clinically significant changes in HIV RNA levels for patients not on ART.

The study represents a major step forward in the treatment of HCV infection in HIV-infected patients. The use of a 3- to 6-month, all-oral regimen that is highly effective, safe, and lacking in drug interactions, sets a new treatment benchmark. Furthermore, it appears to have overcome the treatment disadvantage of interferon-based therapies in the coinfected population.

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LONESTAR: SOFOSBUVIR + LEDIPASVIR FIXED-DOSE COMBINATION FOR HCV GENOTYPE 1 INFECTION

Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomized, phase 2 trial. *Lancet*. 2014 383(9916); 515-523.

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This was a small, single-center, open-label study assessing the safety and effectiveness of a fixed-dose combination of ledipasvir 90 mg and sofosbuvir 400 mg given with or without weight-based ribavirin for 8-12 weeks for HCV-treatment naïve participants (cohort A) and for 12 weeks for patients previously treated for HCV (cohort B). All participants had genotype 1 infection, and none was HIV-infected. Ledipasvir, a HCV NS5A inhibitor, has potent activity against HCV genotypes 1a and 1b. Sofosbuvir has activity across genotype 1-6. The primary end point was SVR12.

Cohort A participants were randomized to one of three arms:

1) ledipasvir and sofosbuvir for 8 weeks (N = 20)
2) ledipasvir and sofosbuvir with ribavirin for 8 weeks (N = 21)
3) ledipasvir and sofosbuvir for 12 weeks (N = 19)

Cohort B participants (HCV protease inhibitor treatment experienced) were randomized to one of two arms:

4) ledipasvir and sofosbuvir for 12 weeks (N = 19)
5) ledipasvir and sofosbuvir with ribavirin for 12 weeks (N = 21)

The study enrolled 100 consenting participants; the majority were men (66%), with a median age ranging from 46-54 years, and 80% were white. Most participants had genotype 1a infection, and while there were no cirrhotics in the treatment-naïve arm, 55% of patients in the treatment-experienced group had cirrhosis.

Overall the combination was extremely efficacious with SVR12 rates > 95% in all treatment arms:

- 99% completed treatment.
- 99% had undetectable HCV VL at week 4 of treatment.
- 100% had undetectable HCV VL at the end of treatment.
- 97% attained SVR12 (arm 1: 95%, arm 2:100%, arm 3: 95%, arm 4: 95%, arm 5: 100%).

The study medications were well tolerated, with < 5% reporting serious adverse events. The most common side effects were nausea and anemia, both of which were more common in the ribavirin containing arms and were managed with ribavirin dose reductions.

All patients underwent screening at baseline for the presence of resistance-associated variants (RAVs) in the NS3 and NS5A regions. Although NS3 protease inhibitor RAVs were detected at baseline in 33 patients (4 [7%] in cohort A and 29 [73%] in cohort B), all 33 attained the primary end point of SVR12, suggesting that protease RAVs may not be clinically significant for patients treated with this protease inhibitor-sparing regimen. NS5A RAVs were detected at baseline in nine patients, seven of whom achieved SVR12; two patients relapsed, both had NS5A RAV detected at relapse. Of note, the presence of cirrhosis did not have an impact on the treatment outcome, regardless of the addition of ribavirin, suggesting that 12 weeks of sofosbuvir plus ledipasvir may be a potential option in this population with difficult-to-treat HCV.

This is one of the first studies demonstrating the safety and efficacy of a single, fixed-dose combination tablet for HCV infection. The regimen was simple, well-tolerated, and highly effective when given for short periods of time in populations with difficult- to-treat HCV. The expectation is that similar outcomes could be expected for HIV/HCV coinfected patients.

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MK-5172/MK-8742 WITH AND WITHOUT RIBAVIRIN FOR HCV GENOTYPE 1 INFECTION IN COINFECTED PATIENTS

Sulkowski M, Mallolas J, Pol S, et al. Efficacy and safety of the all-oral regimen, MK-5172/MK-8742 +/- RBV for 12 weeks in GT1 HCV/HIV coinfected patients: the C-WORTHY study. 49th European Association for the Study of the Liver International Liver Congress (EASL 2014). London, April 9-13, 2014. Abstract O63.

