TREAT NOW OR WAIT? ACUTE HCV INFECTION

Speaker: Leah Burke, MD

11/01/2016
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[video transcript]

[00:00:00]

[Intro music] - [Dr. Brewer] Very fortunate to have Dr. Leah Burke as our speaker. She will be discussing acute Hepatitis C infection management, but first, let me introduce Dr. Burke. She is an Instructor in Medicine at Weill Cornell Medical College in the division of Infectious Diseases. Her career focuses on clinical research aimed at improving the management of HIV and/or Hepatitis C infections, and the clinical care of such patients. Her research interests involve HIV adherence, the use of monoclonal antibodies therapy to treat or prevent HIV infection, and studying the efficacy of new treatment regimens for Hepatitis C infection. She has given several AETC talks discussing the treatment of Hepatitis C infections in patients with and without HIV infection. Just a reminder, today is a CEI cosponsored webinar. We are providing CME/CNE credits at the end. Just so that you know, you will be directed to fill out a SurveyMonkey Webinar via pop-up window automatically when you exit the webinar today. Please look out for the pop-up window. We ask that all attendees today fill the survey out, even if you are not going to be claiming CME or CNE credit. If you are claiming CME or CNE credit, you must fill out the survey entirely by November eighth at five p.m. in order to receive credit. Our next CEO co-sponsored webinar will take place on Tuesday, December sixth, and CME/CNE credit will be offered then, too. So, thank you, Dr. Burke, for joining us today. The microphone is all yours.

[00:01:47] - [Dr. Burke] Great, thank you, Dr. Brewer, for that introduction, and thank you, also, to the audience for allowing me to speak with you today. So, as stated, the title of my talk is Treat Now or Wait? Acute HCV Infection. Throughout this talk, I'll be abbreviating Hepatitis C virus by HCV.

[00:02:05] As far as my disclosures, I do receive research support, which is paid to my institution from the company AdhereTech, for clinical trials regarding HIV adherence interventions.

[00:02:16] And I'd like to start by detailing my learning objectives. So, during this talk, I intend to describe transmission and pathogenesis of Hepatitis C virus during initial infection. I also intend to identify the signs and symptoms associated with acute Hepatitis C virus infections, and discuss diagnostic algorithms and treatment options for acute HCV infection.

[00:02:40] So, let's start by just describing what exactly acute Hepatitis C virus even is. So acute Hepatitis C is defined as the earliest phase of the infection, essentially the first six months of the infection. Unfortunately, this stage of the infection is often a missed or delayed diagnosis because it is frequently asymptomatic, and fewer than 20% of patients have characteristic symptoms, including low-grade fever, right upper quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice, and unexplained elevations in the serum alanine aminotransferase or aspartate aminotransferase levels may be the only laboratory finding during infection. And not only are many of the patients asymptomatic, but even the ones that are symptomatic often chalk this up to the typical "GI bug," and stay home and never actually present to clinical care, so we miss them because we don't even have laboratories on them.
The good news about acute Hepatitis C virus infection is that the majority of patients will spontaneously clear the virus on their own, and not need treatment, so the estimates do vary for this. They vary mostly, as the literature describes, between 40 to 70% with all comers. It’s about 60 to 66% is in the first six months. There are some baseline host characteristics that are associated with a higher probability of spontaneously clearing the virus, and those include female gender, younger age, non-African American descent, being immunocompetent, having an elevated ALT at the time of presentation, developing jaundice, having an infection with genotype one strains, and having this IL28CC genotype. So I’m just gonna talk very briefly about IL28. It does not come up much more during my presentation, but essentially, there are noted to be single nucleotide polymorphisms in the HCV genome located near the gene for interleukin 28, which is called IL28B, and that different genotypes are strongly associated with the likelihood of achieving a cure from Hepatitis C virus infection. A cure is defined as SVR, specifically SVR-12. That stands for a sustained virologic response, which our definition of that is having an undetectable Hepatitis C RNA 12 weeks after completing Hepatitis C treatment. So there are actually three different genotypes for IL28B gene, and those are CC, CT, and TT, and if the patient has an IL28CC genotype, it confers a much higher probability of having spontaneous clearance, and actually also confers a higher probability of having cure, in more so the chronic infection, but also in the acute stage as well. So, in the past, we used interferon based agents to treat chronic Hepatitis C as well as acute, and the majority of our literature is actually using those interferon based regimens. We have the most data on those, and that acute Hepatitis C, the advantage to it, in that previous age of interferon, was that patients had a greater chance of cure with interferon based agents, and could actually get away with having abbreviated treatment course as well. In general, though, knowing how to recognize and effectively treat Hepatitis C in the acute stage of infection is really key to preventing liver related morbidity and mortality, and even more, especially, to decrease the risk of Hep C transmission to potentially susceptible hosts.

So, I'm going to start with a case, and this case is going to run throughout the talk. We're gonna pick it up and leave it at different intervals. So this is a 28 year old male with HIV on truvada and dolutegravir, with a CD4 of 370, and an HIV RNA that's undetectable. He has a history of syphilis that was treated one year ago, and active crystal methamphetamine use, not intravenously. He often has sex with men while taking meth, and does not always use condoms. Labs four months ago showed a normal CBC and normal hepatic function panel. Labs nine months ago showed that he had a positive Hep A virus antibody, he was negative for the Hep B virus surface antigen, positive for the Hep B virus surface antibody, and had a Hep C antibody that was negative, and he feels fine. He has no complaints. The practitioner decides to test him for syphilis and other sexually transmitted infections, and he has no signs or symptoms that suggest viral hepatitis. The question is: should he also be tested for Hep C infection? So, I'm gonna not answer that just now.

