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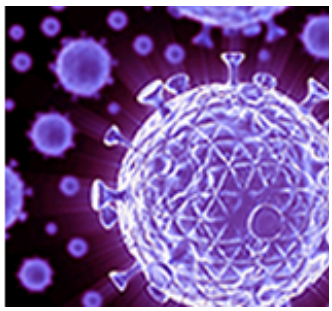



VOLUME 2 — ISSUE 10: TRANSCRIPT

# Featured Cases: Current Issues In HIV/HCV Coinfection

Our guest author is Shobha Swaminathan, MD, Assistant Professor of Medicine in the Division of Infectious Diseases at Rutgers New Jersey Medical School.

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

- Evaluate the use of the HCV direct-acting antiviral agents in the treatment of HIV/HCV coinfection.
- Describe effective management of patients with HIV/HCV coinfected patients who have previously been treated for HCV infection.
- Formulate evidence-based therapies for treating special populations with HIV/HCV coinfection, such as those with advanced liver disease.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of HIV/HCV coinfection in the format of case study scenarios for the clinical practice. This program is a follow up to the Volume 2, Issue 9 *e*HIV Review newsletter — Current Issues in HIV/HCV Coinfection.

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March 26, 2015

**Expiration Date**
March 25, 2017

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### Unlabeled/Unapproved Uses

Dr. Swaminathan has indicated that her discussion will reference the unlabeled or unapproved uses of some newer agents being trialed for HIV/HCV coinfection, including grazoprevir, elbasvir, and daclatasvir, either alone or in combination.

### Faculty Disclosure

Dr. Swaminathan has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of her presentation.

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### LAUNCH DATE

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

Length of Activity: 30 minutes

### STATEMENT OF NEED

- 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.

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**MR. BOB BUSKER:** Welcome to this *e*HIV Review Podcast. Today's program is a follow-up to our newsletter on *Current Issues in HIV/HCV Coinfection*. With us today is one of that issue's authors, Dr. Shobha Swaminathan, Assistant Professor, Department of Medicine, in the Division of Infectious Diseases at Rutgers New Jersey Medical School in Newark, New Jersey.

*e*HIV 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 AbbVie, Inc., Merck & Co., and ViiV Healthcare Company.

Learning objectives for this audio program include:

- Evaluate the use of HCV direct-acting antiviral agents in the treatment of HIV/HCV coinfection.
- Describe effective management of HIV/HCV coinfected patients who have previously been treated for HCV infection.
- Formulate evidence-based therapies for treating special populations with HIV/HCV coinfection, such as those with advanced liver disease.

Dr. Swaminathan has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of her presentation. She has noted that her discussion today will reference the unlabeled or unapproved uses of some of the newer agents being trialed for HIV/HCV coinfection, including grazoprevir, elbasvir, and daclatasvir, either alone or in combination.

I'm Bob Busker, managing editor of *e*HIV Review. Dr. Swaminathan, thank you for joining us today.

**DR. THOMAS SWAMINATHAN:** Hello, Bob. thank you so much for inviting me.

**MR. BUSKER:** In your newsletter issue, doctor, you and your co-author, Dr. Lisa Dever (who's also from Rutgers), reviewed some of the recent publications about the newer direct-acting agents for the treatment of HIV/HCV coinfection. Today, I'd like to discuss how some of that new information can be integrated into clinical practice. So to start things off, doctor, let me ask you to present us with a patient.

**DR. SWAMINATHAN:** So let's talk about a patient that I saw in the clinic a few months ago. She is a 59 year old woman with HIV/HCV genotype 1 coinfection. Her HIV infection is well controlled on tenofovir, emtricitabine, and raltegravir. Her HIV viral load is less than 20 copies per mL and her CD4 is 741 cells per cubic mL. She reports prior HCV treatment with pegylated interferon, ribavirin, and telaprevir two years ago, but her treatment was discontinued because of severe anemia, fatigue, and depression. She now would like to know if she should be treated again now for her HCV infection or wait for more treatment options.