View abstract

This phase 2 study looked at the safety and efficacy of MK-5172 (HCV NS3/4A protease inhibitor) and MK-8742 (HCV NS5A replication complex inhibitor) when used to treat previously untreated HIV/HCV genotype 1 coinfected patients without cirrhosis for 12 weeks with or without ribavirin. This abstract reports sustained virologic response rates four weeks after completion of therapy (SVR4). HIV/HCV coinfected participants needed to have undetectable HIV RNA for 24 weeks prior to entry, a CD4 > 300 cells/cu mm, and stable antiretroviral therapy (ART) with raltegravir and two nucleoside reverse transcriptase inhibitors. ART modification was allowed until eight weeks prior to enrollment.

A total of 59 participants were enrolled, 29 in the arm with ribavirin and 30 in the arm without ribavirin. The demographics in both arms were comparable. The majority of patients were men (80%) with a mean age of ~ 45 years, and 75% had genotype 1a infection. Fifteen percent of participants were black/African American, and 8% were Hispanic or Latino. None had cirrhosis.

The investigators reported:

- All patients in the arm receiving ribavirin had undetectable HCV RNA at weeks 4, 8, and 12 on treatment. One subject relapsed and did not achieve SVR4; 97% of subjects in this arm achieved SVR4.
- In the group not receiving ribavirin, all patients had a negative HCV RNA result at week 4 of treatment — however virologic breakthrough was observed in two patients, and one was lost to follow-up, resulting in an SVR 4 of 90% in this group.
- All three virologic failures were observed in HCV genotype 1a. One of those participants was in the ribavirin arm, and two were in the ribavirin-sparing arm. The two participants in the ribavirin-free arm had virologic breakthrough and low levels of MK-5172 and/or MK 8742, suggesting nonadherence. One of those two had NS5 RAVs detected at baseline and additional NS3 RAVs detected at failure. The second had wild-type virus at baseline and was then found to have both NS3 and NS5 RAV at failure.
- The patient treated with ribavirin who relapsed had NS5 resistance detected at baseline.
- There was no HIV breakthrough reported, and CD4 counts remained stable.

Overall treatment was well tolerated. Serious side effects were reported in two (7%) patients receiving ribavirin and in one (3%) not receiving ribavirin. The most common side effects were headache, asthenia, fatigue, and disturbed sleep, all of which were numerically more common in the ribavirin arm.

Although only SVR4 data are reviewed here, this study suggests that typically populations with difficult-to-treat infections such as those with HIV/HCV co-infection may be able to be treated similarly to monoinfected populations. We await SVR12 data, as well as additional HIV/HCV drug interaction data that will also be needed to apply this regimen more broadly.

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TURQUOISE-1: SAFETY AND EFFICACY OF ABT-450/R/OMBITASVIR, DASABUVIR, AND RIBAVIRIN FOR HIV/HCV CO-INFECTION

RECOMMEND TO A COLLEAGUE

NEWSLETTER ARCHIVE

Sulkowski M, Eron JJ, Wyles D, et al; TURQUOISE-1: Safety and efficacy of ABT-450/r/ombitasvir, dasabuvir, and ribavirin in patients coinfected with hepatitis C and HIV-1. 20th International AIDS Conference. Melbourne, Australia, July 20-25, 2014. Abstract MOAB0104LB

View abstract

This study looked at the safety and efficacy of 12 or 24 weeks of co-formulated paritaprevir (HCV NS3/4A protease inhibitor; formerly ABT-450) /ritonavir /ombitasvir (HCV NS5A replication complex inhibitor) 150/100/25 mg/d plus dasabuvir (NS5B polymerase inhibitor) 250 mg twice daily plus weight-based ribavirin (1000-1200 mg/d) in HIV/HCV coinfected patients with HCV genotype 1 who were HIV virologically suppressed on tenofovir, emtricitabine, and either raltegravir or atazanavir and had not been previously treated with a direct-acting HCV antiviral. Participants were allowed to have Child-Pugh A cirrhosis and had to have an HIV viral load < 40 copies/ml and CD 4 > 200 cells/cu mm or CD4% > 14%. The primary endpoint was sustained virologic response at 12 weeks (SVR12) in both arms.

A total of 64 participants was randomized to the following groups:

1) paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks (n = 31)
2) paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks (n = 32)

Over 90% of participants were men with a mean age of 51 years; ~25% were black/African American. The majority (> 87%) of participants had genotype 1a infection. Roughly two-thirds were HCV treatment-naïve. Sixteen percent were prior null-responders.