We're gonna keep moving on. So, for starters, why do we care at all about diagnosing acute Hepatitis C infection? We have great treatments now for chronic Hepatitis C infections. So most importantly, the knowledge of the status of the patient being positive or negative for Hepatitis C in the acute stages is really critical, because it allows us an opportunity to educate the patient about their risk behaviors, so that they can modify their behaviors and, ideally, reduce transmission to others, and it also allows us the opportunity to do HIV screening, potentially diagnose HIV, and also talk about HIV prevention methods, and PrEP for partners, if need be. And then, lastly, it allows for the opportunity for
Hep B and Hep A vaccination. If a person has one hepatitis, we would like to avoid any further insult to the liver by way of other hepatitises, and what I don't have on this list is we also need to talk to them about alcohol, avoiding alcohol.

So, who is at risk for Hepatitis C infection? This list here is showing the list for both people with acute and/or chronic Hepatitis C infection, but I've actually starred the ones that are mostly seen as receptors for acute Hepatitis C, and the reason for that, why not all of them apply now, for acute Hepatitis C infection, is that we are screening our blood supplies. So, the biggest burden of disease that we still see is from injection drug users, either currently or within the past six months. For chronic Hepatitis C, the next three apply, recipients of clotting factor concentrates made before 1987, recipients of blood transfusion or solid organ transplants before 1992, and hemodialysis patients. Precautions are now taken to effectively screen and limit the risk of transmission from Hepatitis C virus by these three methods. However, persons actually can still have known discreet exposures to Hepatitis C virus. We do see this in our healthcare workers, who have needle sticks from a patient that is Hep C positive and has a high viral load. Also, we do see an increased prevalence of acute Hepatitis C infections in persons with HIV, especially in men who have sex with men. We do know that it can be sexually transmitted, so if you have sex with a Hep C infected partner, there is the potential to get infected, and specifically, there are certain high risk sexual practices, such as fisting or bleeding during sex. Children born to Hepatitis C positive mothers. We don’t see it very often, but still, potentially, it could lead to an acute infection in the child. Blood transfusions or procedures during travel in developing countries, and then, lastly, unsanitary needle practices besides those for injection drug users, also reusing needles for tattooing or piercing is a possible mode of transmission.

So, there’s good and bad news, that overall, currently, there are less cases of Hepatitis C occurring now than there were in the 1980s. However, over the last few years, especially since the year 2000, cases of acute Hepatitis C are on the rise each year, so we’re not still at the same numbers as the 1980s, but they’re basically creeping back up again. So, in the U.S., the CDC actually estimated that 230,000 new Hep C infections occurred each year in the 1980s, which is a very staggering statistic. In 2013, they estimated there were about 30,000 new cases, and the latest data is for 2014, so in 2014, there were a total of 2,194 cases reported of acute Hepatitis C, which was approximately .7 cases per, a zero’s missing, it’s supposed to be per 100,000, and after adjusting for under-ascertainment and under-reporting, the CDC estimated that about 30,500 cases occurred in 2014. So, that’s an estimated increase of about 500 cases between 2013 to 2014, and you can just see, on the right hand side, the graph here, which basically shows that there is a little bit of an inflection point here, and we’re basically on the rise thereafter. Just by way of comparison, currently, in the United States, we have 2.7 to 3.9 million people are estimated to have chronic Hepatitis C infection.

So, who are these cases occurring in? They do occur in people of all ages, particularly adults, but most especially, we are seeing an increase in cases in younger persons. So, there was a CDC surveillance study that examined trends, the instance of acute Hepatitis C, among persons reported between 2006 to 2012. They looked at the urbanicity, their county, and their state, and what was very striking is that, among young persons with acute Hepatitis C infections, 31% resided in non-urban and 67% in urban counties, and that 77% reported a history of injection drug use. In fact, the incidence significantly increased over time, so there was 13% per year incidence with an overall 170% increase
from 2006 to 2012 in non-urban counties, and five percent per year among urban counties. What they attributed this to was mostly the rise in opiate abuse, particularly pill opiates that are abused, prescription and non-prescribed opiates. And you can actually just see here, this broken down by age, and you can see this purple line basically shows that in the 20 to 29 year olds, there's a great rise over the last several years, and also the yellow line, 30 to 39 years, so definitely that age bracket having an increased rate of infection, and also then breaking it down into areas in the United States. The red is the largest increase, greater than 200% increase in the incidence, and you can see certain states are affected by that. It's not necessarily the urban centers that we would expect.

So, I do wanna talk about the epidemic that is ongoing of acute Hepatitis C in patients with HIV. So since 2000, epidemics were reported, pretty much now throughout the world. They were initially reported in Western Europe, Australia, and the United States, and then Japan, and it's been increasing thereafter. It's mostly being seen in HIV infected men who have sex with men, and studies have shown that certain sexual risk behaviors are most likely accounting for this. And so those sexual risk behaviors are unprotected anal intercourse, fisting, enema use, bleeding during intercourse, and non-injection drug use, particularly with crystal meth being frequently used, and you can see that MSM are a large proportion of the new cases within the city of New York, with people with HIV, so basically on the rise here. Data only goes to 2010. There is also data as well, which I'm not going to show here, but that also there is a study in London that was looking at a clinic of MSM, but not HIV infected, and also diagnosed, several cases, of acute Hepatitis C in that population. It's not believed to be as prevalent in the non-HIV population, but also, those patients are not as intensely or as frequently engaged in the healthcare system, so larger cohort studies will probably be needed in the future to try to see what the actual risk is in the non-HIV MSM population.

