Clinical Approaches to HBV Therapy

In our first newsletter/podcast on Current Gaps in Diagnosis and Linkage to Care, learners were knowledgeable prior to the education. However, our post-assessment showed an increase of 15% following the education. We will report the results of issues 3 and 4 in an upcoming podcast.

Our guest author is Daryl T. Y. Lau, MD, MSc, MPH, Associate Professor of Medicine, Beth Israel Deaconess Medical Center Harvard Medical School, Boston, Massachusetts.

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

- Evaluate and manage patients who do not meet current treatment criteria.
- Describe management of chronic hepatitis B during pregnancy.
- Identify patients appropriate for tenofovir alafenamide (TAF) therapy.

Unlabeled/Unapproved Uses

Dr. Lau has indicated that there will be no references to the unlabeled or unapproved use of any drugs or products in this presentation.

Download the podcast transcript
Go to the companion newsletter

MEET THE AUTHOR

Daryl T. Y. Lau, MD, MSc, MPH, Associate Professor of Medicine, Beth Israel Deaconess Medical Center Harvard Medical School, Boston, Massachusetts

Guest Faculty Disclosure

Dr. Lau has disclosed that she has received research funding from Gilead Sciences, Inc. and Bristol-Myers Squibb and that she has served as a consultant/advisor to Gilead Sciences, Inc., AbbVie, Inc., and the Asian Health Foundation.

Release Date: May 25, 2017
Expiration Date: May 24, 2019
MR. BOB BUSKER: Welcome to this eViralHepatitis Review podcast.

I’m Bob Busker, managing editor of eViralHepatitis Review. With us today is Dr. Daryl T. Lau, Associate Professor of Medicine at the Harvard Medical School. Today’s discussion is a follow-up to her newsletter issue on Advances in HBV Therapies here in spring 2017.

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

Learning objectives for this audio program include:

- Evaluate and manage patients who do not meet current treatment criteria.
- Describe management of chronic hepatitis B during pregnancy.
- Identify patients appropriate for tenofovir alafenamide (TAF) therapy.

Dr. Lau has disclosed that she has received research funding from Gilead Sciences and Bristol-Myers Squibb; and that she has served as a consultant or advisor to Gilead Sciences, AbbVie, and the Asian Health Foundation. She has indicated that there will be no references to the unlabeled or unapproved use of any drugs or products in today’s discussion.

Dr. Lau, thank you for joining us today.

DR. LAU: Thank you very much for inviting me.

MR. BUSKER: In your newsletter issue, doctor, you reviewed some of the current literature describing how continuing research into hepatitis B is increasing both an understanding of the virus as well as expanding clinicians’ ability to provide better care for more and more of their patients. Today I’d like to focus on how that information might be translated into actual clinical practice. So, start us out, if you would please Dr. Lau, with a patient scenario.

DR. LAU: I’m going to present a very common case that we see quite frequently in the hepatitis clinic. This is a 55-year-old Chinese male who was documented to have HBeAg negative chronic hepatitis B and has been monitored by his primary care physician for the past year. He has frequent blood work and an abdominal ultrasound every six months. His HBV DNA level has been between 1,000 IU/mL to 1,800 IU/mL and his ALT has been consistently about 80 to 90 units/L.

His DNA and ALT profile appears to fit into the so-called “indeterminant” hepatitis B phenotype. He is treatment-naïve, has no significant medical history and no family history of hepatitis B or liver cancer, he does not smoke or drink, and his serial abdominal ultrasound has been pretty normal.

MR. BUSKER: Doctor, you said “indeterminant phenotype” — that may be something relatively new to our listeners. What does indeterminant phenotype mean?

DR. LAU: That’s a very good question, because usually when we think about the natural history of hepatitis B, we classify the patients into four categories: the immune tolerance phase, the immune active phase, the inactive phase, and the patient’s e-positive or e-negative status. However, in recent studies, we noticed more and more that a large portion of our patient population actually does not fit into any of these categories.
For example, in a recent study published in the *Journal of Viral Hepatitis* by the Hepatitis B Research Network sponsored by the NIH, approximately 38% of cohort patients have the indeterminant phenotype, meaning that based on the DNA and ALT level, they cannot be neatly or easily classified into one of those four usual categories. I think it is important to recognize this, because all the treatment guidelines recommend when to treat the patient and when to monitor the patient, with our treatment based on these same categories.

