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HEPATITIS B AND C: COINFECTION AND REACTIVATION

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Hepatitis B and C: Coinfection and Reactivation

[video transcript]

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Good afternoon. Dr. Ponni Perumalswami, is an associate professor of internal medicine in the Division of Gastroenterology and Hepatology at University of Michigan, and director of the liver clinic at the Ann Arbor VA Health Care System. Her research is focused on overcoming barriers and improved access to care and treatment, and patients living at the intersection of substance use disorders and liver disease including Hepatitis C. Happy to turn it over to you Dr. Perumalswami.

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Thanks so much for inviting me to present today. I'm delighted to speak on The Talk topic of Hepatitis B and C with a focus on coinfection reactivation. But I'll also be sharing some things that are new with respect to Hepatitis B, I don't have any relevant financial disclosures. The learning objectives today will be to start by explaining and reviewing the epidemiology and corpse of a Hepatitis B virus and trying to set this up. In comparison to hep C, discuss laboratory testing and diagnosis of Hepatitis B and Hepatitis C virus, understand the role of heavy wreck reactivation in patients living with chronic hep C, and describe the clinical management of CO infection with Hepatitis B and C viruses. So I always think it's very helpful to try to put things in a perspective. And because a lot of the education initiative in this space is focused on Hep C, I thought it would be nice to compare this to hep B for the for the for, for this topic. So globally, we've actually had an increase in the number of people living with Hepatitis B globally. So that number is actually gone up from around 260 million now up to 290 6 million. And this is somewhat different than what we've seen with hep C globally, where the burden of infection or people living with Hepatitis C has actually decreased down to 58 million. Excuse me, go back. And why this is important is that new cases and mortality related to Hepatitis B, and C, still are major public health problems. So you can see here on the right, highlighted in the red circle, are the number of new cases of Hepatitis B, and C infection annually. And you can see that with C, which is all the way to the right, and with B, it's about 1.5 million cases per year. And this is unfortunately balanced by about 1.1 million deaths, as of in 2019, due to Hepatitis B, and C, and when you break that down, most of those deaths are actually related to Hepatitis B infection 820,000 Compared to 290,000 deaths due to hep C. And there's still a lot of regional variation globally, in terms of how we are doing with diagnosis and treatment, which is shown here at the bottom left. And I think the major messages are that we are still at a point where we are under diagnosing people that we think are living with Hepatitis C, and far fewer patients are getting engaged in treatment. And when you think about Hepatitis B and its relationship to liver cancer, and how this compares to hep C, we certainly see a great majority of liver cancer cases being related to hep B infection when compared to hep C for both men and women. Here in the United States, we certainly have set elimination kind of targets or goals, similar to what has been set globally. And you can see kind of what the elimination strategies and where we are starting with in terms of acute hep B infections on the left and acute Hep C infections on the right. I think what you can see here is that the estimated US prevalence of Hepatitis C infection

the United States is 2.4 million people and with hep B, it's around 880,000 people, although many believe this to be an underestimate, particularly with hep B, and that we probably have somewhere, you know, between 580,000 to 1.1 7 million people living with with Hepatitis B in the United States. So let's talk a little bit about hep B. So when you think about those 296 million people infected globally 68% are actually from Africa and western Pacific regions of the world. About 2.7 million people are co infected with HIV, and most infected persons were born before Hepatitis B vaccine. Seeing was widely used in infancy and there are still some countries across the globe, including countries with very high prevalence of Hepatitis B, that have not yet successfully implemented at birth dose hep B vaccination. So happy really remains unfortunately a leading cause for liver cirrhosis, and hepatocellular carcinoma. And we estimate that close to 50% of liver cancer cases globally, are attributable to Hepatitis B infection. And one of the unique unique aspects of heavy is that you can develop liver cancer in the absence of cirrhosis, which is quite distinct from the other etiologies of liver disease, Hepatitis B, a second tobacco in causing cancer deaths, and it's way more infectious, I would say compared to HIV. Now, who are the populations that are disproportionately impacted by Hepatitis B infection, people who inject drugs, because of blood blood transmission, and then our foreign born communities, in particular Asian and Pacific Islander black non Hispanic individuals. And we've certainly seen an increase in the number of acute infections, which has been related to increases in injection drug use, here in the United States and globally, and lower adult vaccination rates and some patient groups. And in terms of current challenges with chronic heavy Hepatitis B infection, we still see a lot of perinatal transmission. So from mother to child, a lot of lack of awareness of what Hepatitis B is and how it is it transmitted. Testing and Linkage to Care remains challenging in this space, the price of treatment and antivirals, and the lack of curative treatment, although I'll highlight how some of this might be evolving. So we think about Hepatitis B prevalence geographically, I think you guys, a number of you have probably seen this slide in, you know, one, one shape or form. But what you can see here is that areas highlighted in green have the highest Hepatitis B surface antigen prevalence, followed by dark blue, which is about two to 7%, chronic hep B prevalence. And then here are the United States, we're actually considered to be a low have been prevalent in countries but as I just mentioned, some populations that shoulder more disproportionate burden of the infection actually have intermediate or high prevalence here in the United States. So in the United States, I just mentioned globally, we've set targets around Hepatitis B and Hepatitis C elimination. And the goals here are to reduce the number of new chronic infections by 90% by 2030, and reduce deaths due to viral Hepatitis infection by 65%. You can see highlighted in the red circle here, that we still have a lot of room for improvement when we're talking about testing or screening to diagnose people living with hep B, and then getting them transition into treatment is the modes for transmission for heavy, globally common modes of transmission include mother to baby at the time of birth. This accounts for about 50% or more of cases, and this is most commonly in our East Asian communities, horizontal within household during early childhood is still a major cause for transmission. Healthcare unfortunately, so really, I estrogenic causes through reuse of non sterilized needles and syringes and resource limited or poor settings. contaminated blood products has actually improved and is less of a risk factor. And then we surmise additional traditional medicine practices might also contribute, including things like scarification acupuncture. And then in non endemic countries, which include the United States, adult unprotected sexual activity actually accounts for now of 54% of cases, which is the most