**MR. BUSKER:** Treating this patient for HCV now, or waiting — what factors would influence your recommendation?

**DR. SWAMINATHAN:** Many factors can help determine if a patient with coinfection should be treated now or can defer treatment for a few months or even years. Some of those include the stage of her HIV infection. Control of HIV infection is very important in assessing whether a patient is ready for treatment. In this case, my patient is clearly motivated, her HIV viral load is undetectable, and she has a good CD4 count, indicating that she is very adherent to therapy. She has previously been treated for hepatitis C virus infection, and although she failed the treatment, both of those are clear indicators that this is a patient who is motivated, interested, and capable of undergoing hepatitis C treatment again.

The other aspect to consider is to assess the stage of her liver disease, and we have many ways to do that. We can start with the easiest noninvasive test, which is a laboratory study. For instance, liver function tests such as albumin and prothrombin time can both be used to see if she has compensated liver disease or if there is any sign of liver cirrhosis.

Additional tests such as FibroSURE and FibroScan can also be helpful. FibroSURE is a biomarker that takes into account a person's age, gender, alpha-2-macroglobulin, haptoglobulin, apolipoprotein-A, gamma-glutamyl transferase, total bilirubin, and ALT, and it gives a composite number that can then be correlated with the person's extent of liver disease.

FibroScan is another noninvasive test that uses transient elastography to gauge the liver stiffness in the patient. It was approved in the US about 18 months ago, so it's available in select centers in this country.

Liver biopsy is the most invasive of the available diagnostic options and was more commonly used two years ago when our treatment options were limited to pegylated interferon. Today, using liver biopsy in real life scenarios is probably very limited.

**MR. BUSKER:** As you've noted, this is a patient who's had prior HCV treatment. How does that affect your options for current therapy?

**DR. SWAMINATHAN:** Several studies have looked at the success of HIV/hepatitis C virus treatment in patients with coinfection. Some of the studies mentioned in the newsletter include PHOTON-1 and PHOTON-2. PHOTON-1 looked at patients with HIV and HCV coinfection. That study did not include treatment-experienced patients, but the second part of the study, PHOTON-2, did include a small cohort of patients who were treated with sofosbuvir and ribavirin for 24 weeks and had excellent treatment response.

In addition, real-life scenarios such as HCV TARGET included a small proportion of patients with coinfection who were treated with sofosbuvir and simeprevir and reported sustained virologic response rates; in other words, more than 80% had a negative hepatitis C viral load 12 weeks after completion of treatment.

The other two articles mentioned in the newsletter include TURQUOISE 1, which includes a three-drug regimen of paritaprevir, ombitasvir, and dasabuvir given with ritonavir, with or without ribavirin, for 12 to 24 weeks. This study included about 30% of patients who were treatment-experienced. And even that group reported excellent sustained virological response rates exceeding 90%.

The last study presented in the newsletter, C-WORTHY, looked at the protease inhibitor grazoprevir along with the NS5A inhibitor elbasvir with or without ribavirin for 8, 12, or 18 weeks. That study did include some treatment-naïve patients with coinfection and hepatitis C treatment-experienced patients, again with excellent responses.

So in this background, I will say that there is enough data moving forward to state that we can use direct-acting agents, even in patients who have failed previous hepatitis C virus treatment regimens.

**MR. BUSKER:** What additional testing, if any, would you need to perform to determine the best option for this patient?

**DR. SWAMINATHAN:** In addition to the tests already performed, it is very important to make sure we have identified the patient's exact HCV genotype. Although the case presents that it's genotype 1, it is important to know whether it's 1A or 1B. Some studies present evidence suggesting that treatment responses may be slightly superior for genotype 1B than for genotype 1A.

