WEBINAR VIDEO TRANSCRIPT

Partnership for Care HIV TAC

Drug Interactions in Managing HIV/HCV Co-Infection

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STEVE LUCKABAUGH: Good afternoon. My name is Steve Luckabaugh and I'd like to welcome you to the Drug Interactions in Managing HIV/HCV Co-Infection Webinar. This webinar is brought you by the Partnerships for Care HIV Training, Technical Assistance, and Collaboration Center, or HIV TAC.

The partnerships for care project is a three year multi agency project funded by the Secretary's Minority Aids Initiative Fund and the Affordable Care Act. The goals of this project are to, one, expand provision of HIV testing, prevention, care, and treatment in health centers serving communities highly impacted by HIV, two, to build sustainable partnerships between health centers in their state health department, and three, to improve health outcomes among people living with HIV, especially among racial and ethnic minorities.

The project is supported by the HIV Training, Technical Assistance and Collaboration Center, or HIV TAC. Our speaker today will be Dr. Christopher Keeys. Dr. Keeys is the co-founder and president of the Clinical Pharmacy Associates, Inc, and co founder/CEO of Mednovations, Inc. He is a licensed pharmacist, clinical pharmacist, and educator who received his bachelor's of science in pharmacy from Howard University College of Pharmacy, and a doctor of pharmacy degree from Philadelphia College and Pharmacy, and he is board certified in pharmacotherapy.

Dr. Keeys completed his advanced training as a research intern with the Food and Drug Administration, and as a clinician at the Washington Hospital Center. His professional accomplishments include directing both the clinical drug studies for Washington area research group and the clinical pharmacy and drug information program at Greater Southeast Community Hospital in Washington DC.

Dr. Keeys has served on the boards of the Washington Metro Area Society of Hospital Pharmacists, as president of the Drug Use Review Board for Washington DC, and the Chesapeake Research Review Inc. He has also been a member of the Agency for Health Care Policy and Research Group in Clinical Practice Guidelines.

Dr. Keeys is a clinical preceptor at the University of Maryland, and holds an adjunct associate professor faculty appointment at Howard University College of Pharmacy. He serves as a clinical consultant for the Washington DC Department of Health Administration for HIV/AIDS Policy and Programs. He has served as a research fellow at Howard University Center for Minority Studies

and Health Care Services, and he has lectured and published in the areas of drug information, therapeutics, HIV/AIDS quality improvement, medication errors, formulary, management, telepharmacy, and patient safety. Please join me in welcoming Dr. Keys.

CHRISTOPHER KEEYS: Good afternoon, and I thank you for that introduction. I welcome you to the presentation on drug-drug interactions between direct acting anti-virals and antiretroviral therapy and HIV/HCV co-infected patients. I'd like to recognize the collaborative work of my practice fellow Dr. Chen and the completion of the material for today's presentation.

Just by way of disclosure, we have no conflict of interest to disclose with regards to today's presentation. We're excited to be able to discuss what is an extremely timely and important topic. It is a vast and complex topic that has immediate implications for the care of HIV infected individuals, and it's vital knowledge for anyone who's involved in assisting patients in HIV treatment.

But we have some specific objectives for today, and they include to identify the basic epidemiology of chronic hepatitis C infection, and chronic hepatitis C and HIV co-infection in the population, to recognize the availability and clinical importance of newer direct acting antiretrovirals in the medical management of chronic hepatitis C and it's co-infection, to identify and discuss the importance of these new direct acting agents and antiretroviral drug interactions in the management of patients with chronic hepatitis C infection and co-infection, to identify and utilize basic pharmacology and pharmacokinetic information to minimize drug interactions in the care of our patients, and lastly, to recognize and support medication management strategies that limit drug interactions and adverse health outcomes for our patients.

We won't spend a lot of time on pathophysiology or epidemiology, but let's just highlight a few important epidemiologic facts regarding chronic hepatitis C and the hepatitis C virus. It's estimated that 2.7 million persons in the United States have chronic hepatitis C virus infection, and this includes all genotypes, which include 1, 2, 3, 4, 5, and 6. Approximately 75% to 80% of people who become infected with hepatitis C virus develop the chronic form of the infection. And this would be as opposed to what we see in the case of hepatitis A or hepatitis B. I would add that on a global level there is estimated to be over 170 million people infected with the hepatitis C virus, as well as-- so you see there's a global problem as well as an important infectious disease and public health problem here in the United States.

Regarding screening-- people have risk factors in the community, and they're important for screening of high risk individuals, as well as all patients who are HIV infected. Displayed before you is a characterization of the frequency of risk factors and the majority of patients infected with hepatitis C virus. IV drug abuse, or IV drug users is by far the leading category at 60% of the estimated infections, and sexual exposure related transmission, as well as other types, which include occupational exposure and perinatal exposure round out the pie chart with respect to the risk factors.

Let me also hasten to remind you that recipients of blood transfusions and organ transplants before 1992, when we had no reliable screening methodologies to detect a hepatitis C infection, is another risk factor. And in the last couple of years, the CDC has called for testing for baby boomers, those born between the years 1945 and 1965, in as much as the incidence of hepatitis C infection in the population born in those years is about five times higher than any other adult population, and represents about 75% of all of the hepatitis C infected individuals in the United States are born in that period that we refer to commonly as the baby boomers.

About 50% to 90% of our HIV infected individuals who have IV drug abuse are coinfected with hepatitis C virus, as it is the most common mode of transmission. Depending on your population, it may vary, but overall, about 25% of all HIV infected individuals in the United States are coinfected with hepatitis C virus. Important to know, in terms of the seriousness of that statement, that there are some prognostic factors that we would like to remember with respect to the coinfected individual.

First of all, there's a lower rate of spontaneous clearing of the virus after an acute infection, due to low CD4 counts present in the HIV infected population. So just to punctuate that point, a portion of the population, in general, maybe 15% or so, will clear spontaneously the virus and not go on to a chronic state. But that rate of clearance is diminished in individuals who are HIV positive.

The co-infected individual has an accelerated risk of hepatic fibrosis, which is a poor marker for outcomes, including after transplantation, a liver transplantation, to be exact. There's a higher rate of liver decompensation seen in the co-infected individuals, especially in the absence of antiretroviral therapy. And these include conditions such as ascites, and spontaneous bacterial peritonitis seen in the decompensated, co-infected individual. And as you would expect, higher liver related mortality rates are seen in HIV infected patients. In some, data sets related to risk of mortality, hepatitis C represents the single highest cause of death in the HIV infected population in the United States, depending on the source that you're reviewing.

So we have a host of newer agents that came onto market in 2011 that fall into this category of drugs we refer to as the direct acting antivirals, for the treatment of chronic hepatitis C. And just briefly, we classify them but their site of activity. And so I'm going to just briefly share some of the nomenclature related to those classifications as they've been heralded as a dramatic improvement in our armamentarium for the treatment of chronic hep C, both in the general population and in the co-infected individual.