But when we have a patient with indeterminant phenotype, I think it is important for clinicians to know how to monitor them, how to work them up, evaluate them, and when to initiate treatment.

**MR. BUSKER:** So, the patient you just described — a 55-year-old Chinese man who does have an indeterminant HBV phenotype — how would you evaluate him?

**DR. LAU:** If you look at this patient’s ALT level, he fits the treatment criteria because he does have persistently elevated ALT level greater than two times the upper limit of normal of 30 units/L for men. His ALT has been about 80 or higher. However, his DNA level is consistently less than 2,000 IU/mL.

So first we have to make sure he does not have any other common causes of liver diseases that can lead to ALT elevation, because people can have more than one liver disease at the same time. My approach is to carefully take a history and see whether the patient would give me any clue that there may be another disease process going on. We already know that he does not drink alcohol, which is the common cause of liver disease. He doesn’t appear to have metabolic syndrome, which is the common cause of nonalcoholic fatty liver disease. He doesn’t have the risks for that, but I would also make sure he doesn’t have a family history of liver diseases besides hepatitis B and doesn’t have any autoimmune phenomenon that can put him at risk for autoimmune liver diseases. And of course, patients with hepatitis B sometimes have coinfections with other viruses such as HIV and delta hepatitis. So, I think we cannot not just stop and say the patient has hepatitis B and treat him or not without thinking through the other potential causes of ALT elevation.

**MR. BUSKER:** Those “other potential causes of ALT elevation” — would that include hepatitis C infection?

**DR. LAU:** Yes, I think it is crucial for any patients with elevated serum aminotransferases, regardless whether they have hepatitis B, to include hepatitis C in the differential diagnosis. This is especially important because the CDC recently recommended routinely testing everyone born between 1945 and 1965 for hepatitis C. In the past when CDC used the high-risk criteria to indicate hepatitis C testing, they found they missed a lot of patients who have hepatitis C.

This patient is 55 years old, so he does fit into the baby boomer HCV. So definitely hepatitis C should be one of the first things we check, and if he does have hepatitis C with replicative HCV RNA levels, I think we can make a case of treating both his hepatitis C with DAA therapy and hepatitis B at the same time, because his replicative hepatitis B, although not at a very high level, is definitely active.

And recently CDC reported data showing that in some patients with hepatitis C and hepatitis B coinfection, the hepatitis B can reactivate after DAA therapy for hepatitis C. This is a hot topic, and we need to be very familiar with how to manage patients who have coexisting hepatitis B and C.

You mentioned the other coinfection viruses. Delta hepatitis is an RNA virus that can superimpose or coinfect with hepatitis B. Our patient is from an eastern Asian country where delta hepatitis B is not very common, but I usually routinely check for delta hepatitis to make sure we are not dealing with coinfection with another virus.

**MR. BUSKER:** So that patient you described — let’s say that you’ve been able to rule out hepatitis C and delta hepatitis and other comorbid conditions — how do you decide whether or not to treat?

**DR. LAU:** Let’s say all he has is chronic hepatitis B with the indeterminant hepatitis B phenotype, so he doesn’t meet the treatment criteria. However, AASLD also provides a guideline if the patient has significant fibrosis or cirrhosis, in which case we should also consider therapy independent of the DNA and ALT values.

So my next step will be to try to establish the degree of hepatic fibrosis in this patient. In the past, liver biopsy was the standard criterion or the standard modality; however, because of the procedure’s invasiveness and patient discomfort, nowadays we use noninvasive techniques a lot more frequently. I prefer to use transient elastography or FibroScan, as well as MR elastography because both of these imaging-based modalities give very good sensitivity and specificity, over 80% in detecting cirrhosis and greater than stage 2 hepatic fibrosis. However, in areas of the world or in certain clinics when these imaging modalities are not available, we can also use noninvasive serum markers such as the indirect FIB-4 index and APRI, or direct markers such as the Hepascore and Fibrotest. The performance is not as good as the imaging-based techniques, but they have approximately 70% to 75% specificity in identifying greater than stage 2 fibrosis. So, they can definitely be used to make treatment decisions for this patient.

