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RESISTANCE TESTING IN HEPATITIS C TREATMENT

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[video transcript]

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Thanks, Jeffrey. And I'd also like to thank CEI in the New York State Department of Health for this invitation to talk to you about resistance testing, and Hepatitis C treatment. These are my disclosures. So here are our learning objectives. Today, we're going to review the New York State clinical guidelines for treatment of chronic Hepatitis C. With direct acting antivirals. I'll try to summarize the rationale for and clinical reasons we do indications for Hepatitis C resistance testing, described considers eight considerations for resistance testing, and treatment naive and those who are treatment experienced, and then offer some assistance with interpretation of Hepatitis C results to guide clinical practice. So just very, basically, to start off, why do we worry about resistance and Hepatitis C? Well, first of all, is I put here Hepatitis C from A virologic standpoint is designed to develop resistance. And I'll share that a little deeper in a few more slides. Of course, antiviral class and the potency of drugs and impacts resistance and the likelihood of its development. And then clinical considerations are a major part of whether we decide to do resistance testing and whether it has clinical impact. And we'll also cover those clinical scenarios where it may impact our treatment. But the overall theme is that as DEA therapies have improved, and we've gone from our initial days to now very potent pan genotypic regimens, the clinical important importance of resistance testing certainly has diminished, although as we'll show you it is it is not gone. So where we are in 2023, these are kind of the three most common, certainly initial treatment regimens we would use for somebody who's treatment naive with with really out regard to whether they're cirrhotic, or not glecaprevir pibrentasvir and sofosbuvir Vir velpatasvir are the pan genotypic regimens in particular, that are favored in many guidelines, including the unit New York state guidelines. So this just as a way of example, are the New York State Department of Health recommended regimens. listed up top are the regimens, you can see my pointer, this is the generic drug names. And then these are the trade names over here. And as you can see, in terms of preferred regimens for treatment, naive patients that really focuses on our two pan genotypic, regimens. glecaprevir pibrentasvir, for any genotype, and regardless of cirrhosis in a treatment naive patient is eight

weeks. And if you have somebody that has genotype three, that is now actually eight weeks is also available for genotype three, with more recent trials from the expedition eight and then soft velpatasvir, or Epclusa is 12 weeks for almost all patient populations that are treatment naive. So part of the kind of reason that H CV has become so easy to treat now is one because our da regimens have gotten better. But as we've now had TAS available since late 2013, early 2014. The treatment population we see in the clinic now is very different than what we saw at the beginning of the DA era. And this is highlighted here in this study from trio health. What you can just see here very clearly is that the blue bars correspond to the percentage of these different characteristics in December of 2013 and May through May 2014, when they analyze their database. So began the beginning of the DA era you can see only about half the patients were treatment naive, there was a lot of pent up need for new treatments in patients who had already failed interferon based therapies. So most patient a lot of patients were treatment experienced. Whereas then if you fast forward to where we had the introduction and approval of glecaprevir pibrentasvir The last pan genotypic regimen to be approved. Now the vast majority of patients being seen in the clinic were treatment naive If they hadn't been exposed to interferon before they were coming to care have to be treated for their Hepatitis C the first time. So that certainly simplifies things. Similarly, with regards to cirrhosis status, almost 50% of patients back at the beginning of the DEA are being seen in clinics were cirrhotic. They again had been in care and had Hepatitis C for a long time, and many of them had more advanced liver disease, whereas now that proportion at least in 2017, had dropped to about 20% were cirrhotic presenting for the first time to be treated for their Hepatitis C. And then finally, there's been a shift in where the treatment is occurring. Again, at the beginning of the DEA are most of the upside Hepatitis C treatment was in specialized centers, academic centers, and Hepatology Gi, or infectious disease practices. And now that has shifted as well, whereas the minority are treated in academic centers, and most patients are now being treated in primary care or in community practices. So again, the treatment population has certainly shifted to maybe a more straightforward treatment population. of our options, and again, we'll really focus on the bottom two here, the pan genotypic regimens in registrational trials, the percentage of patients that actually fail these regimens are very low. You can see here with soft velpatasvir Epclusa. For non genotype three, the rate of virologic failure was less than 1%. In the registrational trials, there certainly is a signal that remains for genotype three to being somewhat more difficult to treat, you can see here 4% virologic failure rates in registrational trials, very similarly, with glecaprevir pibrentasvir Magaret. For eight weeks, you can see a non cirrhotic populations, genotype one, again, less than 1% virologic failure, again, that same signal of slightly higher rates of virologic failure in genotype three. And then we've had these so called real world studies that look at prescriptions given and then retrospectively look at response rates. And what you can see here very clearly, is that with either glecaprevir pibrentasvir, or sofosbuvir velpatasvir, in general, almost across the board, cure rates are successful treatment rates are in the range of 98 to 99%. across a variety of different population characteristics. males versus females treatment naive or experienced substance use fibrosis stages, even into cirrhotics. You see, in general response rates still around 98 to 99%. Now as you start seeing evidence of decompensated liver disease, so a bilirubin that's abnormal, the treatment success rate dropped slightly. And in this study, in this Italian registry with Epclusa, or soft velpatasvir, you see a slight decrement response rates in persons who inject drugs, a lot of that is due to either discontinuation or loss to follow up so they just didn't weren't brought back to document that

