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HEP B, OR NOT HEP B, THAT IS THE QUESTION: UNRAVELING THE MYSTERY OF HEPATITIS B SCREENING, TREATMENT, AND PREVENTION

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Hep B, or Not Hep B, That is the Question: Unraveling the Mystery of Hepatitis B Screening, Treatment, and Prevention
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Dr Alexandra Abrams-Downey is board certified in infectious diseases and internal medicine. She earned her medical degree from Tulane University School of Medicine in New Orleans, where she also completed her residency in Internal Medicine. She then pursued a fellowship in infectious diseases at the Icahn School of Medicine at Mount Sinai in New York City. Currently, Dr Abrams-Downey is the chief of the Division of HIV medicine at Albany Medical College, where she joined the faculty as an associate professor in the Department of Medicine in 2023 in this role, she oversees the only New York state designated aids center in the region, which provides primary care for people with HIV, treatment for hepatitis C and STI and HIV testing and prevention services. With all that, welcome, Dr Abrams-Downey, thanks for being here today. Great. Thank you so much for having me. And as Jessica mentioned, this is a jam packed presentation. So I will dive right in to hepatitis B or not hepatitis B, that is the question unraveling the mystery of hepatitis B from screening, treatment and prevention, and these are my disclosures. So the learning objectives for today are ambitious, but I think we'll get through it all. So we're going to review the updated recommendations for screening, for evaluation of hepatitis B infection as well as immunity, understand the management of hepatitis B, both in people with and without HIV, and discuss the different approaches to prevention of hepatitis B for people with and without HIV. So starting with a little bit of background, Hepatitis B is an extremely prevalent infection. It is estimated that there are 254 million people who are currently living with hepatitis B, and the estimate ranges anywhere from just over half a million to 2.4 million persons living with hepatitis B in the United States. The issue, both within the United States and globally, is that up to two thirds of people are unaware of their infection. Additionally, chronic hepatitis B is a leading cause of liver disease worldwide. In 2022 alone, Hepatitis B caused an estimated 1.1 million deaths. This is a kind of overall global picture of hepatitis B. So as I mentioned, the estimate is over two 50 million people are currently living with hepatitis B, and you can see that there are particular there are particular areas where there's high prevalence. So the highest is in African countries, where the prevalence of chronic hepatitis B is 5.8% followed by the Western Pacific region, which is 5% and Southeast Asia, which is 3% regarding transmission, Hepatitis B is spread predominantly by percutaneous or mucosal exposure to infected blood in various fluids. This means transmission can occur one of three ways, either sexual transmission, which is predominantly among unvaccinated MSM as well as heterosexual persons with multiple sex partners or contact with sex workers, incidence of accidental inoculation. So this could occur during a variety of procedures, including medical surgical and dental procedures, as well as through intravenous drug use or tattooing, body piercing and acupuncture, and then lastly, through vertical transmission, so maternal to child transmission, and this is mostly the most commonly happens during delivery, so typically associated with antepartum hemorrhage and placental tears. And actual rates of in utero transmission are pretty rare. And while the modes of transmission are very similar to HIV, it is important to remember that hepatitis B is transmitted much more efficiently than HIV. The Natural History disease of hepatitis B itself is kind of really along the spectrum, and there's really two main types of infection. There's an acute infection, which is often self limiting. If patients do have any symptoms, they're usually pretty vague and non specific, ranging from anywhere right

upper quadrant, pain, nausea, vomiting, fever, arthralgias and may or may not have jaundice, and as I mentioned, that's if they have symptoms. Um, most cases, approximately 70% are actually asymptomatic. The case fatality rate ranges from point five to 1% and many adults spontaneously recover and will later develop protective Hepatitis B surface antibodies. However, for those who do not recover, they progress to chronic hepatitis B, and chronic hepatitis B itself is even just a spectrum of disease, often there are no symptoms associated with it whatsoever, but there can be progression to severe, chronic liver disease, which can include fibrosis, cirrhosis or end stage liver disease, and then there is an increased risk of developing hepatic hepatocellular carcinoma. So among um. Untreated chronic hepatitis B, the risk of disease progression increases over time, so meaning the longer you're living with untreated chronic hepatitis B, your risk of disease progression and complications will continue to increase year to year. So the risk of developing cirrhosis over a five year period ranges anywhere from eight to 20% and once developing cirrhosis, the annual risk of decompensation is as high as 20% with an annual risk of developing hepatocellular carcinoma at one to 5% and there's additional other hosts, so additional CO morbidities, as well as viral factors such as HIV, that may increase the rate of disease progression and the risk of developing complications of chronic hepatitis B, and then, specific to the Hepatitis B and HIV co infected population. Globally, it's estimated that about 8% of people with HIV have evidence of chronic hepatitis B, with similar numbers here in the US, ranging from five to 15% there are some important nuances to remember in the CO infected population, compared to the Hepatitis B mono infected typically co infected patients have higher levels of hepatitis B viremia, they will have a lower likelihood of resolving the infection following that acute hepatitis B infection and therefore more likely to progress to chronic hepatitis B, and then additionally, they have increased risk of complications, including hepatitis cellular carcinoma and other liver related morbidity and mortality. So what now? So we know that we have Hepatitis B is an endemic problem. The estimate is that over 254 two 50 million people are living with chronic hepatitis B, but the issue is that only about 13% of that estimate has actually been diagnosed. And then in terms of people on treatment, only 30% of that overpop overall population is actually on antiviral therapy. So this means globally, while we have over two 50 million people estimated to be living with chronic hepatitis B, only about 7 million have actually received treatment. And the concern is, without further intervention, new infections and liver related morbidity and mortality will continue to rise. So this is really going to be the kind of focus of the talk is, how do we make these changes? And it's focusing on these three items, screening, treatment and prevention. So we are going to start by reviewing the updated screening guidelines. So I was going to approach this with a few very simple cases. And as I go through these, I want you to think about what do all these cases have in common? So the first is a 25 year old MSM who wants to start HIV prep. He knows a prior history of syphilis and gonorrhea, which were both treated. He's not currently sexually active, but he's had multiple partners in the past. Case two is a 45 year old man with no past medical history who wants to establish primary care. He's never had a regular doctor, but now has a job with good health insurance, and he wants to focus on his health case. Three is a 65 year old man with hypertension and diet controlled diabetes who presents for follow up. He has no current or past drug use, and he's sexually active with one male partner, and they're in a monogamous relationship. He does say his friend was recently diagnosed with hepatitis B. He thinks maybe he got tested in the past, but if he did, it was a while ago, and either way, he would like to get tested today. And then last case four is a 30 year old woman who's 10 weeks pregnant. This is her third pregnancy, and she reports that she's received the hep B vaccine as