**MR. BUSKER:** One more hypothetical for this patient, doctor: let’s say that, for whatever reason, let’s say that HBV therapy is not initiated. How would you monitor this patient’s infection?
DR. LAU: After careful evaluation, if this patient indeed has relatively mild hepatic fibrosis, I would continue to monitor him carefully, because as we know, hepatitis B is a dynamic disease that can progress over time. The DNA and ALT levels can also change over time. So I would continue to monitor his liver panels and HBV DNA levels, and also do ultrasound every six months for HCC surveillance. If his disease remains stable with no significant change, I would also consider repeating the fibrosis measurements annually to pick up significant fibrosis that doesn’t meet the specific criteria.

MR. BUSKER: Thank you for that case and discussion. We’ll return, with Dr. Daryl T. Lau from Harvard Medical School, in just a moment.

MR. BOB BUSKER
This is Bob Busker, Managing Editor of eViralHepatitis Review.

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

In the month following each newsletter, a case-based podcast discussion, like the one you’re listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to eViralHepatitis Review is provided without charge or prerequisite. Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive eViralHepatitis Review without charge, and to access back issues, please go to our website: www.eviralhepatitisreview.org.

Thank you.

MR. BUSKER: Welcome back to the eViralHepatitis Review podcast. I’m Bob Busker, managing editor of the program. Our guest is Dr. Daryl Lau, from Harvard Medical School. We’ve been discussing how some of the advances in HBV knowledge she described in her newsletter issue can be translated into clinical practice. So, to continue with our patient focus, please bring us another patient scenario.

DR. LAU: The patient is a 30-year-old Korean woman who has HBeAG positive chronic hepatitis B and is currently in her second trimester of pregnancy with her first child. She is at an immune tolerant phase of hepatitis B with a very high level of viremia, HBV DNA persistently greater than 6 million IU/mL, and normal ALT. She’s entirely asymptomatic with regard to liver disease. She has a strong family history of hepatitis B and is very concerned about transmitting the virus to the baby. She is antiviral treatment-naive and has no significant medical history.

MR. BUSKER: What would you tell this pregnant patient about how to minimize the risk of vertical transmission of HBV?

DR. LAU: Obviously, she is very concerned because of her strong family history. Her mother has hepatitis B, and two of her sisters also have hepatitis B. I would first give her some historical perspective. For patients with very high virus levels, especially those who are HBeAG positive, if the baby does not receive any passive or active immunization at birth, the chance of vertical transmission is around 80% to 90%. I would reassure her, though, that now all newborn babies of mothers with hepatitis B would have a combination of hepatitis B vaccine and hepatitis B immunoglobulin shortly after birth, ideally within the first 12 hours. Such measures cut down about 90% of transmissions. However, for mothers who have very high viremia levels as in her case, HBV transmission to the baby remains an issue in about 10% to 30% of the cases.

MR. BUSKER: How would you advise this patient about her care while she’s pregnant?

DR. LAU: For patients with hepatitis B, I have to caution them that some pregnant patients do have active or reactivation of hepatitis B, because during pregnancy the cell-mediated immunity is suppressed so the virus has a chance to increase. And most concerning to me, the ALT level can also increase the so-called hepatitis flare. Increased HBV DNA level greater than 2 log can occur in about 10% of the patients, and in the literature on average approximately 6% to 10% of pregnant women would experience hepatitis B flare, with ALT levels greater than five times the upper limit of normal during the latter part of pregnancy, especially during the postpartum period.

So regardless of whether she had normal or abnormal ALT to begin with, I usually monitor patients very carefully every four to six weeks during the pregnancy. And for patients who have cirrhosis, they are considered high risk patients for pregnancy. With increased blood volume during pregnancy, they can have worsening of portal hypertension, meaning that they can develop ascites, they can develop esophageal or gastric varices which can lead to GI bleeding. There are also
some reports on hepatic decompensation during pregnancy that has, unfortunately, a higher risk for fetal demise, premature labor, and still birth.

So patients with advanced fibrosis or cirrhosis definitely must be monitored very closely in conjunction with the OB/GYN doctor. If the patient does have esophageal or gastric varices by upper GI endoscopy, C-section is usually the preferred mode of delivery, because vaginal delivery can further increase intraabdominal pressure, which can lead to rupture of the varices.

MR. BUSKER: What about the potential effects of antiviral therapy on the baby?

DR. LAU: To being with, in patients with hepatitis B we have to make sure that we use pregnancy class B medications such as tenofovir and telbivudine. We should avoid using adefovir and entecavir because they are class C medications. Lamivudine, interestingly, is considered a class C medication, but it has been used safely in patients with HIV and HBV and has a good track record. But because lamivudine and telbivudine can be associated with drug-associated resistance, nowadays we tend to use tenofovir most frequently. A recent publication in the *New England Journal of Medicine* confirmed that tenofovir administration during the third trimester of pregnancy is associated with 0% vertical transmission of hepatitis B to the baby, compared to 7% of mothers who don’t take antiviral therapy and have high viremia greater than 200,000 IU/mL.

