WEBINAR VIDEO TRANSCRIPT

Partnerships for Care HIV TAC

Pre-exposure Prophylaxis (PrEP), Session #1, Community of Practice

12 July 2016

STEVE LUCKABAUGH: Good afternoon. My name is Steve Luckabaugh, and I'd like to welcome you to the Pre-exposure Prophylaxis, Session #1, Community of Practice webinar. This webinar is brought to you by the Partnerships for Care, HIV Training, Technical Assistance and Collaboration Center, HIV TAC.

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

Our speaker today is Dr. Philip Chan. Dr. Chan is an Assistant Professor of Medicine at Brown University, an Attending Physician in Infectious Diseases at the Miriam Hospital and Rhode Island Hospital in Providence, Rhode Island. Dr. Chan graduated from medical school at the University of Vermont in Burlington where he also obtained a Masters of Science degree. He completed his residency training in internal medicine and fellowship in infectious diseases at Brown University.

Dr. Chan is currently funded by the National Institutes of Health to study HIV epidemiology in the region. Dr. Chan is also Director of the Rhode Island STD Clinic, which offers free and anonymous testing for HIV and other STDs. Dr. Chan also started a Pre-exposure Prophylaxis program at the clinic to provide these new medications to prevent HIV. Dr. Chan serves as Medical Director for the Office of HIV/AIDS, viral hepatitis, STDs, and TB at the Rhode Island Department of Health. He is working with the Department of Health and other community organizations on several statewide initiatives related to HIV and other STDs. Please join me in welcoming Dr. Chan.

PHILIP CHAN: Thank you, Steve, very much. It's a pleasure to be speaking to everyone. Thank you for that very kind introduction. So we were one of the very first PrEP adopters actually. Back in 2013, I directed the STD Clinic here in Rhode Island. We have only one publicly funded clinic located here at it here Marion Hospital in Providence. And back in 2013, we decided to

implement a PrEP program at our site. We've always been very centered around the MSM epidemic and providing services, sexual health, and men's health care. And we saw when PrEP came out that that was an ideal time to implement it.

So today, I want to chat a little bit about PrEP. Just briefly I'm going to mention some of the current trends in epidemiology many of you may be familiar with in the US here, and then really dive into some of the details about PrEP, as well as some of the challenges and successes of PrEP implementation here in the United States.

Just a couple slides on the epidemiology of HIV here in the United States. As many of you know, people are no longer dying from HIV. The medications now are very safe and effective. What I means is that the number of people living with HIV/AIDS continues to increase exponentially as new people are being diagnosed. Unfortunately, the number of new HIV infections over the last decade have decreased slightly, but it is also pretty consistent at about 40,000 new infections a year here in the United States.

When we look at who is being infected with HIV, it's really MSM, so gay and bisexual men. And we see a disproportionate increase among those who identify as Black or Hispanic/Latino. In fact, when you look at all different racial ethnic risk groups across the US, MSM really comprised the number one, two, three risk categories for HIV acquisition. You can see that heterosexual women of African-American descent, as well as black men, are also much more likely disproportionately to be infected with HIV.

When we talk about in HIV prevention, I am going to focus mostly on PrEP today, but I just want to make the point really that when we talk about HIV prevention, it's really a multifaceted approach. There is no one right answer for everyone.

And I really like this slide because you can see these include a lot of the different HIV prevention approaches. And really, the cornerstone of HIV prevention in general is HIV testing. You can see that listed here, counseling, certainly condoms, other harm reduction programs, chemoprophylaxis, prophylaxis with drugs, which is where PEP and PrEP would fall under. But really, we're still learning about how these approaches all fit in together. And again, keep in mind that even though we're talking about PrEP today, PrEP may be right for some people and not right for others. And it's really this combination approach.

I just want to remind people certainly that HIV testing is really recommended. Routine, opt-out HIV testing is now recommended for all sexually active people at least once in their lives. This has been recommended really by all major clinical societies here in America. The recommendations do state annually, once a year, and at least annually if people have risk factors present. For some people that have multiple risk factors and are at higher risk, we do recommend testing up to every three to six months. Certainly there's a population especially of MSM that we do see who we would recommend testing every three to six months.

One of the key successes of the last few years has also been treatment as prevention. And so before I talk about PrEP, I just wanted to mention the second really important prevention approach, which is essentially just getting people tested and on treatment as soon as possible. When people are on treatment, these medications are so effective now that they bring the level of HIV in a person's blood down to almost zero. So that number is known as undetectable. It means in a typical tube a blood that we send out for PCR analysis, the HIV can no longer be detected in that tube of blood.

This study from 2011 out of the University of North Carolina, Mike Cohen down there showed that people who are undetectable, on medications and undetectable, have an almost 100%, much-reduced likelihood of transmitting HIV. So the risk was actually 96% reduced. And even in that one person that was infected, they think that they were infected before, that they were totally undetectable. So let's just say a key concept in preventing HIV is actually diagnosing people with HIV and getting them on treatment as soon as possible.

So that leads us into PrEP, Pre-exposure Prophylaxis. So PrEP, pre-exposure meaning taking a pill before you're ever exposed to HIV. The only medicine currently approved as PrEP is tenofovir emtricitabine, brand name is Truvada. This medication was approved in 2012 for this use. Tenofovir emtricitabine is a combination antiretroviral drug. So this is actually a drug that we use to treat people with HIV currently. So when someone has HIV, we tend to give them this drug plus other drugs.

