JOHNS HOPKINS MEDICINE
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 AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

VOLUME 3 — ISSUE 8: TRANSCRIPT

Featured Cases: AASLD Coverage

Our guest author is Susanna Naggie, MD, Assistant Professor of Medicine, Department of Medicine – Infectious Diseases at Duke University School of Medicine in Durham, North Carolina.

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

- Describe methods of hepatocellular carcinoma screening in patients with hepatitis B to identify patients at high-risk for HCC.
- Discuss decision making on initiating Hepatitis C treatment in the HIV-co-infected patient.
- Identify the complexities in treating the Hepatitis C genotype 3 infected patient.

This discussion, offered as a downloadable audio file and companion transcript, covers progress in the development of new therapies for treating hepatitis C infection, and news about hepatitis B from the 64th meeting of the American Association for the Study of Liver Disease, as well as case-study scenarios for the clinical practice. This program is a follow up to the Volume 3, Issue 7 *eViralHepatitis Review* newsletter—AASLD Coverage.

Unlabeled/Unapproved Uses
Dr. Naggie has indicated that in today's discussion she will reference the unlabeled or unapproved uses of sofosbuvir, simeprevir, daclatasvir, asunaprevir, faldaprevir, ledipasvir and entacavir.

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Faculty Disclosure
Dr. Naggie has disclosed that she has received grants and/or research support from AbbVie, Inc. Achillion Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, Scynexis, Inc., and Vertex Pharmaceuticals. She has also served as an advisor for AbbVie, Inc., Achillion Pharmaceuticals, Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Gilead Sciences, and Janssen Pharmaceuticals, Inc.

Release Date
March 31, 2014

Expiration Date
March 30, 2016

CME INFORMATION

⇩ PROGRAM BEGINS BELOW

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LAUNCH DATE

March 31, 2014; activities expire 2 years from the date of publication.

INTENDED AUDIENCE

The target audience (clinicians) for the HBV curriculum includes:

- Primary: primary care physicians (PCPs), OB/GYNs, physician assistants (PAs), nurse practitioners (NPs), community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence
- Secondary: gastroenterologists, infectious disease specialists, and other clinicians involved in the care of patients at risk for HBV

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Through discussions with experts in the specialty of HBV, a survey of participants from previous Johns Hopkins CME activities, and a review of current literature, the following core learning gaps have been identified:

HCV

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

HBV

- Clinicians do not effectively identify their patients at risk for HBV.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

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General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

HARDWARE & SOFTWARE REQUIREMENTS

PC: Internet Explorer (v6 or greater), or Firefox, MAC: Safari or Firefox

MR. BOB BUSKER: Welcome to this eViralHepatitis Review Podcast.

eViralHepatitis Review is 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., Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

Today's program is a companion piece to our eViralHepatitis Review newsletter reporting on the 64th Meeting of the American Association for the Study of Liver Disease.

Speaking with us today is our newsletter issue author, Dr. Susanna Naggie from the Duke University School of Medicine.

This activity has been developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners, community gastroenterologists, clinicians who care for patients of Asian and West African descent in areas of high hepatitis B prevalence, and other HCPs involved in the care of patients with or at risk for hepatitis.

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Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Describe methods of hepatocellular carcinoma screening in patients with hepatitis B to identify patients at high-risk for HCC.
- Discuss decision-making on initiating Hepatitis C treatment in the HIV-co-infected patient,
- Identify the complexities in treating the Hepatitis C genotype 3 infected patient.

I'm Bob Busker, managing editor of eViralHepatitis Review. On the line we have with us Dr. Susanna Naggie, Assistant Professor, Department of Medicine – Infectious Diseases at the Duke University School of Medicine in Durham, North Carolina.

Dr. Naggie has disclosed that she has received grants and/or research support from AbbVie, Inc. Achillion Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, Scynexis, Inc., and Vertex Pharmaceuticals. She has also served as an advisor for AbbVie, Inc., Achillion Pharmaceuticals, Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb, Gilead Sciences, and Janssen Pharmaceuticals, Inc.

She has indicated that her presentation today will reference the unlabeled or unapproved uses of sofosbuvir, simeprevir, daclatasvir, asunaprevir, faldaprevir, ledipasvir, and entacavir.

Dr. Naggie, welcome to this eViralHepatitis Review Podcast.

DR. SUSANNA NAGGIE: Well thanks for having me, I look forward to it.