common route of transmission here now, and followed by injection drug use, which accounts for about 20% of cases. Now, the outcome of Hepatitis B infection, once it's acquired by an A person is really influenced by the age at which this virus is being transmitted. So what do I mean by that? In newborns, acquiring this infection as a newborn translates into 90% of these babies developing chronic infection. This is quite different than acquiring this infection as an adult, where less than 15% will go on to develop chronic infection it has to do with immune immune systems and how developed they are. And so we we certainly worry more about transmission at a younger age, but you can still develop chronic infection as an adult, acquire During this as well, and I think the one of the main important things to highlight here is that we've had a safe and effective vaccine for decades now. And so one would think that, you know, really focusing on scaling up vaccine availability, particularly at the time of birth, and this has been a large focus for, you know, population based efforts to try to curb disease here.

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Now, acute infection with Hepatitis B can lead to chronic infection, which is largely influenced by age at which this is acquired. With higher risk of developing chronic infection, the younger you are that you acquire it. And this independent of developing cirrhosis, which is a really distinct feature compared to other liver diseases can lead to liver cancer. And, in those patients who develop cirrhosis can develop certainly signs of liver failure. Sometimes, we first start diagnosing still pages and these late kind of parts of this pathway when they develop a very large cancer or decompensated cirrhosis, and then need to be considered for liver transplant if that's an option, or eventually, many of these patients unfortunately, die from liver disease. So we know that the level of Hepatitis B DNA virus is associated with the risk of cirrhosis and liver cancer. And this is based on the revealed study, which many of you are aware of, which was a long term follow up study of untreated people living in Taiwan infected with Hepatitis B. And what you can see here is that the higher the level of the virus, over a 13 year follow up, the higher the risk of developing cirrhosis on the left, which is showing cumulative incidence of cirrhosis. And on the right, what you see here is the cumulative incidence of liver cancer, which goes up with higher amounts of virus over a long term period. Now here in the United States, as I mentioned, about 880,000 people we estimate are living with Hepatitis B, the number of acute Hepatitis B infections has increased by 11%. And most of this is from injection drug use, increases as well as unprotected sexual intercourse. And, again, for adults who are acquiring this infection, you have a lower risk of developing chronic infection, but still up to 15% or more will develop chronic infection. And when we look at, again, thinking about who, which patient groups and populations in the US are really shouldering the burden of this disease, Asian American Pacific Islander populations, black and non Hispanic, actually have the highest rates of death with Hepatitis B listed as a cause of death in US residents. So there are some clear disparities in terms of mortality related hep B, and people who are living with this. So as I mentioned at the beginning, I was going to highlight also what's new in this space. So in March of this year, we've now CDC has now come out with a recommendation for all adults to be tested at least once in their lifetime for Hepatitis B. And this is again, because Hepatitis B can cause liver cancer, and early death, and most people will not have symptoms and know that they're living with it. And so now it's recommended similar to what we went through with hep C, that all adults 18 years and older, at least gets tested once, and for anyone who's requesting hep B testing, they should receive it regardless of disclosure of risk. And this has to do with