So in 2011, we had the introduction of both boceprevir and telaprevir, which are both classified as NS3-4A protease inhibitors. When given in combination with the standard therapy at the time, which was pegylated interferon, with Robert Varn., we saw a substantial improvement in the, what we target as the ultimate projector or measurement of probable cure, which is sustained virological response. And we saw a dramatic improvement with these two new agents.

In 2013, we obtained newer direct acting agents. And here simeprevir came on the market, also known as Olysio, and also we saw sofosbuvir, also known as Sovaldi brand name, that was approved by the FDA. You can see that we've had a very active, what we call, drug development pipeline, with respect to these drugs, because in 2014, continuing on the great development work that had been done in the management of this infection, we see that we have the introduction of a combination pill known as Harvoni, which is a combination of ledipasvir and sofosbuvir, and followed by the end of 2014 by another combination, which was actually a two part combination drug for treatment of chronic hepatitis C, which is ombitasvir combined with paritaprevir and ritonavir. And that's one product. The co-package in the same treatment with an agent called dasabuvir, and that whole product combined is known as the Viekira Pack That was brought on the market in December, 2014.

And then just this year during the summer, we saw FDA approval of two newer agents, which fall into this direct acting antiviral class, which are known as the daclatasvir, or Daklinza. And the combination drug, which you should recognize when I mentioned Viekira Pack, but it's missing [INAUDIBLE] and that is in your slide referred to as ombitasvir, pariteprevir, and ritonavir, which we know under the brand name of Technivie.

So you can see there has been a very robust onslaught of new and exciting direct acting antiviral agents that probably should have been a new era in our management of chronic hepatitis C in the mono-infected patient as well as the co-infected patient. Some of the slides with the information we'll share will be overview to keep us all together with some core principles around the pharmacology and the therapeutics of these drugs, and then we're going to interject, as much as possible, practical applications of that information.

So with respect to the management of the coinfected individual, we really have, in the beginning, in 2011, when we saw the introduction of teleprevir and boceprevir, the first group of oral, direct acting agents, we saw a real, just so called introduction of those therapies into the treatment regimens for the co-infected population. And a predominant reason for that was the many drug interactions that were observed or that were characterized between those newer agents and our antiretroviral therapies.

We also saw significant side effect profiles, which made it difficult, and sometimes too difficult to produce reliable treatment adherence regimens and outcomes in our co-infected individuals with teleprevir and boceprevir. But that being said, there were also problems in the beginning, in that FDA approval was not present for either of those two new agents with respect to coinfected individuals, as well as it was difficult to have good evidence to incorporate that information into our national guidelines, which in my last bullet on the left of the slide, highlights the US Public Health Service guidelines, as well as the American Association for Study of Liver Diseases, as well as IDSA, which is the Infectious Diseases Society of America.

So we had some nationally recognized expert guideline documents that we see clarity around the safe and effective management of the co-infected individual who has the chronic hepatitis

C. And we were challenged heavily around the evidence, in part because of these drug interactions.

On the right side of this slide is, mostly for your visual consumption, we introduced the major drugs within the different classes of antiretrovirals on the left side of the slide, meaning the NRTIs, such as abacavir, the NRTIs, such as the efavirenz or Sustiva, your protease inhibitors, such as atazanavir or Reyataz, and the entry as well as integrase inhibitors, drugs like dolutegravir, or Tivicay, as well drugs like maraviroc, or Selzentry.

So these represent our major armamentarium of therapies to treat our HIV infection. On the right, you see at the top in abbreviated forms, SIM, for simeprevir, DCV for daclatasvir, SOF for sofosbuvir, or Sovaldi, as well as you see the combination drug, which is Harvonia, which is second to the last. And then the last one on this 3D is an abbreviation for Viekira Pak.

What's useful about this slide is that while you're looking to the antiretrovirals, you want to note the landscape, how much green is on the chart, if you will, light pink or pale, and then how much is along the reddish shade. Red refers to contraindicated drug interactions, the lighter pinkish color is where there's a dose adjustment requirement and/or close monitoring. And then green is where we have evidence that there appears to be no significant drug interaction with respect to these combinations.

And so I do want, just for simplicity, for you to note that the drug at the top that's SOF, sofosbuvir, which is Sovaldi, as you look down, you'll notice out of all the antiretrovirals, it's green. Which is suggested that these drugs, particularly from what we call a pharmacokinetic interaction standpoint, though quite clean. Whereas, you can see that a drug to the far left, simeprevir, which is Olysio, it being NS3-A4 protease inhibitor, it has a lot of drug interactions with some of our major therapies to treat HIV.

So this is just one way for us to recognize we have some data, substantial data, which gives us some real warnings around the relative frequency of significant drug interactions associated with some of our major direct acting antivirals. I will spend very little time speaking about the first generation oral antivirals-- that is boceprevir. I mentioned as the 2011 approval an important new addition that did eradicate chronic hep C for many patients, but very few HIV coinfected patients.

So boceprevir and teleprevir are not really mentioned much throughout this presentation, because teleprevir is now off the market. It's disuse has prompted that withdraw, as well as there is boceprevir, which is still on the market, but now relegated to a largely historical drug with respect to the new direct acting anti-virals. And in fact, we anticipate in December for boceprevir to be removed from the market as well.

Not to panic about the technical diagram of this nation, but this is just a couple of quick reminders regarding the hepatitis C virus life cycle. And up in the upper left hand corner, we

have the virion It's required to attach to a cell. In this case it's a hepatocyte, which is a liver cell. And you're looking at the orange outer membrane. It has to attach to that membrane.

It undergoes endocytosis to be taken into the cytoplasm of the liver cell. Within the liver cell, this is a virus that must undergo replication within the hepatocyte. And you see that there is a process that's under way within the cell with the uncoding translation processing RNA replication, the reassembling of the virion particles, the maturation inside the liver cell, and then the discharge, if you will, from inside the cytoplasm of the liver cell back into circulation as a new virus.

So this replication is taking place, and this is obviously the area where we must have some targeted therapies to address the infection itself. Keep in mind that our earlier historic treatment, which included as I mentioned earlier, interferon product and ribavirin. Neither of those are recognized as direct acting against the hepatitis C virus. Though, they are an important part of some of the combination regimens that are being used today.

So just this [INAUDIBLE] on to thinking a little bit more, you'll often hear reference there's a lot of important distinctions between the drug that we were talking about drug interactions with. And so this is just a slide to speak to the fact that we have exploited our knowledge of the different, what we call non-structural proteins, that are found in the hepatitis C virus. And so you see [INAUDIBLE] you see various diagrams-- NS2, NS3, NS-4A. These are non-structural sites of protein sites that are being targeted by our anti-viral therapy to disrupt viral replication, maturation, and recirculation.

