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HCV RE-INFECTION (AND OTHER STUFF)

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[video transcript]

00:08
All right, and now welcome again to HCV Reinfection. I'm gonna take a moment to introduce our speaker, Dr. Martinez and then I will pass it over to him. Dr. Anthony Martinez is Associate Professor of Medicine and Medical Director of Hepatology at the University at Buffalo. His interests are in development of novel treatment modalities for Hepatitis C among people who use drugs. He has worked extensively in the field of Addiction Medicine and specializes in treating patients with Hepatitis C and opiate dependency. Dr. Martinez is the Director of the HCV mini-residency program funded by New York State at the University of Buffalo. A nationally and internationally recognized expert, he has been a principal investigator on numerous clinical trials, and has been involved in the study of many novel agents for HCV, specifically among drug users. He is a member of the American Association for the Study of Liver Disease, where he was recently elected to the HCV Special Interest Group Steering Committee, the European Association for the Study of Liver and the American Society of Addiction Medicine. So welcome, Dr. Martinez. And thank you so much for taking the time to be here and present today.

01:20
All right, thank you all very much for getting on this thing and hanging out with us today. So when they originally told me about this talk, they asked for a talk called Hep C Reinfection. And then, I kind of went off the reservation a little and I named it Hep C Reinfection and Other Stuff, because to understand reinfection, we kind of have to understand all the other aspects of Hep C. So there's all my disclosures. I don't know, I don't like to tell you what you're supposed to learn, but you have to make a slide. So you might know all this stuff already. And it might be old news, hopefully not.

01:59
So some basic epidemiology, in the US we still have like two and a half million people who have Hep C. And I think the most concerning thing is that we have medications that can cure you 98% of the time. And if you look back at like, between 1988 and 1994, when you look at the HCV positivity rates, not a lot has changed, which is actually pretty concerning. So this is from the CDC, of the two and a half million people with Hep C, half don't know that they're infected. So why is that? It's in part because they've never been tested. And that's in relation, in part, to the fact that as providers for a long time, we didn't do risk based screening very well at all. And then we implemented the addition of age based screening, but it still hasn't gotten us quite where we want. There's also varying guidelines. So there's some slight discordances between US Preventive Task Force and the CDC, they don't completely line up in certain categories. And then finally, Hep C, I think most of you know, until it's more advanced, is typically asymptomatic. So you often don't get screened for something that you know, isn't necessarily bothering you. So the rates of Hep C have tripled over the past few years. And this is data from 2016, but these rates are closer to about 50,000 new cases per year. And really, this is owing to the injection drug use crisis. So the slide says it's in the shadow of the opiate crisis. But really, as it pertains to Hep C, what we're talking about is injection drug use as a whole. Depending on where you are in the country, if you're down in Appalachia, they're injecting methamphetamine, for example. And up here in the northeast, or where am I? I'm not in the northeast, I'm in western

New York. Well, you get my point, it is that it depends where you're at, what you're injecting, but injection drug use has always been the primary risk factor. As of today, it's the primary way that you acquire Hep C.

04:00
So here's a little bit more recent stuff, in 2018, you can see 50,000 new cases or acute cases of Hep C. And as we know, 80% of these patients who are acute go on to become chronically infected. Now, hopefully over the next year, I would like to see us eliminate the differentiation between acute and chronic and move toward just being viremic. The issue is that if you find someone who's acute and you wait six months hoping that they clear, especially if they're a person who injects drugs, in that timeframe they can spread infection. So I would like to see us, as a group, move toward being viremic and get closer to a test and treat model for Hep C care.

04:45
So who's getting Hep C? I think most of you, if you do this stuff, you've probably seen this important age group in your clinics. So really what we see now is between ages 20 to 40. This is the key cohort that is becoming infected. And it's like I said, it's primarily attributed to injection drug use. If we break it down by ethnicity, we have a huge problem among the First Nation members, American Indians, and Alaskan Natives, they have a huge problem with opiates on the reservations and in the territories. So we've seen the rates just skyrocket there. But if you go through every group, whether you're white, Black, Hispanic, Asian, the rates are going up across the board. In the old days, Hep C tended to be like 75% male 25% female, and we're not only seeing the skewing toward a younger cohort, but we're seeing more and more women of childbearing age become infected. And this is important because this group, especially female PWID, or people who inject drugs, they're much less likely to be linked into care for Hep C and to initiate treatment for Hep C. So that's an important thing.

05:59
I said that Hep C and injection drug use of traveling partners, we know that injection drug use related admissions are up 622% in patients between the ages of 18 and 29. They're up 250% in women, especially in that young cohort. And Hep C incidence is up 400% in that 18 to 29 group. So you can just see like, this is a trend that has always been, so goes injecting goes Hep C.

06:29
So I told you that injection drug use is the most important risk factor for infection, and this is global. Most people who have Hep C have a history of injecting, even if it's in the remote past, even one time use. The problem is that younger PWIDs tend to share, they don't yet know the rules to the game that you know, that you can't use the same needle. You know, I don't know how familiar you are with using heroin or meth, but typically you have bottle caps or spoons, and you cook it up and you draw it up through cotton filters that they say filters out, you know, impurities, but basically, it just shoots cotton into you. But the Hep C can survive on all of those works. It's much more transmissible than HIV. And like I said, most of these new infections nowadays are related to injecting.