In addition, genotype has a big impact on treatment duration. For example, the PHOTON-1 study looked at sofosbuvir plus ribavirin among patients with genotypes 1, 2, and 3. Patients with genotype 1 received the treatment for 24 weeks, and those with genotypes 2 and 3 received it only for 12 weeks. The cure rates or SVR 12 for genotype 1 were 76% and for genotype 2 were 88%, but for treatment naïve patients with genotype 3, it was only 67%, showing that for genotype 3 shorter duration of therapy was not as effective as the longer duration of therapy. Therefore, PHOTON-2, the second part of the study, which also included patients with genotype 4, extended the treatment duration for all patients with genotype 3 to 24 weeks of therapy.

ELECTRON-2 looked at ledipasvir, the medication that's just been approved by the FDA in the past two months, along with sofosbuvir for 12 weeks for patients with genotype 3, and showed excellent cure rates exceeding 70%. It was 73% in the group with cirrhosis and 89% in the group without cirrhosis.

**MR. BUSKER:** So in the end, for this patient — what treatment course did you recommend?

**DR. SWAMINATHAN:** It was very important for her that she not change her antiretroviral therapy. Her antiretroviral therapy regimen consisted of tenofovir, emtricitabine and raltegravir. Raltegravir is an integrase inhibitor that has few, if any, drug interactions with the currently approved direct-acting hepatitis C agents. As a result, her treatment options included either sofosbuvir/ribavirin or sofosbuvir/simeprevir, which is a protease inhibitor. Simeprevir,

a protease inhibitor, does have drug/drug interactions with many of the HIV medications because it is metabolized through the cytochrome CYP3A4 pathway. As a result, simeprevir cannot be used with most of the protease inhibitors, particularly when they are boosted with ritonavir; cannot be used with the NNRTIs such as efavirenz; and cannot be used with maraviroc. As a result, the only ART regimens that can be used along with simeprevir are the integrase inhibitor raltegravir and the nonnucleotide reverse transcriptase inhibitor rilpivirine.

This patient also did not want to be on therapy for a long time. As you know, PHOTON-1 required treatment for 24 weeks for patients with coinfection. So I discussed the data of the COSMOS study with her. The COSMOS study looked at sofosbuvir and simeprevir for 12 weeks among patients negative for HIV. Although at the time I saw the patient we did not have data in patients with coinfection, because of the lack of drug/drug interactions and because the COSMOS study had SVR rates around 93% to 96%, she really wanted to take that treatment option. This was also aligned with the AASLD guidelines that recommend sofosbuvir and simeprevir as a treatment option among patients coinfected with HIV and hepatitis C.

We also discussed the possibility of waiting until the fixed dose combination of ledipasvir/sofosbuvir would become available, but she did not want to wait, so we started her on sofosbuvir 400 mg once daily and simeprevir 150 mg once daily for a total duration of 12 weeks of therapy. She did quite well on therapy, with few, if any, treatment-related side effects. We repeated her hepatitis C viral load at weeks 4 and 12 during treatment, which remained undetectable throughout the hepatitis C treatment course. At the end of treatment we repeated her viral load, week 4 after treatment and week 12 after treatment was discontinued, and her viral load remains undetectable to date. In a sense, she attained the SVR12 end of treatment and cure outcome. So she was very happy.

You should note that it did take us a while for us to get the medications approved through her insurance company because she had a form of HMO plan, but given the bulk of evidence supporting the need for hepatitis C treatment, we were able to get it approved despite the cost.

**MR. BUSKER:** Thank you for that case and discussion, doctor. And we'll return, with Dr. Shobha Swaminathan, in just a moment.

**JEANNE KERULY:** Hello. I'm Jeanne Keruly, assistant professor of medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the program directors of *e*HIV Review.

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**MR. BUSKER:** Welcome back to this eHIV Review podcast. I'm Bob Busker, managing editor of the program. Our guest today is Dr. Shobha Swaminathan, from the Division of Infectious Diseases, at Rutgers New Jersey Medical School. And our topic is Current Issues in HIV/HCV Coinfection.