And so we have some overlap between the drugs in this regard. And so not to remember specifically where they act on non-structural proteins, but to be clear that they are acting within different target sites on the viral synthesis process to disrupt and can result in the death of the cell. And these are very powerful agents. Keep in mind that the virus that's found in circulation has a magnitude that's higher than the HIV virus that we see. And as much as our patients who have chronic hepatitis C often have viral loads that are in the millions, as opposed to the thousands or hundred thousands, as we typically see with HIV.

So just some practical information that's worth spending a few minutes on with respect to these drugs. If you're used to these therapies, then this will be a quick review. If you're not much experience with these agents, then this might be more helpful.

So just [INAUDIBLE] more common drugs, just to quickly show you. The simeprevir, or Olysio, which is still being used in practice, this gets us to the point of remembering that all direct acting antiretrovirals against a hepatitis C virus are not indicated for all genotypes. That's an example showing that genotype 1 and 4 is where simeprevir is indicated, meaning that's what it's approved to be used for by Food and Drug Administration based on it's safety and efficacy in trials. And it must be given in combination regimens, as do all of these drugs.

If it's not been said, it should be noted that like HIV, hepatitic C virus does require a minimum two drug regimens. And part of that is to treat not only viral suppression, but to reduce the chance viral mutation and resistance, which would be a major reason for treatment relapse in this population.

You can see also, most of these drugs are given once a day. And I'll mention whether or not they're more frequent. And there may a requirement in respect to food.

The next drug, Sovaldi, which, if you see any of these patients, this is a very common drug used. And at one point in the US this was the most common combination drug regimen for chronic hep C-- was Olysio with Sovaldi. Work by two different mechanisms, but Sovaldi is polymerase inhibitor, and it covers multiple genotypes that are found in the community respect to types of hepatitis C infections.

In itself, if given in combination regimens-- and it's worth noting that it is one of the [INAUDIBLE]-- actually, the first drug they got the FDA approval for not only the mono-affected individual, with or without cirrhosis, but it got the indication for the coinfected individual. And you see here it's once a day dosing. And there's common fear regarding dosage adjustments in patients with kidney and liver impairment.

Harvoni only has become a dominant drug in the care of the chronic hepatitis C infection. It is not a stated indication to use it in coinfected individuals. We are aware there's a landmark study that's come out that has supported its use and its high efficacy rate in the coinfected individual, so we don't see many programs or practices where Harvoni is being used in the HIV coinfected population. And this is specifically Harvoni for the genotype 1, which I failed to mention before, but it's the most common genotype associated with chronic hepatitis C infection.

Again, this is a fixed dose combination once a day. And it's convenient in that it doesn't need adjustments for mild to moderate degrees of kidney or hepatic impairment. And then for hepatic, it doesn't need adjustments for any of those degree of impairment.

Viekira Pak, which is a product that if also approved for the coinfected individual with genotype 1, is actually a four-drug regimen. And one of the drugs you may recognize as ritonavir, which is of course what we refer to as a boosting agent. It has no antiviral activity of its own at this low dose in milligrams or hundred milligrams, but it is used because it allows for increased absorption and achievement of higher blood concentrations, which are needed with other agents in this combination regimen, particular is paritaprevir. So hopefully you recognize ritonavir as a drug that's used in combination with our HIV protease inhibitors, such as Reyataz, or atazanavir, or darunavir, which is Prezista.

And then the two newest drugs which I mentioned were just approved this summer. And by the way, approval doesn't mean marketed. And so it takes sometimes a little while to be marketed. So these drugs were approved in the summer, but not immediately available. I believe that they

are available now or around this period. I have not seen individual [INAUDIBLE] receiving them, yet.

But declatsvir, or Daklinza, is a NS-5A protein inhibitor. Genotype 3 is specifically indicated for. And it has not been approved for the coinfected individual. But it's important to note that there has been one study, called the [INAUDIBLE] trial, that did show it to be active in coinfected individuals. And it's likely that Daklinza will be used in many patients for which genotype 3 treatment is being targeted with coinfection.

And then Technivie is a combination drug, as well, for genotype 4, which is infrequent in the population. But it is an important drug, because it represents the only combination regimen when given with ribavirin that can avoid the use of interferons or an injectable immuno stimulant, which is technically an interferon. So Technivie, it is not studied or known to be active or inactive yet in the coinfected individual. But as you'll see soon, the drug interaction profile of this combination regimen, Technivie, makes it a very challenging drug to use effectively and safely in the coinfected population.

Again more for your visual, not for detail. Consumption around the mechanism is important to remember a couple of principles. First of all, most drug interactions that are referred to when we talk about antiretrovirals, as well as antivirals for hepatitis C, are due to pharmacokinetic interactions. And those pharmacokinetic interactions reside largely because of the impact of different drugs in these classes on what we call, proteins that are associated with inducement, or metabolism of drug, or inhibition of metabolism of drug.

And just to back up one step, when we refer to pharmacokinetics, we're referring to what we call, the five phases of how a drug is handled by the body. And if think about an oral therapy, taking a pill or tablet, down it goes. First major phase is called absorption. Once it's absorbed into the body, or simultaneously is being distributed through the body, you have distribution, which is the second phase.

The drug itself will undergo metabolism. Most of these drugs, which means it's being biotransformed, primarily to break down and eliminate the substance. Sometimes it goes biotransformation to be active, and then subsequently be broken down. And then the last phase is excretion, which is elimination of the drug, or to breakdown products of the drug from the body.

For these drug interactions we're talking about, which there are many, the vast majority of the drug-drug interactions within these two classes of agents are due to the pharmacokinetics, and most of it resides at the level of metabolism of drugs. At the metabolism of drugs, we have what we call protein or enzymes, and I'll refer to them a little bit later. And we have transporters. And the slide reveals that in the case of an enzyme, we may have something that needs to attach to an enzyme. And if something inhibits it, it blocks the ability for it to attach. It alters its metabolism.

Or sometimes, there is something that will not block the site for the product or drug to attach, but it will change the conformation or the structure so that it cannot receive and attach appropriately. In either case, whether it's happening extracellularly, which is outside the cell, intracellularly, or inside the cell, or at the level of the cell membrane, we have a potential for there to be a pharmacokinetic interaction. And I think it's pretty common knowledge that we have-- with respect to antiretroviral therapies for HIV, as well as antivirals for chronic hepatitis C-- we have what we call, a therapeutic range, which is the concentrations that are needed to prevent replication of the virus or vis-a-vis [INAUDIBLE]. Ultimately, it's a blockage of replication. And that's with the virus.

And there are concentrations if it's too low, it won't work. And it may even induce resistance by the viruses. If the concentration's too high, it may very well be effective at inhibiting viral replication, but it also is associated with more toxicities. So we have this therapeutic range that we target in clinical care of patients, as well in our research studies.