07:15

Aw man I knew there was going to be, there's always something where you're like, when you see it in real life, you're like, I screwed up. And I'm sorry, you can't see the numbers in the black in the yellow boxes, there is always something. It's never perfect. But the point on this slide is that heroin use has increased across every demographic group. So if you look at gender, doesn't matter, up over 100% in females. Heroin use in that 18 to 25 group, over 100%. This opiate problem doesn't care if you're rich, white, Black, you know, private insurance, Medicaid, across the board. It's touched everyone.

07:53
So Hep C infection rates, they also are attributed to how many partners and how frequently is your use. So every time you bring somebody new into your network of use, you increase the incidence by 5.8 to 6.9 infections per 100 person years. So you know, it's almost a full percent increase every time you add somebody new. Now, if you go from using less than daily, injecting less than daily, to at least once daily, the rate of infection goes up 67%. You know, these numbers are scary. So really important that we're managing two disease states, kind of at once.

08:33
I talked to you a little bit about women of childbearing age, this is a group that we're really concerned about. If you look at this slide, you can just see how, especially in the younger females, they're much more likely to acquire Hep C than older females. And you can see where that skews off right around 2012. And that's kind of when we first saw this opiate thing really grab a hold of the country. And among those women ages 15 to 44, the acute cases are up three fold. So really concerning in this group. And Hep C is a problem in pregnancy because the risk of vertical transmission is about 6%, which is actually pretty high. And that's in an HIV negative female. So if you're co infected with Hep C and HIV, the risk of vertical infection goes up to about 11%.

09:22
Okay, well, where are we? We've seen all these groups, how they're disproportionately affected. So where are we in terms of care? Well, if you look at the care continuum, and this is among PWID patients, the orange is 2015, the black is 2018. And if you look at the folks who have ever been diagnosed with Hep C, when you follow the cascade down, only about 26% have been engaged in the treatment and only 18% have been cured. So these numbers are exceedingly low. A decade ago, the number of patients that were cured was only about 9%. So it took about 10 years, we're still under 20%. That's Seattle. If you go to Philadelphia, this is kind of a similar picture, you go down this care cascade, and you can see that the percent treated, especially if you're young, is less than 10%. If you follow that all the way down, and these again, these are PWID specific numbers. But basically, what I'm trying to show you is that we still have a ton of work to do in this population to get them engaged in care at all. Now, the World Health Organization wants to eliminate Hep C by the year 2030. The US, like many things, is dead last in the world. And there's a lot, I always make coffee when I do these things, and like 10 minutes goes by and it just gets cold, I'm gonna keep drinking, it doesn't matter.

10:45

We rank dead last in the global Hep C report cards. And part of the problem in the US is that we can't eliminate something if treatment access is restricted. And I'm going to show you a little bit more about what I'm talking about in terms of those restrictions in a minute. But really, this is attributed to stigma, who has it and how they acquired it. Hep C is the only disease state, to my mind that I know of, that you have to prove your worth for treatment, you have to demonstrate readiness and all of these things before we treat you. If anybody knows of any other disease where that's the case, feel free to throw it in the chat box. But it's you know, it's the only disease that I know of where this is a factor. And really addiction disorders in general, they're not on a level playing field with other chronic diseases. In the US, we view addiction as a moral failing or a choice as opposed to what it actually is, which is a chronic disease state.

11:45
Okay, I talked to you about limitations and restrictions. So when these medications came out in 2014, every state in the country had some restriction. And the big three pertain to fibrosis stage. So you had to have enough scarring in your liver to be eligible for treatment. Sobriety restrictions, you had to be abstinent from drugs and alcohol for six months. And prescribers restrictions, so you had to be a specialist from GI, hepatology, or ID in order to be able to prescribe. So you can see on the slide, as of 2018, we've made improvements, but there are still states that have these restrictions, especially if you're down in like Texas and Florida. You don't have to wear a mask, you don't need nothing, you can go get yourself some COVID. But if you got Hep C, you're not going to get treated for it. So there's still, you know, room to make a lot of improvement here. But based on the current estimates, it doesn't look like we'd achieve elimination in the US until at least 2037. But I think that at the current pace of new cases of Hep C, I would suspect that this is going to be even longer, especially when you factor in the impact of COVID. And we're going to talk a little bit more about that.

13:00
Okay, that's the lay of the land. How do we find Hep C? How do we screen? It's important that we bring this up because these screening guidelines have been updated. So the US Preventive Task Force and the CDC have evolved their their screening recs, and they now recommend that we screen all adults ages 18 to 79. There's a little discrepancy between the two groups about pregnant women, one says you should screen pregnant women and they leave it at that. And the other says that you should screen pregnant women at the time of each pregnancy. I forget who's who, which one says what, but I think you should screen pregnant women at the time of each pregnancy. There's no statement from either group on children born to Hep C positive moms, we know that is an independent risk factor to attribute Hep C with those vertical transmission rates and half these kids enter into the foster care system. So I would say that you have to follow those children carefully. But this is really a move by both groups toward universal screening. It does not replace risk based screening, you still have to do risk based screening. We have people, kids who age of first use of injecting is 12 years old. So you might have people that fall out of this cohort based on age that still need screening based on risk.