So, a question, which basically asks what is the most appropriate laboratory test to check if considering acute hepatitis due to HCV infection? The choices are HCV antibody test, plasma HCV RNA, HCV genotype, and hepatic function panel. So, the answer to this question is the plasma HCV RNA test, and we're gonna talk more about that.

But first, I'd like to just discuss the laboratory findings in acute Hepatitis C. So, what you see here on the X axis is the time course, from the time of infection, and on the Y axis is the HCV RNA on the left and the ALT level on the right, and then you can see here, plotted out, the change in the Hep C RNA, which is this sort of dashed dotted line, and then the changes in the ALT, which is the solid green line. So, what is seen first is actually that the Hep C RNA becomes detectable, and that can be detected in the serum approximately seven to 21 days after transmission. And then after the Hep C RNA becomes detectable and starts to rise, you then subsequently see an increase in serum transaminase levels at about two to six week period. And then, the Hep C antibody seroconversion goes from negative to positive between a two week to 12 week period. The thing to note about this is that significantly immunosuppressed patients, those who, for example, are in immunosuppression after a bone marrow transplant, those with HIV/AIDS, that antibody can take much longer to seroconvert, and there are cases where, in HIV patients, they've taken as long as a year to seroconvert, so we need to keep that in mind when we are screening our patients and ordering those tests. One hallmark of acute Hepatitis C is that the RNA levels and ALT levels fluctuate greatly during the acute course of the infection, which you can
actually see in these peaks and valleys here, but the Hep C RNA can actually fluctuate greater than one log. You don't see that in the chronic infection, where it essentially levels out and stays fairly constant.

[00:17:06] And that’s what you can see here. So basically, in the days following Hep C acquisition, you see a slow rise of the Hep C RNA, and then it really quickly ramps up in about a 10 to 20 day period, and then, within that first month, later into that first month, it essentially plateaus out and stays relatively stable during the remainder of the acute infection and the chronic infection period. One thing we need to keep in mind about the antibody seroconversion time is that, if we’re testing someone before that antibody has changed over, it may be negative, but they may have acute Hepatitis C, and this is referred to as the window period, which is anywhere from, usually it’s seen within two to 12 weeks, but here, it can be anywhere from about zero to 60 days in most patients. But, as I said before, if they’re highly immunosuppressed, it may take much, much longer for that seroconversion to occur.

[00:18:04] And this is actually, this table’s just taken from the Hep C guidelines that are online at hcvguidelines.org. They are joint guidelines from the AASLB, and the IDSA and IS-USA, and it basically talks about the laboratory findings and what you would see at different times. So, the Hep C antibody may be negative in the first six weeks, maybe delayed or absent when the patient is immunosuppressed, and the presence alone does not distinguish between acute and chronic infection. Generally speaking, once you’ve been exposed to the virus and form that antibody, you have Hep C antibody positive for your lifetime, whether you’re treated, untreated, cured, not cured, or spontaneously cleared, so that antibody pretty much stays with you. The Hep C RNA, as I said before, has great viral fluctuations, which can be greater than a log, and that can actually indicate that you’re in the acute versus the chronic stage, but it can be negative very early on, in the first week or two, most especially, it can be negative. And having a positive RNA also doesn’t help you know whether you’re acutely or chronically infected. We just know that you’re infected at that time, actively viremic, but the fluctuation in the RNA is what’s most helpful. And lastly, the ALT, as I said before, can have fluctuating peaks and valleys as well, but it actually can be normal during the acute infection. We’re used to seeing very high levels, in the high hundreds, close to 1,000, but some patients could have very mild elevations, or even be on the higher end of normal, and we do see this in some of our HIV patients. They, you know, have values of about 70, 69, you know, things that we wouldn’t really think of as acute hepatitis levels, and that may lead us to also miss the infection if we’re relying just on the AST and ALT. And the other thing about the ALT is that, if someone is drinking or taking a lot of Tylenol, for example, that can lead to a further elevation of the ALT that can somewhat skew the picture.

[00:19:58] So, the criteria for acute Hep C diagnosis, there are actually more than one set of criteria, but I’m gonna start by describing the NEAT guidelines, which is the European AIDS Treatment Network. So, they define acute Hepatitis C virus as Hep C antibody seroconversions or a positive Hep C RNA test with a negative Hep C test in the previous 12 months, but you can also use the second set of criteria as well, which is having a positive Hep C RNA while accompanied by an acute rise in the ALT, beyond a threshold of 10 times the upper limit of normal, or you can have the ALT rise greater than five times the upper limit of normal if it has been previously normal in the past 12 months, or 3.5 times the upper limit of normal if the ALT was previously abnormal. So, for example, someone that had hepatic steatosis then has an abnormal ALT to start off with. You can look for a change that is 3.5 times the upper limit of normal, and not have to meet the five times or 10 times greater than the upper limit. And then,
obviously, you would want to make sure that you have been able to exclude and rule out other causes of acute hepatitis.

[00:21:10] So, screening for acute Hepatitis C. Screening has been found to be, in modeling studies, very good in the interferon era, specifically with the HIV population. It was shown to prolong life expectancy and be cost effective. However, there are some limitations to the screening test, and as I referred to before, if you’re using the Hep C antibody for screening, you may not see that turn positive, because you could be in the window period before seroconversion, and that seroconversion can be delayed in HIV infected individuals, and five percent of them can remain negative up to one year after infection. And it seems like something on the slide got moved, here, and blocked over some of the references, but essentially, this box at the bottom is actually taken directly from the Hep C guidelines.org, and actually says that the recommended testing for acute diagnosis of acute Hepatitis C infection is Hep C antibody, and Hep C RNA tested. Both should be done when you suspect acute infection.

