Clinical Education Initiative
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Title: Opioid Dependency, HCV and HCV/HIV Coinfection

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Opioid Dependency, HCV and HCV/HIV Coinfection

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- [Presenter] Welcome to Physicians' Research Network. I'm Jim Braun, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease as well as its coinfections and complications. We hope this recording of Brianna Norton's presentation, Opioid Dependency, HCV and HCV/HIV Coinfection, will be helpful to you in your daily practice, and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants, and membership is open to all interested clinicians nationwide at our website, PRN.org. And now allow me to introduce Brianna Norton, Assistant Professor in the Department of Medicine, and HCV Medical Director of the Comprehensive Health Care Clinic at the Montefiore Medical Center in the Bronx, New York City.

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- [Brianna] Hello everybody, I am going to talk a little bit tonight about treating Hepatitis C, and our Hep C/HIV co-infected patients, particularly in people who inject drugs. So I treat a lot of these patients in primary care, and I'm also medical director for syringe exchange, and so I do a bunch of linkage to care for these folks, and so happy to talk about this today, it's an important issue.

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So why should we care about people who inject drugs when it comes to Hep C?

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So first of all, 80% of the new infections in the United States of America occur among people who inject drugs in this country.

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And 60% if not more of existing infections in this country are among people who inject drugs. Really these people represent the core of the Hep C epidemic in the United States of America. Importantly, people who inject drugs, when asked, in multiple studies,

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have a very high willingness to receive Hep C treatment, even in the era of pegylated interferon, but unfortunately to date we are treating very few of these people. Maybe one to two percent per year. So, what does this have to do with people who are living with HIV?

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So a quarter of your HIV positive patients are likely to have Hepatitis C, and importantly about 80% of people with HIV who inject drugs also have Hepatitis C.

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So likely if you encounter a person in your clinic who's HIV positive who injects drugs, or a former injection drug user, they're likely to also have Hepatitis C, and unfortunately when you're coinfected with HIV, your risk of Hepatic decompensation, Hepatocellular carcinoma, and liver failure is, almost triples when you have HIV coinfection.

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So, as most of you have probably seen this study, this is the D:A:D's cohort and they looked at causes of death for HIV positive people from 1999 to 2011, and I think the take home point was that liver related death was sort of first described as one of the primary causes of death among our HIV positive patients in the United States of America, most of that attributed to Hepatitis C. And even now, in 2014,

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which is much further in time from there this is the cause of death in HIV patients in London, who have a similar demographic to us in U.S., and you can see that after malignancy and non-AIDS respiratory failure, liver-related death still remains one of the primary causes of death.

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So treating our HIV positive patients for Hep C is extremely important from a morbidity and mortality perspective of the individuals. However, unfortunately, this goes beyond the individual.

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Because we continue to have transmission of Hepatitis C from IV drug use in the United States of America. And this is a, these are data showing incident Hep C infection among young people, less than 30 years old, in the United States, and what we know is that between 2007 and 2012, the amount of incident Hep C increased 50% over the nation at large, and in 17 states, the Hep C incident increased by greater than 200% and that is true in New York State. So we also continue to have Hep C transmission,

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and the CDC states that probably in 2014, we have about 30,500 new cases of Hepatitis C. Of which 75% are being transmitted from people who inject drugs.

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So, just like in HIV, what we know is that if we treat people who have Hepatitis C, we can prevent incident infection, and therefore we can reduce the prevalence of disease among a population.

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So these are data, modeling data, that basically show, if we estimate about a 50% prevalence of Hepatitis C among our people who inject drugs, and we scale up treatment, that the more we scale up treatment among people who inject drugs, the quicker and more efficiently we reduce prevalence of

disease within that population. So in this model, they assume that prior to 2002 people who inject drugs were not being treated, and that is because unfortunately guidelines recommended not doing that. And then they assumed a baseline treatment of about one per 1,000 PWID, until 2015, and then they modeled various scale-ups. And the more we scale up, if we scale up to 80 per 1,000 person who inject drugs annually, which is actually not a lot, this is not huge numbers, we're not talking about treating half of our people who inject drugs, by the time we reach 2027, a decade from now, we can practically eliminate Hep C. Now this is a huge feat.

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But most modeling studies show we have to be aggressive in treating people who inject drugs, if we are to truly make a dent in the prevalence of disease. So, the good news is, we actually have meds to give people to do this.