MR. BUSKER: As you described in your newsletter issue, the hottest topic at the recent AASLD meeting was progress in the development of new therapies for treating hepatitis C infection. However, there was also some news about hepatitis B. I'd like to go there first, to hepatitis B infection, if we could, doctor, and look at how the new information you reported on might affect clinical decision-making. So to start things off, let me ask you to describe a hepatitis B scenario for us, if you would please.

DR. NAGGIE: The first patient that I wanted to present was a patient that I've been following now for some time. He's a 45 year old man who was born in West Africa and has now been here in the US for over 10 years. He has longstanding hep B infection and has been on tenofovir now for five years after a switch from adefovir and lamivudine dual therapy prior to that.

MR. BUSKER: In brief: what are your primary concerns for this patient?

DR. NAGGIE: For this patient who actually has done very well on therapy, obviously now being on dual therapy he has had a failure previously to lamivudine and then was switched to tenofovir given good activity and evidence of longstanding activity against the hepatitis B, so he's maintained viral suppression. But he is from West Africa and has had longstanding hepatitis B and therefore would be considered high risk for the development of hepatocellular carcinoma, regardless of whether or not he has cirrhosis, which is a critically important difference between hep B and hep C. So it's critical not only that he maintains viral suppression but that also he receives the appropriate screening for hepatocellular carcinoma.

MR. BUSKER: What kind of regular follow-up testing would you provide for this patient?

DR. NAGGIE: On regular follow-up for a patient like this, certainly liver enzyme testing and usually by this point the patient has been suppressed for over five years, we're usually seeing these folks every six months. So liver enzyme testing, which should include an AST/ALT but then also liver function testing with a total bilirubin and an INR also following hep B DNA quantifications to make sure this patient doesn't have evidence of viral breakthrough which would be suggestive of possible resistance, although generally not reported with our newer nucleoside analogs like tenofovir or entecavir.

Generally in a patient who has been suppressed for this long, those are pretty easy tests and generally those remain suppressed and it's not a whole lot to worry about but it certainly can be a trigger if the liver enzymes becomes abnormal again for concerns of viral breakthrough or something else going on. The big issue here really for this patient is ensuring that he has appropriate risk base testing, as I mentioned previously, in particular, screening for hepatocellular carcinoma.

MR. BUSKER: So to focus on HCC screening — in your newsletter issue, you reported on some Native Alaskan studies.[1] Would the findings from those be applicable here?

DR. NAGGIE: It's difficult to say that they're applicable here, but I think they are generally applicable to HCC screening in other settings. So maybe this doesn't apply to my setting where I practice at Duke University and the Durham VA, because I do have access to the recommended screening by the AASLD, but there are many sites who do not have access to that and really struggle with trying to understand what appropriate screening is. For example, in this patient who is from West Africa, say he were being cared for actually in his native country, access to ultrasound can be quite limited. So this patient would be considered a high risk individual based on the AASLD recommendation for HCC screening which include HBV carriers that are of Asian descent, Asian men over 40 years of age and Asian women over 50 years of age. Certainly any person who has cirrhosis and hepatitis B would be considered very high risk. Patients with a family history of HCC and then patients, again, African patients who are over the age of 20, given that many are infected either at birth or very early in life.

Any carrier really over the age of 40 with persistent or intermittent elevations in ALT or high HBV DNAs over 2000 IU/mL would be considered high risk and therefore should be screened. Now the AASLD's recommendation for screening for HCC is an ultrasound every six to 12 months. I, in particular, recommend every six. And so this is actually a change so there had been a time when alpha-fetoprotein, or AFP, was recommended as part of that, you would do an AFP as well as an ultrasound with an attempt to identify some patients where maybe AFP would be positive before an ultrasound would detect and actual tumor. But that has now been removed as a recommendation although the AASLD does clearly say in areas where HBV carriers may be high risk but access to ultrasound is not readily available, periodic treating with AFP could be considered. And I think that is exactly what this report from the Alaskan Native Tribal Health Consortium attempts to address.

In particular, they attempted to address the use of a two-stage HCC surveillance method and were looking in particular at cost effectiveness which is the primary issue, although again in some research limited settings access to ultrasound, period, is limited, and it's not just about cost, it's more about access. So in this case they attempted to, again, evaluate what if you used AFP as a first stage, a first step, and then ultimately a positive or elevated AFP would lead to an ultrasound for further screening. And what they were able to show is that they, indeed, could save money by using this approach, but the issue was that it failed to identify the majority of cases of hepatocellular carcinoma, at least in the early stages.

