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NEW DAAS AND NEW DDIS: HOW DRUG-DRUG INTERACTIONS CONTINUE TO VEX HCV TREATMENT

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12/13/2016

New DAAs and New DDIs: How Drug-Drug Interactions Continue To Vex HCV Treatment [video transcript]

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- [Jim] Welcome to Physicians' Research Network. I'm Jim Braun the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990 PRN has been committed to enhancing the skills of our members in the diagnosis management and prevention of HIV disease as well as its co-infections and complications. We hope this recording of Charles Flexner's presentation New DAAs and New DDIs: How Drug-Drug Interactions Continue To Vex HCV Treatment will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners and physician assistants. And membership is open to all interested clinicians nationwide at our website prn.org. And now allow me to introduce Charlie Flexner professor of medicine in the departments of Pharmacology and Molecular Sciences and International Health at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

-[Charles] Thanks Jim. We kind of have this idea with HIV that as the drugs get better the drug interactions get fewer and that has not been the case with HCV.The newer HCV drugs do still have their potential for drug interactions and that's what we're gonna talk about tonight. The big difference between treating HIV and HCV in terms of drug interactions is that HIV drug interactions potentially can last for a lifetime whereas HCV drug interactions usually last for 12 weeks. So, that does create a different approach in the clinic and we'll talk a little bit about that tonight.

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Okay, I'm gonna run through some of the newer combos and I'll start with a combination we've been used to using Sofosbuvir/Ledipasvir or Harvoni and then switch very quickly from Sofosbuvir/Ledipasvir to Sofosbuvir/Velpatasvir, the newest kid on the block and talk about what that means with respect to drug interactions.

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Okay, so what do we know about the drug interaction potential of Sofosbuvir and Ledipasvir? Sofosbuvir is a nucleoside analog and like HIV nucleoside analogs it has a very low potential for drug interactions with one exception we'll talk about later. Ledipasvir is an NS5A inhibitor. It has a small number of unexpected drug interactions presumably related to its impact on drug-transport proteins. Especially p glycoprotein and breast cancer resistance associator Protein, BCRA. And drug-transport protein interactions are always harder to remember because we just don't spend a lot of time in practice thinking about what drugs are effected by what drug-transporters unless you happen to be an oncologist, where those interactions can be quite important.

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So, here's the drug interaction warning list for Sofosbuvir. You don't wanna give Sofosbuvir with anti-convulsants that are potent inducers. Carbamazepine, Phenobarbital, Phenytoin in particular. And that's because those anti-convulsants induce a drug-transporter that leads to accelerated clearance of Sofosbuvir. So, a negative impact on Sofosbuvir concentrations. And the same is true for Anti-tuberculosis rifamycins which are also inducers of drug-transport proteins that adversely affect Sofosbuvir. So Rifabutin, Rifampin, Rifapentine, and then finally St. John's Wort. We don't spend a lot of

time in the clinic talking to our patients about herbal medicines complimentary, and alternative medicines, we should because this drug St. John's Wort is a very common component of combination herbals. It's also commonly used by people with moderate to mild depressive symptoms where it has some evidence of clinical benefit. But St. John's Wort is a very potent inducer particularly of some drug-transport proteins and it can adversely affect concentrations of a number of prescription drugs including Sofosbuvir. So, if you're getting ready to start one of your HCV infected patients on a curative HCV regimen make sure you know whether or not they're taking herbal medicines that contain St. John's Wort or if they're taking a combination capsule that they're getting online or from GNC and they're not sure what's in it. Have them stop it for the 12 weeksthey take their Sofosbuvir-containing regimen. Tipranavir's a drug we hardly ever use anymore and for good reason, it's quite toxic. But it also is a very potent inducer of drug-transport proteins and shouldn't be used in combination with Sofosbuvir. But there's one and only one Sofosbuvir drug interaction I want you to remember. Because it's a drug interaction that has the potential to kill people and that is the interaction between Sofosbuvir and Amiodarone. How many people in this audience have a patient in your clinic right now who's taking Amiodarone? Raise your hand. This table over here. Do you all practice at the same clinic? So every time I ask this question it amazes me how may patients being followed by ID Docs or family practice Docs are taking Amiodarone. As a pharmacologist I think it's a terrible drug. We don't really understand how it's cleared. It has a half-life of 120 days. It makes you turn blue. It causes all these crazy arrhythmias. It can cause primary pulmonary hypertension and yet the cardiologists love it because it works for some recalcitrant arrhythmias including things that are common like atrial fibrillation. When amiodarone is combined with beta blockers it can cause bradyarrhythmias and if amiodarone is combined with Sofosbuvir particularly in patients who are also taking beta blockers. It has caused profound, clinically significant bradyarrhythmias including death. We don't know what the mechanism is but we don't think Sofosbuvir is interacting with some drug-transporter that's affecting amiodarone or vice versa. But the bottom line is there have been multiple case reports of life threatening or lethal bradyarrhythmias in patients on amiodarone who were prescribed Sofosbuvir. So this is the one and only thing I want you all to remember about Sofosbuvir drug interactions. Don't ever, ever, ever give this drug with amiodarone.