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So this is Sofosbuvir/Ledipasvir, known as Harvoni, Sofosbuvir/Velpatasvir, known as Epclusa, and Elbasvir/Grazoprevir, known as Zepatier, they're all one pill a day medications. I didn't mention 3D here, although Viekira Pak or 3D is also appropriate. We're lucky in New York in a lot of ways, because Zepatier is a lot cheaper, a lot of the insurance companies will approve the one pill once a day medication. So these are great meds, their cure rates are greater than 95% in HIV coinfected people, it's only one pill a day, as we saw drug-drug interactions, although they exist, are easily, you know, you can easily choose a regimen that can fit your HIV positive patient, and side effects are extremely few.

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So, okay, but we have great cure rates with these drugs, but are the cure rates any good for people who inject drugs? Do people who inject drugs actually complete these therapies, do they adhere? Do we have any data to show that these people do just as well?

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So this is a meta-analysis of over 36 studies, this is in the era of pegylated interferon, and there are nearly 3,000 participants in these studies of all who are people who inject drugs, and you can see that the pooled SVR rate for these studies is 55.5%, which was the, basically similar to all studies in the era of interferon. So most people achieved a 50% cure rate then, and when you take this meta-analysis, people who inject drugs also received a 50% cure rate, and this is even in the most arduous of medications with a lot of side effects. So we do have evidence that people did well, even if they were people who use drugs. Now what about in the era of DAAs? You know some people thought, well that might be true, but you can imagine that if you were a person who used drugs, that to actually say you're gonna take that horrible medication for six months, you probably are a distinct type of person that already shows that you can complete therapy and adhere. But when we're talking one pill a day, are the people who begin treatment really going to do as well?

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So I think what we need to do is first define people who inject drugs a little bit better, because for years we've been sort of lumping everybody in together. So, there's lifetime injection drug use. And then there's current injection drug use, and then there's people who are in drug treatment, or opioid substitution therapy, be it methadone or suboxone. And some of those people are not currently using drugs, and then of course there is some overlap, people in drug treatment who are also currently using drugs. So I think the big point is that most active or current people who use drugs were specifically excluded from all pharmaceutical trials in the era of DAAs. So we have little data on how these people would do. But what we do have is data for a small number of people who are in opioid substitution therapy, and they were allowed in some of these trials. So what we can see is that,

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this is 3D, or Paritaprevir, Ombitasvir, Dasabuvir, or Viekira Pak, or 3D, Sofosbuvir/Ledipasvir, Harvoni, and the newest medication Sofosbuvir/Velpatasvir, Epclusa. And you can see that cure rates in people who were on opioid substitution therapy, methadone or suboxone, were just as good. But if you look, these denominators are quite small. 56, 38, 70 who got Harvoni compared to nearly 2,000 who were not people who use drugs. But I think this is certainly proof of concept that people who use drugs can do well in the era of DAAs, certainly in registration trials. The exciting thing is that Merck went on a limb and decided to have a phase three trial where their entire objective was to enroll people who use drugs.

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And so the C-EDGE CO-STAR trial looked at the efficacy of grazoprevir and elbasvir, which is Zepatier, one pill a day, specifically in people who inject drugs on opiate agonist therapy. So most of these people were in methadone treatment programs. And they gave these people 12 weeks of Zepatier.

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And what you can see is that the cure rates were great, over 95% just like in the other trials with this medication and whether your drug screen, meaning your urine toxicology was negative or positive, meaning whether you were also using illicit drugs at the time, your cure rates were identical. And you can also see that most people were using drugs at that time. And again this is just to show,

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when you look at the cure rates of 95%, a positive or negative drug screen did not alter your cure rate in this trial. So this is great. So a lot of you will say yeah okay, but what about in real life?

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You know, we know that everybody does better in clinical trials. You have research assistants calling people, getting you in, getting you to complete therapy, I mean we all work in HIV clinics, primary care clinics, you know, do we really have the staffing to get these people through treatment like Merck did? So, let me show you a few data about that, but first I think the barriers are obvious.