Truvada does contain two NRPIs. There's been a number of studies done which I'll show in a second which have confirmed that when taking PrEP when you're HIV negative, this medication builds up in your bloodstream and your tissues and prevents HIV from infecting you. So it's interesting that it's already 2016, so it's four years now past when PrEP has been approved, and PrEP implementation has still been considered pretty slow in the United States, as well as across the world.

These were the six studies that led to the approval of PrEP. Most of them were done all over the world. I will draw your attention to the very first study called iPrEx, published by Bob Grant out at UCSF. This was the only study that was done in the United States. It was done in two locations, out in San Francisco as well as in New England, actually, at Boston, Mass, at Fenway Community Health. The other studies have largely been done throughout Africa, including Southeast Asia for the Bangkok tenofovir study.

The iPrEx study was really the only study that that evaluated PrEP among MSM and transgender women. The other studies that looked at women, females, as well as men, heterosexual men, in discordant relationships. The Bangkok tenofovir study was the main study that looked into injection drug users in both men and women. These are all what's known as efficacy trials, meaning that they compared PrEP versus a placebo, so people did not know what medication they were getting.

Some of the studies looked at tenofovir alone. The PrEP medicine that we tend to use is a combination of tenofovir and emtricitabine. Some of the studies look at tenofovir alone, also in comparison to placebo.

These were the efficacy results. So if you look, these numbers were not all that great. I will point out, however, that this was what's known as the intention-to-treat analysis. So what that means is that even though there are people who were supposed to be taking PrEP, they may not have been. And even if they got HIV, they were still counted in the PrEP group. So these numbers are a little bit misleading. But you can see even in the intention-to-treat analysis, the PrEP medicine was effective, certainly above 50% in most of the analyses, in preventing HIV infection.

You will see, interestingly, there are two studies that people cite very often that were not statistically significant. This was the FEM-PrEP study, as well as the VOICE study, study four and five on the slide here. It's important to note that these studies were done among women. And they were done among women in Africa.

When you look at what happened in both the FEM-PrEP and VOICE study, really, the women in the studies were largely not taking their medicines. So essentially, what people believe is that these trials failed because the women, even though they were supposed to be on PrEP, they were not adherent to the medicine. You can see that levels of drug in people, even though they were saying that they were adherent and supposed to be taking it, less than 30% of women in these studies were actually taking the medicines. And that essentially biased the study and made the results non-significant.

When you look at people in the major PrEP studies that actually took the medicine, and they were confirmed to have taken the medicine by checking drug levels, the efficacy of PrEP really rises to 90% or above. You'll see that first number up there, iPrEx had a 90% efficacy level, meaning that PrEP prevented HIV infection in 92% of people in those that were adherent and had detectable drug levels.

There's been a couple of subsequent studies. Those studies were published and done back in 2010, 2011. And there was a study recently published out of the UK called the PROUD study. The PROUD study was also on gay and bisexual men. This was published in The Lancet in 2015. This study looked at a number of health clinics in England during the years specified here, 2012 to '14 and basically randomized people to either immediate or delayed PrEP.

You can see that they found three HIV diagnoses in the group that started PrEP early and 19 in the people that delayed PrEP after 12 months. This gave us a risk reduction around 86%. And you'll notice that STD rates were similar between the two arms. And we'll talk about this is a little bit later.

There's also another study that came out of France that was recently published last year in the New England Journal of Medicine. This is intermittent dosing of PrEP. So at the moment, the

PrEP medication, tenofovir emtricitabine is recommended to be taking one pill once a day. Those are recommended by the CDC. But if people need to take a break from the medicine, you can certainly do that. But it is generally recommended that you take the medicine every day, once a day every day.

This study in the New England Journal of Medicine looked at intermittent dosing. So I do want to make clear that this is not a recommended approach, but it is something that is currently actively being studied and may eventually come to fruition. With intermittent dosing of PrEP, these are people that took two pills within the 24 hours before sex, a third pill 24 hours after having sex, and a final pill 48 hours later.

So this is known as event-driven PrEP and is basically based on a person's sexual activity. If a person continued to have sex for consecutive days, they would take PrEP again 24 hours before they were going to have sex, every day that they were having sex, a third pill 24 hours after their last sexual encounter, and a final pill 48 hours later.

There are some major studies going on at the moment sponsored by the NIH looking at vacation sex. So as with most things in life, sex is not always planned. However, certainly throughout one's life, there are certain periods of times when people may be more sexually active than others. So one can imagine that one of these times may be when you go on vacation.

So there are some studies ongoing look at taking PrEP among MSM when they're on vacation, for example. In general, we do not recommend intermittent dosing, but I want to bring it up just as a point to say that it is currently being studied, and it is an issue that occasionally comes up.

These are a result of the intermittent dosing, the IPERGAY which I just mentioned. It was performed in France from 2012 to 2014. They were essentially randomized to intermittent PrEP with the dosing schedule I just showed versus placebo. They found 14 infections in the placebo arm and two in the PrEP arm, which showed that PrEP really-- the interment dosing had a risk reduction of 86%. So those randomized to the intermittent PrEP dosing were 86% less likely to acquire HIV.

As we move forward in terms of looking at how PrEP is being rolled out in the real world outside of research studies, there's been a number of studies published now showing that PrEP is really very effective. So one of the issues in research studies, as you just saw, was that people don't actually know if they're getting PrEP or placebo. So we think that this led to the less adherence in general for people who are not sure that they're getting the medicine.

