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CHARACTERIZING THE MECHANISMS OF SEXUAL TRANSMISSION OF HCV AMONG MEN WHO HAVE SEX WITH MEN

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Characterizing the Mechanisms of Sexual Transmission of HCV among Men Who Have Sex with Men

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- [Jim] Welcome to Physicians' Research Network. I'm Jim Braun, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease, as well as its co-infections and complications. We hope this recording of Daniel Fierer's presentation, "Characterizing the Mechanisms of Sexual Transmission of HCV Among Men Who Have Sex with Men" 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 Daniel Fierer, Associate Professor in the division of infectious diseases at the Icahn School of Medicine at Mount Sinai in New York City.

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- [Daniel] Well, it's certainly good to be here when it's not snowed out. I had the dubious honor of apparently having the only snow cancellation in the entire history of PRN. So- that's the nature really wanted to hear this talk. All right. So tough. Here it is. So, this is really honored be back every few years, I guess, one of the earliest talks about having uncovered this sexually transmitted hepatitis C epidemic in New York was Jim Barbee, one of the early talks- it's got to be almost 10 years ago now. So I'm circling back with saying that we've made some progress slowly. And, I'm going to start started the end and come back the net so a little earlier data that basically, I hope everyone in this room- actually most people in this room- is sort of ahead of the curve in understanding that we had sexually transmitted hepatitis C among, at least, the HIV infected men have sex with men. And, once that became clear, since there was a lot of skepticism, but even without the skepticism, we need something- some actual evidence- to bring to ourselves to understand it and to develop prevention messages. How can we stop this and so this is really where it's coming in. So I'm going to go back to the beginning and some of this is going to be pretty obvious to many of you, but just sort of follow along with me so I could tell you how we thought about this.

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In the beginning, and really still in many circles, the question when even I talk about sexually transmitted hepatitis C- sexually transmitted hepatitis C- that that's not what we thought. So I want to go back to things we thought we knew about hepatitis C, because it's still relevant when I talk about transmission. So, I've developed, what might be one of my many quirky phrases about sexually professional sexually transmitted organism. So hepatitis C still, I don't think falls in the category of professionals, you know, syphilis, gonorrhea, chlamydia. This is what they do, HIV. And so I think hepatitis C is largely along for the ride but so it's not a professional, but it does a pretty good job in some settings. And so I want to talk to you about- to start off and try to understand transmission where we have the most, you want to call it, data. Let's do some behavioral data from some case control studies and then I'll tell you about the two clinical virological approaches I've taken to try to get a little more actual evidence from the hints

from the behavioral studies. And then the end, I'll tell you about what I think we have, which is a further expanding epidemic and I mentioned this. So coming back to question I think Eric Rude asked me, the Department of Health, years ago about- about whether we have to think about all MSM in addition to HIV infected MSM.

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So, here's somebody I told you guys about many years ago, one of the first people I saw. But we'll start off thinking about a case as usual. 46-year-old HIV-infected man came for his initial medical evaluation- his first HIV visit. This is a few years ago now- he came in with the CD4 count of 427, a very typical HIV viral load. Got hepatitis virus screening and had antibodies already in hepatitis A and then vaccinated against hepatitis B, but had no antibody to hepatitis C and in that time, we talked about it and deferred for come back in three months. And so in three months, I feel great. I know you're little better and talked about some of my social history and that I've had protected receptive and sort of you know, of course with many men, many anonymous, and using meth, coke, ecs, sort of alphabet super drugs really in parties but I don't inject it and slam, and alcohol is not my drug and here he had his ALT was 960, so three months after a normal. LFTs and not jaundiced, had new hepatitis C antibody three months ago was negative and about a six logs of sort of typical hep C viral load genotype 1a, which turns out to be basically the epidemic genotype in the US and in Europe and in Australia. He didn't have syphilis and he didn't have hepatitis B.