stigma. And similar to what we've seen with hep C. Now, the rationale for universal screening is that there's substantial morbidity and mortality. Chronic infection can be easily detected before a development of severe liver disease using reliable and inexpensive screening tests. treatment for chronic hep B can reduce mortality and morbidity, we have methods to reduce the risk of transmission. Part of this is knowing if you're infected. It's cost effective to do treatment, which a number of the studies that led to this recommendation helped influence and screening can again, identify patients who are at risk for reactivation, which we're going to touch on towards the latter part of this talk. And screening might also identify patients who would benefit from vaccination. So people who are not already immune, these are may represent additional opportunities to provide vaccines to prevent screening tests that are now recommended routinely, again, for all adults at least once in their lifetime is happy surface antigen, happy surface antibody and a total happy core antibody. So these are blood tests that can be done at one time. And these, you know can confidently Tell us who is infected with EPI. Now, what is unchanged with these updated recommendation is that all pregnant persons during each pregnancy should still be screened for hep B, preferably in the first trimester, regardless of vaccination status or history of testing. So, so this is an important thing because it can influence and help us distinguish who might be at higher risk, which moms might be at higher risk to transmit this virus to babies up here in Italy around the time of birth. And so it's important to also keep in mind that some groups of people living in the United States have an increased risk for hep B infection and are recommended for periodic testing. And I've included those groups here, along with kind of highlighting who the new groups are. So in addition to people born in regions with Hepatitis B prevalence more than 2%. Now people currently or formerly incarcerated in a jail prison or other detention setting people with current or past Hep C infection, and people with current or past sexually transmitted diseases, or infections, or multiple sex partners, which is relevant given the rise of sexually transmitted infections that we've been seeing nationally. Now, I will also say that there are a lot of inequities and disparities and access to antiviral treatment globally. And so this still remains an important area where we are need to think about how we can improve the reach and access to antiviral therapy, as we're identifying more patients, people living with Hepatitis B. Another kind of key piece of what's new in this space, is that universal Hepatitis B vaccine is now recommended for all adults, aged 19 to 59. So it was already recommended for all infants persons less than 19. So now, this is adults aged 19 to 59. And also for those above 60 and above, who might have risk factors based on sexual exposure percutaneous or mucosal exposure to blood. Some other groups are listed there, including persons with hep C infection, persons who were incarcerated, and then really leaving a door open to just generally recommend this for all adults, including those 60 and above without any risk factors to receive a vaccine. And I just included this slide, which was published last year, which really is a nice population based approach to introducing a vaccine more than 15 years ago, and then antiviral treatment in the last 10 years in Taiwan. And what you can see is in panel a on the left chronic liver disease and cirrhosis mortality in various age groups and how you can see the curves are bending downwards. In the middle you see liver cancer related mortality also bending down from when you compare timeframes going back to 1979 to 2018. And then liver cancer incidence. So you know, these strategies work if we can reach the people to get them, for example, vaccinated and treated. So how do you diagnose Hepatitis B, I just mentioned the Serologies that are recommended for testing and Hepatitis B surface antigen is one of those three tests and if that's positive, that's a marker for active infection. If it's present

for at least six months it by diagnosis you have by definition, you have chronic hep B infection, Hepatitis B surface antibody, the second test listed there is a marker of immunity to Hepatitis B. And Hepatitis B core antibody total is a marker for either previous exposure or sometimes can be a false positive. If you're ever at all worried about acute hep B infection and a patient of yours, the test of choice to check is to also include the Hepatitis B core antibody IgM. Now, once you've checked those tests, you've identified somebody who's surface antigen positive, you want to do additional testing. And I think this is where they're some of this is done in a primary care space. Some of this is done in a specialty specialty, but e antigen testing for Hepatitis B, again, can be a surrogate marker for an earlier stage of infection with a higher viral load antibody to E can really be associated with pre core basal core. promoter mutation tends to be associated with lower viral load, a longer duration of infection. And Hepatitis B DNA virus level similar to like what we do with Hepatitis C RNA levels is your marker for active viral replication. So can I detect virus in the bladder or not? So, again, when we're thinking about lab testing approach for somebody who might have chronic hep B infections, you start with screening if that surface antigen is positive, you want to Get the additional serological markers. And then somewhere that very similar to hep C, I would say you do what you see on the right here, which is look for other parameters to really try to understand, you know, the stage or degree of fibrosis a patient might have. And the degree of fibrosis really does influence