[00:22:13] So, this is a treatment algorithm that I'm not going to go through in great detail, but it is useful to look at, especially if you had a discreet exposure, so for example, a needle stick of a nurse in the hospital from a patient that has known Hepatitis C virus infection, and essentially, they break it down into what to check, checking the Hep C antibody in the RNA, and what you do if both are negative, if one is positive, the antibody’s positive, the RNA is negative, the antibody is negative, the RNA is positive, or both are positive. So, it’s very easy if both are positive, because you pretty much know that you have active hepatitis infection, and that you may very well have a chronic infection, and basically, you can treat with the DAA regimens, the direct acting antivirals that I’ll talk about later. If both are negative, you don’t have Hepatitis C viral infection, but you can say that somewhat guarded, but you do want to actually repeat the testing, because you may be testing too early before the RNA or the antibody have become positive, so it actually recommends to repeat testing in six months. If the antibody is positive and the RNA is negative, in that case, you are led to believe that the person was exposed to Hepatitis C virus in the past, and either spontaneously cleared or was treated, and that you would gather from the history, but they essentially, you would believe, would not need to actually be treated. If the Hep C antibody is negative and the RNA is positive, this is highly suggestive of having acute infection, and you then want to follow the patient to see what happens, especially do they spontaneously clear, because that will help determine whether or not you treat the patient.

[00:23:56] So, I want to just talk a little bit more about HIV and Hep C co-infection. These two diseases are very frequently seen together in patients, so it's estimated that approximately 1/3 of patients with HIV are co-infected with Hepatitis C, so we do need to know how to be able to manage both Hep C mono-infected and Hep C co-infected with HIV patients. There are some things that make the HIV population different, so the Hep C viral set point is increased in the setting of HIV infection, and basically, that means that the Hep C viral load tends to be higher, and it can be more than a log higher than patients that only have Hep C mono-infection. Also, the humoral response to Hep C appears to be delayed in HIV infection, and five percent of cases, as I said, will still be Hep C antibody negative up to one year out. Third, is that, and pretty much most important, is that there are higher rates of chronic infection of certain HIV positive patients. They have a harder time clearing the virus on their own, and the rates of spontaneous clearance range in the literature from about 20 to 40%. And lastly, immunosuppression due to HIV has been seen in some small case reports to accelerate the progression
of fibrosis in HIV infected patients. Generally speaking, when somebody has acute Hepatitis C virus infection, you don't see much fibrosis if you were to do, let's say, a liver biopsy, which not many people do nowadays, or a fibro scan or a fibrosure. However, Daniels here at Mount Sinai actually reported on a number of patients, a small cohort, that were acutely infected with Hepatitis C in the study of HIV, and they already had stage two and some stage three fibrosis, which is quite remarkable, and atypical for the mono-infected population.

So, these are the various guidelines that are available, detailing what should be done to screen for acute Hepatitis C, specifically in patients with HIV. The guidelines all have little differences, but mostly, they have one similarity, which is be on the lookout for it in your HIV population, particularly HIV men who have sex with men, and those who engage in other high risk behaviors, sexual high risk behaviors, intravenous drug use, crystal methamphetamine use, and I'm going to go to the last column on the right first, and basically, this is the IDSA, AASLD, and IAS-USA guidelines, that basically says, when somebody engages into care in your HIV clinic, they should all at least have one time testing for HIV infection, and then annual testing thereafter for those who inject drugs, for HIV patients who have unprotected sex with men, and then periodic testing offered to other persons with ongoing risk factors, and they recommend testing both the Hep C antibody and the Hep C RNA testing when you suspect that there is an acute infection. But it doesn't actually, besides saying the annual testing here, it doesn't talk about, you know, if you think that this person's having really high risk behaviors, and you don’t think one year is good enough. Most of these patients that have HIV that are in your clinic, the advantage is that you are getting labs on them. Most providers are looking at liver function tests, usually, approximately every three months. Some are looking every six months, so hopefully, you'll be able to see a rise in the AST and ALT, particularly the ALT, and that would the reflexively trigger you to do Hep C specific testing, and at that time, you would send both the RNA and the antibody. If you look at some of the other guidelines that are available, the 2011 NEAT consensus panel says that all newly diagnosed HIV infected individuals should be screened for Hep C antibodies, and then particularly, HIV infected MSM who are at high risk for contracting Hepatitis C should be screened every six months with ALT levels, and annually for anti-Hep C antibody. And then, those HIV infected patients that, basically, you're seeing them get sexually transmitted infections, or you note they're having ongoing intravenous drug use, they should be screened three months after their last exposure. The 2015 STD Treatment Guidelines from the CDC says all persons with HIV infection should undergo Hep C testing and initial screening, and then the screening should be with antibody assays at least yearly for those at high risk for infection. Now, as I said before, we do worry that the antibody might be negative for a long time in our HIV population, and they do say that indirect testing with ALT is not recommended for detecting incident Hep C infections, so there's a little bit of a difference there. The 2013 Primary Care Guidelines from HIVMA and IDSA, basically, again say test for Hep C when an HIV person engages into care, and then annually thereafter, and the RNA should be measured in seronegative patients with a history of injection drug use, or unexplained increases in the AST or ALT. And lastly, the DHHS, again, test all HIV infected patients when they engage into care for Hepatitis C, and then for those that are at risk, antibody testing is recommended annually, or indicated by risk exposure, and then, if you see a high ALT increase, you should reflexively check in RNA, so there are subtle differences between these guidelines, but everyone appears to agree that, when the person engages into care, and/or is diagnosed with HIV, they should automatically have some
form of Hep C screening, and then roughly annually at least, if not more frequently, screened for Hep C with an antibody, and also keep an eye out for LSTs. If the LSTs rise, reflectively check the Hep C RNA.