a child and was screened for Hepatitis B during her pregnancy, which was last year. So what do all these cases have in common? They all need Hepatitis B screening. So the Hepatitis B screening guidelines had last been updated by the CDC in 2008 but over that period, there was a growing interest for a universal screening recommendation as well as for expanding the testing recommendations for persons expected to be at increased risk for Hepatitis B that had not been previously included in the 2008 testing recommendations. And with this in mind, the CDC reviewed cost effectiveness analyzes, as well as practicality of implementing guidelines and the overall public health benefits for universal screening. What they found is that the overall risk based testing has been insufficient to identify persons with Hepatitis B in the United States, and has really been a barrier to appropriately screening populations with a disproportionate prevalence of disease. And I think those of us in the HIV world, and particularly HIV prevention world, you know, we know that as providers, we are not very good at assessing risk, and it can be very difficult for patients to really get to those kinds of questions without stigmatizing the patient. So the need to simplify the implementation of screening from a risk based to a universe. Muscle approach may also increase the number of persons aware of their infection. So there was really a call for updated recommendations to consider a simpler and less stigmatizing strategy than the previous risk based Hepatitis B screening recommendations. So in 2023 the CDC did just that. They released new screening and testing recommendations, and the biggest change was a universal Hepatitis B screening. So the new recommendation was that all adults, age 18 and over, should be screened for Hepatitis B at least once in their lifetime. And additionally, the new recommendation was how you do the screening, which is with a three test panel, which includes Hepatitis B surface antigen, antibody to hepatitis B surface antigen, and a total antibody to hepatitis B core antigen. Additionally, the recommendations regarding pregnant people did not change, but the recommendation is that all pregnant persons should be screened with each pregnancy, preferably in the first trimester, and this is regardless of vaccination status or the history of testing, if they had been appropriately screened with a triple panel during and there had been no subsequent exposure, you could do screening with just a surface antigen. But either way, all pregnant persons should be screened during each pregnancy, and then additionally, they did still advocate for risk based testing as in addition to the one time universal screen. And this should be done regardless of age and may require periodic testing. They did expand the groups and persons that were considered at higher risk. And I'm just highlighting here the new recommendations. So for anybody with a history of incarceration in a jail, prison or any other detention facility, they should be screened for hepatitis B. Anybody with hepatitis C infection should be screened. Anybody with any sexual transmitted infections or multiple sexual partners should be screened. And then lastly, anybody who requests it. So that was one of our case scenarios. So you may not fit. You may have already been tested in the past. You may not necessarily fit into one of these increased risk categories, but if your patient comes to you requesting Hepatitis B screening, the recommendation is to go ahead and perform that, and as I mentioned, you're going to do your screening now with the recommendation of a triple panel test. So I just want to go through that in a little bit more detail. So as it's as the name implies, it's three tests that you're going to send. So the first is a hepatitis B surface antigen, and this will actually indicate the presence of a hepatitis B infection. And it will be either acute, meaning the infection has been present for less than six months, or chronic, meaning six months or the duration is unknown. You're also going to send a hepatitis B surface antibody, and this indicates one of two things, either recovery from a prior Hepatitis B infection or an appropriate response to the vaccine. And then lastly, you're going to send your Hepatitis B core antibody. This will