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So this gets back to the dogma about coming into this and say 2006 when it first- this man came to see me. We thought this wasn't sexual transmitted but that's not for lack of evidence. It's actually the evidence of this was sort of interesting. It talks a lot about normative sexual values that's heterosexuals and stable couples, but in fact the evidence was quite good and this was in literature, large studies of discordant couples. The man or the woman who were stable heterosexual couples with one or the other in hepatitis C, they took sexual histories a joke- they're married so then having sex but they had to write that down and they claim to be having sex. And over, really hundreds and hundreds of person years across, actually thousands of person, it's really across these three and there are a couple other studies- these are the ones I usually cite. There were zero transmissions between the couples. Zero. A few people got somebody else's hepatitis C, but nobody got partners hepatitis C. So this is where the evidence of lack of sexual transmission of hepatitis C comes from prospective studies. But, this is stable heterosexual couples. So the other thing is that there's sort of a thought now. Those in the room who know a lot- it's maybe history in retrospect. But in fact, men who have sex with men were pretty good evidence they were not a risk group for hepatitis C or sexually transmitted. You know, we didn't have antibodies to do prevalence studies until the early 90s. But in retrospective studies of serology and in some other ways of doing it, there in fact, in retrospect, was no evidence that there was sexual transmission among MSM in the 70s and 80s, when we had the HIV epidemic was expanding and hepatitis B of course. And the best we can tell if you look at hepatitis C, even subsequently, all the way through the early 2000s and some cohorts, if you can remove those who injected drugs, habitually heroin the seroprevalence is in fact really the same as the general population, and some cases even as low as blood donors, which is the very rarefied group of seroprevalence. So there was pretty good

evidence against there have been much sexual transmission in men who have sex with men, up till about 2000. This latest report here that came out in 2007, you've been looking at Canadian cohort.

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And so, I say things we ought to remember then though, in coming into this is there are lots of kinds of sex, and that things change. And this is so important in medicine and really we're looking at a coalescence of these two things with this particular epidemic.

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And here is my schematic of things changing. So in Europe, just to remind people that the first reports of what looked like sexual transmission of hepatitis C were England, and France, Germany and Amsterdam- there will be a quiz on these- on these flags there, by the way, and don't confuse the French and the Dutch flag. And that, there were a few reports in some journals saying we think we're having sexual transmission a few cases. Just a few years later, there was a case report in San Francisco. We had started seeing cases here, we got published- some scattered in the US through an ACTG study. Lynn Taylor had a lot to do with it, and that in northern and southern Europe and more cohorts- there were published. And down in the southern hemisphere here, don't not look down there at Australia- they, very early on, realized they had an epidemic and in fact, and even in some Japanese clinics in Tokyo, actually one very large clinic had an increase in incidence of sexual transmitted hepatitis C among MSM while the incidence was not as high. So we have both hemispheres, four continents, really within just a few years, were- who had seen this, in many cases, documented incidents increase.

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And so, what comes first. OK. What are the behaviors associated with acquisition of hepatitis C. This is the easiest thing to measure. Maybe easy is not so easy.

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But, so in a study that I did with my colleagues in an association with some of the folks at the viral hepatitis branch in CDC on the first World Hepatitis Day, we published in the MMWR, our case control study of some men we had seen here- many of you are- were your patients and sent them to me and we asked them a number of questions between 2005 and 10. And the main findings, we did actually a pretty significant questionnaire that was quite similar to one done in London and Amsterdam; I put together some- some questions for all that. And the multivariable analysis- there were actually only two statistically significant behaviors, out of quite a number. And it was receptive anal intercourse with ejaculation, that's receiving semen into the rectum, with an enormous odds ratio, although wide confidence intervals because the numbers were not small, and sex while high on crystal meth. And this was interesting because it is not crystal meth use which actually just use outside of sex was not significant between the infected and uninfected men, and this was excluding people who had injected. So I didn't mention that these were not injectors. And it's also not other drugs. So it wasn't KG, alcohol, anything else; it was specifically meth. The others were not significant. So, this is what I call sexualized drug use. Since then, I think it's- English have started calling it chem sex. Although to my knowledge, they never actually published that is true. I think this is the only published report, actually documenting

that this sexualized drug use is significantly associated with acquiring hepatitis C. So this is- this is New York and this is how I was thinking about it: semen in the rectum, while under the influence of meth during sex. And so around that time and then subsequently, there were seven case-controlled studies. So case-controlled studies are reasonably high quality, try to get similar people who don't have a thing compared to those who do have the thing, rather than just listing out risk factors of the people who came to you. And that's a little bit tricky and you'll see a lot of that because people were, for lots of things, but they are called co-linear. You do all the same things at one time, so it's a lot of X. But what is specifically associated with it- that you have to subtract out by doing the multivariable analysis.

