# HBV Treatment Decision-Making

## CMEO Podcast Transcript

**Kris Kowdley:**

Hello, I'm Kris Kowdley. On behalf of CME Outfitters, I would like to welcome and thank you for joining us for Episode 2 of a four-part CMEO cast series on best practices to improve screening and treatment of hepatitis B virus. And today's episode is titled *HBV Treatment Decision-Making*. This activity is brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide.

As I mentioned, I'm Kris Kowdley, Director of Liver Institute Northwest and Clinical Professor at the Elson S. Floyd College of Medicine at Washington State University. I'm really pleased to be joined today by my colleague, Dr. Paul Kwo. Paul is a Professor of Medicine and Director of Hepatology of the Gastroenterology & Hepatology Division at Stanford University in Stanford, California. From today's episode, let's start by reviewing our first learning objective, which is to optimize efficacy and safety profiles of current agents when initiating or switching treatment in patients with HBV. Our second learning objective is to define functional cure for hepatitis B and how it applies to HBV Asians currently in development. Paul, let's begin with a brief discussion of the goals of therapy for HBV.

**Paul Kwo:**

Thanks so much, Kris. And again, thanks so much for the kind invitation. So when we see patients in our clinic who have chronic hepatitis B, we tend to think of multiple goals when we talk about treatment options with these patients. So obviously, when we start at a nucleotide or nucleoside analog on a patient with hepatitis B, we're looking at two immediate biomarkers, the ALT level and the hepatitis B DNA level. And it's our expectation when you use potent first-line therapies that the ALT is going to normalize; that is, you're going to reduce the inflammation associated with chronic hepatitis B. And in addition, the hepatitis B DNA levels are also going to decline. And with our current therapies, Kris, they decline and the expectation is they're going to decline to very low levels or ideally target not detected. And these two responses are associated with an improvement in liver histology.

And Kris, as you now know, since you've been involved with so many of the Seminole studies, we now know that not only does inflammation improve, but also fibrosis improves in individuals who are treated long term with nucleotide and nucleoside analogs for hepatitis B. We often also look at the other benefits with improvement in histology. This means that you will live longer, you're less likely to develop cirrhosis, and we now even know that hepatocellular carcinoma risks also go down with treatment of hepatitis B.

We looked at the serologic markers as well, and we're going to talk a little bit about this and in hepatitis B antigen-positive individuals, which is the minority of people we see, what we wish to observe is a loss of hepatitis B antigen production of e antibody; but ultimately, really Kris, the best marker of functional cure, which we will discuss shortly, is loss of hepatitis B surface antigen. But taken together Kris, all of these lead to reduced morbidity and mortality from hepatitis B, reduced rates of cirrhosis, and again, reduced rates of hepatocellular cancer. Remember, hepatitis B is a carcinogen. It's been classified as a carcinogen by the WHO. It's the leading cause of liver cancer worldwide. And while we want to improve our functional cure rates moving forward, we have the tools now to markedly reduce the morbidity and mortality associated with chronic hepatitis B.

**Kris Kowdley:**

That's great, Paul, for laying out the goalpost and how we measure treatment success in hepatitis B. Now, obviously there are a large number of different guidelines out there and you summarized these extremely well. So please walk us through the AASLD and EASL guidelines for management of HBV.

**Paul Kwo:**

Yes. So let's talk about both of these because both guidelines have evolved over time and, in addition, have included now some flexibility on when to treat some of these individuals. Again, one of the important aspects of treating hepatitis B has been historically that we have treated those individuals with elevated ALT levels and high DNA levels. And this is based to a degree on a Seminole publication, which was the REVEAL study, which came from Taiwan which showed that there's a biologic gradient with DNA levels and the risk of progression to fibrosis and cirrhosis, as well as the risk for hepatocellular cancer.

And the EASL guidelines, which came out in 2017, the AASLD guidelines, which were most recently updated in 2018, both use a strategy where treatment is warranted when the ALT levels go up. And this is true for hepatitis B antigen-positive individuals and hepatitis B antigen-negative individuals. And when the ALT level goes to two times the upper limit of normal and the DNA level is above 20,000 for e antigen positive and 2000 for e antigen negative in the AASLD guidance, we then initiate therapy with nucleoside/nucleotide analog therapy or much less commonly interferon therapy. The AASLD guidance also introduced a new twist in the treatment of those with cirrhosis. So prior guidance documents had suggested that with cirrhosis and if you had a low level of HBV DNA, you didn't need to treat. The AASLD guidance now, in addition to the EASL guidance, both point out that if you have cirrhosis due to hepatitis B, you have a detectable HBV DNA level, then you need to be treated. And again, we typically treat these with nucleotide/nucleoside analogs.