they actually were cured. So I've told you, the population is simplified, somewhat less treatment experience less lower prevalence of cirrhosis and our medications have gotten better. So who still does fail if we see a failure after an initial regimen, this is data from HCV target. I thought it did a nice job of laying out the populations. Although you I will draw your attention to the regimens used here. This would not be with our current glecaprevir pibrentasvir of soft velpatasvir regimens. This is with earlier generation DEA regimens including the dip a sphere sofosbuvir was the prime primary regimen used here or soft sim. So realizing that these are slightly less potent regimens, what you see is patients with cirrhosis do fail at a higher rate. Here you can see almost a 9% failure rate, genotype one a remains a little more difficult to treat, and decompensated cirrhosis certainly. So I think these characteristics still hold true today, although the absolute failure rates are lower with our current pan genotypic da regimens in the range of two to 4%, maybe failure rates and SES to Roddick's or patients with genotype one a or three. So not quite as high as depicted here, but the same population. So I think the message is the same. And then even though you've heard now how good our initial treatment regimens are, when you talk about treating the the several million people in the United States that have chronic Hepatitis C, even with a treatment that is 98% efficacious, you're going to realize a fair number of failures. And this is a modeling study that tried to look at that. So they they published this in 2018. And in their models, which was pretty close to accurate from what we know, from 2014 to 2020, roughly 1.5 million persons in the United States were going to be treated for their Hepatitis C with D A's. And they modeled about an 8% failure rate. So that still means you get about 125,000 DEA failures despite how good our medications are. And this graphically is depicted. So right here, this black line is the number of patients living who have failed Hepatitis C therapy And initially this high number reflected failures of interferon and regimens that were not as efficacious. And over time as those patients had been retreated with more efficacious da regimens and cure, and or they die if patients had advanced liver disease and cirrhosis, some of them obviously, were going to die over the next five to six years. Right now we're reaching really a low point in terms of the number of patients we think, are still out there who have failed a DEA regimen. But on the flip side, those who have failed have now failed more efficacious therapies, and have failed regimens that include an S five A inhibitors, that's this darker blue bar here at the bottom. So you can see here roughly 30 35% of our failures, now we're going to have failed. By 2020, at least were estimated to have failed and as five A inhibitor regimen. And as we'll talk about for resistance, that's probably the group that we have the most issues with the potential for resistance to impact their subsequent therapies. So I just want to do a really quick primer on Hepatitis C resistance, talk about it from the virus standpoint before we go into some actual patient cases.

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And here, I elected to compare Hepatitis C resistance to HIV resistance, something I think we're a little bit used to thinking about. And we're clearly can also have clinical implications. These two schematics are just meant to kind of give you an overview of the viral lifecycle in an infected individual. And so for Hepatitis C here, you have hepatocytes, about 90% of the viral burden in the person is from an HIV infected hepatocytes. And the half life of those hepatocytes is on the order of weeks. So once a hepatocyte is infected, it still survives for weeks, if not months with Hepatitis C, whereas take CD for T cells that are infected with HIV, once they're infected, they don't live very long, a little less than a day. So there's rapid turnover of the reservoir of the cells

that harbor HIV and somebody with chronic with HIV infection, whereas in Hepatitis C, that's a little slower turnover. There's a bigger extrahepatic Reservoir and Hepatitis C, what that is, is still, I would say a little bit of a matter of debate, it may not really be a replicative reservoir, it may just be virus that stuck to other things like dendritic cells that has a slow offerI. But with this churn in Hepatitis C, the virus only lives inside the cytoplasm. And that's an important distinction, whereas in HIV, it integrates into the host genome. And so that's one of the reasons why we don't think Hepatitis C quote, unquote, should have a memory as much, although as you'll see, it still turns out that NS five, a resistance, for example, does persist, largely because those resistant viruses are still relatively fit in an individual, even though there's no way for the virus to actually integrate into the host DNA. So there would, quote unquote, be a long term reservoir. And so taking all that together, both these viruses exist as quasi species. That means within any individual that has chronic infection with either Hepatitis C or HIV, it's not just one viral sequence, it's actually a swarm of viruses that are closely related, but not identical, and have small differences, small mutations that occur randomly over the course of the virus replicating and an individual that caused this quasi species again, this swarm of viruses that are closely related but not identical. And because of there's no cytoplasmic reservoir here with Hepatitis C, no latent reservoir only cytoplasmic replication, we do we know that cure is possible with Hepatitis C. But for now, with integrated pro viral DNA and Long live lately infected cells, these kind of resting are effector memory cells that can live for years and decades, we right now, we're still in the place where we can control HIV, but we cannot cure it, although that's a very active area of research, as you know, but cure of Hepatitis C is possible. And then the last thing I want to point out here is if you just look at how sloppy Hepatitis C is when it replicates, so the the polymerase that replicates the RNA makes errors every day. And then the amount of virus that's produced every day, just by pure chance, the virus replicating in any individual, every single possible single and double mutant viruses created every day in an individual. Now, most of those viruses don't survive, because those mutations incur other costs to the virus, they don't replicate, as well as wild type virus. But before you even start somebody on medication, there's a chance that they have at least a couple of viruses that are resistant, at least have two different resistance mutations to any given medication you might give them and then quickly after the drug is introduced, which creates a selective advantage for drug resistant virus, there's potential to select for that third resistance mutation. So this is why when we talk about starting regimens, and I'll show you some examples, if you don't have a high enough resistance barrier at the start, the virus can break through because those things goal or double mutants probably already pre existed before you started the medication. And I use just two very early examples from our DEA experience. So this is really one of the first trials that showed cure was possible with DEA therapy and a lot presented and published in the New England Journal in 2012. And this was with an NS five A inhibitor declared a sphere, which is still used in many parts of the world. It's a pan genotypic NS five A inhibitor, plus us Dinajpur Vir, which is a protease inhibitor in early generation protease inhibitor, which was pretty much limited to genotype one activity, and is not certainly not as potent as the protease inhibitors we have now. And what you see on therapy is everybody comes down, all the patients came down initially, but of the nine patients with genotype ones, seven of the nine broke through either on therapy, or right shortly after, and they had resistant variants than that were resistant to protease inhibitors and NS five, eight numbers. And this is because essentially, this drug combination presents a two resistance barrier combination, the pretty snubbers not potent enough that it requires multiple mutations.