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So, in regular life, in the real world, you have patient barriers. And our patient barriers are, do they have insurance, stigma, there's certainly a lot of stigma against people who use drugs and getting them treatment, competing priorities, obviously people who inject drugs have a lot of comorbid psychiatric illness, comorbid physical illness. Obviously employment, income, housing, drug treatment, these are all huge problems for our patients in terms of getting them treatment. And certainly there's very Hep C-specific barriers, within our patient populations, and certainly a lot of it is about misinformation. People who use drugs have a lot of mythologies, both true and not true, about Hep C treatment, because they know people who have been treated. So a lot of people don't realize that the new drugs are better or that the side effects are less. And so these are things we need to educate our patients on. And there's certainly provider barriers. You know, HIV or primary care providers not realizing the increase in risk of liver fibrosis progression in terms of our HIV Hep C coinfected patients, not realizing that one pill a day is actually quite easy to achieve, and a lot of perception problems, just sort of referring or treating the good candidates, because of concern for adherence and drug use and risk of reinfection. And finally, the system is a problem, not only with stigma but cost of medications and like I said, is there really sufficient resources to get these people through treatment. So, one of the ways to overcome these barriers is to try to treat these people in clinics that they're already going to. And for us, as HIV providers, this is easy because a lot of our patients are already in care because of their, because they're people living with HIV, and a lot of our clinics have support

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because of ADAP and because we're very lucky and live in New York State, and so we have case managers, we have on-site social workers, we might even have on-site psychiatry or substance abuse treatment, and there's over 1200 federally qualified health centers in the United States who have a very high proportion of people with HIV/Hep C coinfection that can take on this model. So, what we did, and this was presented at CROIs, we looked, did a study, an observational cohort of looking at cure rates among people who inject drugs in primary care, this was a Montefiore clinic in the south Bronx.

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We did have a care coordinator that was funded by New York City Department of Health, and she was essentially there to help with prior authorizations, do reminder phone calls, and re-engage people who were lost to follow-up. And we defined drug use in four ways, again, whether you were currently or actively using drugs and whether you were in or not in drug treatment. So we followed 89 patients who initiated Hep C treatment with DAAs between 2014 and August 2015. And over half of these people were people who used drugs, defined like I said either on OAT or currently using drugs.

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Okay, so here we have no current drug use and no OAT, and that's our people who are not using drugs. And everyone else is defined as a person who uses drugs, whether they're not currently using drugs and on OAT, or actively using drugs on or off OAT. And, here we go, and so we have about 50% of our people are defined as people who use drugs. And if you look, about a quarter of these people are infected with HIV, over a third have cirrhosis, nearly half had psychiatric illness, and these are not people who are just

using marijuana but who are obviously using opioids, cocaine, so these are very traditionally difficult to treat patients. And the take home message is that the cure rates between people who use drugs and people who do not use drugs were identical in this cohort

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after 12 weeks of DAA therapy. And when you look at it by grouping, whether they're

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on OAT or not, again, cure rates were all extremely high and there was no significant difference between any of these groups. So these are some real world settings to show that this can be done and people do well. I think it's important to point out some clinical pearls. You know, how do we assess for treatment readiness,

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in these patients? And I, most of the time I think the most important thing is motivation to be treated, and adherence to appointments. If people aren't able to show up to appointments, they're likely not able to adhere to treatment regimens. However what I don't use is the amount of drug use that they're having, their homelessness, or other things, because if despite drug use and homelessness they're able to adhere to appointments and come into the clinic, then they're likely able to get through therapy, one pill a day, quite easily. As HIV providers, we have a great way to measure adherence, and that is our HIV viral load. So if you have patients who are HIV/Hep C coinfected and they're able to remain undetectable from their HIV perspective, they're probably great candidates for Hep C treatment.

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The one thing I want to mention is that guidelines for Hep C treatment, they recommend a baseline visit, and then, like a treatment initiation visit, and then you follow them week four. I don't do that, and I think a lot of people who also treat people who use drugs might see them first a little sooner. So one of the things I think we're successful is that we do bring them back at week two, just to assess adherence, assess that they have their meds, and then we go with guidelines and go week four, eight, and 12. But I do think that's important, to bring them back a little early, just because sometimes lives are a little bit more chaotic. And finally, this was published in Expert Opinion this year,

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there's been tons of pharmacokinetic data looking at suboxone or methadone in combination with all of the Hepatitis C medications, and the take home message is, there are no drug-drug interactions, there are no dose adjustments needed, and in trials, both in real world and in registration trials there's been no increase in sedation or increase in withdrawal when giving Hep C medications with people on OST. So you don't have to worry about those drug-drug interactions.

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Okay, so another way to overcome barriers for people who use drugs is treat them in the methadone clinic, because many people who are on methadone are going at least multiple times a week, and they're familiar with the system.