And it's important for us to know about drug interactions, because if there are products that patients are commonly receiving, and if those common in therapies are inducing or inhibiting the way the body is handling the drug, then we have a real chance of there being lack of effectiveness or increased toxicity. And/or the inducement or the creation of resistance patterns.

This is a slide that looks really complicated, but I have a theme that I just want to share. How do we generate knowledge about drug interactions? I think that sometimes it's hard to actually believe that drugs can interact in a way that's predictable. Some of us see the studies, or have conducted the studies, and so we are a little bit more comfortable with that concept. Others can treat patients and never see a problem, or what is perceived to be a problem with an interaction. So you may get to the point where it's not believable.

But this is what happens in early investigation of the [INAUDIBLE] antivirals that we've been talking about, where we conduct sample pharmacokinetic studies. And this is an example of looking at paritaprevir and ritonavir, two of the agents that are in a couple of our projects, like Viekira Pak in Technivie.

And what we see here in patients who are being exposed to several different drugs, all to compare what happens to the blood concentration, what we call those therapeutic levels, those blood concentrations, when we introduce a second drug. So that when paritaprevir is being introduced to a drug like gemfibrozil, which is cholesterol lowering or ketoconazole, which many of you may recognize as an antifungal.

But what I really want you to pay attention to is carbamazepine, which is an important anticonvulsant [INAUDIBLE] in the past. But it's also used for a number of other conditions, such as tics and other neurologic disorders. Carbamazepine happens to be what we call, an enzyme inducer. And you can see with paritaprevir, we would have expected the levels to be right here around the middle line going down, like many of the other drugs are, but in fact, what we call, a

much lower concentration of drug in the body, in the blood specifically, because of the fact that carbamazepine has been given to that individual, has caused inducement of the enzyme, specifically, the enzyme is called cytochrome p453a4. And it resulted in a dramatic drop off in the blood concentrations of paritaprevir because of the presence of carbamazepine.

Ritonavir is similar in action, even more dramatic in terms of the drop. Roughly 1/5-- I'm sorry. Roughly an 80% drop in the blood concentration, because of the inducement by carbamazepine. But it's also important to notice many of the other drugs that we tested, sleep-aids like Ambien, diuretics like furosemide, cardiac drugs, that they didn't have an effect.

So we use this methodology of healthy subjects getting tested with two drugs to determine pharmacokinetic interactions as one of our ways of getting at a very important question which is, are there drugs for which they disrupt the blood concentrations, the tissue concentrations that we seek. And if that is so, we really need to know that, because unlike the few of our drugs, we do not follow blood levels of our direct acting antivirals in clinical care. So your patients do not get sent, typically, to a lab to measure levels of let's say, Solvaldi or Harvoni.

So we must use our pre-formed knowledge, and our clinical acumen, and our knowledge of pharmacology to identify how we handle these in advance, and what we do if we suspect interactions.

OK. This slide is useful for showing pictorially. No one's got to memorize these kinds of interacting issues, but here's a slide that deals with a topic I've already talked about, which is pharmacokinetics. Absorption, distribution, metabolism, and elimination. I think I said earlier that there's five. There's only four phases. So those are the four.

And so what you should readily see is that, when you look on the far left column, you look at the antivirals, you'll note that there are substrates they're metabolized by, and they're inhibited by different items. What I want to point out, these drugs have many, what we call, pathways by which drug interactions can occur. Simeprevir or Olysio would be a classic example of that.

Each of these represents a protein pathway that can be interfered with, that could change either simeprevir's blood concentrations, or the other drug that it's being combined with. P-glycoprotein, breast cancer receptor protein, organic acid transport protein, et cetera. CYP3A4. When you see this kind of activity of drugs that can interfere with the pharmacokinetics of any product, you know that there are a lot of drug interactions. And it's got to be carefully addressed in the care of patients.

Sofosbuvir is kind of on the other end. You can see that there are only two here. And the second one is really not that significant. So p-glycoproteins, this one that we pay a lot of attention to, it doesn't have CYP3A4 challenges. So only p-glycoprotein. That's dramatically different than simeprevir.

Just in these examples, you can see that our volume, which is a combination of sofosbuvir and another agent, ledipasvir, has also a very small profile with respect to which pharmacokinetic interactions could occur. Viekira Pak, on the other hand, significant number of potential interactions. Doesn't mean the drug is bad. Has nothing to with whether the drug is bad or good. It has more to do with what we can combine the therapy with, and what we have to do to properly and safely manage the patient.

The new agents this summer that we just talked about, daclatasvir, some interactions are present enough that this is a caution, a drug that has potential drug interactions. We have a summary of the drug's direct-acting agents, and antiretroviral interactions. And that slide that I introduced earlier on that was color-coded in green, red, and pink, that's a great slide for visual recognition of classes of antiretrovirals that are going to have significant, potentially significant, interactions with the direct-acting agents.

Just as a general reminder, most of the nucleoside and nucleotide reverse transcriptase inhibitors do not have many interactions. Tenofovir, on the side, when I say that for a moment. But in general, that's true. Most interactions that occur are occurring with the non-nucleoside reverse transcriptase inhibitors, protease inhibitors, which includes ritonavir at low doses of boosting agent, and the entry agents, such as Selzentry, as well as the integrase strand transfer inhibitors, like [INAUDIBLE], or raltegravir, or [INAUDIBLE], which is [INAUDIBLE].

So just as a general thinking that those are the groups of antiretrovirals where we have metabolic interactions that are substantial for many of these agents. And having said that, we're not going to go through every detail in the chart, but I do want to take time to talk about a few that are being used in practice.

Simeprevir is difficult to use in a coinfected individual. You can see that the antiretrovirals like Efavirenz or Sustiva or a Sustiva-containing regimen, such as [INAUDIBLE], as well as some of the other agents that are listed there are problematic. Including Stribild, which is a four-drug combination monotherapy. And because it has not ritonavir as a boosting agent, but it has cobicistat, which is another boosting agent like rionavir but with really no antiviral activity at any level.

Any ritonavir containing combination is problematic, in large part because these are agents that interfere with cytochrome 453a4. You can see here, the mechanisms. And so these are predictable problems. Some of them though, cause induction, which means the enzyme system speeds up and drops the levels of simeprevir. Some of them are [INAUDIBLE], such as cobicistat or ritonavir and we see levels going up in our research studies. Predictably go up. Not in everyone to the same degree, but they typically go up. And when you see numbers like 350%, that means more than three and a half times the levels that we see in individuals on simeprevir who aren't taking ritonavir-containing combination drugs.

And again, I dwell on this because it is not an uncommon observation in clinical settings for drug interactions to be not easily recognizable in clinical care, and difficult to believe if you've

not encountered any significant drama around a patient in terms of treatment failure. Which is hard to detect if it's a drug interaction, because we're not following the levels of the direct-acting antivirals. It would be more likely to be detected if it was a toxicity that was dramatically increased in a population. Clinicians will pick that up much quicker than they probably would a drop in levels.