develop in all instances of hepatitis B infection, whether it's a resolved or current infection, and this will typically remain reactive for life. And then this was the table from the CDC screening recommendations. There's many different versions of this available, but I particularly liked this one, and it really goes through basically every permutation that you could have of, you know, those three tests and the results and what to do with that. So again, this is just something that, you know, I find myself going back to constantly, because the diagnosis and next steps for Hepatitis B and interpretation of the results can get a little challenging, but that's what we're going to focus on really for the bulk of the talk, I really want to spend a lot of time talking about treatment, and this is going to be both for people with and without HIV. So we're going to do this with a number of cases. So case one is a 57 year old woman with no past medical history who presents to establish primary care. She was born in Vietnam and moved to the US when she was 10. Her new PCP, knowing the updated CDC recommendations, asks if she's ever been screened for hepatitis B, and she's not sure. Her PCP sends the appropriate three test panel, and the results are a reactive surface antigen, total core antibodies, reactive and a non reactive surface antibody. She has follow up lab work sent, which includes an alt of 45 so slightly above the upper limit of normal, which is less than 19. Her AST is normal, and her HBV DNA is 2500 so the questions for this trait case is, do you treat her for hepatitis B? And if you do, what do you use? So the indications for treatment of mono infection, of hepatitis B, traditionally have been pretty complex, and there's been a lot of different approaches. There was the who approach in 2015 more recently updated as LD guidelines from 2018 but they required extensive test. Thing that was costly and pretty complex, and all of that overall led to delays in cares. Additionally, there's a lot of evidence that early treatment may be beneficial to help prevent the integration of HBV DNA in overall reduced rates of oncogenesis. And then there's the concept of using treatment as prevention approach, which is certainly well established in HIV, and that may be an additional benefit for early treatment. And then lastly, but very importantly, we have a lot of information about these antivirals, and we know that treatment of chronic hepatitis B is safe, effective, and importantly, generic, which means inexpensive. So there had been a lot of evolving guideline development that highlighted the need for simplified, up to date and readily accessible guidance for the Manage of chronic hepatitis B. So in 2024 the who released their updated guidelines for prevention, diagnosis, care and treatment for people with chronic hepatitis B infection, and they really highlighted a few priority areas, which included expanding the treatment eligibility for adults and adolescents with chronic hepatitis B, emphasizing the use of non invasive liver tests for the management of chronic hepatitis B, and highlighting what the use of first line antivirals should be for chronic hepatitis B. So the expanded eligibility actually now includes four different pathways that applies to all adults and now also adolescents, which is anyone considered 12 and older with chronic hepatitis B. And I think really importantly, only one of these four pathways requires access to HBV DNA testing. So as I mentioned with the older guidelines, there was extensive and expensive testing that was required to determine treatment eligibility, and these were major cost prohibitive barriers that were making equitable treatment accessibility difficult. So by removing this as a pathway, it will hopefully increase treatment accessibility. And so with these four potential pathways for treatment, there's an estimate to capture a much higher proportion of hepatitis, hepatitis services, antigen positive people, at least 50% and this is much higher than the previous regimens, which captured about eight to 15% So believe it or not, this is actually a simplified algorithm. So I'm just going to draw your attention first to the arm. On the right. This is the small category of people who will be deferred treatment. So this is anybody who has a persistently normal alt, which, for males, is

less than 30, and females less than 19, and they have an HPV DNA of less than 2000 with the absence of any CO infections, co morbidities, immunosuppression, extra hepatic manifestations or family history of liver cancer, cirrhosis. Those are going to be the only cohort that you will defer and monitor. Everybody else will fall into one of four pathways. So the first is evidence of significant fibrosis, which is f2 disease or cirrhosis. You don't need an HBB DNA to make this diagnosis. You can do it based on clinical criteria for cirrhosis or using non invasive tests. So this could be your Apri score greater than point five, as well as the using transient elastography. So things like fiber scan, an additional pathway would be an HBV DNA over 2000 and an alt above the upper limit of normal. So this was the instance of our case, an additional pathway is basically the presence of any follow other kind of CO morbidity which could put you at higher risk for progression of disease. So presence of these disease, regardless of what their APRA score is, HBB, DNA or alt level, this includes co infection with HIV, HDV or hepatitis C, a family history of liver cancer, cirrhosis, immune suppression, co morbidities, including diabetes or metabolic dysfunction, as well as extra hepatic manifestations of hepatitis B. And then lastly, if you don't have access to HPV DNA, but the patient has persistently abnormal alt levels alone, you would go ahead and treat. I want to just bring a quick bit of attention to the ACRIS score, because I think this is really important. You know, transient elastography is a great non invasive way to assess liver disease stage, but it is expensive and it requires accessibility, so using these non invasive tests, such as the Apri score, can really help ensure equitable access to treatment. So it's a very simple calculation. I included it here. You can find calculators online, but it's basically an AST to platelet ratio index. And as I mentioned, it's a non invasive test for detecting fibrosis and cirrhosis, and use a cut off of point five, because anything less than that has a very high negative predictive value to rule out cirrhosis, and the higher the score, the more the more evidence of severe disease. So a cut off of point seven has a 77% sensitivity for predicting fibrosis, and a cut off of one. Has a 76% sensitivity for present predicting cirrhosis. So the other updates to the WHO guidelines from 2024 were now that you have your expanded available access to who should be treated. What do you treat with? So the first line recommendation is monotherapy with either tenofovir, disoproxyl fumarate or TDF or entecavir. And they do note that using a dual regimen such as tenofovir and lamivudine or tenofovir and emtricitabine is an acceptable alternative. And interestingly, because we use these medications like tenofovir, tricytabene for PrEP, it may be actually easier to access dual regimens, and it may be less expensive to get a dual regimen in some countries compared to monotherapy, and then you would reserve using tenofovir, alafedamide or TAF for special circumstances such as renal impairment or osteoporosis. So moving on to case two. This is a 25 year old who presents to initiate prep his HIV antigen antibody test is non reactive. And as part of his prep initiation labs, his provider sends a three test panel that to screen for Hepatitis B and his surface antigen is reactive, his core antibody is reactive and his surface antibody is non reactive. Additional labs include an alt of 45 AST of 20 and an HBV DNA of 2 million. So I think this case brings up a few questions like, What are the HBV testing recommendations for people prior to starting prep? Can people with chronic hepatitis B be on PrEP? What medications should you use for PrEP in that population? And what do you do if the patient wants to stop prep? So screening for Hepatitis B at prep initiation? Yes, ideally, prior to prescribing pep prep, patients should be screened for hepatitis B. I think, first of all, if you think about what the risk factors may be with your CDC, 2023, screening recommendations, they should be screened. But it's also important to know, because you want to make sure that you vaccinate people who are not immune. And you do want to know if anybody has chronic hepatitis B. However, you do not need to wait for