[00:29:25] So, just to go back to our case, so on labs, the patients was noted to have elevated transaminase levels. He was brought in for further testing, which revealed Hep C RNA level of 500,000 and Hep C antibody negative. Based on these results, the practitioner makes a diagnosis of acute Hep C infection. So what next? Do we treat this infection?

[00:29:44] So, there are arguments both for and against treating Hepatitis C in the acute setting. The reasons to not treat acute Hepatitis C is that a majority of patients will spontaneously clear the virus in the first six months, so if you just wait and watch them, you may never need to put them on medication. Second is that acute Hep C is rarely fulminant, so treatment is unlikely to prevent acute liver failure and death, and third, we actually don't have, at this moment, too much data, actually, that is convincing that less intense courses of interferon-free treatments are effective for acute Hepatitis C. In the days of interferon, we did know that treating earlier in the acute setting had a higher probability of cure, and also allowed us to give an abbreviated course of interferon, pegylated interferon and ribavirin. We don't have that confidence right now with our DAA therapies, and more research is needed. The reason to treat acutely, the biggest argument for this is that treating people acutely can prevent transmission, especially if the patient has ongoing risk behaviors, and the second is that special area of HIV infected patients who may have rapidly progressing fibrosis, so if you do an assessment of their fibrosis and you see that they're already at, you know, an intermediate or advanced stage, that would actually push you to want to treat sooner to prevent liver associated morbidity.

[00:31:03] So, some considerations need to be made before initiating treatment, some of which we've already touched on. So one, you need to consider the clinical features. What's their ALT? Do they have jaundice? Do they have female risk? Are they of young age? You know, do they have baseline host characteristics, labs, and clinical factors that would make them a higher probability of spontaneous clearance, and maybe you would want to just watch and wait. What are their ongoing risk factors? What's their potential for transmission? What is their assessment of likelihood to adherence of therapy? As we know, these new direct acting antiviral agents are not cheap, so we do want to make sure that people will actually adhere to them once they get started. We do need to check for drug interactions with HIV medications and Hep C therapy, and there are also not only just HIV medication drug interactions, but also anti-arrhythmics, like Amioderal, and some issues with some statins, and some issues with acid-blocking medications for like proton-pump inhibitors, et cetera. You do wanna know if the patient has HIV or does not have HIV, mostly so that you can diagnose it if it's there, or prevent transmission, and also start antiretroviral therapy, and lastly, pregnancy status. It's not currently known whether women with acute Hepatitis C during pregnancy are at a greater risk of transmission to their child than chronic Hepatitis C, and we don't yet have any post-exposure prophylaxis available to prevent perinatal transmission of Hep C. And lastly, ribavirin is a teratogen, and so, if you're giving a regimen that includes ribavirin, you would not want to give it to a pregnant woman.

[00:32:30] So, another question: what is the minimum recommended time the practitioner should wait to begin treatment if you would like to allow for spontaneous resolution of Hep C infection? The choices are 12 weeks from the time of presumed exposure to Hep C virus, 12 weeks from the time of first
laboratory evidence of Hep C, 6 weeks from the time of presumed exposure to Hep C, or 6 weeks from the time of first laboratory evidence of Hep C. So, the answer to this question is 12 weeks from the time of first laboratory evidence of Hep C.

[00:33:05] So, here are a snapshot of the AASLD/IDSA joint Hepatitis C guidelines. They talk mostly in these guidelines about treatment and management of chronic Hepatitis C, but there’s actually a special section dedicated to the management of acute hepatitis virus infection, and that can be found and hvcguidelines.org.

[00:33:28] And I’m gonna show you here some texts and tables directly from those guidelines. So, they have a box that actually discusses the recommended treatment for patients with acute Hepatitis C infection, and essentially, it breaks it down into whether the practitioner and the patient feel comfortable waiting or want to pull the trigger and start treatment earlier, so if the practitioner and patient have decided that delay in treatment initiation is acceptable, monitoring for spontaneous clearance is recommended for a minimum of six months. When the decision is made to initiate treatment after six months, treatment as described for chronic Hep C is recommended. If the decision has been made to initiate treatment during the acute infection period, so within the first six months, you still want to wait, at least a little bit, you would wanna monitor the Hep C RNA for at least 12 to 16 weeks before starting treatment, and that’s because the majority of people that are going to clear would clear within the first 12 to 16 weeks, with the remainder of the other patients that will clear, will clear between that 12 to 16 week period and six months, so it’s still allowing them some time to basically be observed to see if they will clear before starting treatment. And, as far as what regimens you treat them with, at this point in time, it’s recommended that you would treat just the same as if it has chronic infection, so same regimens and duration, and I’ll talk a little bit later on about trials that have been done and data about regimens specifically studied for acute Hepatitis C infection. So, obviously, at the red box at the bottom, if the patient actually is found to spontaneously clear the virus, their Hep C RNA becomes negative and stays negative, then treatment is not recommended.