So in all these combinations with Olysio just to read this complete, there are no significant effects on antiretroviral therapy. That's a great thing, and that's part of the reason why we tend to need our studies in the HIV community population, as well. Because there are examples of drugs that negate the effective activity of the drugs in clinical care. And so combination class of antiretroviral and antivirals, but it's important to be aware that in addition to the pharmacokinetic interactions, which we tend to be able to visualize because we can draw blood levels in research settings, have less capacity, but we need to be observing in studies whether pharmacodynamic interactions are occurring.

Those are interactions that manifest, largely, outside of the realm of absorption, distribution, metabolism, or elimination. And they are principally associated with things that happen at receptive sites. They can block activity, or they can antagonize activity. So that being said, our pharmacokinetic principles are most important in the discussion of today's subject of drug interactions, but at the end we'll see an example, one case where it's not a pharmacokinetic interaction that's suspected, but a pharmacodynamic interaction, which is more related to the effects of the drugs on tissue, organ, receptor sites that changes the pharmacology of the way the drugs perform.

Bottom line, for simeprevir, and I'm going slow on this one because this is a good example of the significant drug interaction story between these two classes-- bottom line is antiretrovirals work with this agent, but there's many drug interactions. So the groups that are listed on the far left, the antiretrovirals are not recommend to be co-administered with simeprevir because of what we discussed, the effects on blood concentrations increasing or decreasing.

I'll go more quickly through these slides, because we've kind of made the point. But I will share with you that Sovaldi is used in the coinfected individuals, and the drug interaction profile is cleaner, as it is with Harvoni. But particularly with Sovaldi, the problem-- and something to always remember, if someone's only on one drug for chronic Hep C infection, there's a problem, because these are not infections where we treat with a single drug. We may treat with a single combination drug, but not a single drug.

But here, what does stand out is tipranavir with ritonavir can decreases sofosbuvir levels, which you won't know in clinical practice, because we're not measuring them. So it is recommended to avoid. And fortunately, there's not a lot of tipranavir use in most settings that I'm aware of. And so it's not a preferred protease inhibitor in the treatment guidelines for the Public Health Service. So that's a good thing.

Harvoni, which is very popular as the patterns emerge and the way treatments are being done, and it's highly recommended within the guidelines for the settings where it's indicated. And as I mentioned, it is a drug that's used in coinfection, though FDA labelling doesn't specifically state that fact. The guidelines do.

And so we can see there are some drug interactions, and I want to dwell on tenofovir for a moment because I put that aside earlier when I was talking about nucleotides and nucleosides. And tenofovir there does seem to be an increase in tenofovir concentrations because of this Harvoni combination. And so we need to be cautious. Administration is not recommended with Stribild, and, of course, tenofovir is in many products, and Truvada leading the way probably. And we would want to be mindful that what we mostly are worried about with tenofovir being elevated is acute kidney injury, or kidney disease associated with increased levels of tenofovir. And see the other recommendations on this page.

I want to go to another drug, so let's go to the next page. So Viekira Pak, and we haven't talked about cost at all, but as we'll talk about in some slides to come, there is some important discussions around what clients will have access to. And Viekira Pak comes up. A couple reasons. One is because it's FDA approved within coinfected populations for specific genotypes. Genotype 1 is specifically one of them.

And you can see that because it has paritaprevir, which affects many of the pathways we talked about, many of those proteins. And ritonavir, which is a major drug when it comes to interfering with metabolic pathways. And even [INAUDIBLE] and [INAUDIBLE] have some drug interactions. So we have some significant concerns around antiretroviral combinations.

We need to dose atazanavir alone without giving ritonavir booster if they're on Viekira Pak. And that should be obvious, because they're already getting ritonavir. Otherwise, you'd end up with, an example would be, someone on Prezista, which is atazanavir, either alone or in a new combination known as [INAUDIBLE]. We would not see these two together, because fear from two different products. And this would the case if we just went ahead and combined someone who had been on ritonavir-containing atazanavir regimen. And then you gain the Viekira Pak. You have too much ritonavir on board, so that's to be avoided.

Rilpivirine is one to remember, because it is an inducer like carbamazepine, and it's not recommended. Elvitegravir, which is available both alone and in stride will be inhibited by ritonavir. And so they're not recommended to be given together. And cells entry [INAUDIBLE] can be inhibited by ritonavir and not recommended to be given together. So we do have the ability to use Viekira Pak in our coinfected population if we manage our antiretroviral regimen successfully.

Daklinza, as I mentioned, not specifically FDA approved for coinfected individuals. But there's one trial that's published and speaks favorably, as well as the [INAUDIBLE] from the American Association for the Study of Liver disease, and IDSA, they do have a place for this in the management of genotype 3 chronic Hep C. And you can see there are some concerns that result

in dose adjustment in combination with atazanavir to drop the dose. And there's a typo there. It should be daclatasvir to drop the dose to 30 milligrams. Or if they're on efavirenz, or etravirine regimen, alone or in a combination, induces the metabolism resulting in loss of levels.

So per FDA guidelines, we actually increase the dose from the usual 60 to 90. Fortunately, the Daklinza has a 30 milligram and 60 milligram tablet approved. So we can do the 30 milligram easily. We can do the usual 60 milligrams when there's not a drug interaction that's an inducer. And we can go up to 90 by giving a 30 and 60. But as you might imagine, that doubles the cost. You may not notice, but it doubles the cost of very expensive therapies if you use the 30 milligram tablet and a 60 milligram tablet to reach the 90 milligram dose for someone on efavirenz or etravirine.

Now, we've been talking about direct-acting agents in combination antiretrovirals. Because our HIV patients are often on other therapies, we clearly attention to them. This is not a presentation to go through all the other potential drug interactions associated with the direct-acting antivirals. But just some examples that are worth noting very quickly.

When patients are on ribavirin, which is a combination used with drugs like Viekira Pak, it's a pregnancy x-category drug. And so women have to be with effective birth control. So oral contraceptives is one of those. And it has some drug interactions that we have to take into account.

Similarly, if we have immuno-suppressive therapy for transplant patients, there are drugs with very tight, what we call narrow therapeutic margins, such as cyclosporine and tacrolimus, and so we must be mindful of the drug interactions that can emerge in use of our direct-acting antivirals.

Depression seen easily with interferon-based regimen that are for treatment of Hep C. And that's something that still can be used, although it's declined a lot in practice. We have to be concerned about inhibition drug interactions. Individuals who are, we mentioned IV drug abuse is a high risk for Hep C condition, and those who are on Methadone maintenance programs, it's a CYP3A4 substrate, so interactions have to be considered. And obviously, this product has a narrow therapeutic margin with inhibition of CYP3A4, causing methadone levels to go up. You can have an opiate overdose.

Digoxin. Some of our patients, typically our older patients, or patients with heart failure or arrhythmias, may require digoxin. We, fortunately, can follow blood levels clinically in the practice setting because of some drug interactions can occur with our direct-acting agencies.