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So I- talking just about the seven, although there's more, you can see they're across Europe, there's a few in the US and what I spend a lot of time staring at these results, because they're somewhat different. And I'll tell you why and how they're different- I'll show you here and how to think about this. And so, of those who asked about unprotected receptive anal intercourse, five of the studies found that was significant, and two of the studies- one in Germany and one in Belgium- said that wasn't even significant. All right. Group sex- 3 out of the 5 studies that asked about group sex found that that was a significant risk factor. Fisting- four, not in New York. That wasn't significant in the multivariable analysis. Rectal bleeding, on the other hand, only the German study and those two others that asked in mind that didn't publish that in this study. And then sniffing drugs- two of the studies said yes and three no. So you look at this and say well, some would say do a meta-analysis. I say actually, "Don't do that" because we had pretty different studies. And what I see when I look at this is that it's complicated. The tendency, the urges to go and find, "How can we boil it down? We tried to do this in medicine- "What's the single most likely thing, how, you know, what are the possible errors?" And the more I looked at this, the more I said, "Well the praying we have here is we have different countries, we have cultural differences, and we have, what may be something that's unfortunately a little complicated rather than simple. But think about this then, as I'm going out, and this sort of form- how I was going to look at things.

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So I came back to what- what we found here which was receiving semen in the rectum. I thought that that's the simplest explanation for that. So I wanted to take that from behaviors then, to actually understand transmission- body fluids. It's got to come from somewhere. Right. So, how do we think about that? If a two different body fluids, the most obvious through semen because that was the receptive anal intercourse with ejaculation into the rectum. That's where the virus is coming from. Seem fairly obvious. So, and then, that had been done before as it turns out. So we looked at rectal fluid as well, which was something that you wouldn't have seen before.

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So in the first setting, and thinking about the semen, say well, "What do we know about this?" Well it turns out, we know quite a bit about hepatitis C in the semen, going all the way back to 92, practically just after the discovery of the virus. And since then, 14 studies in the US, Europe, South America, over 700 men with chronic hepatitis C and most of the studies was interestingly done for assisted reproduction- they were part of the sperm washing, also those who had HIV and hep B to try to not put

the virus back in mom, essentially. So these we're looking quantifying both- you know, quantifying and just their yes or no. And, the best I can read from them- most of them, although certainly would be possible, most of these were not MSM- it was mostly heterosexual couples bringing the men for what it's worth. And some of them did have worse studies with men with HIV. And so the results vary quite widely. 5 to 57 percent. The studies found hepatitis C in semen, and there were five studies that had men with HIV in it, and it was not definitive all. And I just say that HIV was not clearly associated with having, with being either more likely to shed into the semen, or were having higher levels. That was not, I would say, that with five studies, it was not clearly the case. So I think that that's probably not likely to be a very big effect. It may be a little effect, but I would not consider that an important effect based on the literature. In the six studies that quantified the shedding, the- the range was up to about 3 logs, so 3/3/44 logs, there that would be only a thousandth of the typical blood level. So clearly much lower. And I think that this was, when people who then filtered this out and brought this out, it's considered another bit of evidence that's there. This wouldn't be important- they said, "You know, look. There's a big semen blood barrier. These are low levels- thousands or less blood so that can't be important." And so this is another thing, when that if you don't think something's happening, then you can find evidence that this isn't important. I will then disagree. I think you're going to find, going through this with me.

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So we decided, well, there have been a lot of studies but we're going to do another one. So some years ago, I started working with some of the students who can work with me from Holland and Australia, and started asking men to bring in semen specimens.

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And what we were able to do is get a cohort then of 33 HIV infected men, who had recent and some longer standing hepatitis C infection. All of the ones I'm going to present here had HIV. Since I tend to study recent infection, two thirds of them had recent infection less than a year. And we looked at some with chronic longer than a year. We got 63 specimens total; we tried to do repeat specimens- I asked them to do three; that didn't always work out. And a couple weren't evaluable. There is some semen- turns out to be a little bit difficult to work with as a body fluid- it's a little- a little sticky, and not always- doesn't always go through the machine cleanly. So we just- we lost a few specimens there. And so the results of this are thus I'm going to show it to you in a couple of different ways, so you can think about, and look at.

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Well here go- the number of men here- 21 with recent, 11 with chronic hep C. We did viral load testing on them, and we found that it was detected in 29 percent of those who'd recent infection, 42 percent, but the numbers are very small, here. So, not suggesting there might be an actual difference here but it all come down to basically a difference in the viral load. But overall, a third of men had hepatitis C shed into their semen. So this fits pretty typical into the existing literature on that about one in three men.

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Now looking at it by semen specimen itself- looked at the men who had recent hep C. And what did- this is a plot of the blood viral level, and then the semen viral level. So each gets a corresponding thing here. Somebody here who has a pretty low blood viral level, with some of the recent infections, but has a little bit over a log, while this person here has a very high blood viral level, and a similar semen level. And that the- looking at this is a- are here is the correlation in the statistical test, that between these two, they were both then merging the chronic and recent, there's a fairly strong- I'm going to call this a pretty strong association between the higher the blood viral load, and the higher the semen viral load. Make some sense? This is a blood-semen barrier, and it's somewhat proportional. So it's both more likely to be shed and the levels are higher. Now if you look at people whose blood levels are very typical hep C level of six logs, that's a million. What you find is that most of the people then, who have blood levels that high, had, now semen levels. So, if you have people who have a very typical hep C viral load, they're reasonably likely now, to have shedding into the semen.