This is a study that was published out of the Kaiser system in California after a couple years of PrEP implementation in their state. Basically what they found is that of over 500 MSM, is that there were no HIV infections over a period of one year. This is also what we're seeing here in Rhode Island, in New England.

And when I counsel patients about PrEP, certainly we never tell them that PrEP is 100% effective because it's not, but we tell them that it is very effective. And I personally use the number over 90% effective in HIV. I do, personally, provide PrEP to a lot of gay and bisexual men. And so it certainly is supported by the iPrEx study, the efficacy of PrEP is over 90% in those that are adherent to the medicine. That is an important caveat. But the more literature that's coming out is showing that PrEP is really very effective.

One question that also comes up, both from a public health as well as a critical standpoint, is how many people would we need to treat with PrEP to prevent one HIV infection? So this is known as the number needed to treat. This is an article that was published in Lancet in 2014 by the iPrEx team. You can see that overall based on the iPrEx numbers that about 62 men, gay and bisexual men, would be needed to be treated with PrEP to prevent one HIV infection. However, if you look at the most at-risk subpopulation of that group, men who have sex with men who had receptive anal sex, so that's being a bottom, without a condom, you needed to treat 36 people in the iPrEx study to prevent one HIV infection.

I just wanted to bring up how that compares to other interventions that we use in clinical medicine. So of course, there's a number of primary prevention approaches that we take for things such as cardiovascular disease. You can see in this review here, published a number of years ago, but it's for things like statin and aspirin, and anti-hypertensive drugs, that the number needed to treat to prevent one cardiovascular death tends to be in the hundreds. You can see for aspirin there that, in general, we need to treat 340 people to prevent one cardiovascular death. So in terms of looking at PrEP and HIV prevention, that compares very favorably.

So the first polling question here, this is one of my favorite questions to ask. How effective are condoms at preventing HIV infection? So I'm going to pause for a minute and let the audience click here.

STEVE LUCKABAUGH: OK. Our first poll. How effective are condoms at preventing HIV transmission? 99%, 90%, 80%, 70%, or 50%? Please take a moment to answer this, and we will share the results.

PHILIP CHAN: All results are completely anonymous. So about half the people thought it was 99%, and about 80% believe it's 90% or more. So this is based on a Cochrane Review that was performed a couple years ago. I guess the thing that most people get caught up on is the statement that, if condoms are used correctly and consistently every time, then yes, condoms tend to be 99% effective. That's the line that we often hear. However, there's been a number of studies that have looked at condom use in the real world. And these studies are a little bit hard to do. But the Cochrane Review system tends to be a very robust and reliable system.

You can see here that there are the basic methods, and this was in, I will say, in heterosexual couples. But consistent and constant use of condoms results in an 80% reduction in HIV incidence. So it's not 100%. And this also squares with the rates of condom use for pregnancy as

well. So the bottom line is that, even with people that are reliable and consistent in the use of their condoms, it's not 100%. And this really reflects real-world difficulties with using condoms consistently and correctly every time.

So the point of mentioning this is just to say that a lot of times I hear, and it's certainly great for providers and other counselors to recommend condoms and I certainly do the same, we have to be aware that condoms are not a fool-proof method of preventing HIV transmission. And that's why PrEP is so powerful is because, one, it's in my opinion as effective, if not more, if you take it, in terms of preventing HIV infection. But it's also something that you can take before.

So one of the reasons why many people may not use condoms, or certainly things that we've heard, they're not available at the moment, you forget in the heat of the moment, they're not available when the time for sex is right, etc. So if you think about PrEP, these really overcome a lot of the barriers for condoms.

And again, certainly as we talk about recommending and promoting PrEP, it should be within the context of condom use, but also understanding that some people just don't use condoms anyway. And in my mind, PrEP is a really good fit for those people. And certainly for people that use condoms, we want to recommend continuing condom use. But I do want to make the point that condoms are not, certainly not 100%.

So I'm talking about PrEP implementation. So some of the studies that I just talked about, those where the, quote, "really scientific" studies, the efficacy studies that showed that PrEP works. But how does that really translate into real-world impact? In my opinion, we're really at a really great time for HIV prevention. So we have this new medication, this new tool, PrEP, and we're really looking at how PrEP is being implemented across the United States. We're really looking at widespread implementation of PrEP.

When we talk about implementation of PrEP, or frankly any intervention, there is really three stages. The first are the clinical trials which look at the efficacy of a medicine, so efficacy meaning answering the question does it work? Does PrEP protect against HIV acquisition? In this case, the answer is yet.

The next step and what we're currently in the middle of and sort of transitioning out of are several demonstration projects. So demonstration projects are usually sponsored by organizations such as the CDC and other local and federal sources. And basically, they're looking at more of a real world.

In the case of PrEP, a lot of these demonstration projects, there are some ongoing in San Francisco, Chicago, Washington DC. What they've essentially been doing is providing PrEP, a lot of times free, to people to answer questions such as, are people taking it? How are they taking it? And what's happening to them? It's still within the context of a research study. But it's much more flexible, especially for the reason that people know that they are actually taking PrEP. There is no placebo. There's no sugar pill. People are actually taking PrEP.

The third stage of PrEP implementation is really what we're all here for now, which is implementation of PrEP in the real world. So these are clinical programs. This is talking about billing for PrEP and reimbursements, looking at who's actually taking up PrEP in the real world, in these clinical settings, how to get PrEP out to the masses to people who need it. And we're going to talk a little bit about that now.