So they did show cost savings, but they also showed a greater than 50 percent decrease in life years gained. Now patients didn't die more compared to no screening, but this was compared to ultrasound screening, there was a 50 percent decrease in life years gained, which is the whole idea behind screening is obviously to identify these cancers early so that a patient could undergo treatment, whether that be embolization, ablation, or even transplantation.

That being said, it did result in life years gained compared to no screening and therefore could be considered an option in resource limited settings. Definitely not something that I would recommend in a non-resource limited setting where there is access to ultrasound. I think clearly by the AASLD guidelines we would recommend ultrasound screening unless not available.

MR. BUSKER: Thank you for that recap, Dr. Naggie. To continue with the African patient you described, what other screening would you want to do?

DR. NAGGIE: The primary other thing that we want to think about here other than the things that we have already discussed would be considerations for renal toxicity in the setting of long-term tenofovir use. And this is something that has been recognized, in particular, patients on tenofovir can develop what is called a Fanconi syndrome which is damage to the renal tubules. So I do recommend a urinalysis on these patients once a year, just a UA. Obviously tThey should get a creatinine every six months, and I also look for proteinuria, which is often a first sign of tubular damage in severe cases. Glucosuria may also be present. We also look at electrolytes because often there is phosphate wasting, and these patients can even develop low phosphate in their serum. But from a screening perspective, we mostly look for evidence of protein and possibly even glucose in the urine.

MR. BUSKER: If you do suspect or if you do find renal toxicity from the tenofovir, what would your course of action be?

DR. NAGGIE: This is actually a great question and I think a dilemma that many of us as providers have had to deal with in patients like this. So in a patient who develops renal insufficiency in the setting of tenofovir, your first guess would be to attempt to use another nucleotide analog. And we do have two first-line agents, both tenofovir and entecavir.

The issue here with this patient is that, I previously told you he came to us on a dual therapy regimen of lamivudine and adefovir. So the issue there is it's a clear sign that this patient has lamivudine failure which is quite common to see after up to 5 years of treatment. So the big limitation in the setting of lamivudine failure is that there is and can be cross-resistance between lamivudine-resistant mutants of the hep B virus and entecavir. So there are going to be higher rates of failure in the setting of a patient being switched from lamivudine to entecavir if there is evidence of failure there because of that cross-resistance.

So in this patient's case I think there would be couple of ways to proceed. One, because when he came with didn't have a history of what his hep B genotype was with regards to resistant mutants and now he has a suppressed hep B DNA so we don't have the ability either to detect or test for that.

So ultimately I think you would proceed a couple of ways. One is you would want to make sure that before you blame the tenofovir as the cause for, for example, an elevation in creatinine, decrease in creatinine clearance, that this is indeed due to the tenofovir. Because once you, in a sense, blame the tenofovir for causing a problem and remove it, you've removed probably your best option for drug in a patient with a history of lamivudine resistance and failure. So that's number one is I always like to make sure that I'm convinced it's from the tenofovir and not something else.

If that is the case then, you know, in a setting of full suppression, you can attempt to switch over to an entecavir regimen, but with close monitoring recognizing there is some risk of breakthrough in the setting of possible cross resistance. And then in that setting, you know, we don't have many fallbacks right now with regards to treatment other than an interferon based therapy.

So it's amazing, given maybe for the various options that we have in the setting of HIV and increasingly in hep C, that we are still quite limited in HBV infected patients when you get into one issue and many of our patients have previously failed lamivudine. Especially coinfected patients who were, many of them were on lamivudine monotherapy essentially for their hep B based on old regimens that included Combivir, which included lamivudine and AZT for example.

And the one last comment I would make is that to remember that in an HIV/HBV co-infected patient, entecavir, although it's not an antiretroviral FDA approved for treatment of HIV, it does have antiretroviral activity and can select out for one of the nucleotide resistant mutants, the M184V, and so cannot be used in patient with HIV and concomitant hep B who is not on other antiretroviral therapy. Which was much less common five to ten years ago, much less common now given the recommendations and changes -- recommendations for initiating therapy.

So again, you know, a clear clinical dilemma. Luckily that's not the case in this patient but if it is it becomes difficult and probably proceeding the way I described would be the way that I would move through that case if it did, indeed, happen to this patient. And it's what I've had to do in the past for folks who have developed a renal insufficiency on tenofovir with co-infection.

MR. BUSKER: To summarize this patient if you would for us, doctor: what are the key take-away messages that clinicians should be aware of?