So because likely so many of these were pre existing, the virus quickly broke through. Now contrast this with an early study with psi 7977, which we now know as sofosbuvir, a nucleotide polymerase inhibitor, which even though it's only a single drug, it doesn't mean it only has a one, one mutation resistance barrier. We know nucleotide inhibitors are extremely potent and have an extremely high resistance barrier. The virus cannot easily develop resistance to these. So in essence, despite it's just one drug, it really presents almost a two to three mutation resistance barrier by itself. And what you see is that patients completely suppressed while they're taking the medication and you see no breakthroughs. Now, these were genotype two and three patients that were treated with this plus ribo Viron, some with interferon as well, but it just highlights that the if you have a sufficiently potent enough regimen, you can overcome that pre existing resistance. So what are the key Hepatitis C resistance concepts we want to cover? First, that Hepatitis C resistance associated substitutions or RASS may be present and in all likelihood are present without any prior drug exposure, so they pre exist probably in all patients. Hepatitis C RASS or resistance can impact treatment in specific situations, it really depends on the regimen you're going to use, and what patient population. And as we'll talk about for a patient, it really comes down to what genotype do they have? Are they infected with genotype one, a or genotype three, those are really the two we kind of care potentially about resistance in. And then what I have done here is point four that the patient characteristics really are more important. Are they treatment experienced? Have they been treated before? Or do they have cirrhosis, and really with our modern day regimens, now Cirrhosis is the most important modulator. That might mean you need to do resistance testing. But certainly Hepatitis C resistance here is not absolute. Meaning you may have resistance in a patient to a drug you're going to use in the combination, it doesn't mean, you're going to completely throw away that combination and try to use something else. We very often are using medications, despite some resistance to that medication as a part of the regimen. And again, as I've said before, these newer regimens that are very potent Pangea. tipic have largely obviated the need for most resistance testing. So what about impact of treatment, resistance on initial treatment, so again, now we're talking about patients who have not been treated with TAS before. And here I'll make a distinction between baseline resistant This is that natural variation we've been talking about where just randomly the virus makes mutations. Typically, these are not as big a deal because it's only typically one resistance mutation, at least on a single RNA strand. They don't tend to cause as much as much resistance to an individual medication or a high full change. And they're not prevalent, typically high, high numbers or high percentage of the virus. Whereas once somebody's gone through therapy, and we've quote unquote, selected for resistance, we've introduced that drug exposure, which exerts a selection pressure on the virus. Now we're talking about patients with multiple variants, so multiple NSI NS five a resistance mutations, and in all likelihood, they're quote unquote, linked, meaning the two different resistance mutations are on the same RNA strand. They tend to cause high level resistance, they're highly prevalent once we selected for them, and they're more likely to be enhanced in otherwise difficult to treat patients. So those with genotype one a are genotype three, and those that have cirrhosis.

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So, if we just look overall, what's the actual prevalence of detectable resistance mutations in persons before we start? So this was a large review meta analysis kind of looking at this, of patients that had sequencing done before they were exposed to any and any antiviral URLs.

And you can see here before treatment in genotype one A, maybe up to 40 45% of patients will have some type of Ns three resistance associated substitution. Now a large part of that genotype one A is a q ADK resistance mutation that we don't think really is clinically impactful with our current regimens. So just because they're present in both these slides, most of the the vast majority of these RASS do not impact clinical therapy. They're RASS that caused resistance to older generations of medications that we don't really worry about very much. And S five A you can see here in genotype one a I'll focus on in genotype three, somewhere around 15% are going to have baseline resistance mutations. But what I've drawn out here are the positions we really care about, and what's the prevalence of those at baseline before any drug exposure. And you can see in genotype one a for q 30, position l 31. Or why 93 H er en, they're all present in less than 3% of persons who have not been exposed previously to an NS five A inhibitor, genotype three, a little different story, the tube positions, we really care about a 30k. And why 93 H are present somewhere in 886 to 8% of patients before any drug therapy. So a little more prevalent here. And we'll discuss that a little bit more. So this is really, almost historical data now. So we do still use sofosbuvir, Viola des prosphere, otherwise known as Harvoni. It is available as an eight week treatment for treatment, ie patients with genotype one and a low pre treatment Hepatitis CRNA. So it is still used. But this was really one of the first instance where you could see that in specific populations here, namely patients with genotype one a being treated with this who had baseline NS five a resistance, they did have statistically low response rates about 90% SVRA, compared to 98, without resistance associated substitutions at baseline. Now, I didn't show you the rest of the data, this was really enhanced in persons who are also interferon experienced, and genotype one a. So this was a historical instance, I've listed the Hepatitis C guidelines have a resistance primer in them. And that goes into much more detail about the patient populations. But there was a time when we were using Harvoni, or software Dipa sphere and had a larger population of interferon treatment experience patients with genotype one a that there was at least a conditional recommendation to do resistance testing. And if you had certain key NS five a RASS to lithosphere. To pick something else. We've kind of gotten away from that again, because we have these other options now. And because we just don't have much in terms of interferon treatment experience patients still around. The other historic largely historical instance I want to bring to you is Elvis fear and grows up revere what was known what is known as Zepa tear. This was a regimen that was used fairly frequently in the United States until the arrival again of Epclusa and Magaret. But largely went out of favor because in those with genotype one eight, you had to do baseline resistance testing. And about 1210 to 12% of patients had resistance that would impact therapy. And you can see if they had those resistance mutations, you can see here, the response rate was only about 60% versus essentially 99%. Approaching 100% If you didn't have those resistance mutations. So when this regimen was being used frequently, we were frequently doing resistance testing in genotype one a in treatment naive patients, and if they had any resistance at any of these key positions for elbow sphere, you either again had to switch to the treatment you were going to use or if you continue to use this regimen, you had to extend your treatment of 16 weeks and add Rob of iron, which was really not fun for the provider or the patient. Alright, so first question here, and I'm just going to kind of pose this think about your answer, but we're not going to do an actual polling. So the first question, so which of the following patients would be recommended to have pre treatment resistance testing currently, so genotype one a treatment naive with cirrhosis you're planning to treat with GP or Magaret same