So there is no right or wrong answer to this question. This is our second polling question. What would be your biggest concerns about offering PrEP to people? A, people should just be using condoms. B, people would stop using condoms. C, people wouldn't take it anyway. D, paying for it or insurance issues. E, side effects or long-term safety profile of the medication. F, it promotes promiscuity, meaning people would decrease condoms or have more sex partners. Or G, no concerns.

So again, these are all things that I've heard about. There's no right or wrong answer. If people could go ahead and vote. Great. So I'm going to go over some of these now.

It's always-- so these are legitimate concern, certainly, concerns that many people, across many disciplines have raised as issues for PrEP. So we'll talk about some of them. Again, there is no, of course, no wrong answer with this.

So a number of questions have been raised in terms of how to focus PrEP and where to focus the resources. So, of course, in this day and age with limited public health resources, we want to best get PrEP out to the people who need it most. And so there's no easy way to do this. Some of the populations that we're talking about, MSM in general, certainly sex workers, injecting drug users, these are all populations that have been extremely hard to engage in general and certainly for PrEP as well.

Other things that we're talking about during the early stages of PrEP delivery, including role with other HIV prevention strategies. So this is to say, how should we counsel PrEP? How should we include PrEP with things like condoms? What is the right messaging? And what we've actually seen today is that messaging has been all over the place.

There are some providers that will, say, really strongly encourage condoms or promote condoms in the terms of PrEP use. And there are other providers that will promote PrEP as an alternative to condoms. And so, again, there's no necessarily right or wrong answers. Certainly, PrEP does not protect people against other STDs. There's been some data recently about increasing STDs among people on PrEP. So that's also a concern.

The other issue that has come up in terms of PrEP delivery is who prescribes it? One of my colleagues, Doug Krakower up at Boston, has termed what's known as the paradox of prescribing PrEP. And that is to say that HIV specialists, infectious disease specialists are not comfortable prescribing PrEP because they only want to take care of HIV-positive patients. And primary care doctors don't necessarily feel comfortable with PrEP because it's an antiretroviral,

and they don't have a lot of experience with it. So there's been a lot of talk about who is best to prescribe PrEP.

So as an infectious disease physician, I work out of an HIV clinic. And I have to tell you, when I first started prescribing PrEP to people, there was a little bit of pushback by my clinical staff because they told me that they didn't want to see HIV-negative people. So I had to work through that and around that, of course. And so that's even pushback that I received myself.

I will say most of us do believe that, in terms of really bring PrEP to scale, we really need primary care doctors, community clinics to really be the ones to prescribe PrEP. The problem is is that a lot of places do have these subspecialty sexual clinics, STD clinics, who do reach a percent of the population. And many times they are a higher risk percent of the population. But in terms of really reaching the community at large, and really reaching the MSM community at large, we really need primary care physicians to be willing to prescribe this.

One of the things that we've noticed as a barrier in general to discussing PrEP is just taking a sexual history. And sexual history, what I have up here is the 5 Ps. This is something promoted by the CDC in terms of how to take a sexual history. So before we even start talking about PrEP, one way to start this conversation is just asking a sexual history. And this is something that we've seen many clinicians in the community feeling uncomfortable with, and something that you just have to start asking.

You can see one of the questions here-- I ask a subset of these questions-- but really the questions, do you have sex with men, women, or both? In the past few months, how many partners have you had sex with? How often do you use condoms? Those are really the key questions to help identify people who may benefit most from PrEP.

So our third audience question here. Again, there is no right or wrong answer to this question. Please answer it honestly and freely. A 25-year-old gentleman who comes to your clinic, he reports two to three male partners in the last year. He would like to consider PrEP. He reports using condom use 80% of the time. He has no symptoms. His HIV is negative. What do you think about prescribing PrEP to this patient? A, absolutely. B, yes, but only if he really wanted it. C, I don't think so. D, definitely not. E, unsure.

Great. Thank you all for voting. So most of you said absolutely, B, yes if he really wanted. This is a tough one that I struggle with actually myself. So certainly, again, PrEP is recommended one pill once a day. We do have a number of people that ask for PrEP. But now remember, he has two to three male partners a year. So it would be important to tease out how often he's actually having sexual encounters. If he's having two partners a year and they're spread out over time over many months, taking daily PrEP may not be right for this gentleman. I have a pretty low threshold myself.

So certainly if he really wanted it, I would prescribe it to him, but something to think about. Again, there's no wrong answer on this question. Does it make sense for this gentleman to take

a pill every day as PrEP if he's having two partners a year spread out over many months? Just an issue to consider.

Another option for someone like this may be post-exposure prophylaxis. So if he's having one instance or event a year in which he is having an anonymous partner or is not using condoms when he meant to, one thing that you could counsel him on is post-exposure prophylaxis. So if that happens during the course of a year, please call us right away. We'll get you thinking about post-exposure prophylaxis.

So again, no wrong answer on that. Certainly, I myself would give this gentleman PrEP if he really wanted it. But we do have to weigh some of the risks and benefits. I'm going to talk about some of the side effects in a second.

This is also a scale that some of my colleagues across the country use. This was put out by the CDC. It was based on a number of very large cohorts in the country, the VAXGEN and the EXPLORE cohort, which were gay and bisexual men. This is known as the high risk index for MSM. So essentially, it's a scoring system, and a score of 10 or more people are considered high risk. You can see the negative and predictive value here.