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Okay, Ledipasvir is a little more complicated than Sofosbuvir, it's got a number of other potential drug interactions that we need to talk about. So Ledipasvir is minimally metabolized meaning it is like Sofosbuvir, largely eliminated unchanged although it is eliminated through the bile. Which maybe why it's such a good anti Hepatitis C drug, because the drug is taken orally, it's transported into liver cells and then it's excreted from liver cells unchanged into the bile. And so probably Ledipasvir is getting concentrated in hepatocytes and that may contribute to its excellent anti HCV activity. It is a substrate for a P glycoprotein and so it could be affected its concentrations could be affected by drugs that effect P glycoprotein an intestinal transporter. And it is also an inhibitor of P glycoprotein as well as two other drug-transporters that are commonly involved in drug interactions. The breast cancer resistance protein, BCRP and organic, anion transport protein 1B13 OATP. I don't expect you to remember this alphabet soup but OATP 1B13 is an important transporter in renal tubules. So the Ledipasvir drug interaction profile is really related to drug-transport proteins. PGP inducers, P glycoprotein inducers and inhibitors can effect Ledipasvir similar to the effect expected with Sofosbuvir. This is very convenient because we don't tend to use Ledipasvir without Sofosbuvir and so if you're avoiding rifamycins and anti-convulsants with Sofosbuvir you're gonna be avoiding them with Ledipasvir and that's a good thing. So it's really the same list of contraindicated drugs. Ledipasvir can increase digoxin levels. Digoxin is a pure PGP

substrate. Ledipasvir is a PGP inhibitor. It can make digoxin levels go up. So let me ask another question. How many people here still have anybody on digoxin? Okay, several of you, all right, that's good. So digoxin is a drug that's easy to use. I actually love the drug although I don't think it's all that effective. But in terms of its drug interaction potential it's easy to remember because it is a pure PGP substrate and so there will be no digoxin drug interactions unless you happen to give it with a drug that is a PGP inhibitor like Ledipasvir. So be careful about giving Ledipasvir with digoxin. Doesn't affect cyclosporine or FK506 and so you can give it when people who are liver transplant recipients. And this is just a list of the PGP and BCRP substrates that you might have to worry about with Ledipasvir. Okay, now probably most of us are moving away from using Ledipasvir to using Velpatasvir because it's got a broader coverage for different HCV genotypes.

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So it's a drug that has roughly the same safety profile, it's a very safe drug. But it has a much better activity profile and so the combination of co-formulated Sofosbuvir and Velpatasvir is replacing the combination of Sofosbuvir Ledipasvir in most settings.