patient one a treatment naive with cirrhosis that you're planning to treat with soft velpatasvir Epclusa genotype three a, again, treatment naive but with compensated cirrhosis that you're going to plan to treat with GP? Or finally genotype three a treatment naive compensated cirrhosis that you're gonna plan to treat with soft velpatasvir or Epclusa? Or do we not need to do resistance testing in any of these populations, since none of them have failed? A prior da regiment? Once you think about that for a second, and then we'll go into a case. All right, so our first case is a 63 year old gentleman, he has hypertension, hyperlipidemia and reflux. And he has Hepatitis C genotype three a he's treatment naive his baseline viral load, you can see Here's 1.5 million. So on exam and labs he has evidence of cirrhosis. So he has gynecomastia and spider angioma. He doesn't have ascites that you can detect on his abdominal exam. He doesn't have asterixis his labs are here he's got some mild thrombocytopenia is albumin is low, high and or higher is borderline. And if you put all that together, he's got a pretty high fib for I think I've got it on the next screen. And then you can see his medications here, which perhaps are notable for he is on a ppi, and then receive a statin five milligrams. So now, second question, would you do any additional testing in this patient before you decide on a treatment regimen? So he's genotype three? Treatment naive? We think he's got cirrhosis. So would you do a liver ultrasound? Would you do additional fibrosis staging? So maybe something like a FibroScan, Mr. elastography? If you have access to it or a liver biopsy potentially, would you do NS three resistance testing and as five a testing a combination? You're going to do an ultrasound plus NS five a testing? Or are you just going to go ahead with treatment? So again, think about what you might do in your practice. All right, so we see here his fib four is 5.19. Really, the labs combined with the exam is pretty convincing. This patient has cirrhosis, I don't know that you would really need to do any other imaging, or fibrosis staging. I would be convinced personally, if I was seeing this patient, they had cirrhosis. And so if we calculate a Child Pugh score for him, he's in a six. He doesn't need an ultrasound for HCC screening, right? So you get an ultrasound yes course hepatic texture, a nodule or surface no ascites was seen moderate splenomegaly and no masses. So again, indications of cirrhosis, possibly portal hypertension, and you already had an indication of that as well with this thrombocytopenia. So this patient was treated with soft velpatasvir for 12 weeks. We don't do this anymore on therapy, but at this point he had and Hepatitis C RNA at week 14, at week four, that was 14, sorry. And then two weeks later, he was undetectable or at zero at week six, looked like he maybe was about a week late on his refills. So there's maybe some issue with noncompliance here by his second month, but he did complete therapy. And then in four weeks after treatment, he had already recovered 400,000 was his viral load and you read genotype of many is again genotype three. So did we screw up here? Should we have done resistance testing at baseline. So here's what the New York state guidelines have. So overall, the kind of first here just mentions that not universally needed for most situations, but here focus on the second paragraph, that NS five, a testing is recommended for patients with genotype three, who are being considered for 12 weeks of soft Bell. So that's our patient here. And its treatment naive was cirrhosis, so he should have had resistance testing. at baseline, if we would have found resistance, specifically the wind 93 H resistance substitution, that either we should add Rob of iron or pick something else, like a GP regimen potentially. So now I want to just go into first showing you examples of resistance testing, this is directly from so there's two major sources really nationally that you could do resistance testing, that would be

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LabCorp, which does it through monogram biosciences, and they give you a report that will both give you a genotype. So it will reconfirm the genotype, you do have to know the genotype of your patient before you send off resistance testing, because the primers they use the assay they use will be based on that. So you do have to give them the genotype, but then it's confirmed when they do the sequencing. And then it will typically show you all the variants they detect. So anything that's off from the consensus sequence, the kind of standard sequence, they'll show you, most of those are going to be just random variants that don't have any impact. But then they'll highlight the RASS here and m 28 V, and give you some interpretation. So velpatasvir not expected to cause resistance with a Dipa sphere, not expected, but some of the older ones like elbow sphere that we mentioned earlier, would be expected to cause resistance. And similarly, this is an older example they have but if we had pibrentasvir on here, a component of MeV ret, you wouldn't expect any resistance with an M 28. V. Quest is the other national laboratory that offers resistance testing. Again, it'll spit out what the subtype is, although you have to tell them ahead of time, it'll list the mutation, it'll give you interpretation, like probable resistance here for velpatasvir. I just want to point out that for genotype one A, you can clinically order NS three protease inhibitor resistance testing NS five a resistance and NFIB, polymerase resistance testing, both major laboratories have those assays available for genotype one A, whereas if you're dealing with genotype three, you're more limited. The only option you can order for genotype three is NS five, a resistance testing. Just checking how we're doing on time I'm here. So this is one of the studies and this is the basis for that recommendation we went through for genotype three. So in the initial registrational study with soft velpatasvir, there was I would say a signal noted that patients who were either treatment experienced or had cirrhosis had low response rates to soft velpatasvir for 12 weeks. So then the sick second prospective study was designed that took patients with cirrhosis. So everybody in this study had cirrhosis, a little over 200 patients. And they were randomized genotype three with cirrhosis to soft velpatasvir for 12 weeks, or soft velpatasvir plus Rob of iron for 12 weeks. Most of the patients in this study were treatment naive about 25%, though were treatment experienced as well. And what you can see here is a lower response rate. In patients who did not get robber baron 91% versus 96%. Relapse rates were about a little over double 5% relapsed in the rhyme that did not get rivaled. Or you take one step further and look specifically at those who did NS NS five, a RAS testing or sequencing was done on everybody. It wasn't a decision for how they were treated. But then if you retrospectively look back those with baseline and it's five a RASS, their response rate without Rob barn was only at 4%. Whereas about 11%, higher and 95% If that Rob of iron was included. So this is the basis for that recommendation in the guidelines, the SLD IDSA guidelines have the recommendations that we just looked at, for the New York State Department of Health. And this is the study that's the basis for that. Then in the UK, they went back and look at the registry where they treated patients with soft fell and you can see here these are genotype three patients with compensated cirrhosis. Here, we don't have data on resistance testing, but still with soft velpatasvir 92% SVR, significantly higher when Rob Aviron was included with soft velpatasvir. You notice here glecaprevir pibrentasvir Maverick for 12 weeks without Rob Aviron, comparable numerically not quite as high but 96% rate without Ranjbar. And then, just to kind of talk about GP a little bit more than genotype three, in this integrated analysis that Steve flam did, what you do see here in genotype three is pretty high response rates across the board. You do see in treatment experience patients, maybe just a