The study found: • SVR12 was 93.5% in arm 1 and 95% in arm 2 (based on first 20 evaluable subjects) • one patient in each arm was noted to have a relapse at the end of treatment (end-of-treatment response was 97% in both groups); both had genotype 1a, IL28B TT genotype, and were cirrhotic. They were also observed to have multiclass HCV drug resistance mutations at failure that were not detected at baseline.

Overall, the regimen was well tolerated, with no serious adverse events reported. The most common side effects reported were fatigue, headache, pruritus, insomnia, and icterus (only in patients on atazanavir). Anemia significant enough to cause reduction of ribavirin dose was seen in six patients, without requiring additional erythropoietin or transfusion and all of those six patients achieved SVR, suggesting that this dose reduction did not have an impact on the efficacy of the treatment. A bump in HIV viral load to ≥ 40 c/mL but < 200 c/mL was observed in five patients, but all subsequently achieved full resuppression of HIV-1 RNA without changing their antiretroviral therapy or interrupting HCV treatment.

This is a unique study, since it incorporates the use of HCV direct-acting agents in combination with ritonavir, a commonly used medication for antiretroviral therapy, and demonstrates that short courses of treatment (12 weeks) are very effective in the HIV-infected population. Additional information about drug dosing, particularly for patients using ritonavir with other medications such as darunavir, lopinavir, and for those using twice-daily ritonavir, will be helpful.

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DACLATASVIR PLUS SOFOSBUVIR FOR HCV MONOINFECTION

Sulkowski MS, Gardiner DF, Rodriquez-Torres M, et al; Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014;370 (3):211-221.

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This paper reports the results of an open-label multicenter study of daclatasvir (60 mg), an NS5A inhibitor, in combination with sofosbuvir (400 mg), with or without ribavirin (weight based for genotype 1 and 800 mg for genotypes 2 and 3). Subjects included treatment-naïve patients with genotypes 1, 2, or 3 infection and patients with genotype 1 infection who had failed treatment with boceprevir or telaprevir. HIV-infected patients were not included. The primary efficacy endpoint was SVR12.

Patients (n = 88) were randomized in a 1:1:1 ratio to the following arms:

1) sofosbuvir for one week, followed by daclatasvir and sofosbuvir for 23 weeks
2) daclatasvir and sofosbuvir for 24 weeks
3) daclatasvir and sofosbuvir with ribavirin for 24 weeks

Following a protocol amendment, additional patients (n = 123) with HCV GT1 were randomized 1:1 to:

4) daclatasvir and sofosbuvir with or without ribavirin for 12 weeks in treatment-naive patients
5) daclatasvir and sofosbuvir with or without ribavirin for 24 weeks in patients who previously failed therapy with a first-generation HCV-protease inhibitor-based regimen

The first arm had a lead-in period to determine whether initial HCV suppression with sofosbuvir would reduce emergence of daclatasvir-resistant variants. The majority of participants were Caucasian (83%) men (52%) whose mean age was 52 years. HCV genotype 1a was present in 63% of the subjects, genotype 1b in 17%, genotype 2 in 12%, and genotype 3 in 9%. The favorable IL28B CC gene variant ranged from 2% in previously treated genotype 1 patients to 57% in treatment-naïve patients. The majority of patients in each group had evidence of moderate to advanced fibrosis (Metavir scores F2-F4).

Findings included:

- 207 patients (98%) completed the study.
- Among patients with genotype 1 infection:
  - 98% of 126 treatment-naïve patients achieved SVR12.
  - 98% of 41 patients who had failed prior HCV first-generation protease inhibitor-based therapy achieved SVR12.
- 92% of 26 patients with genotype 2 infection achieved SVR12.
- 89% of 18 patients with genotype 3 infection achieved SVR12.
- SVR12 rates were similar for HCV subtypes 1a (98%) and 1b (100%).
- There were no differences in SVR12 rates based on RBV status (94% with and 98% without RBV).
- SVR12 rates did not differ by IL28B variant status.
- Virologic relapse was confirmed in one patient with genotype 3 (treated without ribavirin); resistance analysis showed a preexisting NS5A polymorphism associated with daclatasvir resistance. This polymorphism (but no others) was also found at relapse.
  - Pretreatment polymorphisms known to confer loss of susceptibility to daclatasvir in vitro were observed in 32 of 204 subjects. Aside from the one subject with relapse, all subjects with these pretreatment polymorphisms achieved SVR12.
- 10 patients experienced serious adverse events; only two required discontinuation of therapy.

