



eLITERATURE  
REVIEW

eViralHepatitis Review  
Podcast Issue

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.



HOME CME/CE INFORMATION PROGRAM DIRECTORS NEWSLETTER ARCHIVE EDIT PROFILE RECOMMEND TO A COLLEAGUE

VOLUME 4 – ISSUE 7: TRANSCRIPT

## Featured Cases: Hepatitis C Treatment in the HIV Coinfected and Dialysis Populations

Our guest authors are Paul Martin, MD, FRCP, FRCPI, Professor of Medicine and Kalyan Ram Bhamidimarri, MD, MPH, Assistant Professor of Clinical Medicine at the University of Miami School of Medicine.

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

- Discuss how direct-acting antiviral agents target the HCV life cycle and how they differ from prior interferon-based regimens.
- Describe the current data on direct-acting antiviral combinations for the treatment of HCV in HIV-HCV coinfecting patients.
- Summarize the current evidence providing guidance on HCV treatment options in patients with end-stage renal disease who need urgent treatment.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of HCV treatment in the clinic in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 4, Issue 6 eViralHepatitis Review newsletter—The HCV Viral Life Cycle and Treatment in HIV Coinfection and Dialysis Populations.

### Unlabeled/Unapproved Uses

Dr. Paul Martin and Dr. Kalyan Ram Bhamidimarri have indicated that there will be reference to the use of direct-acting antiviral agents in patients with severe renal impairment or end-stage renal disease who are on hemodialysis and need urgent hepatitis C treatment.

### MEET THE AUTHORS



**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 Disclosure

Dr. Paul Martin has disclosed that he has received grant support from Gilead Sciences, Inc. and Merck & Co. Dr. Kalyan Ram 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.

**Release Date**  
April 18, 2016

**Expiration Date**  
April 17, 2018

### 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

**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

**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**

*Podcast:* The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nurses**

*Podcast:* This 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hours a total of 3 contact hours for the six podcasts in this program.

**SUCCESSFUL COMPLETION****DISCLAIMER STATEMENT****STATEMENT OF RESPONSIBILITY****STATEMENT OF NEED****INTENDED AUDIENCE****CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS****HARDWARE & SOFTWARE REQUIREMENTS**

Mr. Bob Busker: Welcome to this eViralHepatitis Review Podcast.

Today's program is a follow-up to our newsletter on *HCV Management in the HIV-Coinfected and Dialysis Populations*. With us today, from the University of Miami School of Medicine, are that issue's authors: Dr. Paul Martin, Professor of Medicine and Chief of the Division of Hepatology, and Dr. Ram Bhamidimarri, Assistant Professor of Clinical Medicine and Medical Director for Small Bowel & Multi-Visceral Transplantation at the Miami Transplant Institute.

eViralHepatitis Review is jointly presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, Inc., and Merck & Co.

Learning objectives for this audio program include:

- Discuss how direct-acting antiviral agents target the HCV life cycle and how they differ from prior interferon-based regimens.
- Describe the current data on direct-acting antiviral combinations for the treatment of HCV in HIV-HCV coinfecting patients.
- Summarize the current evidence providing guidance on HCV treatment options in patients with end-stage renal disease who need urgent treatment.

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

Our guests have indicated that there will be reference to the use of direct-acting antiviral agents in patients with severe renal impairment or end-stage renal disease who are on hemodialysis and need urgent hepatitis C treatment.

I'm Bob Busker, managing editor of eViralHepatitis Review. Dr. Martin and Dr. Bhamidimarri, thank you for joining us today.

**DR. MARTIN:** Thank you so much for including us in this exciting program.

**DR. BHAMIDIMARRI:** Thank you for inviting us.

**MR. BUSKER:** Because of the success the direct acting antiviral agents have shown in the general population, the focus has now shifted to those patients who have been termed "hard to treat." As you discussed in your newsletter issue, these include patients with hepatitis C who are coinfecting with HIV, those who have failed prior HCV therapy, and those with significant renal disease. Today I'd like to follow up on that information from a clinical perspective. So start us out, if you would, Dr. Martin, with a patient scenario.