14:22
How do we screen? Y'all know this, I hope. You get a screening antibody test. If it's positive, it doesn't mean you have Hep C, it means you were exposed to Hep C. 20% of the time your

body fights it off, you get rid of it, you don't need treatment, you're not chronically infected. 80% of the time, you become chronically infected. So a lot of places have moved to reflex testing. So if the antibodies positive, they automatically do a viral load test, which will confirm chronicity. Now you could have somebody who's treated and cured, I yelled at one of our fellows the other day, the patient was inpatient and I think it was the eighth time that they've checked the Hep C antibody. It doesn't go away, it stays positive. It's like one of those things, once you got it, you always got it. So quit checking it. So if you have a patient that got treated and cured, or maybe got exposed and cleared and you're doing continued surveillance, you have to do that with a viral load test. So really important that you do that, and a lot of places now are also doing reflex testing for the viral load. So if it's positive, they'll automatically do a genotype test. So a lot of these tests now have changed, not everybody has access to then. But you know, if you have to do the antibody then the viral load, that's fine. It's just two different blood draws.

15:43
HIV patients who are AIDS defined, T cells less than 200, they can't be checked with the Hep C antibody, it may be falsely negative. Those patients don't have a robust enough immune system, so you got to do it with a viral load. Okay, in the old days, you had to do a million tests at baseline to work patients up. There's a new simplified algorithm. And this is really helpful because you know, a lot of these patients are younger, they're unlikely to be cirrhotic or have advanced fibrosis. So this basic algorithm allows sort of decentralization of Hep C care, meaning that you can do this now in an addiction clinic and a methadone clinic, a number of, an FQHC, non traditional sites, with just a few simple tests. So the key things here, the CBC, the CMP, a PT/INR. How do we know if our patient's got more advanced disease? Well, in the old days, you had to get a liver biopsy, that's all gone now. We don't have to do that. It's really cold now, I need a better cup. No more liver biopsy. How do we stage our patients? Okay, I told you on a CBC, the first thing you look for is a platelet count. If the platelets are low, this is the poor man's test for cirrhosis, that is cirrhosis until proven otherwise. Look at the comprehensive metabolic, if the albumin is low and the total bilirubin is elevated, most likely your cirrhotic. The INR, if it's prolonged, probably cirrhotic. So we have all these non invasive tools now. So you can do this thing called an APRI score, or you can calculate Fib-4, they're really easy to calculate. They're actually not easy to calculate, you have to do like advanced mathematics, but they're easy to plug into the app on your phone. I mean, one of them, it's like square root. So you know, I can't do it. But these are really easy, easy tools that you can make an assessment, if your patients likely or not likely to have more advanced disease. Some places have access to a FibroScan. FibroScan, you can see the pictures on the bottom, there's all these different units. We use this as well. It's like an ultrasound, but it tells us two things, if you have fat in the liver and how much scarring that you have. So a lot of non invasive tools at our disposal.

18:04
Okay, so what I've tried to do is kind of lay out what the story looks like so far. So Hep C in 2021. It's really multiple syndemics that are quasi modal. So it used to be just the baby boomer curve. And then it was bi modal with baby boomers and PWID. But really, what we're talking about now is dual disease states. So, you know, amongst the baby boomers, it's kind of yes still conventional just Hep C, there still may be people who have addiction issues. But then we have these other cohorts, the PWIDS, the women of childbearing age, the prison system, children

born to Hep C positive moms, First Nation members, and migrants, especially in Europe. That's a big, big group, where this is an issue. So really how we deal with each of these groups. I'm going to show you a slide, it's a little bit more abstract, but the pillars of how we deal with them are the same in that there's the same fundamentals, but what we do is kind of dependent on what we have. So I'll explain that in a minute.

19:08
How come I've told you, we've only gotten like 20% of these patients in the treatment? I think Hep C in general, it's only about 35% of people that have been taken up into treatment that are chronically infected. How come? We can break the barriers in to three groups. There's patient based barriers, they don't know that it's curable. There's still a lot of misinformation. They're afraid of side effects. They saw a relative or a family member or a friend go through interferon, and they have this sort of interferon based PTSD from what they saw. Their stigmatization, still a huge thing. The stigma of Hep C is still a very heavy burden. They don't like to talk about it. They don't want to go and talk to somebody new about it. So that's still a big issue. And because it's asymptomatic, oftentimes they feel like well, why do I have to treat it? I feel okay. Then there's provider based barriers, there's still a lot of providers out there that are really concerned with adherence and reinfection, which is the topic of today, which eventually, I promise I'll get to. And unfortunately, that narrative among these patients still persists. And hopefully, we can start to dispel some of this with some of the data. A lot of providers not comfortable with coexisting or concomitant mental health disorders or active substance use. And there's still a lot of misinformation and lack of knowledge among providers, there's still providers out there that aren't aware of the newer regimens and what's entailed. Finally, there is systemic barriers, a lot of patients are uninsured or under insured. Less than a third of people who get referred to a specialty clinic show up, not because they don't want to, but because the system's hard to navigate, they don't know how to do it, they don't know where to begin. Transportation is always the number one issue in why patients don't show up. And then the PA process can be complicated. And we've already talked about some of those treatment restrictions.