slight dip here, but what I want to draw your attention to is, so the y 93. H alone doesn't do anything to pibrentasvir in genotype three. And in fact, you don't see any effect of genome of y 93 H at baseline over the A 30k mutation, that other one that's present about 8% of treatment naive patients, there was at least a signal here, it wasn't statistically significant, maybe a slightly lower response rate. The theory is the a 30k kind of is a baseline. And then if you quickly select for the white 93 H on top and get to a double mutant, then you do see some clinical resistance to pibrentasvir prevent potentially. So this was noted in this integrated analysis. I will say in subsequent studies, including even the expedition eight, which looked at only eight weeks of MeV read or GP for cirrhotic patients with genotype three, there was really no signal. In fact, nearly every patient was cured. There was one virologic failure. So this hasn't been consistent in all studies, but I think it's something to maybe keep in the back of your head. Okay, so let's come back to our patient. Would you do any additional testing now prior to deciding on a retreatment regimen? So remember, we've got a genotype three a patient compensated cirrhosis? required, we tried to sell 12 weeks of soft velpatasvir and had a failure, virologic recurrence with the same genotype. So would you do an S five A RAS testing now before retreating? Would you test an NS? Three? Would you do both? And s3 Ns five, a testing? No, I'd retreat without it. Or I'm going to phone a friend and ask for some help. So just think for a second about what you might do. So now, when we're talking about da failures, I think these are the things that you should be thinking about when you approach the patient. First, you need to know what their prior therapy was, What da classes were in that therapy, did they get the appropriate duration? Maybe they were treated too short? For some reason. If they had an indication to get Raghavan, did they get it? Essentially, was the initial treatment, more or less appropriate based on guidelines in the patient care and virus characteristics. Next, you have to think about your patient. Do they have cirrhosis, extreme BMI, BMI, renal disease, anything else? And actually, renal disease really has gone away there was a time where that would limit your options but now really, all of our main options are able to use in in patients with renal disease. And then the other thing I always ask myself if I need to use Rob of iron in this patient, can I do they already have anemia baseline renal disease does come in when you're thinking about Rob of iron and makes Rob of iron dosing really tricky and kind of difficult. So it still is a consideration for other things. Member our patient they were about a week late on their refills after the first month. So was adherence an issue? Do I really need to sit down with this patient really emphasize adherence? Were there any other drug interactions or patient was also on a ppi, we do know PPIs tend to lower the levels of really all our Diaz, it seemed with soft atmosphere, soft velpatasvir and GP glecaprevir pibrentasvir. Clinically, most of the time, we don't think it's a significant interaction, we can kind of work around it with timing of dosing, giving medications, with food, things like that, but it's a consideration. And then finally, is resistance part of this equation? Well, I've already alluded to this, but when you fail, you generally select for resistance, particularly NS five, a resistance. This was data we published from software Dipa sphere Harvoni data, the longer patients has been exposed and then failed, the more likely they were to have resistance. I've just kind of summarized from a number of different studies what the rough rates of having resistance are. So Elvis, fear goes up Revere, high rates of resistance if you fail, here softly the prosphere of soft velpatasvir, probably around 80 to 90% are going to have resistance to NS five A. And then with our next generation, regimens, GP southville, Vox southville, Vox is interesting. So triple bass therapy. So now a nucleotide plus a protease plus and minus five A. And we have data from the Polaris study that when you treat patients like that,

you really pretty infrequently select for additional new resistance mutations, they'll have what they had going into that retreatment. But you won't select for a lot of new resistance. I'm actually going to skip over this, you'll have this table here that you can refer to the most common resistance patterns. As you'll see, the moral of the story is when we're talking about retreating a DEA failure with a triple based regimen like saalfeld, Vox or SOF plus GP, resistance really doesn't matter very much we don't really alter our therapy much based on what resistance the patient has. But this will be here if you want to refer to it. And remember, once we select for NS five a resistance in patients, those resistance mutations tend to stick around for quite a long time, they're still generally present several years after the therapy if the patient's not retreated. So NS three PII resistance is not a big deal. In the interest of time, I don't want to spend a lot of time here, it's mostly because most of the resistant, quote unquote resistant variants we see are kind of more polymorphisms. They don't impact voxilaprevir, or ProCap. Revere are PIs we use now. And then if they are selected, they tend to go away pretty quickly. Because if we do select resistance, it's some of the key positions, the virus tends to be very unfit. And so it goes away quickly.