**DR. MARTIN:** Okay, Bob, we recently saw a 63 year old patient from Pakistan with HIV and hepatitis C genotype 3 with prior null response to pegylated interferon and ribavirin therapy. He came to the clinic and was interested in new hepatitis C treatments. His recent liver biopsy three months ago showed that he has F3 and fatty liver. His HIV is well controlled with a regimen that contains two NRTIs and a PI. His current CD4 count is greater than 700 and his HIV RNA is undetectable.

He has gathered information about new DAAs from various companies including sofosbuvir, simeprevir, 3D, sofosbuvir/ledipasvir, daclatasvir and wants to find out which of these would be effective to treat his hepatitis C and in what combination.

**MR. BUSKER:** This patient, whose HIV is well-controlled, has asked you about a whole laundry list of therapies for his hepatitis C coinfection. Let's back up and let me ask you, Dr. Bhamidimarri, would you review for us how the DAA agents are classified.

**DR. BHAMIDIMARRI:** Unlike the prior hepatitis C agents used to treat hepatitis C, DAAs are direct acting antivirals. These agents directly inhibit hepatitis C at several discrete stages in its life cycle. The discovery of these DAAs was a major breakthrough because of their mechanism of action. They're efficacious, safe, and tolerable and can be given orally. Based on where these agents' targets of action are on the hepatitis C life cycle, they're classified into hepatitis C entry inhibitors, hepatitis C RNA replication inhibitors, assembly inhibitors, or inhibitors of hepatitis C exit out of the cell.

Research for these different direct acting antivirals is ongoing, but the currently available ones have known

target sites on the hepatitis C genome. They're broadly classified as protease inhibitors, which act on NS3 and NS4; NS4A inhibitors, which act on the NS5A part of the genome; and NS5B inhibitors, which act on the RNA dependent RNA polymerase. They are further classified into nucleotide inhibitors and nonnucleotide inhibitors.

These agents are typically named "previrs," which are the protease inhibitors; the "asvirs," which are the NS4A inhibitors; and the "buvirs," which are NS5B inhibitors — for example, sofosbuvir, dasabuvir, beclabuvir, et cetera.

**MR. BUSKER:** A lot of these agents the patient has asked about are combinations, sofosbuvir/ledipasvir, for example. How do you combine DAAs? Dr. Martin?

**DR. MARTIN:** That's a very important point. Similar to HIV treatment, DAAs cannot be used as monotherapy because of the rapid selection of resistant variants as a result of the error prone polymerase of the hepatitis C virus. NS3 and 4 PIs are highly potent and have limited genotype specificity, mostly against genotypes 1 and 4. Newer generation PIs are superior to early generation PIs in regards to efficacy, drug/drug interactions and barrier to resistance.

NS5A inhibitors are highly potent, with multigenotypic coverage and intermediate barrier to resistance. Most NS5A inhibitors are effective against genotypes 1 and 4. NS5B inhibitors are further classified into NI or NNI. NIs have intermediate potency but have pangenotypic coverage and a high barrier to resistance. NNIs, on the other hand, have limited genotypic coverage and lower resistance barrier than NIs.

Therefore, to decide on a combination regimen, different properties of the DAAs have to be considered. These include safety, efficacy, and ability to minimize resistance. Cost effectiveness is also a determinant that must be factored into considering a DAA combination, as current HCV therapies are very expensive.

**MR. BUSKER:** The idea of combining DAAs within the same class — is that commonly done, Dr. Bhamidimarri?

**DR. BHAMIDIMARRI:** That's a good question. Typically, direct acting antivirals of the same class have same mechanism of action. They're generally

not combined because there is no added advantage to doing that. The only exception to the rule is with the nonnucleotide inhibitors, the NNI-NS5B inhibitors. Because these NNIs typically have target actions on different allosteric sites on the hepatitis C genome than the NS5Bs, they can be combined, especially if they have different allosteric sites of inhibition. The current recommendations include combination DAAs either with an NS5B backbone, which can include NI or an NNI; or an NS5A backbone and NS3/NS4 inhibitors can be added with or without ribavirin. A newer generation PI plus an NS5A inhibitor, again without NS5B included in the regimen, is grazoprevir and elbasvir in a single pill, fixed dose combination; this combination has proved quite efficacious in clinical trials.