This is, again, a scoring system that a number of my colleagues at different STD clinics across the country use in terms of identifying people who are at elevated risk of HIV. They actually use this scale in terms of identifying people who are really ideal candidates for PrEP. I thought I would include that here. I can certainly refer you to a reference for more information if you would like to look it up.

There's also a number of other situations which are currently being studied. So this article published last year by a couple of colleagues across the country, people are looking at PrEP in terms of people who are in a serodiscordant relationship where one person is positive and one person is negative. And the negative person is attempting to get pregnant. But certainly, with the increasing number of people who are HIV-positive, many of these people are in long-term partnerships, and many of these people are also trying to get pregnant. So the thought is. Is that the people who are negative in the relationship will have condomless sex, and during that time, they will take PrEP with the intent of becoming pregnant.

I will say that this is also controversial. So again, with the push by many to get people diagnosed and on treatment is that even in these serodiscordant relationships, the HIV-positive person needs to be on medications and undetectable. And I do have a couple colleagues that feel that if that's the case, they time their condomless sex to the point of the cycle when they're ovulating, and therefore, just have condomless sex during that few days that they're more likely to get pregnant, so if that's the case, and they're also undetectable, that really PrEP may not even be needed. So again, this is controversial. People are currently studying it. I, myself, would put the negative person on PrEP as well as an additional protection. But this is something that's actively being looked at.

The only thing I would like to remind the audience is that the medication for PrEP at this time, tenofovir emtricitabine is not approved for adolescents or children, so not approved for people under the age of 18. There are, again, some active studies that are looking at using PrEP for adolescents. But if it were to be used for adolescents, it would be off-label.

Personally, I have prescribed it to a couple people who were 16 or 17 after weighing the risks and the benefits. In the state of Rhode Island, people are able to make decisions about their sexual health without consent. I did confirm this, both with numerous possible administrators and other physicians, so I felt comfortable prescribing PrEP. And again, there were a couple extremely risky young gay men that I saw in my PrEP clinic who were 17 who I did feel like the benefit certainly outweighed the risk, and I did prescribe it. But again, some of this will rely on comfort level of the medical providers. And, again, keep in mind that it is not currently approved for this use and would be off-label in individuals under the age of 18.

The other area that we will sometimes transition people to PrEP is people who are taking non-occupational post-exposure prophylaxis. So as many of you probably know, post-exposure prophylaxis in the occupational setting is if someone has an occupational exposure, a needle stick, a splash of infected blood to the eyes. People can take a 28-day course of a three drug antiretroviral regimen to prevent HIV.

In the non-occupational setting, if people have a risky sexual exposure, you can also take post-exposure prophylaxis to decrease your risk of obtaining HIV. And again, it's a 28-days course. So what people have looked at and are looking at is for people who are requiring post-exposure prophylaxis after sexual encounter, if they're requiring it once or multiple times a year, transitioning these people to PrEP. Just keep in mind that if someone, certainly someone who is presenting multiple times a year for post-exposure prophylaxis, but even people who are presenting once, consideration for these people may be transitioning them to PrEP.

So again, I'll bring up my favorite slide here, just thinking about how to fit PrEP in with the other HIV prevention approaches. I'm going to go over some of the condom data in a second.

An additional question has come up in terms of PrEP implication is if people even want to take it. So one of the issues that we've seen is that a lot of the people who meet indications for PrEP are really young, otherwise healthy 20- and 30-year-old individuals. So these are people that aren't taking any other medicine. They're really, completely otherwise healthy. So it's a challenge in general getting these people to take a medicine. But the other question is even if these young, otherwise healthy guys want to take it.

A second point is attitudes and stigma about PrEP. So there is a stigma that some of you saw in the previous slides about people who take PrEP are being promiscuous. So they're either having more sexual partners or using condoms less.

And finally, one the other challenges of PrEP uptake, PrEP implementation is how to really get PrEP and use PrEP during the highest risk periods of one's life. So as with anything in life, people

sort of go through different peaks and troughs of sexual activity. Ideally, we don't want people on this medication long-term for decades. It is meant to be-- ideally, people would be on it during the high risk periods of their life, and then would come off it once they're at a lower risk. We don't understand exactly when that happens or how often that happens. And this is also an active area of research.

This is a term that some of you may have heard of, but it's something that's being thrown around, especially in the gay community of Truvada whore. So again, this relates to a stigma of people on PrEP who may be more promiscuous.

In terms of adherence and if people are actually taking it. So as I mentioned, PrEP is approved for daily use. It is not currently approved for intermittent. That would be considered off-label. The other question we have to ask ourselves, if people are not taking it every day, how much are they taking it? And is that adherence level high enough to protect them from HIV acquisition?

I will point out that you don't-- and I certainly never tell this to patients or the community. However, as medical providers, you should be aware that 100% adherence to PrEP is not required for it to be effective. So this is some pharmacokinetic data that basically shows that the optimal number of doses per week, you can probably get away with four doses per week. If you take four doses a week, you're going to have a 96% estimated efficacy of PrEP. So that's just to say, if people are missing one or up to two or three doses a week, you're probably going to be OK. So obviously, when I counsel people about PrEP and when you do, you should counsel for 100% adherence, but also understanding that there is some forgiveness and you don't have to take it every day for it to be effective.

When you look back at those efficacy trials that show the people who were, quote, "enrolled in the PrEP arm" were still getting HIV, they were essentially taking the medicine not at all, like they were completely not adherent. What we're seeing-- and this was an article we published just this month. What we're seeing in the real world is that people who are coming in for PrEP generally tend to be adherent to the medicine. And this should make sense to you innately, meaning that if people are coming to you and they keep coming to you for PrEP, they're probably taking it. I.e., why would someone come see you for PrEP and tell you that they're taking it if they weren't really? They would just not show up.