21:07
Okay, so this is kind of the abstract piece that I was saying, if I knew how to use PowerPoint, I would have reversed this. So the screening, linkage, and treatment initiation, those are the key pillars for elimination, so they should be on the left. I don't know how to do it, I'm sorry. But how we achieve what we want to within each of those groups depends on which of these cohorts we're dealing with. It's really a mix and match approach, how we screen a baby boomer could be completely different from how we screen a PWID. Because they access care in different places, they're being seen in different settings. How we link also depends on what cohort we're dealing with, and then the treatment initiation. So the point here is that you really have to recognize that each of these groups is a very heterogeneous group, and they're completely different. So there's no cookie cutter approach to this. I've been saying that for 18 years. And I still hold to it. So like I said, it's a mix and match approach. What we do depends on the where, what those settings have, the resources, and the who is there to do it. So again, mix and match, you might be in a setting, a methadone clinic that can't draw blood. So you know, you're going to have to screen a different way, you're going to have to link to care differently, you might have

a place that has a colocalized system where they can do multiple things. But really, this is highly dependent on these three key variables.

22:41
Okay, for Hep C elimination, there's some key treatment variables. We need widespread access to pangenotypic regimens. There's six types of Hep C, we need to be able to treat them all with high cure rates, low side effects, and minimal drug drug interactions. Treatment in the old days used to be a three hour talk, you had a mess of stuff, and it's now down to a two horse race. So like I said, they're six genotypes. These are assuming you're non cirrhotic and treatment naive. The first is GP or Mavyret. This is basically three pills taken once a day with food for eight weeks. SVR rate is 98%. You can't use this medication regimen in people with decompensated cirrhosis or history of past decompensation. It has a protease inhibitor, that can be dangerous. There's a few DDI, but the one that I highlight here is that it shouldn't be used with EE containing birth control pills. So that's one of the key things with with Mavyret. The other horse in the race is Sof/Vel or Epclusa. This is one pill taken once a day for 12 weeks. The same cure rate, 98%. And the key DDIs here relate to the acid suppressive agents. So this medication, you need a little acidic environment to absorb it. Okay.

24:02
Now this slide here, this pertains specifically to the GP or Mavyret. And the reason that I want you to see this, this came from Europe, this was shown at the European Liver Meeting. The point here is I want you to look at the graph, okay, whether you're cirrhotic or non cirrhotic, whether you're a PWID patient, you have a psych disorder, you're drinking alcohol, you're unemployed, no employed, low education, the cure rates across the board are just like in the clinical trials. At the end of the day, it's 98%. So this is just kind of showing you that as a whole, no matter what subset you're in, you're very likely to get cured.

24:42
Now on this slide, this pertains only to Epclusa. And what's interesting about this one, is that this was a multinational study, and it looked at 122 patients from a couple different countries. I forget I think there's nine countries, oh six countries. And these are all homeless patients. So a notoriously difficult group to treat. We always talk about barriers and why they have all these barriers, which is a thing that in 2021, I'm really working hard to try to eliminate. We perceive them as barriers, but for a lot of these patients, they're day by day reality. So in this case, 122 patients treated with Epclusa for 12 weeks and they all achieved SVR, everybody got cured, so very treatable.

25:29
This is one of my favorite studies that's come out recently. I had nothing to do with it. But I really like the guy who did it. His name is Alan Litwin, he used to be over at Montefiore in the City. And incidentally, Alan lost his wallet. And we found it and I called him, and I hadn't seen him in forever. And we reconnected over his lost wallet, which was kind of cool, pretty random. But he conducted this study called the HERO Study. And this involved 25 sites in eight states. And basically, this was a study dedicated to active drug users. So now they randomized the patients, and this is the largest one, I think it was like 755 patients, something like that. It's the biggest

active PWID study to date. Now, patients were randomized to two arms. So they either did this modified directly observed therapy, which involves not just the therapy itself, but also navigating them through the system. Or they went to this other arm, where they had a peer navigator who helps see them through treatment initiation and then completion. There's a mess of crap on this slide. All I really want you to know from this is that there's a couple important points. Per protocol, the overall SVR rate was about 90%. And these were active users. Now, adherence was better in patients who were over age 40, those who were employed, and those who had a little bit longer period of abstinence. So if they were abstinent somewhere between 5 and 12 weeks, they were more likely to be adherent. So adherence rates though, they were pretty much the same, whether it was the peer navigator arm or whether it was the DOT, that directly observed arm. And then the completion rates were about 80%, which is actually really good, especially in this tough PWID population. Lower SVR rate was attributed or was associated with more frequent injection, injecting more than twice a day, and a shorter period of abstinence, and also poly drug use. So if the tox screen was positive for multiple drugs, they were less likely to do as well. So just really wanted to show you kind of like, how very treatable all of these disproportionately affected groups are.