DR. NAGGIE: The main take-away that I wanted everyone to think about in this patient is the fact that he is a clear high risk patient for the development of hepatocellular carcinoma, and the importance of recognizing in your patient population and the patients that you take care of, what are the indications for hepatocellular carcinoma screening in the setting of hepatitis B, recognizing your patients that are at high risk by the AASLD guideline recommendations, and ensuring that those patients are undergoing HCC screening on a regular basis.

And I think, you know, given some changes in the recommendations by the AASLD, it's important to highlight that the current recommendations for screening include ultrasound every six months and that the alpha-fetoprotein really is now not considered the standard of care with regards to HCC screening, although it certainly can be used in addition and may play more of a role in a resource-limited setting.

MR. BUSKER: And we'll return, with Dr. Susanna Naggie from the Duke University 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 e-mail 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. Bi-monthly 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.

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MR. BUSKER: Welcome back to this eViralHepatitis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Susanna Naggie from the Duke University School of Medicine. And our focus is how new information from the AASLD 2013 Meeting can be translated into clinical practice.

We've talked about a patient with hepatitis B infection. Let's look now at a patient with hep C. So if you would, Dr. Naggie, describe a scenario for us.

DR. NAGGIE: This patient is a 50 year old man who has HIV and HCV coinfection. Like many of our patients these days, he has well-controlled HIV, he is on the fixed-dose combination tablet of efavirenz, tenofovir, and emtricitabine. And when I met this man in clinic he had never been staged and had never been treated for HCV and was now being referred in by his HIV clinician, in fact, for consideration of further management with regards to his HCV coinfection.

MR. BUSKER: So this patient comes in for his first clinic appointment — he's been referred for HIV/HCV co-infection. What are the most important things you need to address in that initial clinic visit?

DR. NAGGIE: When I first meet these patients the first question I ask them all is, do you know why you're here, as it never ceases to amaze me how many times they say I have no idea why I'm seeing you today. And I like to make sure they understand that the reason for appointment is for their hepatitis C viral infection. I spend a pretty significant amount of time with patients to go through with them what hepatitis C infection means, that's it's an infection of the liver primarily.

I like to go through with them to understand how they got it. Many patients, they say "I have no idea where I got this," and they really many times are concerned or confused and want to understand how this happened. And so going through routes of transmission, not only for them to understand how they got it but then also to help them understand how they may be at risk of transmitting it to someone else if they continue to have those risk behaviors that may have led to the initial transmission.

I do like to make sure they understand the natural history of this infection, the rates of cirrhosis, what cirrhosis means. Most patients have heard the term "cirrhosis of the liver," but I try to get them to understand what that means and what the long-term outcome for someone with cirrhosis of the liver could be, including liver cancer and liver failure.

I probably spend at least the first 30 minutes with education about the virus itself, making sure they understandit. I try to get them to engage and understand what this means for them moving forward. I spend a lot of time on education about alcohol use. A significant number of our patients with HIV and hep C use or abuse alcohol and making sure they understand that. You know, and many of them use alcohol thinking it's no big deal, that it's not harmful to them because they previously didn't know they had a liver infection. So I spend a significant amount of time recommending patients discontinue all alcohol use, at least until we get them through treatment if they are a candidate.

I also make sure we understand their prior history of vaccination with hepatitis A and hepatitis B. Understanding whether or not they need vaccination for hepatitis B, which I, in my clinic, use a high dose hep B vaccination with a double dose in all of my coinfected patients. So really a lot of focus on, again, education, prevention, making sure they understand the natural history.

And then at the end of the visit then talking more about how do we understand where you are in the stage of your natural history of your disease, this gets into the staging and then making sure patients understand, I want every patient to walk out of my clinic after their first visit to understand that hepatitis C is a curable infection. That we can eradicate it, that it will never come back, and that's really important for patients to understand. I think when they hear those words, they're generally blown away because they've never heard that before, and then they say, wait, if we can cure this and I want to do this, what do I have to do? Then we get into the issue of what their treatment candidacy would be and what the treatments are and where we are on the treatment path for that patient.

MR. BUSKER: Is this patient a candidate for hepatitis C treatment? How do you assess that?

DR. NAGGIE: I take care of HIV/HCV coinfected patients and I also take care of a lot of hep C monoinfected patients. And to be honest with you, sometimes it's a little easier to assess a patient with HIV for treatment candidacy because they are used to taking HIV medications. And so the idea of waking up and taking pills or medications, and coming to frequent clinic visits is really standard for them, they've been doing this for a long time. For instance, I have seen monoinfected patients who, for many of them, maybe see their doctor once a year, maybe they're on no medications or only a few.