**MR. BUSKER:** Going back to the patient you described, Dr. Bhamidimarri, what would be your DAA recommendation?

**DR. BHAMIDIMARRI:** Now that his HIV is well controlled, he has a hepatitis C genotype 3, and given all the agents that are approved right now, the one that has the highest proven efficacy for genotype 3 patients is a combination of sofosbuvir plus daclatasvir. Of all the agents he has researched, we think sofosbuvir/daclatasvir for 12 weeks would be the right regimen for him.

**MR. BUSKER:** Thank you for that case and discussion, doctors. And we'll return with Drs. Paul Martin and Ram Bhamidimarri from the University of Miami School of Medicine in just a moment.

**MS. JULIE MCARTHUR:** Hello. I'm Julie McArthur, Adult Nurse Practitioner in the Division of Infectious Diseases at Johns Hopkins University. I'm one of the program directors of *eViralHepatitis Review*.

*eViralHepatitis Review* is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to hepatologists, infectious disease specialists, primary care physicians, nurses, nurse practitioners, and other clinicians caring for patients with viral hepatitis.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the exam room and at the bedside.

Subscription to *eViralHepatitis Review* is provided without charge or prerequisite.

Continuing education credit for each issue and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe to and receive *eViralHepatitis Review* without charge, and to access back issues, please go to our website: [www.eViralHepatitisReview.org](http://www.eViralHepatitisReview.org)

**MR. BUSKER:** Welcome back to this *eViralHepatitis Review* podcast. I'm Bob Busker, managing editor of the program. Our topic is Hepatitis C Treatment in the HIV Coinfected and Dialysis Populations. And our guests are Dr. Paul Martin and Dr. Ram Bhamidimarri from the University of Miami School of Medicine. We've been discussing the clinical implications of some of the information presented in our guests' newsletter issue. So to continue, Dr. Bhamidimarri, please bring us another patient scenario.

**DR. BHAMIDIMARRI:** This was another patient we saw in our clinic. He's a 55 year old man with anxiety and depression. He has HIV-1 that is well-controlled on antiretroviral therapy. He contracted hepatitis C genotype 1B from one of his male sexual partners; he thinks he contracted it in 2003. He has failed two prior treatments with pegylated interferon and ribavirin in 2004 and 2007, and more recently he failed boceprevir plus peginterferon and ribavirin in 2011. He recalls that he had significant side effects, including fatigue, worsening depression, work absenteeism, anemia, and leucopenia requiring growth factors and blood transfusions during the prior interferon based treatments. He also recalls that he had F1 fibrosis in 2004, F2 fibrosis in 2007, and recently F3/F4 prior to the boceprevir treatment in 2011. His latest FibroScan results show that his score is around 22 kilopascals, which is consistent with cirrhosis. He's anxious that this fibrosis score has worsened in the last 10 years, but he did not want further interferon-based hepatitis C treatments because he fears side effects. He read about the new direct acting antiviral agents and the options that are currently available, but he is very skeptical about the adverse effects and wants to find out about the new treatment options.

**MR. BUSKER:** Patients who have previously failed interferon/ribavirin now coming back to ask about

DAA therapy — I think this is something many clinicians are seeing today. Dr. Martin, give us some specifics, please: how do these new DAAs differ from the interferon-based therapies?

**DR. MARTIN:** That's a very important issue. We've been fortunate to witness a revolution in the treatment of hepatitis C over the last few years, which has led to an entirely new terminology, which we now refer to as the interferon era and the DAA era. These differences are quite notable in patients with hepatitis C mono-infection, but they also have important implications for patients who are coinfecting with hepatitis C and HIV.