We've been discussing some of the new information Dr. Swaminathan and Dr. Dever reviewed in their newsletter issue and how it can impact clinical practice. So let's continue now, if you would doctor, by looking at another patient.

**DR. SWAMINATHAN:** A 51 year old man with HIV and hepatitis C virus coinfection and controlled hypothyroidism is currently taking lamivudine and abacavir, ritonavir- boosted darunavir, and atovaquone. His HIV viral load has been well controlled for over three years; his most current CD4 count was 129 cells/mm$^3$. His hepatitis C genotype 1B viral load is 124,853 IU/mL. Recent ultrasound of liver shows no cirrhosis.

**MR. BUSKER:** Issues to consider to determine the optimal therapy for this patient's HCV infection?

**DR. SWAMINATHAN:** Among the things to be considered for this patient are, as we discussed in the first case, the level of HIV control. Despite excellent control of his HIV infection, the CD4 remains low, less than 200 cells/mm3. Almost all the studies in coinfected populations have included patients with CD4 greater than 200; PHOTON-1, TURQUOISE-1, C-WORTHy, PHOTON-2 all had minimum CD4 counts greater than 200.

ERADICATE was an investigator-initiated study conducted by the NIH where the lowest CD4 count was 114 cells/mm3, and in that study, despite the low CD4 count, treatment responses were excellent. The other point to note is that this patient is taking ritonavir-boosted darunavir, which would make it difficult for us to use the currently approved protease inhibitor, simeprevir, as part of his hepatitis C treatment regimen because of the drug/drug interaction.

The third point to note is that he had hepatitis C genotype 1B infection. A few months ago it was felt that baseline testing for resistance might be important, particularly for genotype 1A, but those data have not been substantiated in subsequent studies. So at this time for his genotype 1B infection, a treatment regimen that would not have drug/drug interaction would be the most applicable for this patient.

It is also important to note that we can now treat patients with very low CD4 counts, because in the absence of interferon as part of the treatment regimen, there is much less concern of interferon-induced bone marrow suppression causing a further reduction in the CD4 cell count.

**MR. BUSKER:** The timing of the HCV treatment — in the sense of treat now or wait — how would you determine that?

**DR. SWAMINATHAN:** The timing of hepatitis C virus treatment depends on the severity of the patient's liver disease. For instance, people with more advanced liver disease as observed either by liver biopsy or with FibroSURE or FibroScan would have a more urgent need to treat the hepatitis C virus-related liver disease. Patient motivation and interest are also key factors, because they are a marker for medication adherence, which will have a big impact on the success of any hepatitis C virus treatment.

For this patient, although the ultrasound of his liver did not show any cirrhosis, the fact that he was very motivated to start treatment and not wait any longer was a big factor in my decision to start him on hepatitis C virus treatment.

**MR. BUSKER:** So what was your ultimate treatment recommendation for this patient?

**DR. SWAMINATHAN:** After discussing various options with the patient, we decided to treat him with sofosbuvir and ribavirin, and the data to use that comes from the *JAMA* paper that was discussed in the newsletter. That was based on PHOTON-1, an open label study looking at sofosbuvir and ribavirin for 24 weeks.

We chose this regimen because the patient was unable to change his antiretroviral therapy because of previously archived HIV resistant mutations in his past. Hence, we were unable to use simeprevir as part of his treatment regimen, and the only other treatment combination available for use outside of clinical trials was sofosbuvir and ribavirin for 24 weeks.

If the patient had come to me today it is certainly possible that we might have chosen to prescribe the fixed dose combination of ledipasvir and sofosbuvir instead of sofosbuvir/ribavirin.