The EASL guidance is very similar. The threshold for DNA is a bit lower and e antigen positive is 2000, not 20,000. The other aspect for the guidance, both in AASLD and EASL, Kris, is that there are those individuals now with ALT levels that are less than two times the upper limit of normal that we now treat, particularly in the setting of inflammation or significant fibrosis. And as you know, we don't often biopsy patients with chronic hepatitis B. But if we do see substantial or moderate inflammation, or we have elastography study that shows up to fibrosis, if the ALT level is above the upper limit of normal, then these are individuals that you can consider and I certainly do, in my practice, go ahead and initiate treatment for these particular individuals.

Now, in the AASLD guidance, also the ALT levels were defined as 35 for males and 25 for females. And again, we, a few years ago, wrote the ACG practice guidance, Kris, where we also redefined ALT and AST, as you know, that a truly healthy ALT is around 35 for males, and this allows us to account for metabolic syndrome factors, other factors, which oftentimes in outside labs lead to ALT upper limit of normals, it can be 40, 50 or 60. We now know that these individuals often have additional comorbidities. And thus, with an ALT of 35, we can capture those individuals who truly are healthy. So anything above that, we have to look at carefully. And in your practice, you have to keep an eye on this simply because, Kris, oftentimes these values aren't flagged. That's true for AST and ALT and later we'll discuss that's also true for creatinine and estimated GFR.

**Kris Kowdley:**

Yeah. Now, that's a great summary. And of course, as the treatments become more and more safe and efficacious over the long run, the threshold for starting treatment will inevitably go lower. So you've given us an understanding of when treatment should be started. Can you briefly discuss which pharmacotherapies are ideal or less ideal given specific patient characteristics?

**Paul Kwo:**

Yes. Thanks very much. And so let's talk about the preferred or first-line therapies that our practice guidance documents have recommended, and they're pretty uniform across Europe and the US and so our preferred agents are either nucleoside/nucleotide analogs, this is tenofovir disoproxil, tenofovir alafenamide or entecavir and then we do have one immunomodulatory agent peginterferon alfa-2a and these are preferred for those with or without cirrhosis. And those with decompensated cirrhosis, we exclusively use nucleoside/nucleotide analogs as opposed to interferon, which should not be given in anybody who has decompensated cirrhosis. These therapies are all potent. They have high barriers to resistance.

Entecavir, when it was introduced, previously had an indication for the treatment of those who have been exposed to our first nucleoside analog lamivudine, but we now know that we have much better therapies now and those have been lamivudine exposed, that is tenofovir disoproxil and tenofovir alafenamide. And so if you've been lamivudine exposed then entecavir is not a first-line option. However, with people who've never been treated, all three nucleotide/nucleoside analogs are potent treatments with high barriers to resistance. The decompensated patients typically need nucleoside/nucleotide analog therapy tenofovir or entecavir. And again, with hepatitis B, if you initiate therapy in these individuals, as we've now seen, the expectation is that many of these individuals may actually improve and start to show evidence of recompensation with these. So we've got good treatment options, Kris, for those with and without cirrhosis.

**Kris Kowdley:**

And of course, for the patient with cirrhosis, especially if there's a question of decompensation, interferon would not be a good option, right?

**Paul Kwo:**

It would be contraindicated, Kris. We've learned our lesson many times. These are not individuals who should receive an immunomodulatory agent such as interferon if you're decompensated, that's correct.

**Kris Kowdley:**

Well, thank you, Paul, for the discussion of the treatment guidelines and the available agents and sort of how you would choose one class versus another class. That's a lot of information to digest. So for the benefit of our audience, can you summarize the key points of when therapy should be started, changed or discontinued?