these results to come back to start prep. I think what we really want to emphasize in the prep world is if somebody is coming to you for HIV prep, you don't want to delay any care if possible. So you can go ahead and start prep while waiting for some of these Hepatitis B results to come back. So what do you start? The point is, you should start something so people with hepatitis B can, and really should be, offered prep. You just need to do some additional counseling about the potential for hepatitis flares and the importance of appropriate monitoring if and when they choose to stop prep, the options are pretty much the same as people without chronic hepatitis B, so TDF, FTC, TAF, FTC, and of course, you can use the long acting injectable of cabotegravir. Cabotegravir really has no role on any treatment for hepatitis B. So technically, you don't really need to get those Serologies prior to starting cab or monitoring while they're on it. But as I mentioned, it is something you're going to want to get before they start prep. The one regimen you that is contra indicated in people with chronic hepatitis B is on demand prep, or the 211 dosing regimen of TDF, and you this is really designed to be used intermittently, so people will be going on and off of it, and that's when you really have those increased risk of hepatitis flares, that episodic exposure to TDF, FTC. So in that particular instance, you would not recommend two, 111, dosing and chronic hepatitis B, and then the question becomes, what if somebody wants to stop prep? You know, PrEP is a prevention medication, so it's different than what we do for treatment. So people will go on and off of it throughout their lifetime. That's the way it's really designed to be used. The concern is that when treatment for chronic hepatitis B is discontinued, patients may experience clinically significant hepatitis flares. So if you stop prep, you may be having a risk for developing a hepatitis flare. So the recommendation is that all patients with chronic hepatitis B stopping prep should be monitored closely for hepatitis flares. And although those the these hepatitis flares have been documented to occur in people discontinuing their tenofovir containing regimens as part of their chronic hepatitis B treatment. Such flares have actually not been seen in HIV negative patients with chronic hepatitis B who stopped taking TDF containing regimens for PrEP. And we saw this in a paper that was published in 2016 following a study that was part of a placebo, contrived control trial for safety and efficacy for PrEP. So this was almost 2500 HIV negative participants who were randomized to receive TDF, FTC or placebo for PrEP, 12 participants had chronic hepatitis B, including six in the. Tdfftc, arm, but they found that there were no hepatitis flares occurred even after discontinuation of TDF, FTC, and this was monitoring that occurred at four, eight and 12 weeks after discontinuation. So they argued that prep can be safely provided to individuals with chronic hepatitis B. There just needs to be routine monitoring, and of course, there needs to be no evidence of cirrhosis or transaminase elevation or other indications for Hepatitis B treatment. Moving on to case three, this is a 50 year old woman with non Hodgkin's lymphoma who's undergoing further workup prior to starting rituximab. Her results are significant for a negative surface antigen, a reactive core antibody, reactive surface antibody, normal ALT and AST and a not detectable HBV, DNA. So questions for this case is, what is the overall risk of hepatitis B reactivation for this patient, and should she be started on antiviral Prophylaxis. So HPV reactivation in the immunosuppressed is becoming a more commonly countered issue in many disciplines, as we continue to be expanding the use of a lot of immunosuppressive medications. So they're used to treat a lot of different health conditions and additionally most types of cancer, and this includes B cell depleting agents like rituximab. Hepatitis B reactivation is characterized by a loss of immunologic suppression of hepatitis B activity, and it can occur in patients who are either positive for Hepatitis B surface antigen or a hepatitis B core antibody, particularly in the immunosuppressed Hepatitis B reactivation can cause severe liver disease. And so it's

recommended that hepatitis B testing, which in this instance includes surface antigen, core antibody and HBV DNA, be performed before starting immunosuppression, to identify people at risk for reactivation. And from there, you would determine whether or not antiviral Prophylaxis should be considered based on the risk for reactivation. So just earlier this year, the American gastroenterological Association updated their guidelines on the prevention and treatment of hepatitis B reactivation for at risk individuals. And what I really appreciated these guidelines is, even though they were developed by gastroenterologists, they're actually intended for use by the frontline providers. So not the gastroenterologist, not the hepatologist, but the primary care physicians, the oncologists, the rheumatologists, the dermatologists, who are prescribing these medications and following the patients before, hopefully they end up getting to a hepatologist. And so what these guidelines really focused on was simplifying the recommendations for Prophylaxis and really focusing on two key factors. The first is the patient group. Is this somebody with chronic hepatitis B, as opposed to somebody who was previously exposed? And then what the reactivation risk is which is mostly going to be focused on your what medication or immunosuppression the patient's going to be on. And using those two factors, you can look at what your overall risk is and fall into one of three categories of low, medium or high. And so again, believe it or not, this is actually a simplified algorithm from what was just published earlier this year. So when you're evaluating HPV reactivation in any at risk individual, so anybody starting immunosuppression, you're going to try a baseline serology. In this instance, you want a hepatitis B surface antigen, a hep B core antibody and HBV DNA. As you can see, there is no surface antibody on this serology, because when assessing your risk, the presence of a surface antibody is really not pertinent. You may want to consider certainly vaccinating anybody who hasn't been vaccinated, but look at what their actual reactivation risk. It's not going to guide you one way or the other. So first thing you're going to do is determine whether the patient is surface antigen positive, indicating chronic hepatitis B or surface antigen negative, but with a hepatitis B core antibody that is positive. And from there, you want to know what the immunosuppression exposure is, and depending on whether their surface antigen positive or negative, the the risk associated with the various immunosuppressions will change. So things like those B cell depleting agents, like rituximab, are kind of the highest risk. So what you would do is kind of fall what see, where the patient is, what category, what medication they're on, and then do they fall into low, moderate or high risk, and from there, that will help you determine whether or not they should be on antiviral Prophylaxis. So highest risk category, the recommendation is a strong recommendation to be on antiviral Prophylaxis over monitoring alone, and you want to start the Prophylaxis before immunosup. Depression and continue for at least six months after the discontinuation of the immunosuppressive therapy. The exception is among B cell depleting agents, in which case you want to continue the antiviral Prophylaxis for 12 months after stopping immunosuppressant for medium risk patients or moderate risk, there's a conditional recommendation for antiviral Prophylaxis over monitoring alone. So in this instance, you really do want to have a risk and benefit discussion of antiviral Prophylaxis with the patient. There may be some risks associated with antiviral Prophylaxis. You know somebody who may have CKD or other interactions or reasons they can't be on antiviral Prophylaxis. So in that instance, you may want to consider active monitoring, which would be HBV, DNA and an alt every one to three months. And then those in the lowest risk category, the recommendation is to monitor over starting antiviral Prophylaxis. But again, you should have a risk and benefit, discussion with the patient, and the patient may want to start antiviral Prophylaxis to avoid a small risk of reactivation, and if the medication would be well tolerated, and the patient understands that that