So one of the problems that we've encountered is less about it adherence, per se, and more about retention and care. So certainly, some people drop out of care, etc. But what we've noticed really is that when people tell you you're taking the medicine, they are. This was a study that we did out of our clinic and also confirmed it with blood drug levels.

So let's talk about some of the risks of PrEP, of tenofovir emtricitabine. So these include what happens in terms of sexual behavior while people are on PrEP. One of the concerns that some of you alluded to in terms of using condoms less is known as risk compensation or behavioral

disinhibition. This is to say that if people feel protected by PrEP, they are going to compensate or feel disinhibited to use other prevention approaches.

And finally, we'll just talk for a few minutes about different side effects, the concern of drug resistance, long-term safety, and pregnancy. In terms of safety and toxicity of PrEP, it is an incredibly safe medicine. The FDA did approve it in 2012 for this indication, and really adverse, serious adverse side effects are extremely rare. I tell people certainly the thing that you have to worry most about-- a lot of people when they start PrEP will have a little bit of GI discomfort. If you look through some of the numbers, they estimate around 20% of people may have a little bit of GI discomfort. I tell people that this is usually temporary, and usually it goes away after being a day or two on the medicine. And they should push through it. It's not serious.

The one serious thing that we tend to worry about is that the tenofovir can affect the kidney. What we don't see are acute renal toxicity, acute renal failure. We do not see that. What we have seen in our HIV-positive population is over months to years, chronic use of tenofovir can lead to damage to the kidneys, as evident by a decrease in creatinine clearance, increase in creatinine. I tell people that that is something that happens over months to years. It's still pretty rare. It does happen. And then when you stop PrEP, people for the most part return back to their normal kidney function. That is the main reason that we want to see people every three months. That is sort of, to me, the major side effect of PrEP.

The other thing that we occasionally see or is of a concern with the tenofovir is it can decrease bone mineral density. Now, this is something, again, this medication has been approved for HIV treatment since 2004. So in our HIV-positive population of people taking tenofovir, we never see-- I won't never say-- but we really never see fractures due to the tenofovir component. However, when you do DEXA scans and really detailed, in-depth looks, you can see for sure that tenofovir does lead to decreased bone mineral density.

In our PrEP population, we're really less concerned about that, especially among young, otherwise healthy guys. We are not seeing fractures or other concerns for the bone mineral density. The only reason I bring it up, and, frankly, I don't even usually mention it to most guys, but I do occasionally see a patient that has other reasons for bone mineral density problems. So for example, I do occasionally see people with inflammatory bowel disease. I've seen people with other sorts of reasons for calcium deficiency. And in those people, I have brought it up and talked in-depth about the risk for bone mineral loss because of their pre-existing condition, so just something to keep in mind.

The other common side effects that we occasionally see with PrEP are headache and fatigue. I do tell people, and most of the people that I put on PrEP have no side effects whatsoever. Again, it's an incredibly safe medicine.

The other point that I often bring up on the flipside is that any medicine can have any side effects. I have seen a couple weird things. For example, I had one young lady in a serodiscordant couple who got a rash on her lower extremities when she started the PrEP, and

it went away when she stopped it. So clearly, there is a temporal association. There's no other reason. It was a very striking rash. And that's not something that's ever mentioned, in terms of not something we routinely see. But I do also mention that any medications can have any side effects. So certainly keep that in mind as people start taking PrEP.

The other concern that has been raised is for HIV-resistance. So as I mentioned, the tenofovir emtricitabine is the backbone of a number of treatments that we use to treat people who do have HIV. So it's only a true drug regimen. And in general, we always treat people with three drugs, or more sometimes.

What they've seen in the studies is that there was an initial concern that if people converted to HIV, that because they were only on a two-drug regimen, that it would promote or breed resistance because they were not being treated with a three-drug regimen. What they've seen from the efficacy scales, which I presented earlier, is that really HIV drug resistance has not been a concern. If you look at the people who are infected with HIV, less than 10%, if they're are even on PrEP, have evidence of drug resistance.

The other thing that we've seen is that the biggest risk of resistance is if people are acutely infected. So what we've seen in the few number of people that have actually been infected with HIV while consistently on PrEP, the risk of drug resistance is super low. However, if someone comes to you and they have acute HIV infection and it's missed, and their viral load is in the millions, and you start the PrEP at that point, the risk of drug resistance is a little bit higher. So that's one of the reasons why we really want to make sure before we start someone on PrEP that they're HIV-negative. The guidelines do say a current HIV test within the last week. It is recommended for them to use a fourth-generation combined antibody/antigen testing.

I do not personally check a viral load on PrEP initiation. That is something that is mentioned in the guidelines as reasonable to do. I have found, personally, that some of the insurance companies have not reimbursed when sending a viral load in those situations. So I've been a little bit reluctant to. We have fourth-generation now at our sites. And I feel comfortable enough using that, as well as asking people if they've had any recent signs or symptoms of flu-like illnesses to also screen for acute HIV.

This slide speaks to the risk compensation. So in looking at the major studies, if you look at panel A here under the iPrEx, this is the number of partners in the last 12 weeks. If you look at the B panel, that's the percent of people using condoms. Essentially this, and in the Partners PrEP study, you can see that between the people that were actually taking PrEP or not taking PrEP, essentially the number of partners and those using condoms, the percent using condoms was unchanged.