27:48

So La Bodega, this is our shop up here in Buffalo. You might have seen a similar version of this somewhere, I forget, we've shown it in Europe more recently, but our program kind of combines all of these approaches. So in the center it is a colocalized program where it's comprehensive hepatology, the backbone of which is Hep C. And we have a combined addiction program. So I'm trained in both things, in Addiction Medicine, and we do MAT on site. So it all kind of happens simultaneously. We have a number of community sites that refer to us. We work with our inpatient detox and rehab units, some of the local needle and syringe programs. And then we work with primary care and Behavioral Medicine, this is a hospital based clinic, both in the hospital and from outside. Once the patients come in, then it's this colocalized approach. We mentioned in the intro, we have this Hep C mini-residency, I saw a few names on here I recognize that have come through the shop and started treating. We have a social worker and a case manager, Angela and Crystal, like the heart and soul of our entire program. I think Angela is on today. They really quarterback, you know, the whole thing, the referrals, we make the appointments for the patients to facilitate the linkage, we organize the transportation. So we basically navigate the system for the referral based patients. We also use telemedicine, which we have implemented with COVID. We're not doing it quite as much now. It's more of an adjunct, we've been live since June. And this is a small team. We do about 6500 visits a year with a team of six people. But really, it's a number of micro models under one global structure. So all the different things are kind of combined. So this is just a few of the things we presented over the past year. We looked at our active users, we took and followed 429 patients and then we followed them through. The overall adherence among PWIDs was 87%. And what's interesting is that in the same exact model, in the same clinic, we don't do anything different if you're a non PWID, the adherence rates were only 77%. There were 15 patients out of the 429, the overall SVR rate on people who we had data on or who were due to be assessed was 99%. And currently, in the clinic, the SVR rate is 98.6%. We've had 15 people who failed treatment or reinfected. We'll talk more about some of that in a minute. We also have a detox model. So people who are fresh in detox, they automatically get screened. Of those patients who have

come through, 17 of them underwent treatment, they all achieved SVR and they all initiated MAT, equally is important. And then in the telemedicine program, we initially started with phone and video visits. By the second week, almost 90% of the visits were by video. We saw a 51 new patients for Hep C, and 84% were able to initiate treatment having never been met, and having the labs kind of done remotely. So just some interesting findings. But again, kind of trying to emphasize how you need multiple models within your model, and how one size doesn't fit all.

31:09
Okay, this is the part that I think you all came for, half an hour in I'm just getting to it. Let's talk about reinfection. Well, first of all, let's talk about what's cure mean. So cure, you basically you do your treatment, you complete, you wait three months, you check a viral load three months post completion, if it's negative, you're cured. Don't use words like dormant or remission. It's not HIV, it's not Hep B, it's curable. We cannot use SVR 4 as a surrogate yet. So I know there's folks out in the world who are checking a viral load a month after the completion of treatment and saying you're cured. There was an abstract, but the abstract was from the ESL, from the European Liver Meeting, and it only looked at Mavyret and the it was kind of underpowered. So we can't use the SVR 4 as a surrogate yet, I hope we get more robust data because this would be really helpful, because this is where you lose people in the whole cascade, that you can't get that SVR 12 confirmation, but you still have to do it that way.

32:14
Why is reinfection still a part of the narrative? So I don't get this, it happens. And so what? You cancer comes back, you develop CHF again, you have COPD recurrences when you keep smoking, you have a number of different things that come back and wax and wane. I don't know why we spend so much time talking about it with Hep C as if it were a bad thing. I would argue if it doesn't happen, you're not treating the epidemic's core, you're not treating the worst of the worst, the ones who spread. This is a concept of treatment is prevention. You have to treat the people who spread. Do we counsel all the different Hep C groups regarding reinfection the same way? I would argue that when you see a baby boomer, you probably don't sit there for an hour lecturing them about you know, if you relapse, you're going to get it again. Which isn't really fair, in a lot of ways, and I can't think of another disease state that pays as much attention to reinfection before we even read a script as Hep C. Again, we don't tell you, you know, well, you're not going to get your chemo if you keep smoking and we fixed your breast cancer, but you know, if you keep smoking, it's going to come back. Really this narrative is attributed to stigma, it is rooted in stigma and how the Hep C was acquired in the first place. Think about it, you only get reinfected if you keep injecting for the most part, right, but substance abuse relapse happens.

33:41
Finally, reinfection is hard to study long term, the data is rangy. It's historically been all over the place. And it's a fluid population, you have to follow them for a long time. Let's look at the data. This is from 2020. This was a meta analysis from Jason Grably's group down in Australia. Maybe it's not even down in Australia, maybe it's like over in Australia, but Jason's done a lot of work in this area and he looked at 36 studies. Now the overall rate of Hep C reinfection was 5.9 per 100 person years, about 6% among people who were using drugs. But when you break

things down, the rate almost cut in half to 3.8 among people who are receiving OAT, or in our world MAT. But when you stratify this, the rates of reinfection among people on OAT or MAT with no recent drug use, the rates go down to about 1.4 per 100 person years. So what is this telling you? This is telling you that reinfection is really a failure of harm reduction or a lack of harm reduction. Right? So we know and this is part of what I've been trying to point out with this talk, is that Hep C in 2021 among this young cohort, is really treatment of two disease states. Not just Hep C, but Hep C and injection drug use or substance use in general.

35:05
Alright, let's go to Barcelona. Whole mess of crap on this slide, here's what I want you to know, this group embedded hepatologists in a harm reduction clinic. And 845 PWIDs were offered screening, on site they used point of care tests. If they were positive, they didn't have to go anywhere, they could get access to treatment right there on site, very little heavy lifting. 54% of the patients declined to be screened. Now, that's a problem, right? Because that tells me that the people offering the screening are doing something wrong. I mean, you know, if you gave us 900 people, we're going to get them all screened. So that's an issue and that's putting the onus I think on the providers. Okay, well, let's go down and see what happens here. One of the good things that came out of this study, if we look at the graph, is that when the patients initiated Hep C treatment, their frequency of injecting actually decreased. So that's a good thing. And that's a trend that we've seen among PWIDs in the past. We know that once they initiate treatment for the Hep C, their active drug use tends to de-escalate. So that's one amazing finding. One of the problems that we've got here is the risk of reinfection. So now go over to the table on the left, 20% of these patients were lost to follow up, the reinfection rate was 14%, the SVR rate was low, 65%. So why is this? So we don't know, this was only an abstract. We don't know the full details. Were they offered MAT, did they have ready access to it, what the situation was. But here the reinfection rates were high and the screening uptake was low. Same group, this is a different study, they were utilizing a point of care test, trying to validate this point of care test as a way to use it to initiate patients on treatment, but then utilize these point of care tests to confirm SVR or reinfection. And the issue here is, again, when you tease all this stuff out, the overall SVR rate, it was pretty low. It was, I think it was only about 50%. And the risk of the reinfection rates here in this group were 33%. So there's a lot of things that don't make sense to me, especially being that those were done in a harm reduction clinic.