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So this was a study that was done in a methadone clinic, again, these real world data are early data, they've all been presented at international conferences and will be published in the literature probably within the next six months, but real world data is coming out. So these are cure rates for 61 people who were treated in a methadone clinic and about half of them received individual treatment, a third of them actually got group treatment, and 15% got DOT, meaning, the five days a week they got methadone, they also received their one pill a day Hep C treatment.

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Again, these are people with a lot of comorbid illness. And importantly, drug use even during treatment was over 50% for this population.

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And the overall cure rates were 95%. So just again, another setting that even when people are using drugs during treatment, they're able to be successful.

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Okay, so these people do well, but can they even get the medications? So, one great thing, because we live in New York, is most of our HIV infected patients, in New York City particularly, are actually insured. So we have a huge advantage for our HIV/Hep C coinfected patients because most of them have insurance. Now a lot of them have Medicaid, or they have Medicaid affiliates.

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And so this, are the restrictions based on medicating in the United States of America. And basically 75% of states still require that you have a fibrosis level of greater than F2 for therapy. Now if you look from 2014 to 2016, you'll see that that's improving, and I think what's most important, if you look at our state, there are no longer restrictions. So, that's important. On the other hand, there has actually never been restrictions for HIV/Hep C coinfected patients. So fibrosis level does not matter in terms of HIV/Hep C coinfected patients. So we should be able to get the meds, and we do. It's actually quite easy. But what about drug use? We're talking about people who use drugs, people who inject drugs.

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Unfortunately, greater than 70% of states also have restrictions related to drug use, and again that is improving from 2014 to 2016, but many of them require a three to six month abstinence period. Again, this is not a problem in New York State. So in New York State you do not have to send in urine toxicologies, all they ask is that you provide some harm reduction or some drug treatment education to

the patients and that is it. So in New York State, all of our HIV/Hep C coinfected patients should be able to get the medications.

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So, importantly, restrictions are not in line, like I said, in New York State we do not have restrictions. But in other states these restrictions are really not in line with the Hep C treatment guidelines for people who use drugs. And unfortunately,

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so if you look at the AASLD and IDSA Hep C treatment guidelines, they specifically say recent and active injection drug use should not be an absolute contraindication to Hep C therapy, and furthermore, scale-up of Hep C treatment in persons who inject drugs is necessary to positively impact the Hep C epidemic in the United States and globally. So these will not be achieved if we continue to have these restrictions.

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Okay, but what about reinfection? So, we treat them, they get their meds, but is this all in vain, are people just gonna get reinfected if they're people who inject drugs?

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Okay, so this, these are three meta-analyses looking at reinfection rates over multiple studies for people who inject drugs, which is here on the right, history of injecting, and then people who continue to inject drugs post-cure. So if you look, most people who inject drugs, whether current or former, it's very low, the reinfection rates. We're talking like, two per 100 person years. Now that does increase if you're someone who injects drugs even post-cure, it might increase to about five, maybe even seven reinfections per 100 person years. But again most of these are quite small. The other thing to remember though is a lot of these data do come from the era of interferon. And therefore it will be interesting to watch reinfection rate, and certainly we're gonna see publications come out in the era of DAAs. But this was a more recent publication,

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another meta-analysis, that was published this year, again looking at reinfection rates. And the way they did it I thought was interesting, was they categorized people in low risk, meaning not a person who uses drugs, high risk, oh sorry, low risk mono-infected, high risk Hep C mono-infected, and high risk was defined as either current or former injection drug user, so a person who use drugs, recently incarcerated, or an MSM, men who have sex with men. And then they also wanted to look specifically just at HIV/Hep C coinfection. So if you're low risk, your reinfection is nearly nil. If you're high risk, it does go up to about 2.2 per 100 person years, and interestingly in this study, HIV/Hep C coinfected patients had the highest risk of reinfection at 3.2 for 100 person years. Still low, but the highest. The only thing I want to point out is, if you look at the number of studies that they gathered those data from, it's only four studies and those confidence intervals are huge. And one of those studies, which was the largest, was a study of entirely MSM. And what we know, interestingly, is that the population of MSM have a much higher rate of reinfection actually, than the population of people who inject drugs. So the

MSM have a reinfection rate of around nine to 12 per 100 person years, and currently it's more around five per 100 person years for people who inject drugs. I will state, there was a study that came out of Norway and they looked at everyone they treated between 2006 and 2008, and they followed them for seven years. And the people who continued to inject drugs, there was a 4.9 per 100 person year reinfection rate, and so this was in the era of DAAs, it was Sofosbuvir based therapy, which meant that approximately 25% over seven years were reinfected. So when you look at these person years, it's low, it's around five, but that means that about a quarter of those people were reinfected at year seven. So these aren't insignificant. But I will also state, that means that 75% of people who inject drugs and continued to inject drugs remained Hep C free at year seven. Which is actually quite good, particularly when we're trying to reduce incident and prevalence within that group.