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So general conclusions. A third of men, who have hep C that's recent or a little chronic are likely to have- that's what I tell my patients now- a third of men who have a HCV are likely to shed into the semen. The higher the blood level, the more likely to have shedding, and the levels will be higher. What we were looking for didn't find, were people in very early in hep C, like acute HIV, pre -seroconversion- antibody seroconversion- hepatitis C, it's the same phenomena, only two logs higher virus in the blood. And believe it's likely that, I think with my HIV hat here, that the hep C levels would be much higher and the truly acute hepatitis C transmission may be very high. I was unable to get semen on anybody like that and when I proposed this to the NIH they said, "You're just going to treat them anyway, so we're not going to give you the money." So, we have not yet been, you know, that's a very sad thing. Seriously. They did say, "Transmission- who cares- you're just going to treat them." So, I'm currently a little bare bones here on the funding. So finally, it only takes, granted by injection, 10 to 20 particles obviously if you inject that- this is chimp experiments- to cause infection. So, and based on our findings, the average ejaculate, based on a four and a half mL ejaculate by Rehan et al. and 75 would deliver up to about 6,600 IU virus into the rectum of receptive partner. So if you have had seen the semen, there is enough there. I think, based on this, to be rubbed into the circulation. So semen could transmit hep C through unprotected anal intercourse, and condoms would logically prevent this, just like it would prevent the HIV in the semen from infecting the person. A fairly straightforward thing to be, that you can bring home to patients.

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The second part of my fluid decision, I thought, "Boy, you know, while the semen is important, I'd sure hate to miss it- what if there's hep C floating in the rectum and we sure would want to know about that, and that would be terrible if we didn't, if we didn't know that." So I thought, "Well we'll just- here's what we're going to do; we're going to just ask the men if we can do a fairly simple experiment with- with swabs." So, while the case control studies that we did in New York- it looked like semen in the rectum- if you picture the other stories, things like fisting or group sex, there's a tendency to, sort of think that I'm going to address this later about bleeding. But remember, only one of the seven studies was bleeding

statistically significant associated rectal bleeding, associated with hep C acquisition. And one of the reasons maybe, if the rectum bleeds, where does the hep C come from.

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So, since they were transmissions that I couldn't plausibly explain with semen, we went to look there. So I've coined another phrase for you here which is, "penis's fomite". And I said, "Well, what's the difference between an inanimate object like a sex toy and penis or fist, if you're talking about bringing hepatitis C from one rectum to another." And I have anecdotal evidence of that from some of the men who've come to talk to me about group sex episodes that they've had with each other, and we have their viruses and they're the same. So I haven't published that yet but I think this will be compelling evidence. And there was stories from Germany describing, they thought that this could be taking hep C from one rectum into another. And so hence that experiment. And interestingly to me, nobody had ever looked at that. And our paper is still the only one on this. It says something about how I think about this.

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So we undertook that with my colleague, Michael Gaisa, who's an anoscopist at Mount Sinai and was an expert rectal swabber. So I had him show me the ropes to make sure we did it really well. So here's what we did. We just took a swab, put it about seven centimeters and this is just the way you do your chlamydia and gonorrhea swab, gently rotate. What I'll look at is see if there's any blood on it, put it and swish it around some medium, and we bring it to a lab where we run it through the hep C machine. And lower limit of detections of 7 IU. So it's actually the clinical use that the clinical hep C assay.

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And we did account for the putting a swab in, and how much gets absorbed in the swab and how much comes off in the fluid. And we accounted for that when we were quantifying it. So corrected that, we drew the blood levels. The way we had done in the semen. And so this analysis is going to look a lot like our semen analysis, in that we also tested for rectal sexually transmitted infections and for syphilis.

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And we did swabs on 43 men, and founded it in just short of half. So detectable of a little bit higher than the semen in proportion. Median viral level- just short of 3 logs. So the actual median level of this was a little higher than the semen. Still in perspective, three logs lower than blood.