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But what do we know about Velpatasvir and it's drug interaction potential? Well in terms of its metabolism it's actually an awful lot like Ledipasvir. It's a drug-transport protein substrate. It is metabolized. Its metabolites are predominately excreted in the feces and it's not renally excreted. So it's got the potential to be affected adversely by inducers of these drug metabolizing enzymes but it is also like Ledipasvir an inhibitor of the same three drug-transporters P glycoprotein, breast cancer resistance protein and organic anion transporter 1B13. So it really has a drug interaction potential that is very similar to that of ledipasvir. Sofosbuvir we know increases Tenofovir concentrations because of its impact on drug-transport proteins.

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So here's a study that looked at that. These are Tenofovir concentrations on the y-axis in the presence of Ledipasvir and Sofosbuvir with or without these various antiretroviral drugs. So when you give Tenofovir with Efavirenz or Rilpivirine the concentrations are shown on the left. When you add Ledipasvir, Sofosbuvir the Tenofovir concentrations go up. And that's whether the ATR is Atripla and CPA is the Rilpivirine/Tenofovir Emtricitabine/Complera co-formulation. Okay. With Ritonavir-boosted PIs you really see much the same thing. We know that Ritonavir-boosted PIs can increase Tenofovir concentrations and that's shown here compared to the Efavirenz containing regimens on the far left. And when you add Ledipasvir/Sofosbuvir for the most part, you get a further 50 to 30% increase in Tenofovir concentrations. So you really get a big boost in Tenofovir concentrations with Ledipasvir/Sofosbuvir. Especially if you're using that drug with Ritonavir-boosted PIs. And Cobicistat-boosted PIs would be the same, much the same.

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So the current guidelines on using Sofosbuvir/Ledipasvir with Tenofovir given as TDF the old pro-drug, is to avoid these combinations in people who have baseline Cr and an estimated Cr and clearances of less than 60. So that's somebody with pretty significant renal insufficiency. The combination of Sofosbuvir/Ledipasvir and Tenofovir should be avoided with Ritonavir-boosted PIs unless you can't change the antiretroviral regimen and the urgency of treatment is high. So what do you do if you have to give Sofosbuvir/Ledipasvir with TDF and a Ritonavir-boosted PI? Well, you monitor. And what do you

monitor? Well, there's a lot of controversy about this. So what most people will say is do baseline tests for tubular function.

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So that would be an estimated Cr and clearance. Electrolytes and urinary protein in glucose. And then monitor every two to four weeks once you start combination therapy. Including estimated Cr and clearance in urinary protein in glucose. And consider stopping therapy or switching to something else if those things start to go up. How far do they need to go up before you switch? Nobody knows. This is providers judgment. So I personally don't think that's particularly helpful.

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So how dangerous is it to actually use Tenofovir with Sofosbuvir/Ledipasvir in the real world? Well it turns out it's probably not all that dangerous. In part that may be because you're only giving this combination in most patients for 12 weeks. And it takes a while for an elevated Tenofovir concentration to lead to tubular dysfunction in most people.

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And that's confirmed by the study that was presented a little less than a year ago at CROI. I'm not sure if this has been published yet I think it's been submitted. But this is a study that looked at the estimated GFR in groups of patients who were taking Tenofovir with Sofosbuvir, Ledipasvir with or without Ritonavir-boosted PIs. So there were 44 patients in this study taking Tenofovir without Ritonavir or Cobicistat and 25 who were taking it. And what you can see is that at the end of treatment the estimated GFR in these two groups. So the EFR went down a little bit in everybody not very much but the estimated GFR was not all that different in these folks comparing the un-boosted to the boosted regimens. And if you looked at people whose estimated GFR dropped to less than 70. That was a very rare event. 4% with un-boosted Tenofovir and 12% with Ritonavir-boosted Tenofovir. Although, there were three events here as compared to really only one on study event here. And this is just the plot of these two groups over time. So in unselected patients, who had normal baseline Cr and clearance there was a little bit of a drop when adding Sofosbuvir/Ledipasvir to their regimen. But probably not enough to change practice. And it looks like at least in this one study this was a in most patients, a very safe thing to do. Okay. What about Velpatasvir and a TDF?