[00:35:08] As far as monitoring laboratories while on treatment, the good news is we don't have to do very intensive monitoring. Basically, it's recommended to monitor the Hep C RNA every four to eight weeks for six to 12 months, to determine spontaneous clearance of the infection. Now, the one issue with this may be if you don't think a person's going to stay engaged in care. Some providers want to treat the patient if they think that treating them will keep them coming back to the clinic, versus if you just observed them and they kind of fall by the wayside and never reappear again, and then develop chronic infection. One very important thing that we can't forget is that we need to counsel our patients about many things when we diagnose them with acute Hepatitis C infection, so one is we want to, first and foremost, counsel them on what their risk behavior was that allowed them to contract Hepatitis C and to teach them about how to modify that so they don't transmit this disease to others, but we also wanna talk about a possible hepatotoxic drugs. For example, Tylenol, avoiding and limiting use of Tylenol, and limiting and hopefully totally stopping drinking any alcohol, because that can actually accelerate fibrosis. We also wanna talk about vaccinating them for Hepatitis A and Hepatitis B, and then here it says referral to addiction medical specialist is recommended for patients with acute Hep C infection related to substance use. I do this very often in my clinic. A lot of my patients are abusing
opiates that are often not prescribed, such as oxycodone and Oxycontin, and they do need to actually get some substance abuse counseling in conjunction with Hep C treatment.

[00:36:43] So, which regimen is the most well studied for treatment of acute Hepatitis C infection in the context of HIV infection? The options are peginterferon alone, peginterferon alfa plus ribavirin for up to 24 weeks, peginterferon plus telaprevir plus ribavirin, or ledipasvir and sofosbuvir. So, the answer to this is B. The majority of the literature that is available regarding treatment of acute Hepatitis C is actually studying peginterferon alfa plus ribavirin for up to 24 weeks, and it actually showed fairly good cure rates, I should say, in that study of about 70, sometimes up to 80%.

00:37:20 But, we are now in the age of direct acting antiviral agents for Hepatitis C, so no one wants to use interferon anymore. So, DAAs stand for direct acting antiviral agents, and what I have here is picture of the Hep C genome. It is an RNA genome that codes for both structural and nonstructural protease, and these new direct acting antiviral agents essentially target and inhibit certain nonstructural proteins, so I have those highlighted in blue below, and about in green, with the arrows, are different classes of our Hepatitis C DAA regimen. So, for example, the protein inhibitors inhibit specifically NS3 and NS4A, which encode for serine protease, and RNA helicase, as well as co-factors for those. There are replication complex inhibitors, known as NS5A inhibitors, that act on NS5A, and that actually has multiple rows, but it is critical for viral replication assembly, and it also encodes for interferon resistance, which is part of the pathogenicity of the Hepatitis C virus, and lastly, there are RNA polymerase inhibitors, known as NS5B inhibitors, that essentially inhibit the RNA polymerase of Hepatitis C.

[00:38:33] So, here are all the FDA approved therapies for chronic Hepatitis C infection, and currently, none of these agents are actually specifically FDA approved for acute Hepatitis C infection, but as I said before, we do use them. Basically, I have them sorted into the class of agent, the names with their abbreviations up on top, and then which genotypes they are FDA approved for and studied. So, no one really wants to take interferon and ribavirin and sofosbuvir anymore, so I'm gonna kind of move a little bit over, but we have ribavirin and sofosbuvir, plus minus ribavirin with simeprevir and sofosbuvir, not frequently used currently, ledipasvir and sofosbuvir, daclatasvir and sofosbuvir, and this is the PROD regimen, which has multiple drugs in it. Paritaprevir, ombitasvir, dasabuvir, and with or without ribavirin. Grazoprevir and elbasvir, and velpatisvir and sofosbuvir. What I have here in the large, bolded Xs are actually what these agents are FDA approved for, which genotype they're FDA approved for, and I didn't write all the genotypes, partially due to space and partially because genotype one through four are what we most frequently see here in the United States, but what I should note is that velpatisvir-sofosbuvir, which is a coformulated tablet called Epclusa. It's actually pan-genotypic, and is FDA approved for genotypes one, two, three, four, five, and six, so technically, this would go down even further. And then, I have small Xs as well, which are regimens that have been studied, but are not first line recommended FDA approved regimens, currently.

[00:40:17] So, what about direct acting antiviral agents specifically for acute Hepatitis C infection? So, these have been studied, both for patients that are mono-infected, and those that are co-infected with HIV. These are two studies, both of which were presented at the AASLD conference in 2015. The bottom study, I'm actually gonna start with first, by Martinello, the DARE-C II Study actually looked at sofosbuvir
and ribavirin for a total of six weeks in predominantly genotype one patients, and it showed that the SVR4 rate was actually quite low, only 27%. We have better agents available now, and we can also try to avoid the use of ribavirin. The next study, probably more applicable. It looked at both sofosbuvir and ledipasvir for four weeks and sofosbuvir and simeprevir for eight weeks, and then this is broken down in per protocol and intention to treat analysis, so in the per protocol analysis, the sofosbuvir and ledipasvir led to a 100% cure rate. The SVR12 was 100%, all 13. And then, if you look at the intent to treat, it's still quite high, 93%, and then the sofosbuvir and simeprevir also did very well, 100% in the per protocol analysis were cured, and 93% in the intention to treat.

[00:41:34] But what, specifically, about out HIV, sorry, that's actually a typo here. This should be HIV co-infected. And there are several trials that I'm going to talk about here. So the first was presented by Daniel Fierer at Sinai, and it was presented in AASLD 2015, and he looked at telaprevir plus pegylated interferon and ribavirin for a total of 12 weeks. Of note, telaprevir is actually now off the market, so actually can't be prescribed, so this is never a regimen that we would actually use, but it had a pretty good cure rate of 89%, so 32 out of 36 were cured, and notably, that was compared to historical controls that had cure rates of about 64%, and you see an improvement in the treatment group. What is interesting is the next two studies that showed fairly different results, studying both sofosbuvir and ribavirin, so I'm gonna go into more detail about these two studies, but one was by Fierer, and it studied sofosbuvir and ribavirin for 12 weeks, in which 11 out of 12 patients were cured, so SFR12 of 92%, and then Suzanne Naggie presented other data from an ACTG study called the SWIFT-C Study, where, again, patients were given sofosbuvir and ribavirin for a total of 12 weeks, but only 59% were cured. So, we'll talk about what, potentially, could have led to those differences, because investigations are still ongoing there. And then, lastly, by Rockstroh, at CROI in 2016, looked at an abbreviated sofosbuvir and ledipasvir regimen for a total of six weeks, and that cure rate, or I shouldn't say cure rate. I should say SVR4, so that Hep C RNA being undetectable at four weeks, was seen in 85% of subjects, and I'll talk in more detail about this. There is also a planned future trial that will be opening in France, so not here in the United States, but it will be looking at the use of elbasvir and grazoprevir for eight weeks, specifically in patients with HIV and Hep C infection genotype one and four.