As a group, patients with HIV-hepatitis C coinfection were a difficult population to treat with interferon-based regimens. This is reflected in a number of factors, not only accelerated progression of fibrosis, but generally poorer tolerability and lower sustained virological response rates with interferon and ribavirin based regimens, and I think our patient nicely illustrates that.

But importantly for coinfecting patients, direct acting antivirals, especially those approved since the first-generation drugs telaprevir and boceprevir, are tolerable and efficacious and have limited drug/drug interactions, even in patients who take antiretroviral therapy. The SVR rates with DAA therapy in coinfecting patients are identical to those in hepatitis C mono-infected patients, so the former is no longer considered a difficult to treat cohort.

**MR. BUSKER:** Dr. Bhamidimarri, what treatment options are available for patients such as this?

**DR. BHAMIDIMARRI:** Virtually all approved DAA regimens can be used to treat this patient. The ION-4 study, which looked at sofosbuvir plus ledipasvir in coinfecting patients treated for 12 weeks, has shown a fantastic SVR rate of around 96%. The combination is a fixed dose, single pill combination taken once daily for 12 weeks; in our coinfecting patient that could be a fantastic option.

The other option is sofosbuvir plus daclatasvir. The combination of these drugs has been studied in ALLY-2, which showed that a 12 week treatment with the combination has an SVR rate of more than 96%. In one of the arms studied, they looked at shortening the duration to eight weeks in coinfecting patients, and the answer was no, because truncating the treatment to

eight weeks resulted in a marked reduction of SVR12 to only 76%.

One thing to note from this trial is HIV/hep C coinfecting patients should be treated for at least 12 weeks, and daclatasvir was only approved for genotype 3 in the United States; but given the strong evidence seen in clinical trials it is now approved for even genotype 1.

This combination has shown good efficacy not only in genotype 1 but also in genotype 2 and genotype 3, so that is another sound option for patients described in the vignette.

The third option is the PrOD regimen, which is the combination of three drugs plus ribavirin for 12 weeks. This can be used to treat people like our coinfecting patient. But as we discussed in our newsletter, prior PI failures were not studied with this regimen. This patient had failed boceprevir, so probably the PrOD regimen would not be ideal for him. Also, this patient had had severe adverse events from ribavirin, which might recur because ribavirin is included in the PrOD regimen. Finally, PrOD regimen also includes a ritonavir-containing drug, so ritonavir should be withheld if it is part of the antiretroviral therapy for treating the patient's HIV. These are some of the things that have to be kept in mind.

**MR. BUSKER:** The grazoprevir/elbasvir combination was recently approved. Can you give us a little more information about it?

**DR. BHAMIDIMARRI:** Grazoprevir/elbasvir is a combination that has been studied initially in the C-WORTHY trial and subsequently in the C-EDGE trial. Grazoprevir is a protease inhibitor and elbasvir is an NS5A inhibitor, and they're coformulated in a fixed dose combination pill, which was recently approved. Hepatitis C genotypes 1, 4, and 6 can be treated using this combination regimen. However, in this trial they included hepatitis C patients who were treatment naïve, so we cannot extrapolate the results to patients who are treatment experienced. Apart from that, the combination is successful in treating patients who are coinfecting with genotype 1, and treatment for 12 weeks resulted in an SVR12 rate of around 96%. But until more data is available in treatment experienced patients using this combination, I would probably wait.

With this combination of grazoprevir and elbasvir, we also worry about baseline NS5A resistance. Therefore, I would not use this combination in patients who have failed previous treatments.

**MR. BUSKER:** Thank you for that clarification. Now for patients who are on ART, two questions, Dr. Martin. Should all of them undergo HCV treatment? And who should be managing their ART therapy during their HCV treatment?