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tree treatment recommendations because not everybody's recommended for treatment with hep B. And so this graphic here is one again, you've probably also seen potentially in a number of ways, ways shapes or forms and E antigen positive patients are on the left there tend to be a very high virus level in early stages can have a normal LT in some patients particularly those where this is perinatally transmitted Constand this early what we used to call him intolerant do not need treatment Hi replicate replicative phase over time, that Al that DNA level can come down and a multi level can Co Op representing a more immune active phase in which treatment is recommended. And then from that, you can transition from losing e antigen to then transitioning on the right into an E antigen positive or E antigen negative phase. And again, treatments recommended in those patients who are showing signs of transitioning across stages. Now, very few people will lose surface antigen spontaneously less than one to 3% per year. And in those patients that indicates resolution of infection, certainly. So in the first two to three decades of life, as I just mentioned, that immune tolerant with high viral load e antigen positive normal al to your common 180 5% of adults with chronic hep B are in that inactive carrier phase, and 30 to 40% have active Hepatitis. And I said like you said on that saw on that graphic, the time periods to think about when a patient might be meeting criteria for antiviral treatment. As a field we have been discussing how do we simplify what we recommend around Hepatitis B? How can we simplify the message as a guidance for primary care providers to have more capacity building and adoption in this space? So this is like one such approach. You can access this and the University of Washington website. And really thinking through how do we also talk about how do we talk about simplifying our treatment approaches. And I think this is still where there's a lot of controversy, the things do seem to be shifting towards wanting to adopt simplified approaches, with experts, patients also weighing in on this as important stakeholders. So I think if you were to talk about in the screening paid space, we've now shifted right with the CDC recommendations, from the risk based screening to now screen all adults at

least once that's, I think, one kind of example of simplification of care and treatment in this space. And then there is a lot of thought being given to who who we're recommending for treatment. How do we simplify identifying those people who are recommending for treatment. And then, for patients with cirrhosis, one approach that was presented by Dr. tro and others at the liver meeting last year, was really emphasizing the need to treat all those with cirrhosis, compensated and decompensated, regardless of Hepi, DNA and Lt levels. So I think keeping the messages clear, and grounded, and data is going to be an important part of how these these get adopted. Now there are a number of FDA approved treatments for Hepatitis B, you can see the first line treatments at the top here. The most common ones are highlighted in the red box here because of the first line and that's mostly because the peg interferon alpha to a is an injection and and so the antiviral therapies are one pill once a day. Some of the newer medications have more favorable toxicity profiles. And then I've listed on the bottom, the second and third line medications that you sometimes still see patients on for a variety of reasons. Now, there is a lot of discussion and work being done to try to figure out if we can achieve curative treatments for Hepatitis B. And the realistic kind of functional cure is what is really being discussed in most of these circles when we're referring to cures where we could obviously, in an ideal situation have lots of surface antigen and no detected DNA. And I think the the the challenge here has been with part of this virus getting encode loaded into host DNA in the form of this covalent closed DNA so that this would still potentially be detected but not active. And so there's still a lot of work being done here in this space to see if we can really achieve these treatments that would be aimed at a functional cure. There are a lot of drugs in development, I think the point of this talk is to really now take this back to hep C, but I just want to highlight, there are several class of treatments that are being looked at a number of companies that are trying to make antivirals and test them in various stages. And the strategies for heavy cure. And this slide is compliments of Anna lock, is to really think about probably combination therapy with nucleoside, or nucleotide analogs, its backbone therapy. And this might be the strategy we eventually see, but it's will take a little bit more time. Now I want to move to the second part of this talk to really talk about Hepatitis B and C co infection and then reactivation. So how common is Hepatitis B and C co infection? And I think the true answer is we we don't know precisely. But it depends somewhat on the patient population and Rachel prevalence of these infections. In the United States, we think it's around 1.4%. So fairly low. But then when you look at patients who have hep C's, some studies have suggested 10 to 15% of people living with hep C are co infected with hep B, some settings that's as high as 30%. And in additional studies, it's somewhere between five and 20%. And I think this has to do with share routes of transmission increases in these these routes of transmission just epidemiologically seeing a lot more of it in our populations leading to risks around hep B and Hep C infection. And why do we care about dual infection or CO infection? Well, if you have both of these virus, you're more likely to have accelerated disease course with respect to liver disease, so faster progression to cirrhosis, and decompensated cirrhosis. And it looks like there's synergistic risk with liver cancer by all of the studies in the cohorts of patients who have had both these infections. So these are groups that should be really prioritized for treatment, although I think we've really shifted away from kind of that thinking of like, rationing treatment, if you will. But this is a high risk group. And so really engaging with these patients to talk about treatment. And certainly, there's a risk of hep B reactivation as you treat the Hep C. Occasionally, this has been reported to be fulminant, during or after direct acting, no therapy therapy has been reported. We now have the infection among