One concern is adherence. Will this patient show up for their appointments? Will they take their medicines? The medicines that we have now are highly effective, but we're gleaning from data that's coming out of some of these clinical trials is that adherence does matter and patients who do not complete their courses of therapy much higher rates of failure.

So I think about those things very much. Obviously, patients with coinfection in particular must take their HIV medicines, so it's critical that they understand adherence, but adherence is also important based on the necessity of treating their hepatitis C. If a patient cannot show up for their HIV clinics and take their HIV medicines, they are clearly not going to be a great

candidate for taking hep C medicines, especially previously and even today, where most of our regimens still include interferon.

We can use a lot of those tools to help a patient with HIV coinfection to understand adherence, how engaged they'll be, and how well they will do in taking their meds. Obviously, a critically important point for the patients themselves is: are they interested. They have to want to do this. As treatments get easier and better- tolerated, there may be less nonadherence, but until now, patients had to want this for themselves to get through it, to be honest. I think that will still be important, if nothing else because it translates to adherence. But they have to be engaged and want to do this, right?

The last thing is comorbid conditions. When we had interferon as part of the regimen in patients who had hypertension or diabetes, we had to make sure those diseases were controlled. In patients who had cardiovascular disease, we had to make sure they weren't having active evidence of anginal symptoms and make sure all of their comorbid diseases, asthma or COPD, are well controlled, because interferon in particular could flare many of those diseases, which could be a major limitation to starting interferon treatment.

Underlying psychiatric disease, which is extremely common in our patients with HIV coinfection, was another critical comorbidity that we had to address in coordination with their psychiatrist or psychologist to make sure they were appropriately managed for access to interferon-based therapies.

Again, many of these things will become much less relevant as we have interferon-free treatments — significantly less relevant, I believe. In fact, many patients we're identifying for treatment now are patients with psychiatric disease because we now have the options of access to interferon-free treatment.

Those are all the things we think about when considering treatment for a patient.

MR. BUSKER: What about the way you assess and stage fibrosis in these patients?

DR. NAGGIE: The practice has changed quite a bit. Given the approval of new medications that can offer cure rates over 80 percent, even with off-label use, there is the possibility of an oral therapy that can offer cure rates over 95 percent. We used to use liver biopsy quite a bit because we needed to hash out the exact state of liver disease, 0, 1, 2, 3, 4. We felt that anyone who had a stage 2 or higher on the Metavir scoring system should be offered treatment. But now our decision-making is more about can you wait; and most critically, do you have cirrhosis? Because once you cure someone, if they have cirrhosis they still need lifelong liver disease management like hepatocellular carcinoma screening, for example.

And so we've been using I think in clinical practice, more of these noninvasive technologies like serologic markers, the APRI score, which is something you can calculate with just an AST and a platelet count, or a FibroSURE (Fibrotest), an expensive commercial test that costs a significant amount of money. In addition, a new radiologic type of technology called a FibroScan has been approved by the FDA as of April of 2013 that now can also measure liver stiffness. And that actually is an excellent test for differentiating stage 4 disease, i.e. cirrhosis, from all others.

And so staging plays a critical role here but the way that we now stage is quite different from the way that we staged just two years ago, using a lot more of these non-invasive tests and much less liver biopsy because, again, we don't need the granularity that liver biopsy provided and now we really just need to know do they have cirrhosis or not.

MR. BUSKER: Let me ask you to review for us, if you would, doctor, some of the most important new data presented at AASLD and how it would impact your treatment protocols.

DR. NAGGIE: Yeah, so I actually think now understanding the medicines not only that we have today, so two new drugs approved right after AASLD which was a medicine called sofosbuvir, which is a nucleotide analog, the first nucleotide analog that was approved by the FDA, pan genotypic activity, as well as a medicine called simeprevir, which is an NS34A protease inhibitor, so this is a second wave protease inhibitor, similar mechanism of action to telaprevir and boceprevir, but really a drug that is only dosed once a day, fewer side effects. Both of these medications for the genotype 1 patient by the approval still require interferon, but, for example, with a sofosbuvir-based regimen, only 12 weeks of interferon and ribavirin. For a simeprevir-based regimen in a

treatment naïve patient based on futility rules you are talking about 12 weeks of the simeprevir, 24 total weeks of the interferon and the ribavirin. And these medicines are offering cure rates in over 80 percent in patients, which is, so really shortening the course of therapy but also offering much, much higher cure rates for these patients.