37:46
So in the early days, we were just learning really how to retreat people that had failed do therapy, absolutely selecting for resistance meant you weren't going to do very well. Now, this was very early where patients had failed softly dip a sphere, and we came back and tried to retreat them just with a longer course of the exact same medication. Not really a great idea, it doesn't make intuitively a lot of sense. At the time, we didn't have anything else. But you can see here essentially, if you had resistance when you failed initially, and we retreated with the same regimen, essentially everybody who didn't have resistance, got an SVR. Whereas if you had resistance only about 60% responded. So clearly, resistance had an impact if you used a weak retreatment regimen. And that's partly because there's a lot of cross resistance, almost all the first and second generation. And as Fivay inhibitors had pretty much complete cross resistance. Again, as we got to our newer regimens, they were better velpatasvir not quite as much cross resistance. But certainly the white 93 position still impacts it significantly. And pibrentasvir among NS five a five inhibitors really is the standout. Whereas at least for any single position, there's not a significant change in its activity for any of the common single potential single position resistance mutations. So I do think there may be as a little something special about pibrentasvir. In terms of the protease inhibitors, voxilaprevir, Ungol, capillaria, the two we really use now, they have pretty overlapping resistance profiles. And if this case, if anything, maybe VOCs looks slightly better than glecaprevir, but they're pretty comparable. So let's come back to our patient. For the sake of this lecture, let's say we did resistance testing. So actually, remember this is genotype three patients. So we can't do NS three resistance testing, but NS five, a resistance testing was done and they have an A 30k plus a white and a white 93 h we don't know what's a plus plus, we mean they're on the same RNA strands, but in all likelihood they are. And so here's the interpretation causes at least a 50 to 700 fold increase in Val with the 30 and the y 93. Together would cause over 1000 fold shift pibrentasvir less impact, but again, once you get to the double mutant, you do start to see at least a 70 fold shift in the activity of pibrentasvir as well. So in here is the predicted that spit out by the algorithm predicted to have resistance to all these possibly also to have resistance to pibrentasvir? So now we've got this, what would you do genotype three cirrhosis? Failed softball for 12 weeks, we know

they have an A 30k, presumably plus a y 93. H, we don't know what they have an s3? Well, they haven't been exposed to any protease inhibitors at this point. How would you retreat this patient? So just again, think for yourself, you can do Sofitel box for 12 weeks, you can add rival Viron for 12 weeks, you're gonna go longer longer with Rob of iron, or you're gonna go to SOF plus GP with Rob of iron for 16 to 24 weeks. So what would be recommended in the in the guidelines, you can see here. Now this is very specific for soft failures. So soft plus and NS five, eight, or atmosphere goes up here. There is this option to do 16 weeks of Navarette or GP, but only in patients who would have failed SOF plus and NS five, eight, not if they've had protease inhibitor experience like resop Revere. So this would only be an option for a select number of patients. The preferred really, I think, would be soft Bell box. So this triple bass combination therapy for 12 weeks, and then genotype three, as it noted here, you really should consider adding Rhabdo virus in particular if the patient is cirrhotic, like our patient. And here's some of the data data that underlies those recommendations. So Polaris one was NS five experience they were all treated soft pillbox for 12 weeks, no Rob of iron can see overall 96% response 99% of those without cirrhosis, 93% and those with cirrhosis, and all the relapses all the virologic relapses were cirrhotic patients. So again, coming to this idea that it's patient characteristics probably more than resistance in the virus that's determining outcomes to retreatment after da failure. I'm gonna skip Polaris for for now, because they were not in his five exposed which is less common now. And then this is just the resistance data showing that really, pre no resistance pre existing to Vox or Val components of the regimen 98% spr, exactly the same SVR, even with an S five a resistance to velpatasvir. So again, in the context of a triple drug retreatment regimen, resistance really does not seem to be the main predictor of outcomes. Again, it's patient genotype. So genotype three response a little bit worse than one a or other genotypes, and then it's cirrhosis. Does the patient have cirrhosis? That's really what I think you need to focus on if you're doing da retreatments. Here's some real world experience. And I picked each one of these specifically. So there is some evidence from the VA experience that if patients failed soft velpatasvir before, and then you're treating them a soft Bell box. So using two of the three medications over again, maybe they don't respond quite as well. Here from a Spanish cohort, highlight genotype three in the issue. So this is overall genotype three had 80% in this cohort 88% Without cirrhosis, 69% with cirrhosis. So again, genotype three cirrhosis, maybe those who have had soft velpatasvir before do a little worse. And then again, here's the same message more advanced fibrosis, low response rate. And then finally, there's an Australian study again, which looked at genotype three, suggesting they come in right around 90%. So a little bit lower for genotype three and cirrhosis. So that's clearly the problem population, I think, with Da failures and retreatment. I'm going to skip this. Now, I already talked about that this is a potential for some soft and as five and failures, but not patients who have been exposed to a protease inhibitor plus an NS five A in at 16 weeks. So this is the data that belies that part of the recommendation, but I'm not going to spend more time here. And then if we go back to Softail, Vox again, this just highlights for the genotype three patients. All the failures had cirrhosis in that study. Three of the four didn't have resistance. So there may be some modulation there. But again, I think it's the cirrhosis. And why that for this population, genotype three, and S five A failures that you're retreating the Sofo box, I think if you can, there's probably a pretty good indication you should be adding ribo Viron and then Magellan three, I'm going to come back to later this was the SOF plus GP study with Rob Aviron that we did that looked at 16 weeks look very good for genotype three here. 100% of the patients were