MR. BUSKER: What about postpartum care? For example, should the mother breastfeed?

DR. LAU: If the patient decides to breastfeed, I think this is a bit of a controversial area. These medications appear to be excreted in the breast milk in extremely small quantities. Some hepatologists recommend that the mother to continue to use antiviral therapy while they breastfeed, but because it is uncertain exactly how much medication will be in the breast milk, I personally usually advise mothers to stop antiviral therapy if they choose to breastfeed the baby. That is, if they do not have significant liver disease to begin with, meaning they do not need ongoing antiviral therapy. If they do have significant fibrosis or cirrhosis, I usually encourage them to use formula and not to breastfeed the baby. Also, if you discontinue antiviral therapy, it is very important to monitor the patient very closely every four to six weeks, because hepatitis flare can occur during the postpartum period and also can occur with the withdrawal of medication. If they do have flare of hepatitis, I would restart the medication.

MR. BUSKER: One final question about this case — what are the recommendations about testing the baby for HBV?

DR. LAU: The Advisory Committee on Immunization Practices recommends testing babies born to mothers with hepatitis B at the age of 9 to 18 months. So, to backtrack, babies should receive all three doses of vaccine immediately after birth or shortly after birth at 1 month and 6 months. Then they should have testing no sooner than 7 months, and the recommendation is 9 to 18 months. If they develop a good level of anti-HB surface antibody, they are protected. Some babies, especially those who are premature baby or low birth weight, do not develop anti-HBs antibody, even with the three doses of vaccine; in those babies, the recommendation is to give them another series of three doses of vaccine with repeat testing.

MR. BUSKER: Thank you for that case and discussion, Dr. Lau. We've got time for one more patient.

DR. LAU: This is a 61-year-old Hispanic woman with HBV antigen-negative chronic hepatitis B. She also has poorly controlled type 2 diabetes and documented osteopenia on the DEXA scan. She is antiviral treatment-naïve. She does meet the AASLD treatment criteria with persistent DNA level greater than 2,000 IU/mL and ALT level ranging between 50 and 80 units/L.

MR. BUSKER: How would you evaluate this patient?

DR. LAU: To evaluate this patient for therapy, we have to do all the usual baseline liver evaluations, and it is important to routinely check for HIV before considering hepatitis B therapy because entecavir and tenofovir are also effective for HIV. So we make sure we don’t use those antiviral therapies as monotherapy for HIV, because that will lead to drug-associated resistance. And let’s say we have done careful evaluations and have done ultrasound and determined that she does have stage 2 fibrosis and meets all the criteria for treatment; in this case I would also consider the possibility of other comorbid conditions such as renal disease because she had uncontrolled type 2 diabetes, and because she also has osteopenia. I would make sure not to give her any medications that would increase her fracture risk.

MR. BUSKER: What factors would you consider when selecting an antiviral agent for this patient?

DR. LAU: We use entecavir and tenofovir as our first-line antiviral therapy, even though seven FDA approved antiviral agents are on the market. Most recently we have a new prodrug of tenofovir, tenofovir alafenamide or TAF, which is an interesting, newly approved medication that enhances delivery of the active drug to the hepatocyte. Because of that there is 89% reduction in plasma concentration of the medications, so there is decreased systemic exposure of tenofovir to the bone and to the kidney.

So for patients who have renal dysfunction or have risk for osteopenia or osteoporosis, that would be a reasonable first-line
Tenofovir is also a very good medication for reducing fibrosis and has a reduced cancer risk, but in a small percentage of patients, tenofovir can cause reduction of GFR and also reduction of bone mineral density.

Alternatively, the patient can use entecavir, which does not have any bone or renal side effects. With entecavir it is important to remember it must be taken on an empty stomach, so it is inconvenient for some patients to time their medication. And for patients who have a history of taking lamivudine, entecavir may not be the best choice because of cross-resistance.

MR. BUSKER: How would you monitor her during her therapy?