So we clearly make these decisions based on what are our current therapies but then what's coming. And what's coming, and so we've really got a really nice glimpse of what does the future hold in the treatment of hepatitis C, in particular for genotype 1 at that meeting. So, for example, in HIV/HCV co-infected patients, in fact, it's not really what's coming but at that time it was what's coming, the PHOTON-1 study was presented by Dr. Mark Sulkowski.[2] This is the first all-oral treatment for the treatment of HCV in an HIV infected patient population looking at sofosbuvir and weight based ribavirin.

This offered a 76 percent cure rate, SVR-12, which is an undetectable viral load, 12 weeks after the end of treatment, in an HIV co-infected patient population, which is really quite phenomenal. In addition, this study included genotype 2 and 3 patients, and as many of the listeners may know, with the sofosbuvir approval also came a huge change and a paradigm shift from the treatment of genotype 2/3 patients, which is now interferon-free therapies. So that interferon-free therapy of sofosbuvir and ribavirin, now standard of care in genotype 2 patients that are mono-infected, also based on this PHOTON-1 trial, became the standard of care for patients with HIV infection. Showing that HIV co-infected patients with two, genotype 2 and 3, can achieve the same cure rates as an HCV mono-infected patient and cure rates over 90 percent in patients with genotype 2 or 3, 2s getting 12 weeks of sofosbuvir and ribavirin and 3s getting 24 weeks of sofosbuvir and ribavirin.

That 24 week length of treatment not only supported by the PHOTON study which was presented at AASLD, but also the VALENCE study that was presented at AASLD.[3] The VALENCE trial specifically looked at patients with genotype 2/3 infection, this was a European trial looking at sofosbuvir and weight based ribavirin. You know, it's interesting, initially this trial was to look at genotype 2/3 naïve and experienced patients for 12 weeks; however, based on the phase 3 data of this regimen in the registration trial suggested that genotype 3 patients probably needed a longer course of therapy. One of the trials called the FUSION trial investigated 12 versus 16 weeks in treatment-experienced patients, and showed clear benefit. And so the VALENCE made a change to their protocol and ended up treating all of their geno 3s for a total of 24 weeks and really putting forth some really fantastic numbers in terms of response rates for those patients.

So in patients who were treatment-experienced cirrhotics, cure rates of 87 percent, treatment naïve cirrhotics 92 percent, and treatment naïve non-cirrhotics 94 percent. So really fantastic numbers, and again, this now is, per the FDA approved package insert for the treatment of these patients. So these were critical presentations at AASLD that really played a big role ultimately in the FDA hearing as to the approval of this drug and how it could be used.

And obviously, some of the other really exciting regimens that were presented are currently not what we have available but are the regimens that we know are going to be available literally in 6 to 12 months. And so as a provider taking care of a patient in the clinic, what you're going to sit down and talk to them about is here's what we have today, this is basically what I tell them, if I'm going to treat you today, here's what I'm going to give you. But if I'm going to treat you next year at this exact point in time, here is what I'm going to give you and here is what this means. It means even higher cure rates, close to 100 percent in a treatment naïve patient, and no interferon, and this is for genotype 1, no interferon. So those studies that were presented included the trial looking at HCV genotype 1B patients, Japanese patients who received daclatasvir and asunaprevir, this is an NS5A and an NS34A inhibitor combination in nonresponder and interferon ineligible or intolerant patients, really difficult to treat patient population, and this was actually now a regimen that was submitted and I believe is now approved or will be approved very soon for use in Japan, but showing excellent SVR-24 rates of 85 percent overall, which is just really nice for a genotype 1B population.[4]

In addition, we saw evidence of the LONESTAR study.[5] So this is a regimen that includes that drug sofosbuvir that was approved by the FDA in December, and then a combination with another NS5A inhibitor, ledipasvir. So this is I think where it gets really interesting because this regimen, it comes in the fixed dose combination tablet and was

submitted to the FDA for approval last month. So as I'm sitting here with patients, I can actually tell them this drug will be approved in August or September of this year. And the cure rates in this patient population, they did a very interesting study where they actually looked at treatment naïve, non-cirrhotics, and the question they wanted to ask is what I say, and this is: how low can you go. So up to now I think we all argued that 12 weeks of therapy may have been the sweet spot for these all oral treatments but, indeed, they wanted to look at 8 weeks in a naïve, non-cirrhotic patient population. And then in patients who could possibly, who could have cirrhosis or more severe liver disease, they looked at 12 weeks of this fixed-dose combination plus or minus ribavirin. And again, all groups, regardless of cirrhosis and length of treatment, achieved an SVR-12 of over 95 percent. So really impressive, right? Eight weeks, if you are treatment naïve, non-cirrhotic, which in reality is a majority of our patients can achieve an over 95 percent chance of cure in 8 weeks.