would definitely be something worth discussing and pursuing. So last case in the treatment category is case number four. So this is a 55 year old man with HIV. So this is a co infected patient who has, this is more of a co infection case, but who is on bigtegravir, TAF and FTC, who presents for routine follow up. He's been stable on his bigtegraphy or TAF FTC since he was diagnosed in 2017 and his baseline HIV genotype testing shows no resistance. He's interested in switching to the injections. He quote, saw on TV. And in preparation for switching what you interpret to be the injectable cabotegravirin, you send the following tests. His CD four is 525, and his HIV is not detected and well controlled. His AST and alt are within normal limits. His surface antigen is negative, his core antibody is reactive and his surface antibody is non reactive. So I want to take some time with this case to really talk about the management of hepatitis B and HIV, thinking about when are non TAF or TDF ARV regimens contraindicated in Hepatitis B in this particular case, could this patient be safely switched to a non TAF regimen? And then also thinking about what vaccine strategies are recommended for people with HIV exposed to hepatitis B. So firstly, just covering people with HIV and chronic hepatitis B, because this is a really important management point. Anybody with chronic pep with HIV and chronic hepatitis B should be on a combination of tenofovir, whether it's TAF or FTC or tdff, plus either lamivudine or mtricitabine. And this should be part of the NRT backbone of an ARV regimen. This is an A one recommendation from the DHHS guidelines, the use of either lamivudine or emtricitabine alone, which you may see in some single tablet regimens like dolutegravir and lamivudine, which is dovato, is not recommended because there is a concern for emerging Hepatitis B resistance when they are on a mono therapy and not on a tenofovir, including regimen if For whatever reason, the patient can't be on TAF or TDF, maybe it's due to underlying CKD, then you would want to do renally dosed and tech of your as an alternative Hepatitis B therapy. And then, additionally, anybody with hepatitis B and HIV co infection should be advised against stopping Hepatitis B active treatment, and that is because of the risk of HBV reactivation hepatitis among people with chronic hepatitis B and HIV in the setting of withdrawal of treatment. And I just want to do a quick plug, very quickly, on HCC screening in people with HIV and chronic hepatitis B. So for anybody with chronic hepatitis B, this is whether they're mono infected or also living with HIV. HCC surveillance should be performed every six months, and this includes an abdominal ultrasound with or without an AFP for people who are with chronic hepatitis B and either have either cirrhosis or are at increased risk of developing HCT. And that includes Asian males who are over 40, Asian females who are over 50, and males who are over 20 from Sub Saharan Africa. Now, as we know and we've discussed, people with HIV are at increased risk of HCC in the setting of chronic hepatitis B, so there are some expert recommendations. Patients, it's a b3 level recommendation that people with HIV and chronic hepatitis B over the age of 40 would fall into this increased risk category and should be receive ongoing, semi annual HCC for surveillance. So something that important to remember in your co infected patients. But switching gears slightly to what the instance of this particular case is. And you know, an issue that has come up a lot very recently is the management of people with HIV and prior exposure to hepatitis B. Now, the Hepatitis B status should be evaluated in all people with HIV before the initiation of any NRTI or sparing or NRTI limited ARV regimen, and this includes regimens like the long acting cabinooviralpivirine injections, single tablet regimens such as dolutegravir and rilpivirine, or dolutegravir and lamivudine and HBV reactivation has report been reported in people with HIV and prior exposure to hepatitis B, when these HPV active agents are withdrawn, and anybody consider prior exposure. So what that means is they have a positive core antibody, they have a negative surface antigen, and they can either have a