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Well, a couple of interesting things happen with Velpatasvir in combination with ARVs. And I will say, my talk tonight is mostly gonna be about DAAs and antiretrovirals because that's where most clinicians in my experience have problems with drug interactions, with DAAs. Is understanding how to juggle a patient's antiretroviral regimen and their DAA regimen. So point number one. A big difference between Ledipasvir and Velpatasvir because Velpatasvir is partly metabolized by Cytochrome P450 enzymes you can't give it with Efavirenz.

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So Efavirenz and Ledipasvir is fine to combine. But Efavirenz and Velpatasvir leads to a significant reduction in Velpatasvir concentrations because Efavirenz is a hepatic drug-metabolizing enzyme inducer. So this changes how you think about using ARVs in people who are gonna be on the Sofosbuvir/Velpatasvir co-formulation. Other ARV regimens look quite safe. Here's Rilpivirine, FTC TDF. Here's Dolutegravir, here's FTC TDF Raltegravir. Really no change in Velpatasvir concentrations. Now

what about Tenofovir? Well these are Tenofovir concentrations and if you add Sofosbuvir/Velpatasvir you pretty much increase Tenofovir concentrations with all of these regimens. In fact, with the Efavirenz with the Atripla co-formulation you pretty much double Tenofovir concentrations in the presence of an Efavirenz regimen. So these dots here, the blue is the AUC area under the curve the yellow square is the CMAX or peak. And the triangle, the C tau is a trough. So C tau is the concentration at trough. And so what you can see is that Velpatasvir is increasing all of these PK parameters. So it's probably increasing Tenofovir bio-availability when you give Tenofovir orally as TDF. So that's potentially worrisome especially in somebody who starts with some baseline renal insufficiency.

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So here's a more detailed look at the combination of Sofosbuvir/Velpatasvir and a variety of now boosted regimens. So this is Elvitegravir/Cobicistat TAF Elvitegravir/Cobicistat TDF boosted Atazanavir, boosted Darunavir and boosted Lopinavir.

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And so again, same scheme. Blue circle is the area under the curve. Red square is the peak and green triangle is the trough. So Velpatasvir concentrations in the presence of all of these boosters you get a big boost with Atazanavir. 2.4 fold increase in concentrations. And that's probably because Atazanavir inhibits both drug-metabolizing enzymes and drug-transport proteins. Although the authors of this study who worked for Gilead their conclusion is that they don't think this increase is clinically significant based on what's known about the safety profile of Velpatasvir. Which in fact, it's a pretty safe drug. So what about the effect of Velpatasvir on these other antiretrovirals?

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So what happens with Velpatasvir. You get a big increase in Cobicistat concentrations curiously and again, that's probably because of Velpatasvir's effect on drug-transport proteins. But because the Cobi half life is short, only three hours the increase in concentrations over the course of a 24 hour dosing interval is only 20 to 30% even though the trough is increased by 100%. So again, the conclusion from the investigators who in this case, work for Gilead is that they don't think this is clinically significant and I think that's probably fair based on what we know about the safety of Cobicistat which is generally speaking, quite a safe drug except for its potential to induce drug interactions.

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So how about the effect of Velpatasvir on Tenofovir concentrations in the presence of all of these other drug combinations? And here, the conclusion is a lot simpler. It looks an awful lot like Ledipasvir. So one of the advantages of Velpatasvir over Ledipasvir is not decreased potential for drug interactions. It's pretty much got the same drug interaction profile as Ledipasvir. Now there's one exception in this study. This is again a study presented a little less than a year ago at CROI. And that is TAF. So what happens to Tenofovir concentrations if it's given as TAF? Well if it's given as TAF there's really not very much change. In fact, if anything there's a slight decrease in Tenofovir concentrations. So that looks pretty promising. The problem here is we don't have a comparison with Ledipasvir. We don't actually know what Ledipasvir does to TAF because the study was never done. And we also know that because the TAF dose is so much lower than the Tenofovir dose than the TDF dose. Maybe this is just simply a reflection of the fact that you're combining these drugs with a much lower dose of the Tenofovir pro drug. But it's encouraging if you have a patient with renal insufficiency and you want to treat that

patient with a Sofosbuvir/Velpatasvir regimen that you could use you could deliver the Tenofovir as TAF rather than TDF, and not worry about a drug interaction.