**Paul Kwo:**

Yes. So when to start therapy? So the key clinical considerations include an elevated HBV DNA. And if you're seeing a hepatitis B antigen positive individual, it's above 20,000 International Units, if they're hepatitis B e antigen negative, which is the majority of individuals you'll encounter in your practice, it is HBV DNA level of 2000 International Units or greater. And you want to also have evidence of an elevated ALT or significant disease on elastography or liver biopsy. And again, historically, we had higher thresholds to initiate therapy, but with better therapies and with better understanding of the natural history of hepatitis B, the thresholds for treating are starting to fall now, but these criteria help us select appropriate candidates who will benefit from treatment for hepatitis B.

**Paul Kwo:**

When to stop or alter therapy? So this is very interesting. So our practice guidance... Let's talk about the hepatitis B antigen-positive individuals to start with. So if you're hepatitis B antigen positive and you initiate therapy, the traditional endpoint is zero conversion. And this means, Kris, that you lose e antigen, you produce hepatitis B antibody, and you have undetectable HBV DNA. There's typically then a consolidation period. And this consolidation period can be anywhere from one to three years or longer with longer consolidation periods being associated with greater durability when you stop your nucleotide or nucleoside analog. However, there are some individuals now who are trending to continue therapy even after you've had your period of consolidation, hoping to clear surface antigen, which is we can discuss a bit later, is the so-called functional cure.

For hepatitis B antigen-negative individuals, right now the expectation when you sit down with your patients, the expectation is that you are going to be on long-term therapy, chronic suppressive therapy. And I make the analogy with our patients who initiate therapy, who are hepatitis B antigen negative, that this is like treating your high blood pressure. Right now, we know that long term our current first-line therapies are very effective. There's incredibly low rates of resistance and the clinical benefits have been described already, as we did earlier today.

Now, what about when to otherwise stop therapy? What about an inadequate virologic response, that is, you don't suppress virus? With our first-line therapies, this would be extremely uncommon. And if this were to occur, I would be looking very closely at a patient's compliance. This is not to say that resistance or primary non-response can't occur, but it would be extremely unlikely nowadays in a patient who's taking their nucleotide or nucleoside first-line therapy appropriately. The same thing is true for resistance. With our current therapies, it's extremely rare. There have been essentially no reported cases yet of resistance with the tenofovir disoproxil or tenofovir alafenamide. And with entecavir, again, it's also extremely low in treatment [inaudible 00:14:53] individuals really only occurring and those who've been previously exposed to lamivudine. Moreover, the other possibility is that we will be now introducing novel agents into our clinics to try and treat and lead to functional cure. And certainly, we would encourage our patients to consider exploring these as well.

**Kris Kowdley:**

Thanks for that great summary. So you mentioned that entecavir and tenofovir are first-line therapies for HBV. The tenofovir disoproxil fumarate or TDF and entecavir differ in their association with the risk for hepatocellular carcinoma in patients with hepatitis B.

**Paul Kwo:**

Oh, yes. This is a very topical conversation right now. And so I would like to just spend a little bit of time and perhaps review some of the data. So in Korea is, as you know, a few years ago, there was a very interesting observation that suggested that those who are taking tenofovir actually had a lower risk of incident hepatocellular carcinoma compared to those who are taking entecavir. And again, these observations can sometimes be very difficult to interpret. Your entecavir has been around much longer than tenofovir for hepatitis B; but nonetheless, this was statistically significant. And to help answer this, we've had several meta-analyses that have now been reported.

And there was one recent meta-analysis that looked at 13 observational studies in over 85,000 individuals with chronic hepatitis B. And they compared the incident rates of hepatocellular carcinoma. And what they found was that tenofovir seem to be associated with a slightly lower risk of hepatocellular carcinoma than those who were treated with entecavir therapy.

**Paul Kwo:**

And so this benefit seemed to be most associated in their meta-analysis in those with cirrhosis and the same observation was not made in chronic hepatitis B patients who had no evidence of cirrhosis. So that was one very interesting meta-analysis. It was recently published.

There have also been a few other ones, Kris. And in fact, there was one recently published, just a month ago, that looked at a much larger group of individuals here. And this involved over 119,000 individuals and this particular study looked at a variety of pooled studies, they adjusted covariates, and what they found was that tenofovir and entecavir were associated with no difference in the risk of hepatocellular carcinoma over five years. And their conclusion was that you should select your therapy and guide it by patient tolerability as well as access to therapy.