**DR. MARTIN:** These are very important questions because often these patients have complicated antiviral regimens for the HIV. ART is not a prerequisite to undergoing hepatitis C treatment in coinfecting patients, but ideally the patients should have good control of their HIV infection before embarking on hepatitis C therapy. The DHHS guidelines recommend ART control of HIV before beginning hepatitis C treatment. Importantly, there is no clear evidence for a CD4 count threshold, but patients who are not on ART should preferably have a CD4 count of greater than 350 to anticipate similar efficacy that was reported in clinical trials.

Coinfecting patients can be managed by an HIV expert or a hepatitis C expert or both. It varies with individual clinical practice and it is not generally uniform. In our practice in Miami we have two clinicians who independently manage HIV/hepatitis C coinfection, whereas the rest of the clinicians co-manage the viruses with the patient's HIV care provider. It is, however, important that coinfecting patients with baseline advanced fibrosis or cirrhosis remain in the HCC and follow variceal screening surveillance protocols at their respective practices to comply with standard of care.

**MR. BUSKER:** Thank you, Dr. Martin. I'd like to look at one more patient now, Dr. Bhamidimarri.

**DR. BHAMIDIMARRI:** Now that most of the previously known specific populations are no longer specific populations, like the coinfection patient, what about the patient with end stage renal disease and dialysis? This is a patient we met in the last week's clinic, a 58 year old woman from the Bahamas who had IgA nephropathy resulting in end stage renal disease and underwent a deceased donor kidney transplantation in 2000. Her renal graft failed because of rejection, and she's been back on dialysis since 2010. She is undergoing an evaluation for a second kidney transplant, and her son is being evaluated as a

potential donor. She was found to have chronic hepatitis C genotype 1A that was diagnosed three years ago.

Her labs revealed a hemoglobin of 9 gm/dL, ALT of 65, albumin of 3.8, platelets of 160 K, INR 1.1, and creatinine 4.6; she's on dialysis. An ultrasound of the abdomen shows an echogenic liver without ascites but she has mild splenomegaly.

Her FibroScan reveals a score of 12 kilopascals and a transjugular biopsy was done which shows HVPG of 7 mm and an F3/4 METAVIR fibrosis. An endoscopy did not reveal any esophageal or gastric varices. She has been listed for living donor kidney transplantation for the past eight months and is eager to get a transplant at the earliest possible date.

**MR. BUSKER:** Dr. Martin, what are the current options to treat the hepatitis C in these patients with renal insufficiency?

**DR. MARTIN:** Treatment options have expanded with the recent licensing of grazoprevir and elbasvir to treat patients with hepatitis C who have end stage renal disease, including patients on dialysis.

The other regimens are safe to be used down to a GFR of 30 mL/min, but there are some important caveats. One of them is with the 3D regimen, ribavirin would be required for a patient with genotype 1A. Ribavirin is excreted renally, and its accumulation can lead to a profound anemia. So caution is required for its use.

Simeprevir, ledipasvir, and daclatasvir are not eliminated renally and can be used in patients with advanced chronic kidney disease. But importantly, these drugs need a sofosbuvir backbone, and there is no optimal dose recommendation for sofosbuvir below a GFR of 30 mL/min.

**MR. BUSKER:** Dr. Martin mentioned sofosbuvir. Dr. Bhamidimarri, what are the data on sofosbuvir in the ESRD setting?

**DR. BHAMIDIMARRI:** NS5B nucleotide inhibitors like sofosbuvir have a complex process of drug metabolism, and in the newsletter we have detailed it to an extent. But to cut it short, the NS5B NIs must be administered as a monophosphate prodrug, which enters the hepatocyte and is converted to an active triphosphate form. PK data for sofosbuvir 400 mg in

the end stage renal disease setting shows that sofosbuvir drug levels and its inactive metabolite, GS331007, reach significantly high levels in patients who have GFRs less than 30 mL/min and also in the dialysis setting.

However, sofosbuvir 200 mg has been studied only in patients who have a GFR less than 30 mL/min in the nondialysis setting. The sofosbuvir drug level is similar to the 400 mg dose, but its metabolite level is significantly lower than with the full dose administration. Current data shows that the SVR<sub>12</sub> is around 40% with sofosbuvir 200 mg daily plus ribavirin in a nondialysis setting in patients whose GFR is less than 30 mL/min.