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So here's the summary from that study. It's safe to give Velpatasvir and Sofosbuvir with these NRTIs, Emtricitabine, TAF. It's safe to give it with TDF with the caveat that you need monitoring because the concentrations go up. Safe to give it with Rilpivirine. Safe to give it with all of the approved Integrase Inhibitors. Safe with Atazanavir, Darunavir and Lopinavir with the caveat that Atazanavir makes Velpatasvir concentrations go up a little bit more than two-fold. And safe to give with Cobi and Ritonavir. There's another problem with Velpatasvir. And that's also a problem with Ledipasvir we haven't talked about yet. And that is its interaction with acid-reducing agents.

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So Velpatasvir absorption is pH dependent.

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You need to separate antacids from Velpatasvir by at least four hours. You need to avoid H2-blockers. If you have to use them, give a famotidine dose or dose equivalent of 40mg BID or less. And avoid proton pump inhibitors completely. If it's critical, you can give an Omeprazole dose. You can give proton pump inhibitors at an Omeprazole dose of 20mg and make sure you administer with food. And these are the same restrictions that are already in the package insert for Ledipasvir. So this is something that flies under the radar screen that a lot of people don't think about when they're prescribing drugs for HCV. We're used to thinking about proton pump inhibitors particularly for antiretrovirals. You can't give Rilpivirine with proton pump inhibitors. But we haven't been used to thinking about this for HCV DAAs, and here's an example of a setting where you really have to start to think about this. Be very careful giving Sofosbuvir/Ledipasvir or Sofosbuvir/Velpatasvir, with acid-reducing agents because of the deleterious effect on the concentrations of the NS5A inhibitor. And if you want to make sure you're gonna cure your patients either get them off of these drugs for 12 weeks. Make sure they separate these drugs. Make sure they, if they're taking antacids separate by four hours. Or make sure you use the lowest possible dose of the acid-reducing agent while they're on their 12 weeks of HCV therapy.

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Let's talk a little bit more about TAF. Shouldn't we always be using TAF instead of TDF when we try to cure HCV? Well I'm not gonna answer that question but I'll talk to you a little bit about why TAF has some real advantages over TDF when it comes to drug interactions.

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So here's the scheme for the metabolism or the pharmacology, if you will. The absorption and uptake of the different ways of delivering Tenofovir. So Tenofovir, if you give it as the nucleoside the bare nucleoside, it's just not very well absorbed. In part because of its chemistry but in part because it's a substrate for exclusionary drug-transport proteins. TDF is rapidly absorbed, but it's converted very quickly in the plasma to Tenofovir and it's the Tenofovir that gets taken up into the target cells where HIV resides. But TAF is very different. TAF is well-absorbed, but it does not get converted to Tenofovir in the plasma. It gets taken up into the cells as the pro-drug TAF which is then rapidly converted to Tenofovir which is phosphorylated and exerts its anti-HIV effect. TAF can be given at a much lower dose because of this. Because it's so well-absorbed. Because it's well-absorbed and efficiently taken up into

cells. It's given at about one eighth the dose of Tenofovir. Or achieves one eighth the concentrations of Tenofovir in the plasma. The assumption is that because the Tenofovir plasma concentrations are so much lower the renal tubular toxicity is also lower because the component of Tenofovir that's causing renal toxicity is the parent unphosphorylated drug being taken up by renal tubular cells and exerting toxicity on those cells.

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And this is just a look at the comparative concentrations of TAF vs TDF when combined with drugs that are known to boost plasma Tenofovir concentrations. Namely, Cobicistat and Ritonavir. So here's TAF in the purple and here's TDF in the red. And what you can see is that Tenofovir concentrations in the presence of Sofosbuvir and Ledipasvir when combined with Cobicistat were increased by 27%. But because you start at such a lower level it's felt that this is still a safe combination. So the area under the curve for Tenofovir delivered as TAF instead of TDF was only 20% of that seen with, for example an Elvitegravir Cobi TDF co-formulation. So that's it, that's all I'm gonna say about Sofosbuvir, Ledipasvir and TDF. Now I want to move on to a couple of the other newer DAAs and DAA combinations.