And so when you look at these large meta-analyses, and there's also a third one that was recently reported that didn't show a difference, what we see is that some of these studies have suggested there may be a benefit in reduction of hepatocellular carcinoma with tenofovir; others have suggested there's no difference. It is certainly true, Kris, that no study has shown that entecavir is actually associated with a lower risk of hepatocellular carcinoma. But right now, what we can say is that if there is a difference here, it is probably slight. And the data do seem to suggest in the largest trials that there is not a statistical difference in incidents of hepatocellular carcinoma at this time.

When you look at the two therapies, my analysis is look at some of the other virologic, biochemical and other benefits when giving entecavir or tenofovir. And one recent meta-analysis suggested that tenofovir versus entecavir, there were slightly improved virologic response rates with tenofovir. With regard to normalization of ALT, entecavir may have had a minimal benefit, although the trend didn't quite reach statistical significance. And finally, there were no differences in serologic response rates.

So the totality of the data is both of these treatments are excellent first-line therapies, and you should be able to use these with competence. And hopefully moving forward, we'll be able to use these medicines in combinations with others, not only to suppress virus and provide the clinical benefits that we've discussed, Kris, but also ultimately to lead to functional cure, which is what this is really about, that is, clearance of surface antigen.

**Kris Kowdley:**

Yeah, that's the goal that we have to keep in mind as our ideal goal. Now there's this new agent tenofovir alafenamide, also known as TAF, it's been around in the HIV therapeutic area, and now has been approved for hepatitis B. What does the data revealed in terms of switching patients from TDF to TAF?

**Paul Kwo:**

Yes. So we have used tenofovir disoproxil, as you have said, Kris, for years, and tenofovir alafenamide is a newer agent. Because of what it is complex to, you can use lower levels of tenofovir and you have potentially fewer off-target effects. And these two agents have been compared in a randomized controlled trial. And what it showed was that the viral suppression rates for tenofovir disoproxil and tenofovir alafenamide, TDF and TAF, are identical. The viral suppression rate, that is HBV DNA levels less than 20 International Units, is identical between the two. There are extremely low treatment failure rates as well. And one of the most interesting things about these two drugs are that when you are treated with tenofovir alafenamide, there seems to be a higher rate of ALT normalization when you either initiate tenofovir alafenamide therapy or if you switched from tenofovir disoproxil, TDF, to tenofovir alafenamide. And this is something that has been consistently observed in these trials that have looked at switching TDF to tenofovir alafenamide.

**Kris Kowdley:**

Yeah. It's interesting. No one has a very good explanation for it. My personal theory, purely subjective based on no data, is that it may be that higher intrahepatic concentrations may actually suppress virus to a greater degree, but to a degree that we're not able to measure. But anyway, what have we learned about the safety of switching from TDF to TAF? I think the main appeal of TAF has been the potential favorable effects on bone, renal, and kidney function. Can you share the information available in hepatitis B with regard to switching?

**Paul Kwo:**

Yes. So let's talk about this. It's just what you said. So, because we use lower amounts of tenofovir, you have fewer off-target effects. And so tenofovir disoproxil over time in some individuals can lead to renal tubular dysfunction and also to metabolic bone disease issues including osteoporosis or osteopenia. And there are now data looking at the safety of switching from tenofovir disoproxil to tenofovir alafenamide and what they've been able to show, Kris, when you switch is that you seem to recover your renal function more significantly when you switch over from tenofovir disoproxil to tenofovir alafenamide.

And in addition to the ALT normalization, bone mineral density also seems to improve and this has been shown both in hip and spine measurements. And this has been, again shown over two years, there was 21% and 38%, respectively, improvement in osteoporosis scores. And again, there were very few individuals who actually had their bone mineral density worsen when they received tenofovir alafenamide. And again, as our population ages to some degree, we need to be mindful of some of these metabolic abnormalities that can potentially occur when we treat those with chronic hepatitis B. And this is certainly a reason in select populations, why we should be contemplating if you're on tenofovir disoproxil changed over to tenofovir alafenamide.

**Kris Kowdley:**

Yeah. Excellent point. So we know now from several observational studies that patients with chronic HBV who may be immigrants from countries with high endemicity and immigrated to the US and after years of living in the US, their metabolic profile, regrettably starts to look a little more like the metabolic profile of the American population at large, which is overrepresented with metabolic syndrome, chronic kidney disease, et cetera.

So you have enormous experience in treating hepatitis B. You also have a major role in directing and teaching other students, fellows, et cetera, in terms of treating hepatitis B. What guidance do you provide, from your own perspective, about how do you individualize treatment selection for patients?