The data presented with sofosbuvir 400 mg or 200 mg is only in of clinical trials and has not been approved for clinical use in patients who have end stage renal disease or whose GFR is less than 30 mL/min.

**MR. BUSKER:** What about using sofosbuvir in combination with another DAA? What do the data show, Dr. Martin?

**DR. MARTIN:** Obviously this is an important issue. Simeprevir is the only DAA that has been studied with sofosbuvir, although other DAAs like daclatasvir and ledipasvir, which are not renally eliminated, could also be used in combination with sofosbuvir. Clinical trials are ongoing to clarify the role of some of these combinations.

There is limited data in the form of case reports and case series with simeprevir plus sofosbuvir 200 mg or 400 mg daily in patients with advanced chronic kidney disease, which suggests that this regimen is feasible, efficacious, and importantly is ribavirin-free. Reported SVR rates are between 87% to 100%, but the sample sizes in these studies are small —15 to 17 patients. Ongoing clinical trials will expand our information, but other combinations that include sofosbuvir are needed in patients with advanced chronic kidney disease.

**MR. BUSKER:** Dr. Bhamidimarri, what other treatment options are available for the patient you described? What else might be considered?

**DR. BHAMIDIMARRI:** That's a very important question, Bob. As we all know, hepatitis C is

associated with several poor outcomes in a kidney transplant recipient, and obviously the timing of hepatitis C treatment is key in patients who are waitlisted for kidney transplant, because any patient who undergoes a kidney transplant and has normal or optimal GFR posttransplant can be treated with any of the approved DAA regimens.

So in our patient within the living donor kidney transplant setting, we know that the patient already has advanced fibrosis and early cirrhosis, so this patient is going to get a healthy graft, and we would like to treat her hepatitis C before the kidney transplant because we can avoid all the negative outcomes that we already know that can happen in a patient with active hepatitis C after a kidney transplant.

Grazoprevir/elbasvir is a ribavirin free regimen that has recently been approved. It is a very viable option to treat this patient prior to the kidney transplant. Transplant teams should be involved in making the decision, especially if the patient is going for deceased donor kidney transplantation, because they could ideally receive a kidney from a hepatitis C-positive donor and can minimize the duration of the wait time during their prekidney transplant phase.

The ease and success of hepatitis C treatment post kidney transplant has given us a new strategy of transplanting hepatitis C positive donor kidneys in hepatitis C positive recipients. Thus, we are increasing the use of such organs and abbreviating the wait time. Hepatitis C prior to kidney transplant in waitlisted patients therefore offers a practical disadvantage because of longer wait times for a nonhepatitis C positive organ. Each case has to be individualized, and we strongly recommend that transplant teams be involved in making such critical decisions about a waitlisted patient.

**MR. BUSKER:** Doctors, thank you both for today's cases and discussion. Let me ask you to take a moment now to share your thoughts about the future of HCV treatment. Dr. Martin?

**DR. MARTIN:** Despite all these exciting advances, we cannot guarantee 100% of patients a cure of their hepatitis C infection. In part, this is related to some patient characteristics, for instance, patients with more advanced liver disease. It also reflects the innate qualities of the virus. For example, we're now seeing

resistance associated variants emerge in patients who failed DAA therapy. What I'm looking for in the future is even more effective regimens that are tolerated in each patient group with hepatitis C.

**MR. BUSKER:** Dr. Bhamidimarri?

**DR. BHAMIDIMARRI:** There is increased research, especially to offer standardized treatment across all genotypes. As Dr. Martin said, we want to concentrate on specific populations, especially those with decompensated cirrhosis, people on dialysis, and resistant associated variants. We're also seeing more and more people who have failed newer DAAs. Eventually we will want to bury ribavirin, so we want to eliminate any regimens that can eliminate the use of ribavirin. The shortened duration can also mean to improve cost effectiveness to treat one patient and achieve hepatitis C cure. That will also be part of the equation in the quest for new drugs.