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And let me say a few words about the Abbott 3D and 2D combinations Paritaprevir, Ritonavir, Ombitasvir and Dasabuvir with antiretroviral drugs. So here's the metabolism and renal elimination profile for these three drugs.

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Several of these drugs are substrates for drug-metabolizing enzymes. So this is very different from, for example Sofosbuvir and Ledipasvir. And several of them are also either substrates and/or inhibitors of drug-transport proteins. However, because these drugs have to be given in combination with Ritonavir as a boosting agent for Ombitasvir the drug interaction profile of the 3D and 2D combinations are overwhelmed by the impact of the Ritonavir.

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And so, not surprisingly, if you give these drugs with nucleoside analogs FTC Tenofovir you don't see much of an effect because Ritonavir doesn't have much of an effect on nucleosides. If you give these drugs with Raltegravir you don't see much of an effect because Ritonavir doesn't affect the enzymatic pathways that affect Raltegravir. If you give these drugs with Rilpivirine you do get a significant increase in Rilpivirine concentrations because of the Ritonavir and therefore that's not recommended because of the theoretical concern increased Rilpivirine concentrations. What about other antiretrovirals? What about boosted PIs?

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Well, there's one big problem with boosted PIs where the booster is Ritonavir. Because you're already taking Ritonavir with your 3D or 2D. You have to stop the booster that you would have normally combined with your other protease inhibitor. So for example, Atazanavir or Darunavir you need to stop the extra Ritonavir. With Lopinavir/Ritonavir co-formulation the recommendation is not to co-administer with 2D or 3D because you can't pull the Ritonavir out of the Lopinavir/Ritonavir colitra co-formulations. What about Darunavir with the 2D or 3D regimens?

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Well here's a real world study from a year ago at CROI looking at the combination of boosted Darunavir with 3D with Ombitasvir/Dasabuvir and Paritaprevir with or without Ribavirin. And what they found was that there was a reduction in Darunavir concentrations which is seen when you give these drugs with Darunavir in healthy volunteers. But despite that, 100% of these patients achieved SVR so their HCV was cured. Two patients had HIV blips between 40 and 200 copies per mL. But those did not appear to be related in those patients to reduced Darunavir exposures. And so the conclusion here was that it looks like at least in this first cut of the combination of these drugs in patients with HIV, HCV co-infection their clinical outcomes were quite good with respect to both their HIV and their HCV. So that's reassuring. There is a larger Phase 3 study that is in process that I think is gonna be presented at CROI in February.

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So let's move now to the new MURC Anti-HCV DAA combination Grazaoprevir and Elbasvir. What do we know about the pharmacology of these two drugs?

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Grazoprevir, it's a HCV protease inhibitor. It's metabolized in part, and mainly excreted in the bile. And again, this is a recurrent theme. Effective HCV DAAs tend to be excreted in the bile and that probably is telling us that these are drugs that are getting concentrated in hepatocytes where we want them to be concentrated. No detectable circulation metabolites and minimal, less than 10% renal excretion. But Grazoprevir as a protease inhibitor is a substrate for cytochrome P453 A4. It's also a substrate for OATP 1B1/3 this drug-transporter we talked about earlier and a potential inhibitor of breast cancer resistance protein and CYP 3A4 although a weak one.

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Elbasvir is a similar story. It's an NS5A inhibitor. It is also partially metabolized and mainly excreted in the bile. Less than 10% renal excretion. No detectable circulating metabolites. And like Grazoprevir, it is a substrate for cytochrome P450 3A4. So this two drug co-formulated combination is very different with respect to its drug interaction potential from the Sofosbuvir combinations. Sofosbuvir/Ledipasvir or Sofosbuvir/Velpatasvir in that both of these drugs are substrates for hepatic drug-metabolizing cytochromes. And specifically 3A4, the enzyme most commonly involved in human drug metabolism.