**Paul Kwo:**

Sure. So when we see patients in clinic, the important considerations in seeing our hepatitis B patients are that you should be aware of potential complications and those who are older, that is, above the age of 60. For bone disease, you want to be quite careful in those who have to receive chronic corticosteroid use or any other medicines that can worsen your bone density. Those with a history of osteoporosis or osteopenia, you want to be staying away from tenofovir disoproxil. And most importantly, Kris, we also need to track very carefully our renal function, and this is true throughout liver disease. But again, if you have a GFR that's less than 60 milliliters per minute, you need to be very careful and make sure that you're selecting agents which minimize the renal toxicity.

**Paul Kwo:**

The important teaching point here, that I always go over with our residents and fellows, is that look at the GFR not the creatinine, Kris. So that, for instance, if you're a petite Asian female and your creatinine is 1.2, then your estimated GFR is actually not normal. And you are somebody that we need to, if they require hepatitis B therapy, Kris, that this is someone that should not be receiving tenofovir disoproxil, and we should be thinking about tenofovir alafenamide, entecavir not. And then, of course, you still have to monitor renal function, but you'll be much more likely to have less of an effect on your renal function. This is also true for individuals who are on hemodialysis as well, those who have any kind of substantial proteinuria, these are all individuals where tenofovir alafenamide, I think, is a better choice than tenofovir disoproxil. And again, with our current demographics, as you said, we do see large numbers of these individuals.

**Kris Kowdley:**

Yeah. So of course, with treatment, Paul, comes a need to monitor the effectiveness of that treatment, both from an efficacy and a safety perspective. We've talked about the safety monitoring with regard to bone, kidney, et cetera, inflammation and hepatocellular necrosis are predisposing factors for liver cancer or hepatocellular carcinoma highlighting the need for monitoring. What is your recommendation regarding when and how monitoring should occur?

**Paul Kwo:**

Sure. So typically the first year, Kris, we do hepatic panel and renal panel every 12 weeks. And again, the expectation is that we are going to see the ALT level normalize. We also check HBV DNA levels and, for the first year, I check them every 12 weeks. This is not because, with our current first-line therapies that I'm worried about the efficacy of the treatment, I just want to make sure the patients are actually compliant with that. And after the first year, if everything is suppressed, then I'd switch over to every six months and follow DNA levels. Then, in addition, that's a liver panel as well every six months after the first year.

What about hepatitis B serologies? Well, if you're e antigen positive, I typically look for the e antigen serial conversion after the first year of therapy. And again, in those who are e antigen negative annually, I check the hepatitis B surface antigen level particularly in those who have undetectable HBV DNA, whereas hepatitis B surface antigen clearance or functional cure is as an uncommon event in e antigen-negative individuals, it certainly does occur.

We typically... Again, if you're taking tenofovir disoproxil, you do need to be looking at the renal function regularly. And again, there is another nucleotide, which is not first-line therapy, which is adefovir, which hopefully should be an almost unheard of occurrence nowadays. But if you're using either of those, you should be looking at the serum creatinine regularly as well and making sure that these individuals don't have worsening proteinuria as well. And so if you do these, then you should be able to not only suppress well your virus, Kris, but you should also be able to make sure that there's minimization of any unintended off-target effects.

**Kris Kowdley:**

Well, great. Many patients with chronic hep B are of child-bearing age, and it's always difficult to know exactly what to do in a patient who is thinking about getting pregnant or pregnant. So what is your approach to management of HBV during pregnancy?

**Paul Kwo:**

Yes. So again, a common occurrence. Now we see young people with chronic hepatitis B. So obviously first you need to stage the disease. And if you find somebody does have advanced fibrosis, that cirrhosis stage IV or V fibrosis, or they have significant hepatitis either a flare or they meet the standard criteria for treatment of hepatitis B, you should be treating these individuals with tenofovir disoproxil. And these people are then treated throughout the entire pregnancy.

Now, what about those that are the more typical presentation that you have a young woman who is pregnant, but does not have active chronic hepatitis B at this time? These individuals get monitored without treatment, and I typically monitor them during their first two trimesters, but ensure that they return at the end of the second trimester for a quantitative HBV DNA level. And if their DNA level is less than 200,000 International Units, Kris, then they can go forward with their planned delivery. They need to make sure that their infants receive hep B immune globulin and the hepatitis B vaccination series. And typically it's within 12 hours of birth, but actually if you can do it within one hour of birth, Kris, that does seem to be even more effective.