positive or negative surface antibody. Either way, overall, the risk of HBV reactivation is low. It's less than 1% and that's for HBV reactivation. There's an even lower risk of a clinically significant HBV reactivation hepatitis, and then that risk is even further reduced in people who are positive for both core antibody and surface antibody. So a lot of this was based off of a presentation that was given at ID week back in 2023 this was a retrospective chart review of people with HIV in the VA aging cohort study. So overall, that cohort has over 60,000 people enrolled, and they looked at specifically anybody in that cohort who was Hepatitis B core antibody positive, and that was just under 21,000 participants. And their particular, particular inclusion criteria was for this at risk cohort, Was anybody who switched to an ARB regimen without Hepatitis B activity. So this mean meant people that were switched to a regimen that contained no tenofovir limiting or M tricida B, and they were, these were people who were at risk of reactivation, so there was no evidence of chronic hepatitis B. And overall, that was just under 6000 people. So the primary outcome of the chart review was looking for any Hepatitis B reactivation, and they define that as new surface antigen positivity, or newly detectable HPV DNA. And overall, of this almost 6000 participants, there were only 39 cases, or point 7% of HPV reactivation. And of those 39 cases, 37 had follow up labs, and only less than a third had an alt of greater than 100 at the time of HPV reactivation. The median time to reactivation was pretty extended. It was about 292 days, but the majority of the reactivation occurred at 180 days after the ARV switch, and that's what you can see here. So overall, there were 939, cases of hepatitis B reactivation. As I mentioned. The median time to reactivation was pretty long, 292, days. But that was really due to some of these outliers that you see here towards the end of people who were reactivating at 1200 1400 1800 days. But really the majority of the reactivation occurred at 100 and aids or less after the ARV switch. So in response to this, the DHHS ARV guidelines were updated in September of 2024 and this was really responding to this increased interest in switching people to NRTI sparing or NRTI limiting regimens, which we've been seeing particularly with the advent of the long acting injectables. These updated recommendations stress the importance of screening for Hepatitis B before switching to NRTI or NRT limiting regimens and people who are not known to have Hepatitis B infection, recommending vaccination for those who are found to be non immune to hepatitis B, and then particularly providing guidance for monitoring and managing people with prior exposure to hepatitis B. So they recommended, it's a b3 level recommendation, but a monitoring, monitoring strategy that is safe and effective, a safe and effective way to assess Hepatitis B reactivation in low risk people. So this low risk category was group defined as people who were had demonstrated prior Hepatitis B exposure, so core antibody positive and they. We're switching from a hepatitis B NRTI containing regimen, so TDF, TAF or entecavir, to a non NRTI regimen, so long acting injectables like cabinet cabinetry, dilutepivirine and dolutegravir and levied. So the monitoring strategy that they consider reasonable and feasible is to incorporate alt testing into your follow up monitoring. And you would do this check an alt every one to three months for six months, as I mentioned, the timeline for reactivation is not clear, but as we saw from that VA cohort study, the majority of reactivation did seem to occur within six months of the ARV switch. And then basically you're looking for an increase in alt. So if the alt goes up, you'd want to follow that immediately with HPV DNA testing to really assess for HPV reactivation. And if there is HBV reactivation, you would want to initiate HPV therapy immediately. The other strategy that you need to think about in people with HIV with prior exposure to hepatitis B is vaccination. And we see this pretty commonly in people with HIV, with HIV who have an isolated core antibody positivity, and there really seems to be a lack of an amnestic response among people with HIV and prior exposure to

hepatitis B and an inability to really create that surface antibody protective effect. So what the recommendation is that any people with HIV with an isolated anti Hepatitis B core antibody, they should be vaccinated with one standard dose of hepatitis B vaccine. You then want to check the titers one to two months after, and if the titer is actually less than 100 you want to go ahead and complete the series. And this is an important distinction, because we usually consider a surface antibody titer of greater than 10 as protective, but in those with isolated core you really want it to be higher, at 100 and this was based on data that came out of a prospective multicenter study. This is a group that's basically the French equivalent of the AC, T, ACTG. And what this study did was assess the immunogenicity of hepatitis B vaccination in people with HIV with isolated core antibody. These were stable HIV patients. They had isolated core antibody and no prior Hepatitis B vaccination. They received a single dose of the recombinant hepatitis B vaccine, and then had follow up monitoring of surface antibody titers at week four, week 28 and then finally, month 18. And what they found is that all responders who had a surface antibody of greater than 100 at Week Four maintained that surface antibody protective response as far out as month 18, and this was compared to only 23% of participants who had a titer of anywhere from 10 to 100 at Week Four maintaining that surface protective response at month 18. So then lastly, I just want to, in the last 15 minutes or so, wrap up with vaccination, because there's actually been a lot of recent updates of vaccination for both people with and without HIV. So again, focusing with a case. This is a 50 year old man with stable HIV, SC four of 800 viral load not detected for many, many years on big tigravirtaf and FTC, he's interested in switching to long acting injectable cabotegravir and ropivirine. His provider checks a three panel testing because there's no results within the last six months. He notes that the surface antibody is nonreactive, but then goes back through the records and notes he did appropriately complete a three dose series of the double strength recombinant vaccine. So questions for this case, and just vaccination in general, is, what are the current recommendations for HBV, for dentin, both in people without HIV as well as people with HIV, and then, particular to this case, what are the recommendations for hepatitis B vaccine in people with HIV who are, quote, non responders? So looking first at HIV, hepatitis B prevention in general, what we've seen is the number of cases of acute hepatitis B have actually increased, particularly among older adults. So those over 40 from 2011 to 2019 and in addition to that, we know that the Hepatitis B vaccination coverage among adults is low, and this is based upon guidance for vaccination determined by risk factor assessment. So again, similar to the screening story that we mentioned at the beginning, the idea of removing the risk factor indication for eligibility and expanding to a Universal Recommendation for vaccination could decrease Hepatitis B cases and increase the number of persons who receive vaccination. So back in 2022 the CDC and a CIP expanded Hepatitis B prevent. And recommendations to include universal hepatitis B vaccine for all adults ages 19 to 59 and that includes also, and this is an addition to vaccination for all infants, all persons less than 19, all persons over 60 with risk factors for hepatitis B. And then even on top of that, anybody over 60, even if they don't have known risk factors for hepatitis B vaccine, they can also get vaccinated too. So really a pretty universal vaccination recommendation, the risk factors for the adults over age 60, again, pretty similar to what you want to think about with your Hepatitis B screening. And then the question becomes, what do you vaccinate with? So the preferred regimen is the recombinant adjuvanted hep B, CPG vaccine, or heplisaf. This is dosed at zero and one months. It was approved by the FDA in 2017 and recommended by a CIP in 2018 there was an important update in I think it was in September of 2024, so late last year, where the FDA approved a request to update labeling for indicated use among pregnant