cured. It is 16 weeks and soft plus GP with Rob of iron so everybody got robbed of iron in this study. So it's a little longer duration and it does include gradual firing. All right, so come back to our patient. How did we treat them? They were approved for soft bellabox for 12 weeks, we did add Rob Aviron held the PPI the patient was okay with that you got to talk to patients some patients can really get pretty bad rebound reflux symptoms if you hold a PPI patient took this for 12 weeks. You can see here 22 week for undetectable weeks. Nixon did achieve SVR 12 Alright, in the next five minutes I kind of want to go through one last case. This is a 65 year old woman with hypertension, diabetes GERD and genotype one a. She also has cirrhosis, Child Pugh, a six, and C the viral load there on a map Rizal Metformin, insulin and receive a statin 10 but very treatment experience. So we've got GP for eight weeks, which is what is recommended now for cirrhosis if they're compensated. So we've got eight weeks of GP failed that and then was retreated in 2022 was soft bellabox for 12 weeks did not get pretreatment wrasse testing did not get robbed of iron with that retreatment. So she said updated HCC screening and ultrasound without masses but consistent with cirrhosis. So now if we do wrasse testing here, in NS three has an A 156 T, it's actually a mixture and T but that's right at the active site, and that that mutation does cause high level resistance to both voxilaprevir and glecaprevir. Here's the resistance interpretation. And then an NS Fivay has kind of a weird pattern, but a Q 30 and y 93 S. individually. As it's common in these positions, they cause a moderate full change in velpatasvir. But not significant change in pibrentasvir. We kind of looked with this patient, we were looking to find a any studies that had this dual mutant to know my guess would be that the dual mutant would probably cause significant shift in both these medications, but we just don't know. So how would you retreat this patient? Again, the capsule on the right gives you the summary genotype one a cirrhotic compensated has failed GP eight weeks saalfeld box 12 weeks has dual resistant and s3 and s5 A probably high level resistance. So here are your options soft mailbox with rye but 1224 GP plus soft with Rob a 1624 weeks? Or would you go all the way to 24 weeks but not use Rob of iron? Or would you do something else? Just think about that briefly. So here's what the New York State Department Health recommendations will be these are for GP failures, or I would throw in multiple da failures here. So glecaprevir plus pibrentasvir, with Robern and sauf. I think this has been updated now, but that's the phosphate has got to be in there. And that's key in this population. And 16 weeks is really because that's what was studied. That was the study duration. So that's really all the data we have soft pillbox, certainly you could do. For a GP failure, there's a fair bit of data that that works pretty well. I think if they're non cirrhotic, or even genotype one with cirrhosis, whether you added Rob of iron would kind of be a plus or minus but in general guidelines recommend adding it if there's cirrhosis present.

47:44

This again is the study that looked that I mentioned that use 16 weeks aside anybody with genotype three, or if before they failed GP they had failed another da regimen they automatically got 16 Weeks was robbing barn. Here's the response rate in those arms 95% There was only one failure, which was a genotype one a all the genotype three patients were cured in this study. And then there is some real world data this is from Germany retrospective. Now these are soft Val box failure. So patients who fail multiple da regimens including this triple regimen. And here they retreated it with GP plus off with or without Rob of iron had an 80% response rate. But I will say of these three failures. Two of the three failures were patients that

died, they had decompensated cirrhosis, and they died from other liver related issues before they could be evaluated to see if they were actually cured. So it was only one documented failure here. And then using Val soft plus Reverend wouldn't make a lot of sense to me. In this case, it was probably done because patients had decompensated liver disease. And it is I would say risky, and only should be done in a monitor transplant setting. If you're going to use a protease inhibitor with somebody with decompensated cirrhosis, that's really for transplant centers and transplant hepatologist under the watchful eye if it's even done. And then I kind of looked at a few other case reports and combined them. So overall, the data is pretty promising using either GP plus off with Rob of iron for at least 16 weeks, some of these studies went longer, or soft mailbox with or without Robert Viron for various durations anywhere from 12 to 24 weeks. Anecdotally, in case reports in small case series, it seems to work pretty well. This is just highlighting again that the beneficial effects of effects of extending your treatment, adding in Rob Aviron. And in particular for genotype three, adding and Rob of arms. So these are the strategies which we can use when we're kind of at the end of our rope. We've been through all the treatment classes, they've had multiple DEA regimens and you're faced with retreating somebody, I think you're at the point where you try to add Rob of iron if you can, and go as long as you can, with ideally three different classes of drugs, nucleotide plus a protease plus an NS five A inhibitor. These are just a summary of what the guidelines recommend for initial NS five a failure so GP or soft Val, generally they go to solve Fill box or soft plus TP. And then when you get down here, these are soft dough box failures or multiple da failures. Here, pretty much everybody is recommended using ripe Aviron if you can, and going for as long as you can really, especially if you've got self Build Box failures 16 to 24 weeks if possible. There's lots of footnotes here, I'm not going to go through them. You know, the the easel and eex recommendations do recommend doing resistance testing, although again, to me, it's not clear what you do with that, because you're already in the position where you're going to use all three drug classes and you're already going to use rival Viron. Really kind of regardless of what your resistance pattern shows you. And then finally, I'll just end with these two case. Kind of case reports. This is one I did with Daniel fear or retreated where we retreated or Daniel really retreated a multiple failure and a patient who was also living with HIV, failed multiple day regimens, ultimately was cured with soft plus GP and Rob of Ireland for 24 weeks. And then Stuart Gordon and the group at Henry Ford just recently published this in hepatology. He had a patient that was genotype one a treated with Harvoni for 24 weeks, then GP plus Radovan for 12 weeks. He was actually in the Magellan three study our study. GP plus SOP was robbed after 16 weeks and failed history was Sofo. Vox plus ran for 12 weeks and failed, had extensive resistance. And Stuart kind of came up with this regimen of just continuous da treatment for over a year using essentially whatever they could get. It started with soft declared a sphere plus interferon arrived virus so interferon kind of as a backbone to prevent breakthrough. When they could no longer get approval for this they switched to Epclusa. Again with Rob of iron interferon intermittently as the patient could tolerate it. Then they went to Navarette or GP, they added soften on top of Navarette for over 24 weeks, and then did some more soft velpatasvir. Again, all the time giving interferon arrived Varnes tolerated. Stuart treated him for over a year, and finally ended up killing this gentleman who had been through four or five different da regiments. So even in kind of the most hopeless of cases, it's possible to get a cure. So um, you know, in the last couple of minutes, I want to leave time to go to some questions. We've only got about five minutes left. So I put in some other stuff here about determining relapse versus reinfection.