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Now, to show you about again, similar kind of idea- possibly a barrier, we as a blood rectum barrier. If you look again here, blood viral load gets higher as you go in this direction, and then the rectal viral load gets higher in this direction. And you can see here that the scale here, 6 logs is almost as high as the blood levels. And so doing the statistical analysis, just looking if you have five logs of hep C in your blood, which is really most people have chronic infection. That's only 100,000. That would be very low- very strongly associated with having, shedding into the rectum. And, if you go to six then, it's a very, very strong association. So a typical, chronically infected person or person who has recent infection with a higher level of viral load is very strongly associated with that. And in fact, above six logs, 86 percent of

men who had typical, bland old chronic level HCV viral load, and a detectable hep C in the rectum. And some of the levels here are actually fairly robust in the- more than 4 log range.

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Hep Cs shed into about half of the rectums of men who have hep C and HIV with recent or chronic hep C. The higher the blood viral load, the more likely it is to be in the rectum. And the higher the level that's in the rectum into very, just typical range. It's not crazy high viral loads- just regular old viral loads. 86 percent of men had- in the rectum with antitypical blood viral load. And so, same hypothesis here- much higher in the blood during the true, acute seronegative early phase of hep C, we may have very high levels in the rectum. Thinking about it the same way- same inoculum size, thinking of very low. The average- we made a calculation with the surface area of the average human penis would be, and we coated with about 2,500 units of- there we go, the schematic there- of hep C, and that would be coded for the duration of intercourse. So I've asked people who say, "Ah, you know, that's not really very much, and you know, penis would be hard to infect inside, invite all the male versions of that. So yeah well, here why don't we just take your penis- we'll dangle it in 2,500 units and rub it around for a while," and I haven't had any takers on that one. We'll follow you with viral loads for a while, right? So- and so I think that this is pretty reasonable evidence- direct evidence- that there is enough to be covering a penis, removed, or a toy or a fist. Fist has a bigger surface area, from one rectum to another in a group sex setting; we're simply sharing a toy that hasn't been cleaned in between. It could conceivably infect the inserted penis so I think that, again that would be the penis is a little bit, you know, being mostly stratified, good stratified epithelium is fairly good. We know that you have to have a reasonable abrasion to get hep C. But nonetheless, I said, "I don't think there's anybody in the room would be willing to do that experiment with me." If there is, come up quietly afterwards, you don't have to say anything right now and we'll- we'll do that. And so I think that this is again, the sort of other piece that can tell people about "penises' fomite" in a group sex setting or fist or actual sex toy.

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So I've been trying to think of what a model looks like for this. And here is a very early attempt at this. That- that you may find unsatisfying because I'm not quite ready for that yet. So to declare this real, so I put the body fluids and then sort of how to think about it. I think nobody else has really been talking about fomite in the middle. We talk about blood and everyone thinks, "Hep C blood, hep C blood," It's almost like a blindness thing we have, and that was when we were less susceptible to that I think because of our HIV experience, but I think we can to put that aside. Yes, sharing blood, injecting blood- very infectious. 6 plus logs. We know that. Very infectious. But, the interesting thing- even the men who are injecting- I think it's ironic to me because everyone knows that's how you get hep C. So I'm sure if you talk to your patients about how they slam, they'll know that hep C is that way. And they- you know, we live in a great city for these. You just walk to that pharmacy and say, "Give me a box." It's cheap, you know, points are cheap. Getting into the language there. Syringes are cheap and- and they put sharpies and mark- this is mine, this is yours. Put it in your shoe. Everyone's' got a system. And unless you're really high, you usually don't lose track of them. And so, I- pretty much all men that I see use slam, maybe 15 percent of men I see, maybe 20- by now it's going up a little bit over time- have a really good system, and are pretty darn sure they didn't share. But they're so sure that hepatitis C is transmitted