The statins, like Lipitor, or Crestor, and all these statins that we have. Clearly, some of them are being used for just patients with co-morbidities of hypercholesterolemia. But we also may see individuals who are receiving the statins to manage the hyperlipidemias associated with the antiretrovirals, such as many of the protease inhibitors or the boosting agents, like ritonavir. And so we need to be aware that there could be a substantial drug interaction in statins, which

can have difficulties with tolerance in some people. They can be a serious risk of things like rhabdomyolysis. If some of the statins go too high, it can cause muscle kidney injury, and put patients in hospital with this extreme.

And then our patients who are on prophylaxis for opportunistic infections, particularly Biaxin or clarithromycin. But azithromycin is less of a problem, but we do have interactions there that we need to be mindful of, as well as if patients are on azole antifungal agents like fluconazole or ketaconazole or the like.

So when we have two drugs, we have a tighter story of how to manage drug interactions. If we have three, four, five, the research tends to be not robust enough to greatly predict the consequence of a mutli-drug interaction. And so in that case, we have to use our training and skill, and we have to try to navigate away from them as much as possible.

In the early slide when we were talking about the objectives of today's presentation, we used a term, which is commonly used in systems approach to medication, which is called medication management. And medication management has a few major steps involved.

The first one is prescribing. The idea of selecting an agent that's appropriate for an individual. And we've been speaking today principally around the drug interaction concerns, and therefore, that's a dominant reason for the prescriptions or the orders that will be placed to treat patients with direct-acting antivirals in the coinfected state. We also want to remind our listeners that we have to know what the genotype is. We need to know it's consistent with FDA labeling. And usually, it's consistent with FDA labeling and with guidelines, such as the Public Health Service in the case of management of chronic Hepatitis C.

Much of the Public Health Service references to the American Association of the study of liver diseases in IDSA, which are leading the way in the evidence-based, inquiry [INAUDIBLE] to the practice of managing the chronic Hep C individual.

We do have to pay attention to comorbidities in addition to the HIV status. Prior treatment is an important consideration. The stage of fibrosis is usually weighted in terms of the risk benefit because it is an important prognosticator of the advanced conditions of Hep C, which include obviously, cirrhosis, [INAUDIBLE].

Prior to 2011, our regimen were based on injectable regimen led by interferon. Today, our regimen are principally oral. And there are some combinations with both. Duration of treatment is an important part of the consideration in drug interactions. Drug interactions can affect the duration, but we typically have durations based on standard evidence. Eight weeks, 12 weeks, 24 weeks, 48 weeks. [INAUDIBLE] on the clinical setting.

Contraindications and ones with cautions are critical, as well as adverse drug events. We have done a phenomenal job in our care models for trying to minimize the adverse events and the morbidity and mortality that can be associated with antiretrovirals for HIV. And we're working

very hard to do the same with the direct-acting antiretrovirals for Hep C. So this remains a very vital part of overall quality of care rendered to our clients.

And then access. I mention this because these direct-acting agents have brought great promise, and in fact, delivered on the promise for many patients of today. Many of you are aware that they represent one of the most expensive treatment regimen released in the US, with single-dose tablets of some of these combination regimens being $1,000 a day. So we have regimens that can be $75,000 to $150,000 or more to treat a single patient with direct-acting antiretroviral drug.

Cost varies, as well as the formulary status of these drugs. So that helps to define the prescriber's decision making is what's available within the benefits for pharmacy products.

I bring up the second step, which is dispensing. And I should've said in the earlier slide, but no need to go back. Prescribers benefit from having electronic prescriptions generated, especially if they allow for drug interaction checking to be done at the prescribing environment, or electronic health record. Pharmacies have also electronic pharmacy profiles and drug interaction screening. It is something that's common and part of the standard of care for pharmacy practice to appropriateness of selection of agents. While we're continuing to be responsive to [INAUDIBLE] patient access to drugs. Let's say, in the acute care, ambulatory setting, as well as they may move through a continuum of care between whether it be incarceration or at a nursing home, or to a nursing department, or a hospital, a skilled nursing facility.

But the dispensation of the drug is a key point where drug interactions can be done. That requires a complete and up to date patient medication list, including over the counter products and herbal products. Something that was on an earlier slide that I did not emphasize is St. John's wort which has been a commonly used herb for management of mood, typically depression, that is a major inhibitor. Think of it like ritonavir with respect to its drug interaction capabilities.

And there are other herbs that we have to concern ourselves with. So that's part of the practice actually at both prescribing and at dispensing. At transitions in care, we see disruption. One of the most notorious times where disruption in care in terms of drugs and the appropriateness of drugs is at times when they transition. Let's say, out of hospital or into the hospital. Or between care settings, or even between providers. Change doctors, go to different providers, and different prescriptions are generated. So medication reconciliation is a process that's critical to screening and to maintaining the integrity of the regimens that are deployed for chronic Hep C.

Particularly around a drug interaction, because we have to communicate with prescribers and other health care providers. And providers have to speak to pharmacists. And patient education needs to be there, because we have characterization from our research both the pharmacokinetic studies done before marketing, what we call phase one, two, and three trials. And also after marketing, in what we call phase four, or pharmaco-vigilance trials.

But we do need to listen to our patients. And particularly around adverse events, around adherence. It's difficult to determine treatment failure from listening to the patients in the role of dispenser. But it is something that we are also aware of.

And then again, education around direct-acting agents because we have come out with more to come. They are representing dramatic outcomes, but there's some safety concerns. There's evolving [INAUDIBLE] a couple of studies to show that. But it's something that remains a critical point of optimal health care.

We talked about the prescribing. We talked about the dispensing. The next [INAUDIBLE] management process is administration. And we have, mostly for my FDA approved package labeling and guidelines, we get some guidance. If it needs to be revisions to that, it typically comes out slowly. But the administration of drug is a point where we do concern ourselves about drug interactions, particularly as it relates to bioavailability or the absorption of drugs. I want to hasten to say that, with respect to antiretroviral and direct-acting antiviral drugs, that the administration phase is not a phase where we see a lot of activity on this end, but I do want to share some points that you check for and be thinking for in regards to interactions that affect absorption.

One may be if there's anything common in medications that should not be administered at the same time. There are plenty of examples of that in antiretrovirals. Several good examples. One would be Complera or rilpivirine where protein pump inhibitors like Prilosec, and Protonix, and lots of drugs just cannot be given with it without impairing absorption and the ability to eradicate the virus. So we do pay attention to that. That's not the case with any of the direct-acting agents today.

Spacing of medication, we ask is that important? Specifically for the direct-acting agents. We have no strict guidance around that for drug interactions that affect absorption. [INAUDIBLE] several slides that spoke to whether they should be taken with or without meals. That's an FDA labeling that should be adhered to so that absorption is maximized based on the taking or and not taken with meals. And that's been developed through the drug development process, and emerges as part of the approved FDA labeling.