- The most common adverse events were fatigue (37%), headache (29%), and nausea (19%).
- Anemia was more common and severe in RBV-treated patients.

This study demonstrated that an all-oral regimen of daclatasvir and sofosbuvir without ribavirin was associated with high rates of SVR12 across all patient groups studied, including those that had previously failed telaprevir or boceprevir, and was well tolerated. Although HIV-infected patients were excluded from the trial, there is reason for optimism that that the combination will be effective in coinfected patients.

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VANIPREVIR FOR HCV GENOTYPE 1 INFECTION IN TREATMENT-EXPERIENCED MONOINFECTED PATIENTS

Lawitz E, Rodriguez-Torres M, Stoehr A, et al. A phase 2B study of MK-7009 (vaniprevir) in patients with genotype 1 HCV infection who have failed previous pegylated interferon and ribavirin treatment. *J Hepatology*. 2013;(59):11-17.

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Vaniprevir, an HCV protease inhibitor, was evaluated with peg-interferon (peg-IFN) and weight based-ribavirin (RBV) therapy in non-cirrhotic patients with genotype 1 HCV infection who had failed prior peg-IFN/RBV therapy. The trial was randomized, placebo-controlled, double-blinded, and multinational. Primary endpoints were efficacy (SVR24) and safety.

Patients were randomized to five treatment arms:

1) 24 weeks vaniprevir 600 mg twice daily plus peg-IFN/RBV
2) 24 weeks vaniprevir 600 mg twice daily plus peg-IFN/RBV followed by 24 weeks of peg-IFN/RBV plus placebo
3) 48 weeks vaniprevir 300 mg twice daily plus peg-IFN/RBV
4) 48 weeks vaniprevir 600 mg twice daily plus peg-IFN/RBV
5) 48 weeks peg-IFN/RBV plus placebo (control)

Patients were stratified into four categories based on previous prior response to peg-IFN/RBV: null response, partial response, breakthrough, and relapse. The study enrolled 211 patients, with 41 to 44 in each treatment arm. Across all treatment arms the majority of patients were Caucasian (78%) men (62 %), and the mean age was 50 years. HCV genotype 1b was present in 57%; genotype 1a in 42%.

Reported results included:

• 190 patients (90%) completed the study.
• SVR24 rates were 71% (arm1), 84% (arm 2), 67% (arm 3), 78% (arm 4), and 19% (arm 5) • SVR24 rates for patients on vaniprevir + peg-IFN/RBV were statistically superior to peg-IFN/RBV plus placebo in all treatment groups ($P < 0.001$).
• The highest SVR occurred in patients stratified as partially responding or relapsing. • Most patients (80%) had non-CC IL28 genotypes. The effect of IL28 genotype was not significant when considering only vaniprevir treatment groups.
• Drug-related adverse events occurred in 90 to 98% of patients receiving vaniprevir vs. 83% in the control arm.
• There were no significant differences in the rates of anemia or rash between the study arms.
• Patients receiving vaniprevir had higher rates of gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to controls.

This study, while excluding HIV patients, demonstrated the safety and efficacy of a HCV protease inhibitor in a difficult to treat population that included prior peg-IFN plus those

who did not respond to RBV and those with unfavorable treatment prognostic factors (HCV genotype subtype 1a and non-CC IL28 gene variants). Vaniprevir, however, has considerable gastrointestinal side effects, and SVR rates for this medication in combination with peg-IFN and RBV are lower than those reported for other DAAs. The regimens studied here will likely be rendered obsolete in the era of all-oral DAA therapy.

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LAUNCH DATE

February 26, 2015; activities expire 2 years from the date of publication.

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- As the demographics of HIV have shifted to include many older adults, clinicians require education regarding the treatment of common comorbidities.
- Clinicians may be unclear about issues specific to the diagnosis and treatment of women with HIV.
- Many clinicians require education regarding current treatment and new emerging hepatitis C medications in patients coinfected with HIV/HCV who require antiretroviral therapy.
- Clinicians may need an update on current recommendations for the treatment of HIV with HAART.

INTENDED AUDIENCE

The target audience (clinicians) for this initiative includes infectious disease (ID) specialists, primary care physicians (PCPs), nurse practitioners (NPs), physician assistants (Pas), and other health care practitioners whose work/practice includes treating patients with HIV.

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Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
(Updated 4/09 and 3/14)

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Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

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This activity was developed in collaboration with DKBmed.

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PHYSICIAN POST-TEST

NURSE POST-TEST