And then if you thought that that was kind of the best that we could do, the SYNERGY trial,[6] which is actually an NIAID-led trial investigating not only the fixed dose combination but then they tried to add on another drug, so the fixed dose combination plus either an NS34A protease inhibitor or this fixed dose combination plus a non-nucleoside polymerase inhibitor. And they, in fact, showed that they could cure 100 percent of patients, small numbers, 20 patients per arm, but 100 percent even in six weeks with one of these triple combinations, all DAA, no ribavirin, no interferon.

And so recognizing that this is the future, you really have to sit down with a patient and say, for example, you have stage 1 disease, you have no significant damage, you've had this disease for 25 years, it is highly unlikely that you would even die from complications, but the bottom line is waiting one more year for these really phenomenal all oral, anywhere from 6 to 12 weeks of therapy, it really is worth waiting for. And so when we make these decisions and have discussions with the patients, it really does involve what do we know is coming and we talk to them, it's amazing, that you can practice with almost a crystal ball, because one of these has already been submitted to the FDA for approval. So it's not like sometimes when you're having discussions and they're on phase II trials and you don't know how many of them are going to survive, and wow, it's years away. But in this case we actually know that at least one of these highly effective all oral therapies will be available in the coming year.

And so this is why staging is, having some feeling of the severity of liver disease is so important because you really want to be confident that you can tell a patient to wait, but I absolutely recommend in stage 0/1s waiting, and anyone who has higher stages of disease, I kind of give them the option but the bottom line is if they don't have cirrhosis I recommend that they await these all-oral therapies.

MR. BUSKER: You've mentioned genotype 3 patients — let me ask you to focus specifically on those now, if you would, please.

DR. NAGGIE: I think a number of us probably have a couple of these genotype 3 patients who previously failed PEG and riba treatment. We know that geno 3s have higher failure rates to taking riba than geno 2s, and many of them have severe liver disease. And I have a patient who's 50, genotype 3, previously failed treatment, and has been awaiting interferon free therapies and he had cirrhosis on a liver biopsy 3 years ago, and now like many of our patients has signs of early portal hypertension. So he has a large spleen on ultrasound, his platelet count is now down to 110, and so a difficult to treat patient here.

MR. BUSKER: Difficult-to-treat genotype 3 — tell us about your approach to patients like this.

DR. NAGGIE: The first and most important step here is not so much to focus on treatment but to make sure this patient is getting adequate care for his severe liver disease. Making sure he's getting appropriate hepatocellular carcinoma screening and esophageal varices screening, and, of course, in this setting, making sure that all patients have adequate testing for HIV and ruling that out as a co-factor here as well as HBV vaccination if possible. But really the big focus here is on managing this patient's liver disease, making sure that they have at least q.6 month liver function tests, bilirubin, INR, albumin, and making sure that this patient isn't someone, for example, who needed to be considered for liver transplant.

In addition, I think once you have all those ducks in a row, this is a patient you really must prioritize for therapy. And as I mentioned, genotype 3s with severe liver disease are the more difficult to treat patient

population right now. In fact, we discussed earlier the VALENCE trial, and with 24 weeks of treatment these treatment experienced cirrhotics do have lower response rates and in that trial 60 percent. And so that's that very sub-specialized patient population where cure rates are going to be lower and because of that, considering other options.

So the only one study that I would want to quickly highlight from AASLD was the LONESTAR-2 trial, and this looked at very difficult to treat genotype 2/3 patients who had previously failed therapy. Over about 50 percent of them had cirrhosis and they looked at an interferon inclusive regimen which was sofosbuvir, interferon and ribavirin. Clearly in a patient with portal hypertension, you have to be very careful about giving interferon because of the risk of decompensation, but those cure rates were in the over 80 percent range versus 60 percent if you don't include that interferon. And so really in this sub-specialized patient population there has to be a consideration of an interferon inclusive regimen to improve that cure rate.

MR. BUSKER: So Dr. Naggie, your specialty is infectious disease. Do you usually involve your hepatology colleagues in the care of patients like the ones you've been describing?