American patients with hep C infection. This was a study we did many years ago in the VA looking at VA patients who had both hep B and Hep C infection. And what it was a you know, the stage of fibrosis in the 26 co infected patients and we compare these two mono infected Hep C patients, you know, again, in an observational way suggested these patients living with both had much more fibrosis than those who just had mono infection. And so we have some theories as to the viral interplay between these two viruses. The host immune response probably plays a significant role in controlling viral replication. If you were to look at the viral loads, and people who are co infected, usually one virus dominates. Most typically, most of the cohort studies, it's Hep C. Eradication of hep C or immunosuppression of the host could lead to reactivation. And the three main theories here here have to do with either direct inhibition of hep C to hep B replication, increase in available replication space after you, for example, are curing Hep C and reducing that viral burden of one virus and the last of host immune responses to one of the viruses usually hep B, or pre production of an immune inhibitory signal to improve replication over the one over the other. So moving along to hep B reactivation. So this is a really important concept, I think, for people to have awareness around. It's a clinical syndrome it's defined by characterizing defined by sudden increases in hep B replication due to a loss in immune control. And it can occur in people who are surface antigen positive so have chronic epi and or patients are surface antigen negative but core antibody positive so they've had a marker that tells us they been infected before right and happy activation in surface antigen positive patients is reasonably defined as one of the following. So greater than or equal to two log increased and happy DNA compared to wherever they were at baseline

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or happy DNA greater than or equal to three log in a patient with previously undetectable level, or epi DNA greater than or equal to four log in I use PrEP. Well if that baseline is unknown. And the reason why we've tried to establish some criteria, many of the early studies in this space used all kinds of criteria that weren't, didn't really allow us to compare the cohorts across the studies very well. Now for surface antigen negative patients who are just core antibody positives, that patients who don't have chronic infection, but have a marker that they were infected at some time in the past, the criteria is hep B DNA is detectable, okay, because they they didn't, they don't have chronic infection, they had it in the past, and now they have a DNA that's positive or reverse of surface antigen seroconversion. So reappearance of the surface antigen in the setting of what are whatever else is going on with this reactivation case at the time, no Hepatitis flares reasonably defined as an able to increase more than or equal to three times the baseline level, and or over 100 units per liter, and incurs in surface antigen patients that are positive, less commonly with resolved infections, so you're more likely to see reactivation and people with chronic epi who are surface antigen positive, compared to those who were just core antibody positive, who you know, had cleared, quote unquote, infection in the past. Now, the presentation of reactivation can really be quite a wide spectrum of presentation or disease, it can be on one end, very minimal Hepatitis, to acute or acute on chronic liver failure, where people die from this. So anything that's really the thing to highlight here, why there needs to be a lot of attention on this, even if it's not as commonly seen is that the stakes are high if it does develop for some patients. So I just mentioned silent reactivation elevated viral load without a vert Hepatitis is one under Omaha, that one end of the spectrum of how this can present. On the other end, you have fulminant liver failure, with full blown as if