**MR. BUSKER:** And the patient's overall response to this treatment, doctor?

**DR. SWAMINATHAN:** Overall, the patient tolerated treatment very well. He had few, if any, side effects on treatment. At week 4 of treatment he had a negative hepatitis C viral load, and he remained negative throughout his treatment course. Around week 8 to 10 of treatment he developed anemia, which was most likely related to ribavirin. His hemoglobin dropped at the lowest point to 9.5 gm/dL. At that point, we reduced his ribavirin dose to 400 mg per day.

We did not start him on erythropoietin because in PHOTON-1, where 15% of patients developed ribavirin dose-related anemia, anemia was managed with ribavirin dose reduction alone without erythropoietin and growth factors to stimulate it. This did not have an impact on SVR treatment response rates, and patients, despite ribavirin dose reduction, did just as well as those who maintained the ribavirin

dose. Hence, in our patient we only reduced his ribavirin dose, and as his hemoglobin improved we were able to increase his ribavirin back to the 1,000 mg he started with.

**MR. BUSKER:** Thank you for that case and discussion, doctor. We've got time for one more patient — so if you would, please.

**DR. SWAMINATHAN:** The patient is a 60 year old man with well-controlled HIV infection. He has advanced liver disease from his chronic hepatitis C virus infection. Two years ago localized hepatocellular carcinoma was diagnosed and he underwent successful radiofrequency ablation; he has since had no recurrence of his HCC. He has declined HCV treatment in the past because of concerns about interferon-related side effects. His HCV viral load is 395,000 and his genotype is 1A.

Other pertinent laboratory results include a low albumin, 2.4 gm/dL, elevated total bilirubin of 2.5 mg/dL, serum creatinine of 1 mg/dL, and an INR of 1.3. He also has elevated liver enzymes: his AST is 105 IU/L and ALT is 65 IU/L. His HIV is well controlled, with a viral load less than 20 and CD4 at 513 cells/$mm^3$.

**MR. BUSKER:** So — a coinfected patient, with compromised liver function due to hepatitis C, as well as a history of hepatocellular carcinoma. What's your approach to treating this patient, doctor?

**DR. SWAMINATHAN:** We should approach patients who have signs of advanced liver disease very cautiously. Some of the things we can use to gauge the extent of liver disease include calculation of MELD, a calculated score that stands for Model for End Stage Liver Disease. It was initially developed to predict death after TIPS (transjugular intrahepatic portosystemic shunt) procedures in patients with advanced liver disease and has since been used to predict post transplant mortality.

Papers have shown that even among patients infected with HIV and hepatitis C viruses, the MELD score can be an independent predictor of transplant mortality, suggesting that MELD can be used in this patient to calculate his risk. The MELD score includes creatinine, bilirubin, and INR, and it also takes into account whether a patient received dialysis in the past week.

Our patient's MELD score was less than 10, suggesting that despite what appears to be advanced liver disease, he has a very low likelihood of death in the next few months.

**MR. BUSKER:** Are there data that support using the newer direct acting antivirals in a patient like this?

**DR. SWAMINATHAN:** A lot of data has emerged in the past 12 to 24 months supporting use of these new direct-acting agents in patients with both compensated and decompensated cirrhosis. In the newsletter article, we reviewed a paper that looks at daclatasvir, an NS5A replication complex inhibitor that has had genotypic activity across genotypes 1, 2, and 3. Although that study included only patients with hepatitis C monoinfection, more than 50% of patients in the treatment-experienced group in that study had moderate to advanced liver disease. And even in that group of patients, the SVR12 response rates were in excess of 95%. It's also important to note that using ribavirin in this group of patients did not necessarily improve their hepatitis C treatment response.