DR. NAGGIE: I'm lucky, I trained with the hepatologists here, even though I'm not a hepatologist. I did clinics with them and they trained me to do liver biopsies. They've been very engaged in working with me and taking care of these patients. In fact, both of my clinics at the VA and Duke are multidisciplinary clinics where I have hepatologists involved in the care of the patients. But we don't need them to see all of these patients; we primarily have them see patients with severe liver disease — cirrhosis, portal hypertension, patients at risk of decompensation. They are the ones who would be managing these patients through liver transplantation and we like to make sure that they know all patients with portal hypertension and their MELD scores. The MELD score was initially studied in patient populations with refractory ascites being considered for a TIPS, which is a portal vein shunt, but now we use MELD to help us define a patient's mortality in the next three months, so MELD is now used as a marker for liver transplant listing.

Any patient with a MELD over 12 in our center should be referred for transplantation, but we make sure that the hepatologists see all of these patients. In the peritransplant setting we now have some options for possible treatment, as that's part of the FDA package insert for sofosbuvir. But any patient with cirrhosis, in my opinion, should be comanaged with a hepatologist, because even if we cure their hep C and then as infectious disease providers may become less interested, but those patients still need long-term liver care.

MR. BUSKER:I want to thank you for today's discussion, doctor. To wrap things up, let's review the key points of today's podcast in light of our learning objectives. So to begin: hepatocellular carcinoma screening to identify high-risk patients with hepatitis B.

DR. NAGGIE: I think the most important thing here is to recognize that you're caring for a patient who meets those criteria for high risk screening and in that setting the AASLD recommendation is for an ultrasound every six months. Again, in resource limited settings, in many clinics where they don't have access or where cost is a major limitation, the considerations of a two stage approach with alpha-fetoprotein then triggering an ultrasound if the alpha-fetoprotein is elevated, is a consideration, but again, recognizing although more cost effective will miss HCCs at an earlier stage of disease and does not provide as much of a life-years benefit as ultrasound screening does.

MR. BUSKER: And the decision-making process in initiating hepatitis C treatment in a patient co-infected with HIV.

DR. NAGGIE: I would argue that all HIV co-infected patients should be treated for their hepatitis C, and I think very important to review candidacy with the patients, and in particular, again, getting to the issue of staging. It's critically important to know if these patients have cirrhosis. One is right now patients with cirrhosis should all be treated with what we currently have available but also that those patients that need lifelong liver management.

The decision-making on initiating therapy really is driven primarily by whether or not they have severe liver disease because any patient without severe liver disease should be able to wait the one year to get

access to what would really be the standard of care moving forward, which is all oral DAA therapies. I think the future of hep C treatment is one or two pills that may involve two to three direct acting antivirals for hep C. Many of these will not require ribavirin, although some will. None of them will include interferon. And we're looking at somewhere between 6 to 12 weeks of therapy for a genotype 1 patient. Genotype 2s and 3s now can be cured at high rates with sofosbuvir and ribavirin for 12 weeks as a 2, and 24 weeks as a 3, and I think those are the critically important points to think of in making decisions about treatment for any patient but certainly for an HIV co-infected patient.

MR. BUSKER: And finally: the complexities of treating the Hepatitis C genotype 3 infected patient.

DR. NAGGIE: With FDA approval of several either pan-genotypic or multigenotypic DAAs, what we have found is that now genotype 3 patients tend to be the patients who have the lower responses to these treatments primarily given just less efficacy of these drugs with this genotype. In a sense we have now used the term this has become the new genotype 1, the patient who is a bit more difficult to treat.

Overall, the current standard of care — sofosbuvir and ribavirin for 24 weeks — works extremely well for all of these patients, with the exception of the treatment-experienced cirrhotic genotype 3, and this is the one patient where you may consider the addition, if possible, of interferon. So the LONESTAR-2 looking at 12 weeks of a triple combination with sofosbuvir, PEG-interferon, and ribavirin offered the highest cure rates.

Other than that, I think these patients can do very well, but there is that select patient population. And again, remembering, for any genotype, patients who have severe liver disease, really needing to think about making sure their HCC is being screened for, that they're being referred to hepatology for co-management, as well as consideration of liver transplant, is critically important and why all of these patients need to have least some sort of a test, noninvasive mostly, that can tell you cirrhosis yes/no with a high level of confidence to make sure you're managing that patient's liver disease appropriately if they, indeed, have it.

MR. BUSKER: Dr. Susanna Naggie from the Duke University School of Medicine, thank you for participating in this eViralHepatitis Review Podcast.

DR. NAGGIE: Thank you so much for having me. As you can tell, I love what I do and enjoy taking care of these patients, and I hope we can get more ID practitioners out there doing the same.

MR. BUSKER: 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.

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Thank you for listening.

eViralHepatitis Review is supported by educational grants from AbbVie, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., and Genentech, Inc.

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