somebody's coming in, you know, it's like a Tylenol overdose kind of failure. And then in between, you can have somebody who has, you know, elevation in their liver test and viral load, and kind of what we would say, biochemical or clinical or histological Hepatitis if we were to biopsy them. So why does reactivation Is it important entity to talk about, especially with respect to hep C? It's rarely been described it as and really think of it as an unwanted, unwanted but possible effect of hep C treatment. So in the very early studies that described this with direct acting antivirals, there were 29 cases globally that were reported of happy reactivation in the setting of hep C treatment with direct acting antivirals. Two out of three patients actually died and one out of three of those D compensated cirrhotic patients needed a liver transplant. So this client, obviously a lot of needed attention. The time to reactivation was somewhere between four and eight weeks, there was no specific DEA regimen that seemed to have higher risk, no specific Hep C genotype, and 28%. So over third had clinical illness and six were hospitalized. And that led to this blackbox warning for direct acting antivirals to say you need to screen everybody with for, for heavy before you start Hep C treatment. And again, the patients who were really at highest risk were the patients who were surface antigen positive. Now, again, the theories here that the Hep C core protein might be interfering with gene expression of Hepi. Once Hep C is treated, the hep B has more space to replicate, which kind of gets into also number two there. And then finally, Hep C can induce interferon abundant state that inhibits hep B replication. And once Hep C is gone, the interferons relax, and then the hep B has a chance to kind of replicate out of control. So there have been additional studies after that initial database kind of look at all of the patients who had reactivation when DBAs were first, you know, approved and introduced. And so this was like looking at 28 studies, 884 patients had chronic hep B 292. Were just core antibody positive so they had been infected before but were not chronically infected. And they were looking at who had happened had just been reactivation. And what they found was that, you know, 14% plus had a reactivation rate, and that the patients who were highest risk were certainly those who were surface antigen positive. And they've now looked back in time to see people who are treated with interferon based regimens, which we no longer do, and then just the direct acting antiviral regimen, so there doesn't seem to be a whole lot of difference, although maybe a little bit higher with interferon. Now, there have been additional studies since then, trying to describe those with chronic hep B infection compared those two core antibody positive people with resolved infection you can see here, far fewer patients with chronic hep B infection and much more with the history of core antibody, and the risk of heavy rock reactivation was 24% in patients with untreated chronic hep B infection and less than 2% in those with the result infection. So the risk really has to do with with the patients who have surface antigen or chronic epi infection. Now, I know a number of folks have tried to really drive home the point of it's important to screen how to for happy before doing treatment for hep C, and what you should do with this information. What are different strategies we can apply to try to have an algorithm for example for managing hep B infection. And so one proposed approach that was published a several years ago was in the surface antigen negative patients who are core antibody positive so don't have chronic infection were infected in the past can be monitored with alle T alone, while they're undergoing Hep C treatment until the SVR 12 visit. And that they could be it should be tested with surface antigen and hep B DNA only if the LT goes up. So this is what we tell a lot of the providers we work with here in the community that use your alts your signal, right, and if that staying normal, there's no reason to then check surface antigen and DNA. But if that goes up during treatment, as your Hep C virus is coming

down or not detected, that should be a cue a cue in to say, hey, we need to check the hep B surface antigen status again and what's going on with that. Now in patients who are surface antigen positive, so people who have chronic infection, but don't have detectable virus, who are being treated for hep C, they should be considered for either pre emptive hep B treatment or monitor with alle T and happy DNA levels until SVR 12. And again, these are the highest risk group of patients. And then the final group here is those who are surface antigen so they have chronic hep B infection, they had detectable virus so you know that they have a virus there already, you're treating their Hep C, and these patients should be started on pre emptive hep B treatment. So kind of three different approaches depending on where your patients might fall when you're thinking about hep B Hep C treatment. Now, the ASL D IDSA. Hep C guidance does have some information on this as well. Patients with low or undetectable hep B DNA again can either receive prophylactic hep B, a treatment for the duration of their Hep C treatment until SVR 12 are monitored at regular intervals for heavy and reactivation with heavy DNA testing. And if monitoring is elected, have B treatment kind of needs to be started on demand if the hep B DNA level increases. And so I think you know, the again, should be in our back of our mind as we're approaching our patients and thinking about hep C treatment. So the only way we're going to really have awareness around this is to be proactive and look for it. So all patients and now with the CDC recommendations, all patients should be tested at least one time in their lifetime. But certainly prior to PEP BC treatment to screen them with the three blood tests, you think about stratifying risks based on the neurological data. And then tailoring the management. And the is regimen here really gets into additional groups of patients who might be at risk. So again, this is just like another slide highlighting, really need to test all patients initiating Hep C, their therapy for Hepatitis B and how you can approach trying to manage these patients based on their surface antigen hep B DNA level.

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Now beyond Hep C treatment, there's also a risk of reactivation with hep B with immunosuppressive agents, which is what that is referred to two slides back. And the scenario in which we see this most commonly is with cancer related treatments, but we have a lot of immune modulatory treatments. Now they're used for a number of chronic diseases outside of cancer care, including inflammatory bowel disease, for example, for example, dermatological conditions, rheumatological conditions. So we're actually seeing more of these therapies being used in a variety of different spaces outside of cancer, the risk of reactivation goes up depending on the level of immunosuppressive agents that you're dealing with. So the highest risk groups are those who undergo stem cell or solid organ transplants because of all of the immunosuppression, we give them at the time of transplant and after. And on the other end of the spectrum, there are some what we would consider immunosuppressive agents that really represent much lower risk steroids are somewhere in the middle there as you can see. So in those patients who are receiving immunosuppressive or cytotoxic drugs, ASL D does have some guidance in the heavy guidelines document. So again, your highest risk patients are those who are chronically infected with hep B. And the patients with the most potent immunosuppressive therapy, including those anti CD 20 therapies need to be on treatment for six months, you know, during treatment and for six months to 12 months after completion of treatment. And patients are still recommended for prophylaxis with entecavir, tenofovir or TAF. These have higher potency and high resistance barriers. And those who are lower risk which