If your DNA level is greater than 200,000 International Units, or there's a threatened preterm labor, or there's some other reason such as a previous childhood immunoprophylaxis failure, then these individuals need to be initiated on therapy in the third trimester typically with tenofovir, but you can certainly use lamivudine or telbivudine, though these are not preferred agents beginning at the third trimester. These individuals also, in addition to starting tenofovir-based therapy, should also receive hep B immune globulin and hepatitis B vaccination series. And again, preferentially, you should give it within one hour of birth.

And if the patient does deliver, then breastfeeding is certainly something that can be done if you are on tenofovir therapy. And again, once you've delivered and your patient has had to initiate tenofovir therapy, you can either give it up to delivery or one to three months postpartum. Again, first-line therapy is certainly tenofovir disoproxil right now, Kris. I typically give it up to delivery and then taper these individuals. You do need to monitor and very rarely will you see an ALT flare, but typically my experience has been that you don't need to reinitiate tenofovir-based therapy in the vast majority of these individuals.

**Kris Kowdley:**

Well, that was an excellent summary. The World Health Organization has set a goal for HBV elimination by 2030. Since we don't have a cure or a sterilizing cure for HBV as an achievable goal at the present time, focus is now on functional cure. Can you walk us through what is a functional cure and how do we achieve that? You've certainly been at the cutting edge of a lot of the clinical trials with new therapies, so I look forward to your comments.

**Paul Kwo:**

Sure. So functional cure is a goal, Kris, that I think we should be able to achieve. And so typically when you start hepatitis B therapy, as you know, we're able to suppress the DNA levels, we're able to press the ALT levels, but what is more problematic is to clear surface antigen. And what we tend to believe is going to be the achievable cure rate is when we're able to clear hepatitis B surface antigen, which is defined as a functional cure. Other definitions of cure that we can certainly contemplate is going to be something such as a sterilizing cure, where you're able to remove all DNA, all evidence of hepatitis B from the host hepatocytes. That includes also getting rid of integrated hepatitis B DNA, making the hepatitis B core antibody titers go to zero. I think all of these are going to be a bit too ambitious unless we develop truly new techniques to try to suppress and rid hepatocytes of chronic hepatitis B.

**Paul Kwo:**

But again, using multiple different mechanisms of action, Kris, we should be able to not only suppress hepatitis B DNA levels, but the expectation is that with a variety of technologies, we should be able to clear surface antigen as well.

**Kris Kowdley:**

Thank you for that great summary. So thank you for providing us with a great discussion on opportunities for HBV screening, diagnosis and management, explaining the concept of functional cure, management of HBV in pregnancy, and emerging therapies. Now let's close with our smart goals that is specific, measurable, attainable, relevant, and timely goals. Paul, what key messages do you hope clinicians listening today will take away from this podcast?

**Paul Kwo:**

Sure. Thank you, Kris. So importantly, we have the tools now to effectively suppress hepatitis B and improve clinical outcomes, Kris. And you need to consider the safety and efficacy profiles of our current available therapies when you make your treatment decisions in your patients you follow with chronic hepatitis B. The AASLD guidance documents do provide flexibility and a framework on whom to initiate therapy including populations, Kris, that years ago in practice guidance documents we didn't necessarily treat. And it's important that you stay abreast of these, particularly in patients who may have relatively seemingly normal ALT levels, but may have more advanced fibrosis, including patients with cirrhosis with low levels of virus, make sure that you implement the AASLD-directed guidance in your practice.

And finally, in your patients who are pregnant, make sure that you apply your best practices. Check the DNA level at the third trimester in addition to vaccination to eliminate hepatitis B, to achieve WHO guidance goals, Kris. Obviously, preventing transmission of hepatitis B will be a substantial portion of that strategy as well.

**Kris Kowdley:**

Thank you, Paul. To receive CME and CE credit, click on the link identified here to complete the post-test and evaluation online. Thank you for joining us today for Episode 2 of our four-part CMEO cast series. To view additional episodes on community-based efforts to improve screening and treatment of hepatitis B virus, please visit cmeoutfitters.com and thank you again for participating and thank you for providing the best care for your patients.