If there's any time the daily timing of medication administration that maximizes benefits, it usually will convey that. That doesn't seem to be the case with this class. As well as if there's any timing of medication administration that minimizes adverse events. Such as if it's to be taken in the morning, or in the afternoon, or in the evening. It comes up in clinical practice, and may not be readily recognized, often is not with direct-acting agents when the clinical trials take [INAUDIBLE] drug to market.

If it's used in pediatrics, for which none of these drugs are currently FDA approved, but which there clearly will be tube feeding, and how we navigate the administration of drugs for the absorption, and there's no drug interactions there. Swallowing. And then, if there's a chance

that there's drugs that [INAUDIBLE] sound alike that could cause medication errors to drug interactions, then we would pay attention to that.

One example of that would be Viekira Pak, which is for Hepatitis C, sounds like the brand name for [INAUDIBLE] like [INAUDIBLE], which is called, and they look very similar when you see the two names side by side.

We're coming toward the end. I just want to--

Monitoring is the phase here. And speaks to something I think we're readily aware of, which is adherence. We need to monitor for adherence with the direct-acting agents in the coinfected individuals. That includes the ongoing monitoring for the [INAUDIBLE] on a virus, which is typically quantitatively tested at week four, and re-evaluated at week six, looking for suppression or consideration of stopping the drug, or adjusting the therapies.

Week twelve is typically [INAUDIBLE] for which therapy is required to continue longer, primarily because of things like cirrhosis or transplantation. And those go out typically 24 weeks, but can be as long as 48 weeks depending on the drug. We also look at other measures that go beyond the scope of the day, but there's other measurements of adherence, such as prescription fill records, refill records, something we refer to in pharmacy as mean possession rates. And then direct observation of whether patients are taking their medications properly.

We need to be aware of the toxicities. As I mentioned, that will be something we will note. If levels are going up because of drug interactions, or interaction is clearly one of them, we should be doing laboratory monitoring for those that are recommended by the FDA, such as CBC counts, basic metabolic panels, liver functions tests, and bilirubins.

And then in the case of typically, liver enzyme elevations, because we were talking about Hepatitis C, that we look very closely at that as part of the disease monitor as well as the drug monitor. And we see significant elevations in our liver enzymes, such as AST, or hyperbilirubinemia, which is clearly associated sometimes with antiretrovirals by themselves, such as atazanavir but they can be worse in combination with direct-acting agents. That something that's a point of distinction in terms of monitoring for toxicity.

The adverse events here. I think, a couple of very broad statements. One is that there is clearly hepatotoxicity risk that is infrequent, but should be thought of with the direct-acting agents. And would be one of those things as I just mentioned as part of the monitoring that goes on at medication management for detecting drug interactions that could be problematic. Some of the more common ones are listed on this slide, such as fatigue, headache, nausea.

In the case of skin reactions or photosensitivity, simeprevir/Olysio is a problem there. We should be aware of that. And the last one, we have a case to emphasize, but amiodorone, a cardiac drug which is commonly used for arrhythmias, is a problem combination drug, which we'll talk about in a moment with some of our therapies.

OK. A couple of themes to drive home some of what we discussed. Appreciate the potential for drug interactions. This is a study by Patel, et al., that was conducted in 2015, where they looked at HIV-Hep C coinfected patients. Patients in their medical record that they were on the lexicon drug interaction software, which is a authoritative direction screening tool that's used commonly in practice.

And they documented how often, and what types of contraindicated drug interactions were identified before and after [INAUDIBLE] of either simeprevir or sofosbuvir to the regimen. Before any Hepatitis C regimen was introduced to the HIV population, they had 20% of patients had a contradicted drug interaction noted. Addition of simeprevir, it went up to 88.4% of patients had a contraindicated drug interaction. Contraindicated, in all of our minds, that it's not to be given. These two products are not safe to give together. And it's rarely a justification for giving the two together, so it shouldn't be done.

Sofosbuvir had a much better story. It went up to 24.5%, consistent with earlier statements I made, which is sofosbuvir is less likely to cause significant drug interactions. Simeprevir much more problematic. But the use of drugs for chronic Hepatitis C treatment was, in either case, increasing the potential of patients to have contraindicated drug interactions, which brings about safety concerns, as well as diminished efficacy of the drugs to treat the Hep C. So screening is critical in detecting the potential for contraindications before patients are initiated on therapy.

This slide is emphasizing how we predict interactions. And I've kind of already went to this point. But I do want to make sure that we again, emphasize we have, in the FDA labeling, which therefore means would be in all the authoritative references, specific dose adjustment guidelines for certain antiretrovirals, which should be followed in clinical practice. If it's not followed, there should be some expert reason why that's not being done. And you see one of the things is to avoid contraindicated drugs, but in the case of we don't have to avoid drug interactions, such as use with Sustiva or efavirenz, you do have to up the dose to 90 milligrams of daclatasvir per day.

Failing to do that would be ineffective medical error. Follow FDA labeling around appropriate dosing for drug interactions that have been laid out based on the science.

OK. I earlier mentioned a drug that you may be familiar with, maybe not, called amiodarone. It is the main drug used for management of chronic atrial fibrillation, and it's used for other cardiac arrhythmias. Prior to its release of sofosbuvir or Sovaldi to the market, it was not known that this interaction existed. But now, the FDA labeling, as the first bullet notes, that there's a warning of severe bradycardia when administering this agent, sofosbuvir with amiodarone.

Keep in mind, sofosbuvir comes alone. It also comes in combination with Harvoni, and it is part of combination regimens, like with daclatasvir. So it's a popular direct-acting antiviral. The example here is after amiodarone and propranolol were given to a patient, two hours later, sofosbuvir and daclatasvir were started for Hep C, and the patient experienced within a two

hour period, a dramatic drop in their heart rate to 27, knowing that typically 60 or 70 is normal for most of us.

They stopped the amiodarone and the propranolol. They continued the direct-acting agents for three days. Each time the patient received sofosbuvir with daclatasvir, the bradycardia occurred again. It was only after discontinuation of the direct-acting antivirals that no bradycardiac events were observed. Ten days after the patient stopped the amiodarone and another beta blocker, called atenolol, which is another cardiac drug, the patient was challenged again with their sofosbuvir and daclatasvir. Bradycardia was again recorded.

When we see a [INAUDIBLE] like this, it becomes highly probable that it's the drug interaction that's causing this. No bradycardiac events were observed following a challenge eight weeks after Amiodarone was stopped.

So couple of themes here. Drug comes on the market. We need to remain vigilant about updates to drug interactions and warnings, as in the case of this. Two, important to have those who know about the drug included in the case when this occurs, because amiodarone is a very, very long acting drug. It takes a long time to come out of the body. So just stopping it and then starting back the direct-acting antivirals would not be sufficient, because it has what we call a half-life of about a month and a half. So it takes a while for the body to break it down and remove enough of it that it doesn't cause a problem anymore.