that way, they come and tell me, "Oh, I got it from that slam I did." And I said, "Really? Was anyone else in the room?" "No." "Where did you get your point?" "I just bought it." Was it fresh, and they opened it?" "Yeah." And they opened it. But yeah, the whole thing. No share, no nothing. But we've hammered into people so strongly that hep C is blood that they're sure that spontaneously generated in this brand new syringe from that's, you know, tapping a little crystal in there that that's how they got it. Unfortunately what that means is that they tend to get reinfected by having semen in their rectum, because they're so sure that they're- that it's the share. And so I've had that one guy even come and tell me that I was right. He didn't believe me at first. And he came back and it was reinfected. He said, "Doctor, right. Said I didn't share, and got infected." That's not the kind of right I like to be. So anyway, so- so that's all came with this model. So we know that we have really clear evidence that blood will transmit hepatitis C, and that receptive anal intercourse- these are for our case control studies. And I would just put to you that other things that you'll talk about- nasal drug use, even fisting. When one says, "Oh, this blood!" OK, but where's the, you know, the hand doesn't bleed in the rectum, right? The penis- penises don't bleed into rectums. They just don't, right? And so if the rectum bleeds, where is the hep C coming from? It's the bottom who's being infected. So that could be obviously a much worse fomite. If you have bleeding, that it's easy to get it on somebody else. So I would put these as thinking about even nasal drug use. You get a little blood on your nose, you have hep C, and you give it to somebody else- I don't want to personalize your hep C. One, somebody else has a hep C, and you know, it gets- so you get the blood on from somebody else's nose. That's again, that's a fomite transmission. But semen does explain a lot of it, and having semen there- what can break down the barrier? So some of these other, I think, are interesting observations, although not consistent across all. Things like douching prior to receptive anal intercourse. So this is extremely common as you know, and we have one case control study in Belgium that found that it was a very high risk, and another in Amsterdam, which is European geography- they're right next to each other in countries, and share of culture didn't find it to be the case. But one can imagine that that could wash out bacteria. We know that increases STIs, in some cases and there's some studies that it's weakly associated with acquiring HIV. So we can imagine that bacterial STIs' possibly ulcerating. You know, you don't know where the chancre is and the syphilis, maybe it's in the rectum, and that allows things to get any easier. All these things are possible. I don't think they're necessary. I think that's really important. So, things that increase risk- we know, it's the same thing for HIV. What increases risk? Ulcerating things, making the portal of entry, softening up the area as it were. But probably not necessary. So these are just things to think about and how you would counsel. We clearly now demonstrated. And I put in yellow things that we have actual, now physical lab data on that there're semen and a third of men; there's rectal HCV that could directly, in fact, probably more likely to be fomite transmission mechanism.

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All right. So you can see why that's an imperfect model. But it gets me to be able to talk about this. So we talked about- here I've told you about behaviors that the behaviors are actually quite different in different countries. I think that's true. I think that that associations in different places with different cultures and over time, as behaviors change, as awareness changes. All those are maybe real, rather than pooh poohed. "Oh, they just did the study wrong." These are pretty good people. There are probably some statistical differences, but I think that many different behaviors in different places can be associated with hep C acquisition, if you consider where the fluids come from. So body fluids- I think, I

hope that you've seen now, that rectal fluid and semen- these are the two body fluids, really exchanged during sex. A question that gets asked that I can address, here, you know, and you can ask more questions about, "Well, you know, what if there's a little blood?" I said, you know, "OK." I mean you- you may have talked to your patients about how much bleeding. People are pretty sensitive that; most recognize blood on your penis for instance and stop. That's been my experience. And, at some point, you say well, what is rectal fluid? Well, it's actually the red part is not of blood, is not where the virus is, right? The virus isn't in the red cells- it's in the serum circulating the plasma, right? So this is this is where our body fluids come from. It's not from the blood part. So we are in equilibrium, right, in many of the body fluids between blood and semen- blood and rectal fluid. So, well maybe it's just blood. Well, it is blood. It's just an exchange with the blood. But what we're thinking about is trauma in the red stuff. You don't- so you don't have to leak red cells in there. But I think- so, it's important to consider that this doesn't have to be something that causes red blood cells- big enough to puncture because red blood cells to extravasate. You can just have the fluid extravasate. So, with those thoughts, I would put you- we're talking about HIV infected men in all this. Why is a HIV necessary at all? And I've thought for a long time that it's not necessary.

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But, it was hard to show when we weren't really seeing it. And so people would ask me, "Why is it that these men all have HIV pretty much, before when they get hep C? What is it about the HIV?" Well we can posit that the- the rectal mucosa is changed forever. Once you have HIV, you have a massive destruction of the CD4 help that happens immediately and immune dysregulation. And we know that that is never completely restored from the work of Marty Markowitz- these guys up the street here, and other groups. That's never completely restored, even a long term antiretroviral therapy. So it may be that it's more the barrier is decreased a little bit. And we know that there is more endotoxin and other bacterial products that come through, and people who have HIV infection even very well controlled. So it might be a little weaker and therefore a virus might get across more easily. That's certainly possible. But if seminal hep C can cross through the rectal mucosa and rectal hep C can infect that inserted penis possibly or through deposit in another rectum, then it seems to me that there's no reason this would be restricted to HIV infected men. And so, here is how to think about why it appears to be this way. Well the first and clearest reason- well, let's not say first reason. Let's just say that HIV infected MSM at this time are the reservoir among MSM. And this has entered this population for various behavioral and historical reasons. So, this is where they hep C is and where the HIV is. Now, HIV itself is much more infectious through sex than hep C is. The converse is true, we know very clearly, in hep C. We know that injection use of injection drug users in Newark for instance, 90 percent became infected in the first two years of injecting. But despite continued injecting, only a third ever got HIV. So HIV even when injection drug users, is actually a lot less infectious. But the converse is- is true that hep C is much less infectious. Therefore, if you're having sex with men who have both HIV and hep C stochastically, you're going to get HIV first- maybe a hundred times maybe 50 times- before you'd get hep C. It's just a statistical phenomenon. There's more HIV in the semen, there're more receptors- it's just more infectious. It's a professionally sexually transmitted organism- virus. And so for those simple reasons, that's all you need to explain why these men really all had HIV before they had hep C, because that's what you get when you have sex with people who have both. That's- and the HIV prevalence is actually probably higher as well. So again, I think this is a stochastic phenomenon- not something about some sort of impermeable