37:23
Well, let's go to Canada. This program is based out of Vancouver. Now, it's a clinic that's more comprehensive. There's infectious disease folks. Everybody's trained in addiction. MAT is widely offered to everybody, they have on site Behavioral Medicine. So they looked at a cohort of patients, 5700 patients who had been treated for Hep C over a period of time and they followed them out. And the rate of reinfection was 1.28 per 100 person years. Now, what's interesting is that among the patients who had uninterrupted OAT or MAT, the reinfection rate was zero, they were no reinfections. As long as you stayed on the OST. The risk goes up to 3.42 per 100 person years for those who did have interruptions. So you can see again, the opiate substitution therapy is a critical aspect of this. So reinfection is really a failure of harm reduction, in my mind, it's as simple as that. And it's critical to manage both of these disease states, we're talking about two different things, substance use disorder and Hep C. You can't do

one without the other or you can, but the likelihood that they reinfect will be higher. And to minimize this reinfection, patients need open access to OST or MAT uninterrupted. You can never use the right term, OST, OAT, MAT, whatever you put on the slide, inevitably I get like 50 emails, somebody's pissed off I didn't use the right one. So sorry, but for the purpose of this, I stayed with OST. Anyway, MAT. They need uninterrupted, continued OST, access to needle syringe programs. And not just clean syringes, but clean works, like the entire work kits that they use, and they need access to substance use and mental health treatment.

39:18
Okay, how do we work reinfection? Step one, you got to check the genotype. Is it the same? If it is, well, now we got to get some additional details, what regimen was used previously and was SVR confirmed? So you got to do some forensics. Is it a new genotype? Now if it's a new genotype, your job just got easier because it indicates that it's a new virus. Alright. This is just directly from the Hep C guidelines. It's all online, you can access that if you are wondering about it. But if you have a patient who is on a Sof based regimen, so these patients that maybe got Harvoni, maybe they got Epclusa, and they failed treatment, the recommended re-treatment is with something called Vosevi. It is a triple, it is Sof/Val/Vox, three medications in one pill for 12 weeks. As an alternative, you can use the Mavyret, provided they never had a prior NS3 protease inhibitor. You can use a Mavyret for 16 weeks. It's not recommended to be used with the genotype 3s, though, however. And really nobody really uses the 16 weeks, in this alternative option, this is primarily going to be Sof/Val/Vox.

40:41
Nole asked for someone with a serious alcohol problem, can the doctor refuse treatment until they get better or not? I mean, sure, you can do whatever you want, you know, you can do whatever you want, I guess. But I would argue you shouldn't do that. Because if they have alcohol use disorder, they have two hepatic insults, the drinking piece and Hep C, and you have the ability to eliminate one of those hepatic insults 98% of the time. So I would argue treat their Hep C, which will reduce their likelihood of accelerating to more advanced disease and try to sort out the alcohol as well, obviously, but I would not use that as a barrier to not treat their Hep C. In all professional societies, ASLD, IDSA, they no longer recommend any period of abstinence from drugs or alcohol to initiate Hep C treatment. So hopefully that answered the question. I'm multitasking, can you see that, in the chat thing, and anyway, pretty proud of myself.

41:44
For patients who maybe got treated with Mavyret, so this is the GP regimen. So maybe you got MAvyret for eight weeks, and you failed treatment, you can retreat them again, either with Sof/Val/Vox or Vosevi for 12 weeks, or you can retreat with the Mavyret plus ribavirin for 16 weeks. In most of these cases, again, we utilize the Vosevi. And think about this too. These are like, it's pretty rare. I mean, the cure rate is 98%, no matter the regimen, even with incomplete adherence or imperfect adherence or variable adherence, there is all these buzzwords now. The cure rate is still very high. So you know, I don't want you to get the idea that treatment fails all over the place.

42:31
This is relatively new in these guidelines. This is for patients, this is when you're right off the the reservation here, these are people who have failed multiple DAA regimens, including things like salvage therapy with Vosevi or Sofosbuvir plus Mavyret. So these patients that are just you know, yikes, they need quad therapy for 16 weeks either with Mavyret plus Sofosbuvir plus Ribavirin. Or 24 weeks with just Sof/Val/Vox Vosevi plus Ribavirin. If you're in this territory, you should probably refer the patient out, I don't think that you're going to be be treating them.

43:20
Colleen asked, how adherent does someone need to be to still achieve SVR? I believe HERO has data on this. So there is data on this in HEOR and there's also data on this in Simplify. Now, keep in mind, both of those regimens were Epclusa based regimens, so there's no answer to your question in general. How adherent, it depends on the regimen. It depends when did they miss? Did they miss early on versus later? How much did they miss? Did they miss a month, two months? So it's a hard question to answer. I can't give you an answer for that. With incomplete adherence, in Simplify, in ANCHOR, in HERO, even with imperfect adherence, they still achieved SVR and I believe it was like 88 to 90% of the time.