persons. So this was based upon post licensure observational, retrospective cohort study, which included 75 pregnancy with known outcomes, and there were no increased risk for major birth defects and miscarriages. So there had been a warning against using the Hep bcpg vaccine in pregnant persons, but it is now approved by the FDA to be used in pregnant persons. The alternative regimens remain the recombinant vaccine, which is dosed at 01 and six months, or the combination of hepatitis A and B vaccine, which is also 01 and six months, and then focusing on hepatitis B vaccine among people with HIV. These vaccination recommendations were recently updated in the HIV ma IDSA 2024, primary care guidance for persons with HIV. And this was based on interim analysis of data from the ACTG, 5370 9b enhancement of HBV vaccination in persons with HIV, or what's known as the beehive study. And this was a phase three prospective open label two group study. And the two groups were people with HIV who were hepatitis B vaccine naive, as well as people with HIV with non response to prior hepatitis B vaccine so the first data that was published was back in 2023 these were people with HIV who were hepatitis B vaccine naive. It was a pretty small group of about 74 patients in the open label single arm, all with well controlled, stable HIV. And they all received three doses of the recombinant adjuvanted hep B CPG vaccine at 04 and 24 weeks. And from there, they measured the zero protective response, which was considered a surface antibody over 10 and what I highlighted on the bottom is just the dosing. So it was at entry Week Four and week 24 and then they looked at the surface antibody for a seroprotective response. And this was an interim analysis, but at week 28 you could see that 100% of participants had a surface protective response with a surface antibody greater than 10

48:29
This was followed up with

48:31
looking at the the second cohort, which was people with HIV with a non response to prior hepatitis B vaccine. And this was just published in January, earlier this year in JAMA. So just a couple months ago, this was a slightly larger group. It was a population of 561 people, open label, randomized, well controlled HIV, and they were randomized to one of three arms. They were either in the traditional hep B alum vaccine, which was dosed at 04 and 24 weeks, or they received one of two dosing regimens for hep bcpg vaccine, which was either zero and four weeks or 04 and 24 weeks. And then, importantly, all participants had documentation of appropriately administered hepatitis B vaccine, but were surface antibody negative and therefore considered non responders. So again, this was an presentation of the interim analysis, so 28 week data. But what you can see here is in the green box, this is the zero protective response within the bars. The basically, the darker the colors the higher the it surface. Antibody response. The top bar is the participants who received the three dose hep B alum vaccine. And at the interim analysis of 28 weeks, 80.6% had a serial protective, protective response. This was compared with the hep B, C, P, g2, dose and. Cohort, which was 93% seroprotective, and in the hep, bcpg three dose arm, which was 99.4% seroprotective. And then most recently, there was end of study, or 72 week data that was presented as a late breaking abstract at co just a couple months ago in March, and they presented both groups. So Group A was the non responder groups randomized to three arms, and group B was that hep B naive group. And basically what you can see here, so the three arms on the left is the group A the prior non responders in the traditional three dose alum series, at week 72 only 57% of people had a seroprotective

response. This was compared with those in the two dose CPG arm, which had an 86% seroprotective response. And then finally, in the three dose CPG arm, there was a 97.20 protective response. And again, remember, these were the people who had previously been vaccinated and were considered non responders. And what you can see really in that three dose CPG arm is they actually were very similar in their overall seroprotective response to Group B, which was those who were hep B vaccine naive, and they also demonstrated a 97% zero protective response. So with this information, the primary care guidelines for people with HIV were or updated. So for those who are vaccine naive, the preferred regimen is a recombinant adjuvant, or hep B CPG vaccine with two doses at zero and one month, if you cannot give that regimen, the alternate is the traditional recombinant vaccines. But it is important to remember, in anybody with HIV, you want to do the double strength dose, and you would do that for all three doses at 01, and six months. You can consider the hep a and hep B twinrix vaccine as well. And remember, no matter what regimen you choose, you always want to check a surface antibody titer one to two months after the last dose with a surface antibody greater than 10 considered seroprotective among those who are non responders. So if they did not fully respond. Respond after a full series of the recombinant vaccine, the first thing you want to do is preferably do the two doses of the recombinant adjuvanted hep, B, C, PG vaccine, and then really, you know, thinking, especially after that data that we saw most recently presented at the late abstract, the late breaking abstract at CROI, you may want to consider a third dose at 24 weeks, particularly in somebody who maybe had lower CD four uncontrolled viremia. Again, if you cannot do the recombinant adjuvant vaccine, you would do three doses of the double strength, recombinant hepatitis B vaccine. And you may even, again, want to consider a fourth dose of the double strength if there's no response. And you also want to think about why they might not be responding. So even though it's safe to give the hepatitis B vaccine in any formulation to people with a CD four count less than 200 you may just have a blunted response. So you may want to wait to revaccinate them until their CD four is over 200 So just in summary, you know, that's kind of a whirlwind tour of screening, treatment and prevention in people with and without HIV, but I hope I was really able to cover a lot of the kind of burning questions that have been coming up with HIV, HPV, and kind of where we're at and where We need to be going. I think the really important factors are the shift to universal screening and vaccination. I think these recommendations serve to reduce the stigma, while also increasing rates of diagnosis as well as prevention. Switching to using a simplified, non invasive testing algorithm will serve to reduce barriers to treatment, prevent progression of liver disease and reduce overall transmission, and that we need to continue to have understanding of hepatitis B reactivation. This includes risk of reactivation, the role of monitoring and the indications for antiviral Prophylaxis, as this is critical to preventing liver disease complications. So with that, these are my references, and I want to thank you and my bad Hamlet jokes. So with that, I'm happy to take any questions.