So people have pointed to these early studies as evidence that there hasn't really been a change in sexual behaviors in people that get on PrEP. However, I will say anecdotally that, certainly, there's a subgroup of people that I've prescribe PrEP to who have used condoms less since getting on PrEP. It is a real concern, for sure. I will say, though, that most of the people

who get on PrEP have the same behaviors that they did before, meaning that they're not having more partners and that their condom use remains about the same.

I find it very rare that anyone uses condoms 100% of the time. There's certainly a subset of people. But I haven't found any changes before and after, except in the small subgroup of people. Again, those are anecdotal experiences. And this is an active area of study, as PrEP is implemented in the real world, what is happening to people.

Finally, some very broad public health questions about PrEP implementation. Is PrEP cost-effective? What is the impact on HIV incidence? And, importantly, a question that has not really been addressed yet, but really what's the percent of people in your community that are at risk for HIV that actually need to be covered for PrEP in order to impact HIV incidence?

There's a number of well done studies that have looked at-- these are some groups, both at MGH and otherwise, that have looked at cost-effectiveness of PrEP, and found that it is cost-effective, especially when focused on people who tend to be higher risk, i.e., men who have sex with men. These are the references for those studies. I'm going to also refer people to the CDC guidelines on PrEP, which came out in 2014. This is a very comprehensive manual. Some of the slides and the pictures that I have been going over are taken directly from these guidelines.

The PrEP guidelines do state it as 1A evidence of PrEP in people in both MSM, heterosexual, as well as injection drug users. These are the recommended indications for PrEP use by MSM, essentially men who have sex with men. And this includes any man who has had any male partners in the past six months, and has had sex without condoms, anal sex without condoms in the past six months, has been diagnosed with an STD in the past six months, or is in an ongoing sexual relationship with someone that is HIV-positive. Obviously, these guidelines are kind of broad. But they can provide some guidance in terms of considering PrEP in this group.

The heterosexual criteria for using PrEP per the guidelines are a little bit more restrictive. Essentially, they recommend heterosexual individuals who have had sex partners in the past six months who, for female, who has a male partner who is bisexual, or has a partner who has other risk factors of HIV. So these include people that are injection drug users, bisexual men, or an HIV-positive partners, so a little bit a more restrictive. And this really reflects the epidemiology of HIV that we're seeing across the United States.

I will mention, of course, that as you think about who to provide PrEP to, it should really be focused and helped to be developed by your local surveillance statistics. So here in Rhode Island, we actually have only a couple new cases diagnosed each year that are injection drug users. So we don't do very much PrEP outreach towards injection drug users.

Now, that may be very different in other urban settings. And so you really have to tailor your PrEP implementation and outreach to where the epidemic is hitting you must. In injection drug users, people that are actively using, who have shared any needles in the past six months, or

importantly also been in a methadone, buprenorphine, or suboxone treatment program in the past six months as well.

When we do have someone on PrEP, so the first time that I see them, we certainly do a lot of education and counseling related to PrEP, as well as sexual risk. We, again, as I mentioned, really want to evaluate for HIV infection, both with an antibody test, plus or minus a viral load if there is suspect for acute HIV. For women, we want to check a pregnancy test. We also want to check kidney function tests, as well as other STDs.

The other important thing to remember to check are hepatitis B serologies. So it turns out that the tenofovir and emtricitabine are both actually active against hepatitis B. In some people, especially those who are HIV-positive, we use this as a treatment for hepatitis B. However, the concern is not treating hep B. It's that we treat someone with hep B and we don't know it, and then take f off this medicine, sometimes the hepatitis B can flare up and make people really sick. So certainly before we start someone on tenofovir emtricitabine, we want to know there hepatitis B status.

We want to follow these people every three months. The CDC guidelines do say it is reasonable to check in with people at one month, if needed. What we do here personally is every three months, where we want to do a behavioral assessment check for adherence, just asking them essentially if they are taking their medicine, any issues in taking it. You want to check an HIV antibody test, as well as a renal function tests, creatinine, as well as check for other STDs as needed.

This is a short article that we published in this last month as well, looking at retention and care across a couple of the studies, types that we had, including St. Louis, Missouri, as well as Jackson, Mississippi, and here in Providence, Rhode Island. Again, what we found is that a significant number of people are not being retained in PrEP care for various reasons. I'll refer you to this article. It has been a challenge. And as we think about implementing PrEP towards the future, one of the challenges and one of the things that a lot of people are starting to focus on is keeping the young people retained in care, whether it's for PrEP or otherwise. So I'll refer you to this article for more information and the exact statistics that we ran.

So again, I'll just end on my favorite slide here. HIV prevention is really a combination approach. PrEP is one of those puzzle pieces, but certainly we need to remember and keep in mind the other approaches as well. And here's my contact information. I'm happy to answer any questions in the few minutes we have remaining. Thank you.

STEVE LUCKABAUGH: All right, thank you. If anyone has any questions, please answer them now in the questions pane one the Go to Webinar toolbar. We did have a couple that came in. How do you handle situations where clients come in specifically for a PrEP prescription with no intention of having a provider as their PCP? Will insurances pay for a PrEP prescription referral?

PHILIP CHAN: So great question. And the bottom line is it varies. So for Medicaid patients, which some of these young people are, again, Rhode Island is a Medicaid expansion state, you can see these people and you can prescribe PrEP. So if you think about it, again, a lot of these people, especially in their 20s who are coming in, they really have no other medical problems. These are people that their entire primary medical problem list is really sexual health. So I do see us providing PrEP to these people as really as an ideal opportunity to engage them in health care in general, as well as provide other aspects of primary care.