44:19
Brett asked, if you're unsure of SVR 12 status, do you ever use resistance testing to help determine reinfection versus true treatment failure? Brett, I'm glad you asked. Because this leads us to our cases. These are real cases. And the disclaimer here. I got 15 minutes. I'm almost done. I promise. I'm kind of almost done. These are real cases. The disclaimer is that, you know these two individuals are outliers. We've treated 1000s of patients and the reinfection rates are I think about, there's 9 that we're aware of out of maybe 2500 people. These are two of them. These are the two most difficult people I've had in 18 years of doing Hep C stuff. So please, you know, I'm showing you these because they're pertinent to what we're talking about, and they're complex. But I do not want you to think that this is the normal, I know this is recorded. Make sure you put that in the transcript because somebody is going to see this and be like, 'oh my god, no way am I doing this!' These are outliers.

45:28
Okay, case one, patient one. This is a 30 year old white male, in 2019 he was genotype 1A. He was prescribed treatment with Mavyret for eight weeks. He completed treatment, we thought, and he relapsed to heroin. So he came in and three months post treatment, he was due for his SVR assessment, and he turned out to be viremic. And he was, again, genotype 1A. So now the question is, and this is something that Brett just brought up, was this reinfection versus treatment failure? Well, when we sat back down with him. And this is a case, Brett, where I was going to do resistance testing, until he admitted that he only took four weeks of treatment. So I didn't think this was a true reinfection, this was more likely a treatment failure being that he was incompletely treated with only half the treatment course. But because of the fact that he was exposed to Mavyret, we had to retreat him with Vosevi. Now there's no clinically significant resistant variants out there that can't be treated through. So in this case, we didn't do resistance testing, he got retreated with the 12 weeks of Vosevi. So in August 2020, he had completed therapy, he had his SVR assessment, and he was in fact cured. Unfortunately, a month later, he

shows up in detox and he had relapsed again to heroin. And his Hep C RNA was again detectable. And he's again, genotype 1A. His girlfriend is also positive, and she's also geno 1A and they relapsed together. We confirmed that he had SVR on Vosevi, he had three fills that were delivered by specialty pharmacy, we had documented RNAs because we were following him really closely. He was on Suboxone with me. So we were able to see him every month. We confirmed that this was a true SVR on Vosevi. But it looks like a new infection, but now this is I can't 100% prove that it's new infection. So this is a kid that I would definitely do the resistance testing on, he may need a quad regimen that I showed you. But unfortunately, he is lost the follow up right now. We haven't seen him since I think September, and we're trying to find him. So this is an issue with him right now. But this is an example of the different regimens and some of the forensic work that we had to do.

48:00
Our second case, our second patient, this is a 26 year old Caucasian male, in 2017 he was genotype 3A. He got Mavyret for eight weeks. He was lost to follow up, he received meds, we lost him, he relapsed to heroin. He didn't resurface for two years. And when he showed up in 2019, he was viremic. And he was genome 3, but he couldn't be subtyped. Hard to tell, is this just a Quest thing? Is it a new virus, same virus? And he admitted he took some of the Mavyret, but he couldn't remember how much, how long he did it for, but he knows he didn't take it all. So again, we had to retreat him with Vosevi. I couldn't prove that it was new infection. I had no idea how much he took, it could be treatment failure, could be new virus. And we retreated with Vosevi. Now he only completed eight weeks of that, he never took the third month. So he relapsed within there, he was in detox again. He surfaced again in October of 2019. And at that point, he was well past three months of treatment with the Vosevi, even though he had only taken eight weeks and we checked them again. He was confirmed to be SVR, he cured with only eight weeks of retreatment with Vosevi. He gets lost to follow up again. August 2020, he surfaces again in our clinic. He had been in a long term rehab in New York in the City, he relapsed in the City. He was homeless, made his way back to Buffalo. We rescreened him and he was viremic, but this time he was genotype 1A. Now previously, he was a 3. So this is a confirmed new infection. Treatment course number three, he was prescribed Epclusa. Now he had Mavyret, he got Vosevi, he cured on Vosevi, and now we're on round three with Epclusa, being that it's a new infection. And he was prescribed the 12 weeks, he transitioned to methadone. He decided he didn't want to do the Suboxone anymore. In November of 2020, he was on week 10 of 12, and we were following his viral load closely when he would tox each month. We would also check the viral load to know he was taking it. But unfortunately in November, he left the residential facility he was in, he relapsed with the same girlfriend, his Hep C viral load remained undetectable. And unfortunately, he did not show up for his appointment in December 2020 and is currently lost to follow up. So we're hoping that we can track him down and hopefully confirm that he cured on the Epclusa. But two cases just to kind of highlight some of the forensics that you have to do and how to navigate some of that. And again, these are outlier cases.

50:48
Okay. How is COVID going to impact this whole mess? This is the end I promise. We've seen increased rates of anxiety and depression. People cohorted together in quarantine, programs

closed, they couldn't get to meetings, they couldn't get their MAT, rates of relapse and overdose have gone through the roof. And we're also starting now to see an increase in the rates of incident Hep C. Now COVID's had a huge impact also on overdoses. This was from OD Map, the blue is pre lockdown, and the orange is post, and there was about an 18% increase in just a few months time span, pre and post lockdown. And like I showed you earlier in the talk, as goes overdosages to opiates, goes new cases of Hep C.