And just to heighten your awareness on this, so all sofosbuvir containing regimens now, Harvoni, sofosbuvir with Olysio, sofosbuvir with daclatasvir, any other combinations like that, if someone cannot have amiodarone taken off of their regimen, then they have to be hospitalized to start this combination regimen. Monitored, and then they have to be monitored regularly afterwards for several weeks. And this is all based on new FDA labeling. So this is just an example of not a pharmacokinetic interaction, but a pharmacodynamic interaction.

And an example of how new information emerges around drugs and specifically, drugs that have interacting concerns. And then we, as a clinical community, have to be vigilant, embrace it, employ it. And also we have to be observing it, because fortunately, outside of research, some clinicians recognize this as a probable drug interaction and shared it with the manufacturer, the FDA, and now we're all informed about it. So we have to listen to our patients, especially since we know these are products that have significant potential drug interactions. Before I open for questions, just simply put, there are no direct-acting antivirals for treatment of chronic Hepatitis C, in the monoinfected or coinfected population, have no drug interactions. They all have some.

We saw dramatic variability and good guidance on some of the interactions, but it's not a subject that's one for intensive care. It requires engagement on the part of the clinical community and the patient. And we need to be vigilant, especially to avoid missteps with breakdown in transitions of care, because that's often where we see the breakdown after good initial planning that over time, I mean, eight, twelve, 24 weeks, things introduced into the

patient's regimen, or behaviors change. Or clinicians change, and we have varying understanding of what's going on with patient care. And so I would just say, again, all of these drugs have significant interactions.

With that, I'll stop and I'll turn it over to you, Steve, for any questions from the audience.

STEVE LUCKABAUGH: OK. Thank you, Dr. Keeys. We would like to open it up now for questions and answers. If you have any questions, please type them into the questions pane on the GoToWebinar toolbar. We did have one that came in that reads, have any organizations had any experience with setting up clinical decision support via their EHRs for medication management, for HIV and HCV coinfected patients?

CHRISTOPHER KEEYS: That's a great question. And I suspect that there's others in the audience who may want to comment. That sounds like kind of a polling question for the entire body on the call. But I would just share that all EHR records that have e-prescribing capabilities within them, there are only less than a handful of vendors that provide the backbone to electronic prescribing in the United States. And in the electronic prescribing capabilities within the EHRs-- I'll just mention one of the major ones, which is First Databank, but they're not the only one-- they do have drug interaction software capabilities for the HIV and the direct-acting antivirals.

A few cautions, though. There's a lot of interactions in many facilities. Two, things to the clinical decision support, meaning turn off or suppress alerts, because there's too many in the physicians or prescribers have great difficulty accepting those as valuable and time-efficient. I just wanted to share that. So there is that built into e-prescribing capabilities. If the clinical support has been introduced, and turned on, and is useful. I'll leave that thought as it is for any others who type in some other responses.

STEVE LUCKABAUGH: OK. If anyone would like to add to that, go ahead and type your comments in the questions pane. I don't see any more questions right now. We can give folks a few minutes.

CHRISTOPHER KEEYS: I also want to mention to our group is that there are some centers that go to great lengths to keep track of these kinds of interactions. One of them is University of California San Francisco, they have a website that is a database of antiretroviral adverse drug-drug interactions. And it does include the [INAUDIBLE] things, which all but includes many of the direct-acting antiretroviral drug interactions.

And so I would encourage you to Google it. It's the Database of Antiretrovirals at University of California San Francisco. And it's still actively up and running. But it's not integrated in the facility electronic health record that I'm aware of. Maybe is at their institution, but not across the country.

STEVE LUCKABAUGH: OK. We have another question. What has been your experience regarding HCV and HIV coinfected patients who have renal failure, and receiving dialysis weekly? Treatment successes, or drug-drug interaction?

CHRISTOPHER KEEYS: That's an excellent question. Let me go through evidence. From an evidence standpoint, we do not have randomized control clinical trials that have sufficiently answered the question of best regimen for treatment of renal failure patients on dialysis with direct-acting antiretrovirals. Those considerations are mostly expert opinion combined with pharmacokinetic and pharmacodynamic considerations, which are designed for a patient.

So as we do for antiretrovirals, we do have, for some of the direct-acting antivirals for chronic Hep C, we have guidance on dose adjustment. But we are weak overall in chronic Hep C dose adjustment guidelines for direct-acting antivirals. And so the evidence I would say, from our standpoint, is primarily clinical case reports, case series, and expert opinion, using pharmacokinetic principles for which of these drugs have been used. But we are really, I think, overall inadequate, because all of these new agents have principally excluded from the trials the population that the questioner posed, which is dialysis patients.

So I wish I could add more, but our personal experience is so seldom that we don't even have enough in our practice, enough of them to say we have a case series that we can speak to efficacy, which I think was an important part of the question that was posed is so what is the efficacy?

What I would say is that we don't have evidence that they fail. We assume that if we can get therapeutic levels in the range that they will have good, sustained response. But it's probably not going to be at the same level that we see in the monoinfected patient, or the coinfected HIV patient who doesn't have renal failure.

STEVE LUCKABAUGH: OK. And if anyone else has any questions, please enter them into the questions pane right now. We have another minute or so. All right. I'm not seeing any further questions. Did you have any closing thoughts before I close it out here?

CHRISTOPHER KEEYS: I'm just picturing myself in all of the settings where I'm speaking to, and I'm hoping that there is a keen engagement, where discussion is going on between the different providers, because it's very difficult to successfully do this piece of what we're talking about, the managing of drug interactions. Kind of separate and apart from doctor working with nursing, and case managers, and pharmacists, and patients.

So if you find yourself isolated, then reach out to your providers who are doing the phases of medication management we talked about. The prescribing, the dispensing, the administration, and monitoring. So that you can coalesce around a team dynamic. That's pretty essential for successful management of these, and to reduce the chance of errors.

STEVE LUCKABAUGH: All right. I think that will do it. Thank you for participating in today's webinar. We hope that you're able to find the information provided useful as you continue your P4C project. And we ask that you take a few moments to complete the Feedback Survey that you will receive when you close out of this webinar. You will also receive it in the follow up email.

Today's webinar was recorded, and audio and video versions of the entire webinar will be made available on the P4C website within the next few weeks. Copies of all our prior P4C webinars are currently available on the website on the P4C Resource Materials page at P4CHIVTAC.com. You will need to log in to access the materials.

If you need log in credentials, send an email to P4CHIVTAC@mayatech.com. Thank you again for participating in today's webinar. And thank you Dr. Keeys for that excellent presentation. If you have any additional questions for the P4C project, or for Dr. Keeys, please email us at P4CHIVTAC@mayatech.com.

Take care, everybody. And we'll see you next time.