54:31
Thank you so much. Dr Abrams Downey, we really appreciate it. We do have a couple of questions. First, goes back to the beginning. If you have chronic hepatitis B, are you always considered infectious?

54:47
So that's a good question. I think you really need to think about what the, you know, the the Hepatitis B DNA is, you know, that's kind of almost similar to what we think about with with HIV. Higher Hepatitis B viral load, the more infectious you will be. You do want to still counsel people on the risk of transmission. And as I mentioned at the beginning, with hepatitis B, it transmits much more efficiently than HIV. So you know, you do want to take a little more caution. And we do even counsel against people like sharing things, like sharing toothbrushes with partners. It because you can be at that higher risk of transmission. So yes, you can still be considered infectious, but there's kind of gradations of how infective you can be.

55:32
Great. Next question, I think, is a good way to summarize what you just mentioned about vaccination. So in patients who are on PrEP and have evidence of hep B vaccine in childhood, but negative surface core and antigen. Do you vaccinate and recheck titers or go with the vaccine evidence?

55:56
So I would still go with this. You know, if you're checking a surface antibody and it's non reactive, I would go ahead and re vaccinate them. You know, protect certainly, yes, in people with HIV, that would definitely be what you would want to do with some of the older vaccines. We do just kind of not see that surface antibody response when you check it routine and there, you know, you can kind of have, again, a risk and benefit conversation with the patient. You know they're they likely would have a response to they do, likely do have immunity against Hepatitis B, where they expose, but I don't have the surface antibody to clearly say that. So the risks of getting the vaccine, particularly with the newer adjuvant, the recombinant adjuvant vaccine, it's pretty low. So you can have that conversation, and there'd be no harm in revaccinating them with the newer version.

56:45
Great. Thank you. Another question here, like big tarvi, do any of the injectable arts prevent hepatitis B?

56:57
So that is an excellent question. No, they do not. So the only current there's really two injectable regimen for for HIV treatment there one is the full combination, full treatment regimen, which is the cabotegravir rilpivirine, and that has absolutely no protection against hepatitis B. So I always want to make sure, for anybody that I'm switching to that that I always check my three panel titers. If they are not immune, I do go ahead and get them immune. And again, that is where you maybe want to do more of your risk assessment. Scenario of the patient, you know, if they're kind of low risk for acquiring hepatitis, being the amount of time that it would take to get them immune, I'll go ahead and do the switch. If they're at a higher risk category that they may potentially acquire Hepatitis B in that period, I would want to make sure that they're fully immune before I switch them to a NRTI sparing regimen. Okay.

57:56
Wonderful. Another question about you mentioned using double dose of the Hepatitis B recombinant vaccine in folks with HIV, would you also use a double dose of the twinrix vaccine, the combined hep A, B, yeah, you know, I think that's

58:12
a good question. I think it might, I don't know if you can even do that as a double dose. You know, you can get the double dose of the like, for example, the enderex or the recombinant. I'm actually not 100% sure if you can do that. I tend to stay away from it because of that very reason. So I don't have a great answer for that, but it is a good question,

58:34
and we've got one minute, so I'll do the last question that came in here. How can you compare at this point, very briefly, sort of how you think about frequency of screening for all the viral hepatitis? Because it seems like some folks kind of just do them all together every three months, but probably for some of them where chronic infection is really the issue that that may not really be necessary, yeah. So

59:02
again, you know, I know, I mean, I think move to a universal screening is great, but when you have, when you think about your kind of higher risk patients, you know, I tend to do, maybe, certainly with hepatitis C, I tend to do every six months, at least with my higher risk hepatitis B, I would probably do annually for the higher risk patients. So again, particularly, you know anybody who's coming in to me for PrEP, that's usually my routine, screening schedule.

59:34
Alright, wonderful. Again, we are at time. It's exactly one o'clock. So thanks, Dr, Abrams Downey, we really appreciate it was a wonderful talk, and thanks everyone for joining us today.

59:45
Thank you so much for having me. This was great. I really appreciate it. Thank you

59:51
and Jess and Gail. I will defer to Jessica on when it's okay to close.

59:59
Yeah. All looks good. Just getting some thank yous in. So wanted to say that I don't see anything else coming in, so I think we're good. Gail,

1:00:08
thanks everybody.

1:00:10
Great. Well. Thank you again. So much. You guys made this so easy. I really appreciate it. Thanks. Ellie, take care. All right. Take care. Bye.
[End Transcript]