51:36
This was from Europe pre lockdown, you can see the impact on attendance in the harm reduction clinics and Hep C program recruitment. 28% of patients missed follow up visits, linkage into the programs just get decimated, absolutely decimated. Reinfections also went up, 23% of reinfections coming after the lockdown. Ambulatory Care Clinic, screening in these settings, we've made a lot of progress, we were doing well with this. COVID lockdown you can look at that scatter chart, and you see whether it's birth cohort or outside the birth cohort, it just it gets waylaid. COVID is absolutely dismantled our Hep C care cascade. This is another European clinic. What I wanted to show you here is the table with the bars. And again, this is just showing you the impact of the lockdown, you can see the green bars pre lockdown and then post, attendance gets hit hard, huge reduction, almost a 20% reduction. Treatment initiation goes down to almost zero. Missed follow up visits goes through the roof. Now there was a reduced frequency of injection in this group, but what's concerning is that there was an increase in unsafe injection. So they weren't using as frequently, but they were injecting more recklessly and they weren't coming into the clinic. So COVID is going to have a huge impact on this thing.

53:09
Okay, last slide. I'm done. I feel like I should just skip this so you can ask questions. You can read this, but really, we have to do a better job with all of these three pillars screening, linkage, and treatment initiation. It's going to take a mix and match approach. I can't emphasize enough this thing about reinfection is really a failure of harm reduction and the need to deal with the ongoing addiction. That's one of the biggest things. There's another question that popped up in the chat. 'I work with women in correctional facilities. They've been fortunate in that they've been able to cure the ladies before they go home, sometimes a year or two prior. Should they get tested again, once they return home?' Yeah, not a bad idea. You get treated in prison or in corrections, and when you come out, yeah, it's always good to rescreen them if they have ongoing risk factors, especially. But sometimes also just for peace of mind, you know, corrections is a whole different animal. There's a number of risk factors in there. Even things like you know, going to the barber shop or things like that, getting tattooed. Don't get tattooed in jail. It's terrible idea. But yes, I would say sure. It's a good idea. It's not a hard and fast rule.

54:31
Nole, 'we have experienced doctors who don't want to go through the prior auth process. And also the cost of the medication is so high that they don't want to tangle with it, is the price of Hep C meds still high?' Nole, this stuff's all at parity. Right now, there is authorized generics of the Sof/Val. New York State Medicaid, I presume everybody on this thing is from New York State. I could be wrong. But in New York, we're actually pretty lucky, we have a very, very good

Medicaid system. If you have Medicaid, you are you are eligible for Hep C treatment. It's covered, we don't have people that have to pay anything. So you have widespread access.

55:20
Somebody asked, 'when people miss dosages, after how many days of missed drugs do you stop treatment? Or do you continue treatment and add drug at the end?' Boy, this question always comes up, there's no data. In general, you know, when you anecdotally ask people out in the world, you know, what do you do, I think the cutoff for most people is in that 10 to 14 day range. You get past that you really, you're running the risk that you're going to either introduce resistance, or that they're just not going to get cured. That said, a lot of patients, somebody mentioned, insurances refusing to cover Vosevi, for example. So you know, that becomes an issue. And you really, sometimes you think maybe they're only gonna get one chance at it. So you really try to push them through. As far as missed dosages, one thing that we see is, in general, what they tend to do is not shorten the treatment regimen, they actually tend to prolong it, which is interesting. So this is something we've seen among PWID, where they take an eight week regimen and they turn it into 12, or they take a 12 week and turn it in to 20. And it's really still one of the last frontiers for Hep C research. You know, to look at the importance of when you miss and things like that. Okay, let's see. Trying to scroll through the questions.

56:54
Yeah, no, you don't need to do prior auth Yeah, in New York, you don't need to prior auth. Now there's two boxes of questions. Holy crap. Yeah, you don't need, you don't need a prior auth in New York, that's over. And I believe May, the Medicaid stuff is going to change again where you can pick basically what regimen that you want.

57:22
Julia Hunter, one of the folks who came through the program with us, she's out there in Binghamton, she's treating Hep C. That's awesome. Baby and Chavez work in San Francisco. I guess not everybody is from New York! Cool.

57:36
What can I give verbally to get patients attention? You know, I find man that like most of these patients want to get treated, they want to do this. They're afraid, a lot of them are afraid, and a lot of them don't know how to do it. And Fabian has indicated that he's one of the bilingual health educators and our Latino population is a disproportionately affected group that we really need to do better with our Spanish language, educational materials, and addressing some of the reasons that they don't want to engage or haven't engaged into therapy. And some of that has to do with cultural stuff and things like that. So, I don't know that there's like an overt verbal prompt, but most of these folks, I promise when you sit with them, they want to do this thing. It's kind of just they got to know they're in a safe place, a stigma free place, which I know if you're on this thing, most of you probably work in clinics that are like that, but that goes a long way. You know, there's no magic bullet for this stuff, right? It's kind of just treating people as people. This is like the hug the tree portion of the talk. But I think that's the main thing is, is they can tell when you're authentic and when you really care about them and want to help them and do this stuff.

59:03
Thank you so much for a great presentation.

[End]