[00:43:42] So, let's dig a little bit deeper into the sofosbuvir and ribavirin trials that I talked about, that had differences in their cure rate. So, the first is the Fierer New York study, looked at a total of 13 patients that were actually observed in the acute stages of their infection. One of those patients did spontaneously clear the virus before 12 weeks of observation was completed, so that one did not undergo treatment. The remaining 12 subjects were treated with sofosbuvir and ribavirin for a total of 12 weeks, and notably, there were delays in actually procuring the drugs to treat the sofosbuvir, to treat these patients, so they were all treated roughly around 20 to 22 weeks after the time of their diagnosis, so there was an adequate delay there, to look for spontaneous clearance. So, about half the participants were white. Two were black, two were Hispanic, and one was Asian. The median age was 43. All had genotype one, with the majority being subtype 1A. The median Hep C RNA was 32,000 copies, but there were two that had a very high viral load, greater than 10 million, and all of these patients were HIV co-infected, and were on antiretroviral therapy except for two. Sorry, all but two were on antiretroviral therapy, with undetectable or low HIV viral load, and the median CD4 was greater than 500 at 545. So, of the 12 patients that underwent treatment, 11 of them actually achieved SVR, and that one remaining patient actually experienced a relapse, which was between weeks four and nine after being treated.
About that patient specifically, that patient had a low peak ALT before treatment, and had a baseline Hep C RNA that was greater than a million before starting treatment, and also, they had previously been treated with interferon based regimen and failed during their primary infection. So, the most common adverse events were irritability and insomnia, but these did not limit treatment. Because this is utilizing the older drug of ribavirin, and we have more potent therapies, we believe, available with DAA combinations, the decision is made to not pursue this regimen in a larger trial.

And that's because there was the ACTG SWIFT-C Study, known as A5327, that actually showed something very different. So, this was an open label, two cohort trial. They aimed to enroll 44 total patients, so the first cohort looked at a regimen of sofosbuvir and weight-based ribavirin for a total of 12 weeks, and that cohort was completed in the data I'm going to show you here, and then there's a second cohort that received sofosbuvir and ribavirin for a total of eight weeks. That cohort is now closed to enrollment, and we are awaiting data from that. Just to talk about those patients, so the median age was about similar to the New York study, in the mid-40s. All of these patients, all 17 of them, were male. The majority of them were Hispanic or Latino, 65%. 24% reported ever using IV drugs. 24% had IL28CC, which is the favorable genotype. The majority were genotype one at 88%, and all of them, it was believed to be their first Hepatitis C infection, and then, the median Hep C RNA was, in logs, 5.6, plus or minus 1.76. And if you look down here at the viral suppression rates, it goes through the weeks of treatment, and then after treatment, which is the SVR12, which is looking at the Hep C RNA 12 weeks after finishing the therapy. So, basically, at the end of the treatment, at the end of the 12 week treatment, 100% of them had the Hep C RNA suppressed, but then, when you get to 12 weeks after treatment, only 59 of them had the Hep C RNA suppressed, and this was actually due to a high rate of relapses. There were seven relapses, and the study team tried to figure out why that would be, and one possibility is that they saw that ribavirin concentrations were 52% higher in those that achieved SVR, and that was statistically significant, and there was no statistical differences in those that achieved SVR versus relapse in regard to race, weight, or inosine triphosphatase, which all these can affect ribavirin level, or even patients' reported medication adherence. So, it's not entirely known, right now, why we saw such a difference between these two studies, but it did definitely pique curiosity in the field, and we are now awaiting the data from the week eight arm.

So, the Rockstroh study, which I had mentioned before, that was presented at CROI, looked at six weeks of ledipasvir and sofosbuvir, and this actually did quite well. This, again, was looking at HIV infected men who have sex with men, so they gave them a total of the six weeks ledipasvir and sofosbuvir, and then waited 12 weeks to assess for virologic cure. Some similarities here in the age. Low 40s here. Majority of all the patients were men, and the majority were white. 46%, so a higher percentage in this study, had the favorable IL28 genotype of CC. Majority were 1A, but there was also a pretty fair presentation of genotype four, at about a third of the patients. Here, the median Hep C RNA was about 5.4 logs, and a median CD4 was 678. They even also broke it down into the antiretroviral regimen, which I'm not going to go into too much detail about that, but we, in this field, are often concerned about drug interactions with antiretrovirals, and Hep C therapies.
So, you can see here, this is the post-treatment data, so they looked both at Hep C RNAs at four weeks after treatment and 12 weeks after treatment, and what they saw is that there were four virologic failures and then, subsequently, after the four weeks, between four and 12, they lost two patients to followup, so if you're not accounting for the two patients lost to followup, they had about 85% cure, but then they lost the two to followup, which drove the overall cure down to 77%. And they broke down, here, into whether they were relapse, reinfections, and whether or not they achieved SVR4 or SVR12, and basically, there were three relapses, which is this kind of maroon red color, and what was interesting is that those relapses occurred in patients with high Hep C RNA treatment initiations which were greater than nine million. So, there is some suggestion here in the data that having a very high Hep C RNA level in acute Hepatitis C infection before starting treatment can predict a lower probability of cure.