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Okay. But because it exists, I think probably the most important thing is to incorporate harm reduction in conjunction with HCV treatment. Now this is a bit of a, convoluted slide. But I will try to navigate you through it. So this is modeling studies based on data of increasing treatment among people who inject drugs, and also increasing harm reduction, meaning opioid substitution therapy, and needle exchange programs. And looking at how that can affect your overall prevalence within the community. So one thing to note is that even if you, and this is assuming a baseline prevalence of around 60%, which it is in our community of people who inject drugs. I think what's interesting is based on modeling studies of what we know, is that if you increase needle exchange programs to where you're covering like 80% of folks, which is quite significant, you still actually, oh I'm sorry, I'm not, this is after 10 years, change in prevalence after 10 years. That if you increase to 80%, and you go up here, you'll see that after 10 years you're really only gonna be able to reduce your prevalence rate in the community by about 40%. So after 10 years of really high impact harm reduction, it's hard to make huge reductions in prevalence. However, if you combine coverage of harm reduction with treatment, and like I said not a ton, 40 per 1,000 people who inject drugs, you can get significant reduction. So if you increase coverage of harm reduction by about 40% and increase treatment of people who inject drugs by about 50 annually, you can get a reduction of about 70% prevalence in 10 years. So we really need to be thinking about how to combine treatment of people who inject drugs with harm reduction. And, what has been said over and over is if reinfections don't occur, then we aren't treating the right population. Because we need to be treating the people who are transmitting disease. So we're going to expect some amount of reinfection, and I think the question will be, as we get more data, how much will we allow, and how much will it affect the reduction in prevalence?

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So, what about harm reduction by a medical provider? So, I think it's important that if we treat these people who inject drugs we do provide harm reduction ourselves, so certainly you want to educate the patient about the possibility of reinfection. And so I always say to the patient, your Hep C will never ever come back. Because there's always confusion around that. However, you may get Hep C again, if you share syringes or, have a high risk behavior. So just letting people know. I think it's important to not stigmatize the drug use, but instead say, if you relapse to drug use, or you're continuing to use drugs, to really emphasize not sharing syringes, cookers, cottons, water, crack pipes, or snorting devices. All of it,

a lot of people don't realize that we've definitely seen Hep C transmission through snorting devices or crack pipes. It certainly is not just syringes, it's the cookers and the cotton, and all of that as well, and if you know your community syringe exchange contacts or addresses, it's even better. Certainly there's the Lower East Side syringe exchange, there's NYHRE in the East Harlem and throughout the Bronx, and all of them have vans and places where people can get syringes. But on the other hand, you are completely empowered as physicians to write a script for your patients, and what I often do is write a simultaneous script for the Hep C treatment, with syringes, so that patients really take you seriously that harm reduction is part of this treatment plan. And often patients, you know, one cc syringes, patient will know what syringes they use. So they can educate you. I think another thing that's important is really to treat their partner. If someone has a partner that they do drugs with, then it's a lot, then it's really gonna be not beneficial if we just treat one of them and then they continue to go back and live together and use drugs together. So I would treat a partner or, you know, a friendship circle if people are using drugs. And finally, if you can get the patient into an OST program or prescribe them buprenorphine yourself, we can, again that is one way to increase harm reduction while at the same time increasing treatment of people who inject drugs.

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So, my final thoughts, essentially people who inject drugs really represent the core of the epidemic of Hep C in the United States. We know that they can achieve high cure rates even in real world settings, reinfection is low but it certainly exists and so we need to incorporate harm reduction, and in order to reduce the transmission and prevalence of Hep C in the U.S., we really must actively and aggressively treat people who inject drugs, and finally, in New York State, we're lucky in that coinfected patients really are covered almost by all insurance companies, and there should be no restrictions for those patients. Go forth. Thank you.

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