barrier or any kind of reason there. But, pre-exposure prophylaxis against HIV, Truvada: great HIV prevention, terrible hep C drug. And so this is I think, a natural experiment that is now happening. And I'll show you my anecdotal, wildly anecdotal, super anecdotal experience.

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Before PrEP year, and some of you out here really early adopters. So these are going to be overlapping. So five men- I'd say, a few hundred HIV-infected men, five HIV uninfected men, who came in with their primary hep C got- that appeared to be sexually acquired. So0.6 a year. Even saying that is almost suggested that I have better numbers, that's almost statistically illegal. And the PrEP year- I'm going back to 2013 because a couple of men were on PrEP here saw me- 8 HIV uninfected men who were on PrEP who got hep C, and then 2 got reinfected- two of those. And so that's 10 infections in about this four-year observation period. So, I think that based on just this, you say, "Look, that's just, you know, referral bias. You were- we knew you better in 2013 through 16. Maybe we didn't- we didn't think you wanted to see those guys before something," and I'd buy that. But I'm quite worried about this. And talking to colleagues around the country when I sort of have a poster or talked to them in different meetings, pretty much, the big PrEP prescribers said they all seen a couple of cases. But of course, we may be looking for this more now. And there was a letter to the editor in Clinical Infectious Diseases about a year and some ago- Kaiser Northern California, where they found three cases in there. But they told me, also anecdotally, since then, that they really haven't- maybe only seen one. So we- I don't know the answer to this, but I can just say that, which is the same thing I said early on in this- in this among HIV infected men that once you have a mechanism for transmission and once something is happening during sex, when was the last time you saw that go away? So I would just present that while this may not be true, and I'm not saying, "Boy, would I like this not to be the case," that just keep an eye out.

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And that- I think that we have to be concerned. So here's my message. Take care. Show this every time because I just love this World War II poster. VD in the old days, right? But now I'm going to say, "Take care. HCV.

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And let me go through the conclusions of my talk here, with those things in my time. So while in stable, heterosexual discordant couples- there was no hep C transmission. So, hepatitis C is not sexually transmitted- that doesn't mean that's the case for everybody. And in fact, there is reasonable evidence that people just sort of push them on the carpet that- that heterosexuals who had multiple partners had much more hep C than others. But that was conveniently brushed around. You have to go look for that and the CDC doesn't really have that much up on their site now, because it's not a very clean message. But similarly, before about 2000 or so, MSM had similar HCV prevalence to the general population. This is, I think, is reasonable evidence this is a fairly recent, that is 21st century- I like saying that because it's the modern century- we're seeing the hep C transmission that has increased. And probably not in every city in big cities. But there are some studies that said, "We didn't see much of an increase." The just- I didn't mention this before but in a way of thinking about it, if you see a study like that, MACS, so the Multicenter AIDS Cohort, published in there. But they're in Pittsburgh. Most of their people were