are the surface antigen negative, but core antibody positive people who don't have chronic infection but have signals of, of past infection should be carefully monitored with hlt, Hep B DNA. And again, thinking about this on demand therapy approach that I just explained. And monitoring these patients, even after they stop is important to look for reactivation. I think this is maybe one of my final slides, but you know, should have be coinfection impacts selection of hep C treatment. I think the short answer really is these treatments seem to work fine with one another sofosbuvir and velpatasvir velpatasvir does increase tenofovir area under the curve by up to 80%. No effect on the pharmacokinetic parameters sofosbuvir or blood pedosphere. So you can keep continuing on treatment and monitor friction off of your associated adverse reactions. I think the bottom line is most of these treatments are safe. They can kind of just monitor these patients closely to you know report anything if they're experiencing on treatment and treatment. Now, durations for hep C is so short for a lot of our patients that this doesn't end up being an issue. And tap has not been studied, but no clinically significant interaction is expected between Taff and Hep C D A's. So I'll just end by saying that hep B is a major public health concern it's associated with increased mortality from liver cancer and cirrhosis, especially with those infected at birth. Remember heavy can cause liver cancer independent of cirrhosis, which really sets it apart from other liver etiologies, which you develop liver cancer risk by way of cirrhosis, hep B and Hep C co infection can be common in some high risk groups. And there's likely viral interaction between hep B and Hep C. So that one is more dominant. And we're at why this is important is that if you're thinking about treating one need to monitor for reactivation, and then testing for hep B, prior to hep C treatment initiation is really important. As I just mentioned, it's now recommended for all adults at least once in their lifetime, but prior to hep B treatment, and then to think about treating if at risk for reactivation based on some of the strategies that I shared. With that, I'll end.

43:35
Thank you so much penny for this excellent talk. We already have several questions coming in. So maybe starting with Penny at the highest level, you know, there's such a push to simplify Hep C treatment and offer it in low resource settings. Is there ever an opportunity to bypass the hep B screening if, you know, maybe heavy screening is not readily available? Or if it's a really low prevalence? You know, setting or must have be screening be part of pre treatment for hep C?

44:12
Yeah, I think that's a great question. I think when I think about resource limited settings, it also makes me think about risks around hep B potentially being different. You know, there are some groups of patients that are just higher risk. And you know, here in the United States, it's certainly a lot of our immigrant populations, which could also fall into these kind of low resource settings. So they in some ways, you could be dealing with some populations that are even higher risk right for hep B, where you really don't want to forego screening. I think it would be great to have home testing simplified testing point of care testing for heavy which we just haven't realized yet. So I think there's still so much work to be done in that space. To see how Do we get to a more simplified place, but it right now, because you might be sitting there testing somebody for hep C? Now we can do point of care, you know, PCR testing for the RNA for hep C. And then you're saying, Well, we have to do a phlebotomy, to screening for hep B. And this does represent a

barrier, an extra step and extra challenge that I wish wasn't there. But I don't think we're at a place where we can say we can forego testing. I think the stakes are too high. And I would say some of these groups might be even higher risk. Yeah.

45:29
Thank you. Question about terminology might be more appropriate for the term reactivation to be reserved for patients with a history of negative hep B surface antigen, and new onset of detectable hep B DNA and exacerbation be used for patients with history of hep B surface antigen, whose viral loads increased to the extent defined in the current working definition.

45:56
I'm just going to read it again. So it might be more appropriate for the term reactivation to be reserved for those patients who are surface antigen negative, then get a new onset a detectable disease and exacerbation for those who have chronic hep B. And the viral load goes up. I think it's like a it's like a word debate or nomenclature debate kind of reactivation. And I think there was a lot of discussion when this was first developed. But as I mentioned, there was so much like, how this was being studied all over the place, that the definitions weren't very clear. And I think this is a logical exacerbation versus reactivation. And, you know, I'm not the one that comes up with a definition. So yeah, I think it's a logical, logical kind of way to think about it and trying to make a distinction between these two things. I think that's the important thing the the commenters trying to make that these are not the same groups of people, people with chronic hep B are different than people that passed infection with EPI. Yeah.