Other studies such as PHOTON-1 and PHOTON 2 in patients with HIV/HCV coinfection have included anywhere between 10% to 25% of patients with cirrhosis, and have both shown that treatment can be safely administered with these direct-acting agents in these complicated patients. It is, however, important to note that in the PHOTON-1 study, SVR rates were somewhat inferior in patients with cirrhosis. For example, SVR was only 65% in those with cirrhosis compared with 88% in those without, and the same was true with subgenotypes 1A and 1B, where SVR rates in those with cirrhosis were 62% or 75% respectively, and for genotypes 1A and 1B in those without cirrhosis, response rates were much higher, 87% to 100%.

Two other studies, SOLAR-1 and C-WORTHy, both discussed in this newsletter, included patients with advanced liver disease who were successfully treated with these newer agents. Given these data, patients with advanced liver disease can be successfully and safely treated with the newer direct-acting agents.

**MR. BUSKER:** So in the patient you presented — HIV/HCV coinfected, compromised liver function, history of HCC — what were your treatment recommendations and what was the outcome?

**DR. SWAMINATHAN:** I discussed the two treatment options with my patient. At that time the only option available was sofosbuvir/simeprevir or sofosbuvir/ribavirin, or we could have waited for ledipasvir/sofosbuvir. With the evidence that I discussed with the patient, he wanted to wait for the fewest number of pills with the fewest drug/drug interactions, so he decided to wait for the fixed-dose combination, ledipasvir/sofosbuvir. When it came on the market, we started him on therapy.

He has been on therapy at this point for six weeks and he had a negative viral load at week 4 of treatment. I will have to wait for an additional 8 weeks for him to complete therapy of total of 12 weeks, and then 12 more weeks post-treatment to get his treatment outcome. Thus far though, he has tolerated treatment extremely well and has had no treatment-related side effects.

**MR. BUSKER:** I want to thank you for today's patients and discussion, doctor. To wrap things up, let's review what we talked about today in light of our learning objectives. So to begin: the use of HCV direct acting antiviral agents in the treatment of HIV/HCV coinfection.

**DR. SWAMINATHAN:** I think overall the treatment response rates with the newer direct acting agents in patients with HIV/HCV coinfection are comparable to those of the patients with hepatitis C monoinfection. Providers and physicians taking care of patients with coinfection should be aware of the drug interactions between these new hepatitis C virus DAAs and the HIV treatment regiments to ensure they are compatible.

Drug interactions are particularly concerning with the use of some commercially available protease inhibitors such as simeprevir, the new protease inhibitor paritaprevir, and the NS5A inhibitor ombitasvir, which uses ritonavir as a boosting agent. Both of those groups use the cytochrome CYP3A4 enzyme system to metabolize, which is similar to many of the HIV protease inhibitors and some nonnucleoside reverse transcriptase inhibitors. Hence, treatment regimens using both of these should be used in caution with the full awareness of the drug interaction data.

**MR. BUSKER:** And our second learning objective: the effective management of HIV/HCV coinfected patients who have previously been treated for HCV infection.

**DR. SWAMINATHAN:** As discussed in the podcast, I think a wealth of data is emerging that despite previous treatment experience either with interferon-based therapies alone or even with the use of first-generation protease inhibitors, patients can still be successfully treated with a combination of the newer direct-acting agents; past treatment failure should no longer be a contraindication to treatment options with the newer HCV DAAs.

**MR. BUSKER:** And finally: the evidence basis for treating special populations with HCV infection, like patients with advanced liver disease.

**DR. SWAMINATHAN:** Although the data are limited, there are certainly enough data to support the use of hepatitis C virus treatment in patients with coinfection, even those with cirrhosis, both compensated and decompensated liver disease, because these patients are likely to benefit the most from successful hepatitis C virus treatment.

**MR. BUSKER:** Dr. Shobha Swaminathan from the Division of Infectious Diseases at Rutgers New Jersey Medical School, thank you for sharing your clinical expertise in this *e*HIV Review Podcast.

**DR. SWAMINATHAN:** Bob, thank you so much for inviting me to do this podcast.

**MR. BUSKER:** To receive CME credit for this activity, please take the post-test at www.ehivreview.org/test.

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