enrolled in Pittsburgh and the suburbs of Chicago and some in LA and in Baltimore. And so they found- they said, "Well, it was relatively flat over time." Now, we can say, "Well in the time you looked at- it wasn't happening in those cities." And that's not that surprising. But I can tell you that in New York and in San Francisco, that's a different thing. And so they looked in a place where they didn't see much. So things will probably change. Now, we've seen there are many studies in many cities and I showed you the map, where the sexual transmission has become epidemic. Many case control studies have shown different kinds of results among them. None of them agreeing completely. In fact, none of them agreeing that closely, leading, I think, to multiple possible mechanisms and a couple of which I've addressed. And I actually think that between these fluids, it probably addresses most of them. In this city, the epidemic- at least when we did the study, and that questionnaire study actually ended kind of a while ago, we had that- those data done by 2010 I think. So I haven't revisited this. But at the time, it was driven by receiving semen into the rectum while using meth- high in meth sex, high in meth sexualized drug use. And I just found that to be anecdotally that was true and that's continued to be the case. The men that I talked to. And not everybody, right, it's a statistical association, but it's common. And so we went on to investigate the hep C body fluids, we found hep C in a third of them, rectal fluid in a half, have really gone through that carefully. Therefore, it can be transmitted via semen and sex with one or multiple partners, and the rectal fluid could get spread around the party pretty quickly. And so, the data really don't exist that- what phrase that I'm going to go "beat up on," which I read in many of my colleagues in a lot of papers. So I read "traumatic sex." And I kind of ask, "Well, what is that?" And the data that I see- I just see being bottom as what it is, as- as the as the main- bottom and semen. And so, I'd hate to call that traumatic sex. I'm very much against that. So I'm going to try to remove that word or even the idea that traumatic sex is necessary. I think, sure if you have your rectum bleeding, then hep C could get in a lot easier. Blood coming out- something could get in. But that's a very unusual report in most of cities- it was really basically just in Berlin. And, so I want to just completely not think of it, and I think it's right- I think it's misleading, and it makes people think, "Well, I don't do that." So, you know, just- just bottom and I get semen in my rectum. Well that's where the hep C is. So I'm going to suggest avoiding it. I think it's pejorative.

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OK. So, in some, many ways men get hep Cs- semen, rectal fluid- I'm here to talk to you all about this. This will then, you can bring this back to patients. So how do I purchase? Well I think that quarterly liver tests are still a good idea. I don't have a cost effectiveness analysis on this. But as we've gone, our HIV visits have become- so I've even called it that. Our care of HIV infected men who has sex with men and others is so focused on HIV, that we sometimes forget- busyness, that other things happen. I sort of think it was the AIDS PTSD, those old enough to live through the AIDS era maybe have it the worst. Oh well, we don't have to follow a CD4 count. We call them CD4 visits and their viral visits. "Oh we don't have to do that very often- the drugs are so good, they're not toxic- I basically don't have to see anybody- just keep writing that prescription." And we forget that behaviors are changing, other things are changing, and of course, we have to remember aging and check the cholesterol here and there. So, I think that one of the things we really miss by not seeing people, is you don't see their LFTs go up and down, and even if you test their hep C antibody a year later, they've had it for a while, if they've got it having sex, and they've been having sex since then. So be thoughtful about whom you might want to see more often and why you're seeing them more often. And I would consider that for the men on PrEP too.

So I think that men who are going to start PrEP need to know that they can get hepatitis C from getting semen in their rectum. I think this is good enough evidence to say that. Early diagnosis by seeing people more often can decrease further infections. This is treatment as well. This diagnosis and treatment is prevention. This is just old hat to everyone in this room. Some years ago, I got up and I believe to be the first person to say, "Treatment when-" I said, "We've got to treat these men early. Don't sit on it for a long time. Don't fart around. Treat. Because that can prevent further infections." And I still believe that. And it's getting that interval- I've been showing you treatment data. But the earlier you get people in, the more likely are to cure them. And ah, my homage to Steve Jobs- the anvil. We need to keep doing that work. And so, all you out there, prescribe the antivirals, especially non-toxic ones for 8 to 12 weeks is easy. And you guys could just see all the guys can do hep C, and just treat them all. And I suspect that's happening. I'm gonna make a little plea, that I hope you don't take it self-serving, but without each individual person coming to see me, it's all referral bias- massive referral bias. But you guys in the room who have sent me individual people, I think this person's fairly, newly infected. Even if you're not brand newly infected. Maybe it was last year and we just picked it up or something like that. I would ask you, please continue to just send me those people. Try to get virus in the freezer, I've asked the CDC to look at if we can compare the viruses, we can learn a lot from the science. And even just having them basically signing up and being part of the experience counting. This is the only city in the country, I'm kind of the only person in the country, which is sad- the Europeans are doing a good job- who is doing this. Where is Eric? Maybe had to leave. Eric- I was back there- at the Department of Health. So I try to work with those guys but they have their own thing. So really, do this because I think we need to know. And if all those individual people you said hadn't come in and filled out their questionnaires and done this, we wouldn't know anything about this at all. We wouldn't be here telling you- this is from each individual person. This was not other people- these are you guys. And so, I won't be putting anybody particular on the spot. Many of you do, but please do. Even though you can treat them easily, maybe just send it to me and say, "Don't mess with them. Don't teach them. Don't treat them." Whatever. Just take their virus and get whatever you want to do. But just consider that. All right. So that's my final impassioned plea for how we have to do this. And thank you for coming and sitting through that.