DR. LAU: After starting antiviral therapy, I usually check with the patient in the first month. Because of distance, some patients may not find it convenient to return in a month, but I would make sure they can contact me if they have any uncertainty about how to take their medication or worry about any side effects. If they tolerate the medication very well, I will see them every three months until their HBV DNA level has reduced to a low level. I would like HBV DNA to continue to reduce to less than 20 IU/mL, but I think if they gradually have reduction of the virus to less than 1,000 IU/mL, I can lengthen their clinic visit to every six months and continue to do abdominal ultrasound for HBV surveillance and continue to monitor their disease activity every six months.

For patients who have a history of any renal dysfunctions or abnormal serum creatinine level, one also needs to check the urea, creatinine, and GFR every three to six months. That’s the advantage of TAF, because it reduces plasma circulation and reduces systemic exposure, so we don’t really need to give the adjusted renal dose of the medication to patients with renal dysfunction.

MR. BUSKER: Thank you for today’s cases and discussion, doctor. Let’s wrap things up now by reviewing what we’ve been talking about today in light of our learning objectives. So, to begin: evaluating and managing patients who do not meet the current treatment criteria.

DR. LAU: As we discussed, approximately 40% of the hepatitis B population does not meet the treatment criteria because they belong to the so-called indeterminate HBV phenotype, meaning that their DNA and ALT levels cannot classify them into the traditional categories. However, we need to systematically evaluate and monitor them, because hepatitis B is a dynamic disease. If their DNA and ALT levels change, or their hepatitis B reactivates, we need to catch them early and initiate therapy. Furthermore, we need to establish their hepatic stiffness or degree of hepatic fibrosis because that may meet criteria for therapy, regardless of their DNA and ALT levels.

MR. BUSKER: And our second learning objective: the management of chronic hepatitis B during pregnancy.

DR. LAU: Pregnant women are a special population. Hepatitis flare can occur during pregnancy and also during the postpartum period, so we need to monitor the pregnant woman very closely every four to six weeks during pregnancy. Another major concern is vertical transmission of hepatitis B, even though it is on universal recommendation that infants born to mothers with hepatitis B should receive passive and active immunoprophylaxis. In a mother with high-level viremia, we should also consider antiviral therapy during the third trimester of pregnancy to further prevent vertical transmission of hepatitis B.

It is equally important to provide immunoglobulin, hepatitis B vaccine to the infant and also remember to test the baby for hepatitis B at age 9 to 18 months to ensure that they did not acquire hepatitis B.

MR. BUSKER: And finally: identifying patients who may be appropriate for tenofovir alafenamide, or TAF, therapy.

DR. LAU: Currently entecavir and tenofovir are the front-line therapies for chronic hepatitis B. In November 2016, a new prodrug of tenofovir, tenofovir alafenamide or TAF, became FDA approved. TAF has been shown to have an improved safety profile compared to tenofovir for patients with renal dysfunction, and those at risk for osteopenia or osteoporosis. So, for our patients who have concerns for renal toxicity or bone loss, TAF would be an alternative treatment option.

MR. BUSKER: Dr. Daryl Lau from Harvard Medical School, thank you for participating in this eViralHepatitis Review Podcast.

DR. LAU: It's my pleasure to be here today. Thank you very much.

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

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

This activity has been developed for primary care physicians, gastroenterologists, infectious disease specialists, OB/GYNs, physician assistants, nurse practitioners and nurses, and other clinicians diagnosing or managing patients with viral hepatitis.
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

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

This educational resource is provided without charge, but registration is required. To register to receive eViralHepatitis Review via email, please go to our website: www.eviralahepatitisreview.org.

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

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

eViralHepatitis Review is supported by educational grants from Gilead Sciences, Inc., and Merck, & Co., Inc., and AbbVie, Inc.

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

CME/CE INFORMATION

ACCREDITATION STATEMENT
Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT
Physicians
Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credits)(TM). Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
Podcast: This 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE
It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

INTERNET CME/CE POLICY

INTENDED AUDIENCE

DISCLAIMER STATEMENT

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY
<table>
<thead>
<tr>
<th>STATEMENT OF RESPONSIBILITY</th>
<th>PARTICIPANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>STATEMENT OF NEED</td>
<td>HARDWARE &amp; SOFTWARE REQUIREMENTS</td>
</tr>
<tr>
<td></td>
<td>COMPLETE CME INFORMATION</td>
</tr>
</tbody>
</table>

All rights reserved - The Johns Hopkins University School of Medicine. Copyright 2017.

This activity was developed in collaboration with DKBmed.