Certainly for people a bit older, it's also an opportunity to get them into primary care. We have found that certainly some of the insurance plans, they don't let us bill their insurance unless they're referred by a primary care doctor. In those situations, we've called the primary care office and gotten the referral.

But I really see PrEP more as an opportunity to engage a lot of these young people in the medical process, many of whom would otherwise never being engaged. So I think it is an important question, but I also totally see it as an opportunity to get them involved. And we also link people, for people that come to us, and I start on PrEP, and I'm the first doctor that they've seen in 10 years, I do, all the time, use that as an opportunity to link and refer people to primary care. We actually do not do primary care on site here. I also make it the point to say that I'm happy to keep prescribing the PrEP for you, but certainly any doctor can. And your primary care doctor, if they were comfortable, could offer to do it. So I give people options.

STEVE LUCKABAUGH: OK. Is there info on whether or not corrections facility are implementing PrEP?

PHILIP CHAN: So this is a great question. So we're actually working with our local Correctional Institute. So the answer is not yet, and no, not that I know of. We have a very strong correctional setting focus here. One of the problems that we've found is that it's a little bit of a hotbed political issue. So people in corrections shouldn't be having sex. So theoretically, there's no need for PrEP while people are incarcerated. So the question would be, if prior to release, if people wanted to get on PrEP.

So I think what the audience member is alluding to is that certainly the post-incarceration period is one of the higher risk periods in general. It's been shown in numerous studies that when people get out of prison, that they participate in higher risk activity, which, of course, makes sense to me. So the question that's coming up is how best to link people post-incarceration to PrEP care. To my knowledge, that has not been studied. We are looking at several options here in Rhode Island. But there is no place that I'm aware of that has a good program to do that.

STEVE LUCKABAUGH: With a less than 4% chance of getting HIV in serodiscordant couples with the HIV partner undetectable, would you still advise PrEP for the negative partner?

PHILIP CHAN: So this is an absolutely fantastic question that many people disagree on. So I just want to add the disclaimers so that different, quote, "experts" will give you different opinions. So there is no right or wrong answer. Essentially what you have to do is lay out the pros and cons to people, and have them decide, and have an educated discussion. My philosophy, personally, is that I try to recommend two prevention approaches to people.

So what does that mean? It means that when someone is in a serodiscordant couple and the HIV-positive partner is undetectable and totally reliable in taking their meds, that to me is the most important thing to do out of everything. So that's one way to protect and prevent.

If that couple is also using condoms 100% of the time and they swear up and down, and they seem like they're telling the truth, then I try to dissuade them from using PrEP. So I feel like if people are using condoms 100% of the time and the partner is undetectable, then that's enough and PrEP is not needed.

That being said, if someone really still feels strongly like they really want PrEP, I will prescribe it because it is still a risk, condoms break, as I mentioned. The other thing is that over time, people can still become detectable even when you're undetectable. And this is something that needs a little bit more study.

So at the current moment, we're seeing HIV-positive patients every six months. However, there's certainly a concern that during that six month period, you may become detectable before it's picked up again. So that's really the risk that we're talking about. What is the risk that someone will become detectable even though they're undetectable at the current time?

If people are not using condoms in a serodiscordant relationship, I'm much more comfortable with giving people PrEP and offering it to them. So if they're not using condoms, even though the partner's undetectable, I will encourage PrEP in that situation. But I do feel like if people are using condoms 100% of the time, and the partner's also undetectable, that PrEP is a little bit of an overkill in my opinion. Different people will give you different answers to that.

STEVE LUCKABAUGH: OK. And one person says, I work with a patient who is in a serodiscordant relationship, two middle-aged men, HIV partner wanted PrEP. Thinking about your comments about using PrEP during highest risk periods in life, couple together exclusively for several years. HIV partner had been married to an HIV-positive man in the past who died of AIDS. Was PrEP appropriate in your opinion?

PHILIP CHAN: So if I understand the question, it's if two negative people are in a monogamous relationship, is PrEP right for them?

STEVE LUCKABAUGH: No, I think one was positive. One was negative And the positive wanted the PrEP.

PHILIP CHAN: So the positive one wanted the PrEP for the negative person?

STEVE LUCKABAUGH: Right.

PHILIP CHAN: So we do-- that sort of relates to the prior question in terms of I do give it out. So I think it's reasonable in any serodiscordant couple, if someone really wanted to give PrEP. However, the first and foremost is to make sure that the partner with HIV is undetectable. And again, to my prior point, if they're using condoms for anal sex 100% of the time, I usually try to discourage PrEP unless they really want it and really make a strong case for it, then I usually give it. But I do try to talk people out of it. Again, PrEP, very safe medicine, but there are still some side effects and risks to it.

STEVE LUCKABAUGH: OK. That's all I'm seeing right now. If anyone else has any questions, now would be a good time.

PHILIP CHAN: If anyone wanted to email me, too, on the side, I'm happy to answer any questions if people additionally have any. Thank you everyone.

STEVE LUCKABAUGH: A couple of comments. Excellent program. Thank you. And I'm not seeing any more questions. Did you have any final thoughts before I wrap it up?

PHILIP CHAN: I do not. Thank you everyone for their attention.

STEVE LUCKABAUGH: Take care everybody. We'll see you next time.