So, going on to our case, so the patient chose to defer treatment to see if his acute Hep C infection would spontaneously resolve, and during the observation period, he committed to safe sex practices and abstinence from drugs. However, after six months, his Hep C RNA remained detectable, so he was treated with ledipasvir and sofosbuvir for 12 weeks. He was a genotype 1A infection, so that’s a regimen that is FDA approved for a chronic genotype 1A infection. So, for him, his Hep C RNA remained undetectable 24 weeks after completing this therapy, which essentially meant that he was cured. On a subsequent followup visit, it was learned that he had resumed using crystal methamphetamine and having unprotected sex.

Which of the statements is true about this patient's risk of future Hep C infection? Choices are: the patient is not at risk for future infection because his infection has been adequately treated, the patient is at risk for infection because he has IL28CC genotype, or the patient is at risk for reinfection because of his ongoing high risk sexual practices, and the answer to this one is C. He is at risk, because he’s resumed his risky behavior, and can become reinfected. So, reinfection is definitely possible, and it is definitely seen and reported in the literature, and it's mostly seen in people with ongoing risk factors, especially intravenous drug use or unprotected intercourse, especially with MSM, so there is the MOSAIC Study, which stands for MSM Observational Study of Acute Infection with Hepatitis C. Trial was done in Amsterdam, and it actually showed a high incidence of Hep C reinfection in the HIV infected MSM population. So, these patients were previously diagnosed with sexually transmitted acute Hep C infection, and they were Hep C RNA negative following treatment of the primary infection.

And they defined reinfection as a new, detectable Hep C RNA after a successful treatment, and accompanied by a switch in the Hep C genotype or clade. And they found the incidence of Hep C reinfection in this group was 15.2 per 100 person years, with a cumulative incidence of 33% within two years, which is very significant. I have seen, I would not say often, but I have seen patients that have been reinfected two and three times, and we have to think about that, because like I said, these regimens, while they're becoming easier and with less side effects, they're also not cheap, so we need to use some discretion in, you know, if the patient is having ongoing risk behaviors, is a good idea to treat them now to prevent transmission, knowing that they might get reinfected again? And that actually becomes not even just a monitoring economic question, but also an ethical question at times, as well, and there's much conversation going on in the field about that.
So, in conclusion, acute Hepatitis C infection is increasingly recognized among young persons and HIV infected men who have sex with men, and is linked to recreational drug use and high risk sexual behaviors. Annual testing, at least annual testing, is recommended for HIV infected MSM. As I said earlier, the Hep C antibody can remain negative for a longer time period in HIV infected patients, so if there is a high suspicion for acute Hepatitis C infection, we always wanna check a Hep C RA, that's actually what we need to make the diagnosis, and also, for Hep C patients engaged in clinical care, we should be checking the liver function tests, ideally, every three months, and if we see a rise in the ALT that's otherwise unexplained, we should reflexively check the Hep C RNA. Guidelines recommend waiting up to six months before commencing Hep C treatment. That will essentially allow us time for spontaneous clearance, and that we do need to consider, weigh the risks versus the benefits of waiting versus treating now, especially in our patients that may transmit this disease to others. If you treat during the acute period, at this time, the recommendations are to use the same regimens with the same drug components and treatment duration as those for chronic infection, but more data is coming down the line for regimens specifically aimed to treat the acutely infected population, so that may change in the future. Lastly, patients that remain at risk for Hep C acquisition after treatment should undergo routine testing with at least serial ALT tests, and possibly Hep C RNA tests.

I just wanna draw your attention to the CEI line, where you can actually call in if you have questions about various things, not even just Hep C, also HIV, PEP, PrEP, and STDs. The number is listed here.

So, at this point, I'm going to pause and take any questions.

- [Audience Member] Dr. Burke? From the primary care perspective, so I'm treating mostly, I do see Hep C patients, but I also see, you know, your run of the mill primary care patients as well. What are your suggestions for when a patient just comes in and, like you said, has the vague GI upset, sort of like a stomach flu? Should we all be doing LSTs right off the bat, or giving them a couple more chances to prove themselves a little bit more?

- [Dr. Burke] Yeah, I think that's a great question. I think it really comes down to risk factors. If someone has no risk factors for Hep C acquisition, I would not necessarily send the lab. If they look otherwise, you know, fairly well, if you don't think you need to admit them to the hospital, they're not septic, you know, just kind of a run of mill, fairly mild GI infection, I would not, in every instance, reflex to LST testing, but I do think that I would ask about possible risk factors. If the patient, on that, you know, questioning comes up to be high risk, and they're telling you yes, you know, I'm MSM. I'm having unprotected intercourse, and had some of these high risk sexual behaviors, or uses IV drugs, in that case, yeah, I would, actually check LSTs in that setting, and you know, kind of keep an eye out for how high that ALT may be, and if the ALT does look, you know, fairly noticeably, significantly high, especially if it's in the high 100s or reaches 1,000, that right there, you know that you have probably an acute viral hepatitis, or some sort of, you know, toxic ingestion, like Tylenol abuse. Then, in that case, yes. If you see it very high, and it's in the context of this sort of viral GI setting, I would check the LSTs and then reflex to a Hep C RNA.

- [Dr. Brewer] Thank you, Dr. Burke, so much for spending time with us, and for your very informative talk. [Video End]