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So that explains their drug interaction profile. Don't give Grazoprevir and Elbasvir with strong cytochrome P450 3A4 inducers like the anti-convulsants and the rifamycins I just described for the Sofosbuvir combos. So those drugs, the strong enzyme-inducers are just bad news with HCV DAAs in general. And you either need to figure out alternatives or treat those patients with an alternative DAA regimen. Strong cytochrome P450 3A4 inhibitors like Ritonavir and Cobicistat can increase the concentrations of these two drugs and also should be avoided. Grazoprevir and Elbasvir increase Tacrolimus concentrations by a small amount, about 43% and midazolam by about 34%. We don't know what the mechanism of that is and so it's a small increase and it probably it's okay to give these drugs with those drugs. But it's an indication that there's possibly something going on with these drugs in the drug interaction arena that we don't really understand yet. That includes the fact that these drugs can increase statin concentrations. In fact, they can increase atorvastatin concentrations by almost two-fold. Rosuvastatin by a little bit more than two-fold and rosuvastatin I think is Crestor and pravastatin

by not so much, only about a third. But you need to be careful in using Grazoprevir and Elbasvir in patients on statins. And this was a question you were asked in your pre-test and most of you got it wrong. So when you go back and answer that question after the session tonight. Make sure you remember that Grazoprevir and Elbasvir can increase statin concentrations by an unknown mechanism because it's potentially clinically significant particularly in patients taking high dose statins. And so you may either want to compensate for this by lowering the statin dose or perhaps for example, if you can change the statin from something like atorvastatin or rosuvastatin to pravastatin for 12 weeks. Efavirenz again, is a bad actor with Grazoprevir and Elbasvir as it was with Velpatasvir. Efavirenz decreased the Grazoprevir area under the curve by over 80%. And so don't give Efavirenz with these two new drugs. And again, that's probably related to induction of drug-transport proteins.

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I'm gonna finish with treatment of acute HCV infection. It's not something we often think about. Some of you may see patients with acute HCV and you may wonder about treating them. There was a study presented last year at CROI on the benefit of Sofosbuvir and Ribavirin for acute HCV infection. They use Efosrivir Ribavirin because historically, acute HCV infection's easier to cure than chronic HCV infection and they thought maybe this would be enough.

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It turned out to be quite disappointing. This is the HCV RNA, and a bunch of patients on a study with acute HCV infection. All of these people had their HCV suppressed at week 12 when the treatment was stopped. But the majority of them rebounded. 60% of them rebounded. So very disappointing result. And in fact, that outcome was no better than using peg/riba for acute HCV infection. So why didn't this combo work any better than peg/riba for acute HCV infection?

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Well here was a study, again presented at last year's CROI. Trying to understand why Sofosbuvir Ribavirin did not work for acute HCV. And what this figure is looking at is Ribavirin concentrations in these study participants. And they looked at Ribavirin concentrations in plasma and red blood cells at week two, week four, week eight and week 12. And the red circles are the people who had an SVR. They're in the 40% who were cured. And the blue squares are the people who relapsed. And what you can see here is that the people who relapsed actually had lower ribavirin concentrations. Low ribavirin concentrations are a bad thing if you're trying to use ribavirin to cure acute HCV infection. Now, the interesting question is why? Is this simply a surrogate marker for poor adherence? Or is there something specific about this 60% of the acute HCV patients who participated in this study that led to them having significantly lower ribavirin concentrations in plasma and cells. And the answer is nobody knows. Presumably this is related to adherence although, in this study adherence was monitored by self-report and adherence by self-support in this study was quite high and there was no difference in self-reported adherence between the relapsers and the curers.

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So that's the end of what I wanted to share with you tonight. I do want to thank Jennifer Kiser at the University of Colorado. My long time collaborator who shared with me some of these slides, including the primary data from her Ribavirin/Sofosbuvir studies. Thank you for your attention.
(audience applauding)
[Video End]