And also treatment interruptions because I find that's a very common question we get my patient missed five days a week, do I stop? Do I restart what to do? And I'll just say that DEA regimens are very forgiving. I kind of came up with my own framework for presentation. And now there is a section in the ASL D IDSA. guidance as well, addressing specifically treatment interruptions. I think the moral is if they've missed less than a week, and you think everything else is okay, they're going to be able to restart and be compliant, I would just restart without hesitation in the one to two week range, I still tend still tend to restart generally depends on where it is and their treatment. If it's you know, they took five days and then this two weeks, I say Alright, what's going on, let's stop, regroup. But otherwise, I think you can still pretty safely restart. If they're in that one to two week range, but get an RNA to check, make sure they didn't already break through. If they've missed more than two weeks again, then it really depends on where they are. If they took 10 weeks, they were very easy to treat patient and they missed their last two weeks lost their medication. And they were non cirrhotic genotype two that we gave 10 weeks of you know, soft velpatasvir I would just stop and assess for SVR at that point, but it depends. So again, there's a section in the guidelines to really tackle that. So here's the summary. I'm not going to belabor this right now you all can read this, I think we've we've gone through the keys. The key is genotype three is the only time and a treatment ie patient with cirrhosis that you need to really be thinking about pretreatment resistance testing and somebody who's not da experienced. So don't forget that. And then once the RDA experienced since we have these triple mechanism, action combinations, resistance testing really doesn't play a big role. And it gets really their characteristics. And are they cirrhotic? And are they genotype three, then you need to be thinking about extending your duration to the maximum possible and using Rhabdo virus. All right. With that, let's see if we can get to some questions to answer. Let's see.

54:20
Thank you so much, Dr. Wiles. We have a few questions. The first question is whether you can comment on the timing of resistance testing. Sometimes when we do resistance testing, we see wild type no resistance. Do we believe this is da do we believe this in da experience patients? Or is this because we have lost the window of selection pressure? Is interpretation dependent on genotype or cirrhosis?

54:48
Yeah. And so you know, kind of I think is we ran through NS five A, it depends on where you're looking right and what the genotype is, and what they were treated with. But if you're talking about NS five, a resistance those generally Stick around if they're selected for for two to three years and most patients. So I think if that's what you did resist testing and you didn't see it, they may not have selected for it. The other good part of this is again, as we went through, if you're talking about da failures, particularly like soft velour GP failures that now you're going to be true retreating with saalfeld, Fox or another triple based combination regimen. To be honest, the resistance testing is probably not going to change your approach too much. And in a treatment naive patient, I would take it at face value. If they didn't find it, it's probably not there at significant levels.

55:37

Thanks. Thank you. There's a question in the past GP was not recommended for people with compensated cirrhosis because of the PAI has has changed what has changed.

55:50
So actually, it was always an option for those with compensated cirrhosis Child Pugh, a. You know, it was done in the studies and was never was not was always recommended or an option in that point. It's really the D compensated cirrhotic. So Child Pugh B and C. So somebody who's had very steel bleeding, ascites encephalopathy, or even based on their labs that you SCORM out, they have an elevated INR, and they would they would score out as a Child Pugh B, I would avoid those still. I will say at the recent liver meeting ASL D, they took another look at this. And it's always been a question, is that truly a class effect of protease inhibitors? Or was it more early protease inhibitors? You know, brozovic Revere, which had a signal for potential some hepatic toxicity and higher doses cemap, revere things like that. And they found not a lot of evidence that with modern regimens, there was a difference in rates of liberty, compensation, or issues in patients with Child Pugh B and C. I wouldn't recommend it. But yes, Child Pugh a compensated cirrhosis, absolutely fine to use, GP or Maverick.

56:56
Thank you. Because one thing I can extract a while is very practical. As I know, sometimes medical providers are being asked by insurance companies to do resistance testing when it's not indicated. Can you give some guidance on how you deal with that in your practice?

57:11
You know, that's interesting. So I practice in Colorado, and I see mostly Medicaid population at Denver Health. And so actually in Colorado, although I felt like New York, largely, you know, prior authorizations for most of the days have gone away. Um, occasionally, with private insurance, we'll run into cases where we have to have a genotype, we've gone away from routine genotyping, viral genotype genotype one, three, we generally get that I have not run into a situation where an insurer has asked me specifically to have RAS testing. I guess what I would say though, is just my general Fallback is if is to point them to guidelines as long as it's not recommended the guidelines which are only should be genotype three that you're going to treat with soft velpatasvir. That's my typical first I guess, salvo back to the the insurers the payers is this is not according to guidelines and see what they say. You know, I mean, I guess ultimately, it's only more cost for maybe the insurer, but it is a hassle for the patient have to come in and it does, probably takes, you know, on average, at least 10 days to two weeks to get the resistance results back so it could delay your therapy. So

58:19
thank you for that. Thank you so much, Dr. Wyles for this excellent presentation.

[End Transcript]