46:59
Thank you. Question for folks at high risk, such as MSM and other groups, if vaccinated? Do you need to check titers to make sure hep B vaccine is still protective? How long does it mean that they last?

47:12
Yeah, so I think there's some area of debate here. I think for patients that you're concerned about whether or not they might be immunosuppressed, like I work a lot with patients who have very advanced liver disease, they don't always make the antibodies that are recommended to be protected, right? Because they, they have even a smaller tolerance, right for if they were to get hep B and they already have cirrhosis. So I do a lot of testing. But that's because I work with a group of patients that, you know, I will not always make an antibody because they're immunosuppressed. I wouldn't doubt a recommend to test it's not a recommendation globally to be testing people to see if they have antibody. But if you have concerns about a patient and whether or not they made an appropriate response, and their high risk, right, even if then I think it does make sense to me to be checking for immunity.

48:06
Next question is for someone who's happy core antibody positive and surface antibody positive, happy antigen negative? How concerned should I be if I could not get any in on treatment labs?

48:19

Ah, um, I think this raises a great question. I think these patients are very low risk. And, you know, I think we're hoping we're learning from things like the min mon study, where I mean, we don't really know what the optimal testing and monitoring and treatment really is now, that antiviral treatment is so short for hep C. So I think these patients are very low risk, I think. Yeah, like, if you can't get them in for a blood draw, you can't get them in for a blood draw. And I don't think it should detract us from saying we're not going to treat these patients for hep C. Best practice is to do some monitoring of those patients. I think they're very low risk, though, and you're not likely to see a lot of reactivation of hep B for that group of patients.

49:08
Thank you. Okay, we'll go to Scott Springer has several questions for us. How frequently during Hep C treatment, should al T and or Hepi DNA be checked? I know there's a risk of reactivation of hep B at any point during treatment, even after conclusion of treatment. But is there any trend to when in the course of treatment reactivation has been seen to occur?

49:32
Yeah, so I think based on those studies, it tends to be between weeks four and eight. So maybe Abby, even going back to your question before, if you could get one blood test, maybe do it in the second month based on what we know. But Scott, I think this is also a really great question. And remember, you can just monitor the ELT for those that don't have chronic infection who are just core antibody positive right. And if the alts going up as your is your Hep C you Patients taking treatment and you know are presumed to have seen it to come down, you start to see that go up that should raise a suspicion that there could be reactivation that you need to rule out and in those patients check surface antigen and hep B DNA. Now for patients who are surface antigen positive, so that chronic hep B and chronic epstein, you're treating the Hep C, then monitoring them for the LT and hep B DNA. Now, your specific question is about how frequently so they left it open and the guidelines because I don't think we quite honestly know. But again, if you think between four and eight weeks, do it sometimes in that second month of hep C treatment, it's an eight week course do it once. Now that the guidance does say to do it through SVR 12. So you with if they come back for, you know, end of treatment labs or SVR for 12 depending on you know, everybody's kind of really tailoring this appropriately now to their patients. Getting that hlt level will be part of what you're doing anyways, when you check their Hep C viral load, I imagine. But it is recommended through SVR 12 on that guidance. Yeah. But they leave it open.

51:12
Thank you. Scott is asking now, if you've ever seen any bizarre changes in heavy Serologies after a patient received IVIG therapy.

51:20
I think there have been actually some core member I've mentioned in one of the early slides in terms of interpretation, that testing one on one slide, the first step, that core antibody positivity, by itself is usually a marker that you've some point in the past and Hep C infection. But there are some patients, we believe this to be a false positive. And the patients who are more likely to have false positive are these patients who get IVIG or something else. That's kind of just

influencing markers in the blood. So I think there's been case reports actually, of that, with hep B core antibody being positive. For example, I've never seen like a false surface antigen positive though from IVIG. Like I haven't seen that yet. And again, the way to confirm that would be to I always repeat first. And then I also will check the the the to the second step labs, the E antigen, the hep B viral load in the antibody to understand is what's the full spectrum. I had one patient who had rheumatoid arthritis. And I think she's had she has a false positive she had one time false positive on a surface antigen. She never made antibodies never had DNA. And ever since then the s the surface antigen has been indeterminate. And she's had zero risk factors she reports to me. So it's a little bizarre, but I think you know, these antibody test Serology tests do have some imperfection and I just wonder if some of these patients who have other immune related conditions are getting immunotherapies if there's you know, I don't know if we're going to see any changes with growth of immunotherapy for example, use in patients to

53:07
Okay, thank you so much, Ponni. Really amazing presentation.

[End Transcript]