**MR. BUSKER:** Thank you, doctors. Let's wrap things up by reviewing the key points of today's discussion in light of our learning objectives. To begin: how direct-acting antiviral agents differ from prior interferon-based regimens. Dr. Martin?

**DR. MARTIN:** I think it's true to say that when we were using interferon with ribavirin, it was a blunderbuss approach. In other words, we were using antiviral agents that weren't terribly specific. The beauty of the DAA regimens is that we're targeting specific parts of the hepatitis C life cycle to shut off replication and allow viral elimination. We've gone from a nonspecific therapy to highly specific therapies, and that is reflected in the excellent efficacy we now see with these new treatments.

Importantly, with these new DAA regimens, despite their relative complexity, they're actually much better tolerated than interferon/ribavirin regimens, so that has a number of implications. One of them is that patients who are more difficult to treat — for instance, those with advanced cirrhosis; our patients with HIV; our patients with advanced kidney disease — are now going to be good candidates for antiviral therapy.

**MR. BUSKER:** Thank you. Dr. Bhamidimarri, our second learning objective: the current data on DAA combinations for the treatment of hepatitis C in HIV/HCV coinfecting patients.

**DR. BHAMIDIMARRI:** Previously, the HIV/hepatitis C population was considered a population or special population because treatments with interferon/ribavirin, as Dr. Martin said, have been very difficult, associated with low SVR rates and high rates of adverse effects, but thanks to the revolution in the treatments for hepatitis C, we now have very tolerable regimens and with very high SVR rates. Therefore, the coinfecting population is no longer considered difficult to treat.

Right now all the approved agents like sofosbuvir/ledipasvir or sofosbuvir/daclatasvir, the PrOD regimen which is the 3D regimen, and recently approved grazoprevir/elbasvir, all have shown a very high SVR rate and very tolerable side effect profile in treating these coinfecting patients.

**MR. BUSKER:** Finally: HCV treatment options in patients with end-stage renal disease. Dr. Martin?

**DR. MARTIN:** For the patient with end stage renal disease, evidence is accumulating that these newer regimens are well tolerated and are highly efficacious in this challenging group of patients. Importantly, the decision to treat a renal transplant patient should be made in conjunction with the renal transplant program to optimize the patient's care, not only in treating the hepatitis C but also in access to renal transplant.

**DR. BHAMIDIMARRI:** I totally agree with what Dr. Martin said. A patient with hepatitis C who is on the transplant wait list now has options for hepatitis C treatment, but the timing that hepatitis C treatment has to be decided on a case by case basis, and the transplant team should preferably be involved in making those decisions.

**MR. BUSKER:** From the University of Miami School of Medicine, Dr. Ram Bhamidimarri and Dr. Paul Martin, thank you for participating in this eViralHepatitis Review Podcast.

**DR. BHAMIDIMARRI:** Thank you, Bob, for inviting us to participate in this podcast.

**DR. MARTIN:** Bob, thank you for your great questions, which I think really highlighted some of the key issues in managing hepatitis C.

**MR. BUSKER:** To receive CME credit for this activity, please take the post-test at [www.eviralhepatitisreview.org/test](http://www.eviralhepatitisreview.org/test).

This podcast is presented in conjunction with the eViralHepatitis Review newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with viral hepatitis.

This activity has been developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners and nurses, and other clinicians diagnosing or managing patients with viral hepatitis.

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. The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit(s)*.<sup>TM</sup> Physicians should claim only the credit commensurate with the extent of their participation in this activity.

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.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive eViralHepatitis Review via email, please go to our website: [www.eViralHepatitisReview.org](http://www.eViralHepatitisReview.org).

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

---

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

eViralHepatitis Review is supported by educational grants from Bristol-Myers Squibb, Gilead Sciences, Inc., and Merck, & Co., Inc.

This program is copyright with all rights reserved, by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing.