Bob Leahy: Hi James. Thanks for agreeing to talk to PositiveLite.com again, this time on the PARTNER study. Now I read your analysis of the interim results – Positive Lite.com published it here – which took me back to the day the news first broke from CROI that we finally had data about the risk of HIV transmission involving gay men with an undetectable viral load. I was really excited that day. Would you agree that this was ground-breaking stuff?

Yes, I think the preliminary results from this study are very important. Ever since the HPTN052 study released its results in 2011 – showing that antiretroviral treatment can significantly reduce the risk of HIV transmission through vaginal sex – there have been unanswered questions with regards to its implications for populations which mostly have anal sex, such as some gay men and men who have sex with men. The preliminary results from the PARTNER study help answer some of these questions.

But we did have some pretty good ideas about the very slim likelihood of transmission occurring involving undetectable viral loads prior to PARTNER, didn’t we. The fact that so few known transmissions were occurring in the studies of heterosexuals that Mona Loutfy looked at was well established, wasn’t it? And many people were talking about it.

Well, we knew from HPTN 052 that the risk of HIV transmission through vaginal sex could be drastically reduced by starting treatment, but it was unclear exactly what this risk was reduced to. Because of this, Mona Loutfy – a physician and researcher from Woman’s College Hospital in Toronto – conducted a review of the research on serodiscordant couples to determine how many HIV transmissions had occurred when the viral load was undetectable.

Her research team identified six studies of heterosexual serodiscordant couples where the HIV-positive partner was on ART. In these studies, no HIV transmissions occurred when the viral load was undetectable. This was a significant finding because the couples in these studies were followed for a long period of time, a total of almost 3,000 couple years of follow up (equivalent to following 3,000 couples for a year with no HIV transmissions).

The findings from this review got a lot of attention and it was definitely good news. However, the review also had its limitations. The main one being that the couples in these studies reported using condoms the majority of the time. This made it difficult to know the extent to which having an undetectable viral load, and not condoms, was responsible for the absence of HIV transmissions. In other words, it didn’t answer the question of what the risk of HIV transmission is when the viral load is undetectable and no condom is used. This, as you know, is a question that many people want the answer to.

Also, Mona’s review didn’t provide any information on what the risk is reduced to for anal sex, as the studies her team identified only enrolled heterosexual couples. There is the concern that – even if the reduction in risk is the same for anal sex as it is for vaginal sex – that the risk when undetectable may still be higher for receptive anal sex (where the HIV-negative partner takes the receptive position during anal sex, also known as bottoming) compared to other types of sex. This is because the risk of HIV transmission through receptive anal sex is much higher than other types of sex when the viral load is detectable. Therefore, there is the possibility that the risk could also be much higher when the viral load is undetectable.

In the face of these research gaps, uncertainties, and unanswered questions, we have seen expert consensus
statements playing an important guiding role in translating the research we have available into useful messaging. You may remember that, shortly after the HPTN 052 results were released in 2011, the World Health Organization released an expert consensus concluding that treatment also reduces the risk of HIV transmission through anal sex, but the risk-reduction may or may not be the same as for vaginal sex.

More recently, but prior to the results of the PARTNER results, the British HIV Association released an expert consensus saying that the risk of HIV transmission through both anal and vaginal sex is “extremely low” when the viral load is undetectable and other conditions are met. These conditions included the absence of STIs, having had an undetectable viral load for at least 6 months, regular viral load testing and complete disclosure within the couple about sexual relationships outside the partnership.

So on to PARTNER. Do you want to summarize briefly what PARTNER told us, James?

Sure. The purpose of the PARTNER study was to answer the question: "what is the risk of HIV transmission through anal and vaginal sex when the viral load is undetectable and no condom is used?" This was a question that had not previously been answered.

To do this, the study enrolled heterosexual and gay male serodiscordant couples that had previously made the decision - for whatever reason - to stop using condoms consistently. In fact, the couples who ended up enrolling had already been having condomless sex for an average of two years prior to entering the study. It is also important to note that the study only enrolled couples in which the HIV-positive partner was on treatment. The study did not enroll a “control” group of couples who were not on treatment.

The preliminary analysis of the PARTNER study was presented in March 2014 at a conference in the United States and included information on 767 couples followed between September 2010 and November 2013. During this time, couples engaged in approximately 44,000 condomless sex acts when the viral load was undetectable. This included 13,728 receptive vaginal sex acts, 14,295 insertive vaginal sex acts, 7,738 receptive anal sex acts, and 11,749 insertive anal sex acts. No HIV transmissions occurred.

Interpreting these results is challenging. Since there was no control group, it is difficult to know how many HIV transmissions would have been expected if the HIV-positive partner had not been on treatment and had a detectable viral load. However, based on results from previous studies, I would have expected about 10 infections each through receptive vaginal sex, insertive vaginal sex and insertive anal sex. So, for these sex acts, the preliminary results weren’t super compelling because not many infections would have been expected anyways. Also, for vaginal sex, these results are less compelling than the results for vaginal sex from the HPTN 052 study.

The most compelling result from the preliminary analysis is that no infections occurred despite participants engaging 7,738 receptive anal sex acts. As I mentioned already, when the viral load is detectable, receptive anal sex is much higher risk than other types of sex. In the PARTNER study, I would have expected about 80 HIV infections through receptive anal sex if the viral load of the HIV-positive partner had been detectable. This is a significant number of HIV infections and therefore the preliminary analysis provided the first direct evidence that treatment can dramatically reduce the risk of HIV transmission through receptive anal sex.

But simply because there were no HIV transmissions in the study does not mean that the risk going into the future is zero?

There is always the possibility for chance to influence research results. In general, the larger the study, the less likely that the results are due to chance. For example, if the participants in the PARTNER study had engaged in a million sex acts with no HIV transmissions, the potential role of chance would have been much smaller and the researchers could be more confident that the “true” risk is zero. On the other hand, if this analysis had only included 100 condomless sex acts, then the potential role of chance would have been much larger and the researchers would be less confident that the “true” risk is zero.

To understand the role that chance may have played in the PARTNER study, the researchers calculated upper confidence limits for their results. Confidence limits are basically a tool that researchers can use in order to take into account the potential effects of chance and produce a range of values in which they can be very confident that the “true” risk lies.
I will use the results for receptive anal sex as an example for how these confidence limits can be interpreted.

In the preliminary analysis of the PARTNER study, the upper confidence limit for the risk of HIV transmission through one act of condomless receptive anal sex when the viral load is *undetectable* was calculated to be 0.05% (equivalent to 1 transmission per 2000 exposures). This means that the “true” risk through one act of condomless receptive anal sex when *undetectable* is extremely likely to be lower than 0.05%. This is very significant because the average risk through one act of condomless receptive anal sex when the viral load is *detectable* is 1.4% (equivalent to 1 transmission per 71 exposures). The reduction from 1.4% to 0.05% represents about a 96% change in risk, which is a dramatic reduction and equivalent to what we saw in HPTN 052 for vaginal sex.

While the “true” risk is more likely to be closer to zero than the upper confidence limit, the researchers could not statistically rule out the possibility that the risk is as high as 0.05%. This is concerning to some extent because 0.05% is similar to the average HIV transmission risk through one act of condomless vaginal sex when the viral load is *detectable*, an activity that is generally considered to be “high risk” for HIV infection in most guidelines.

It is important to point out that receptive anal sex had a relatively high upper confidence limit because, during the study, relatively few of these sex acts occurred (about 7,000 compared to over 11,000 for each of the other types of sex acts). Therefore, chance could have played a greater role in the results for receptive anal sex.

As the PARTNER study continues, and more condomless receptive anal sex acts occur, the upper confidence limit will begin to “tighten” and move closer to zero (assuming no transmissions occur). This will allow the researchers to be more confident that the “true” risk is closer to zero and not potentially as high as 0.05%. This is why the study is continuing and plans to enroll more gay men.

I know this can all be pretty confusing and difficult to interpret, but I think we can boil it down to two main conclusions. First, the analysis told us that the change in risk of HIV transmission for anal sex is equivalent to that for vaginal sex. This is great news and something we didn’t know. However, the second conclusion is that the study could not rule out the possibility that receptive anal sex may still be higher risk than other types of sex when the viral load is undetectable. This is unfortunate and something we hope the full analysis will rule out.

**OK, in the past, we have qualified what we’ve known about transmission risk by saying it could be affected by STIs, in other words the presence of STIs in either partner could increase the likelihood of transmission occurring. Does PARTNER tell us anything about whether STIs still represent a complicating factor?**

We have strong evidence showing that STIs can increase the risk of HIV transmission, whether it is the HIV-negative or HIV-positive person who has the STI. Unfortunately, most of the studies looking at STIs didn’t keep track of the viral load of the HIV-positive partner, so it’s unclear whether this is true when the viral load is undetectable.

In the PARTNER study, 16% of the gay men and 5% of the heterosexual men and women were diagnosed with an STI at some point in the study. While it is reassuring that no HIV transmissions occurred despite the presence of STIs, it is difficult to come to a more definitive conclusion. This is because the conference presentation on the preliminary analysis didn’t include much information related to STIs. For example, the presentation didn’t include anything about the type of STIs, their location, their duration, whether they were treated or untreated or how many of the 44,000 condomless sex acts occurred in the presence of an STI. Hopefully the final analysis of the PARTNER study will include more information so we can better understand the potential impact of STIs on the risk of HIV transmission when undetectable.

It is also important to note that the HIV-negative and positive participants in the study received regular care every six months, which included testing and treatment for STIs. This may have helped limit the impact of STIs on HIV transmission. So, for now, I think our messaging needs to continue to state that STIs *may* increase the risk of HIV transmission when undetectable.

**What about the semen issue? We’ve always made the point that virus in the semen may occur when it is not measurable in the blood, How important is that a factor now given that there were zero transmissions recorded in x number of sexual acts in PARTNER, even though it seems virtually certain that there was virus in the semen of at least some otherwise undetectable participants? Granted we don’t know at what levels and what is enough to cause transmission. But surely if virus in the semen**
mattered as a significant risk factor we would have seen some transmissions?

We know that people who have an undetectable viral load in the blood can sometimes have detectable (although lowered) levels of the virus in their other bodily fluids, including semen, vaginal fluid and rectal fluid. However, as you point out, the implications of this phenomenon for HIV transmission are not well defined.

While some studies show that the viral load discordancy between blood and other bodily fluids is common, others suggest it is uncommon. Unfortunately, the PARTNER study didn’t monitor the viral load in the genital and rectal fluids, so we don’t know how common this phenomenon was among participants in the PARTNER study. This makes it difficult to come to any definitive conclusions. However, it’s very likely that at least some of the participants had detectable levels in their other bodily fluids, so it is reassuring to some extent that no HIV transmissions occurred.

What about “blips” in viral load? Does PARTNER tell us anything about the significance of those?

The preliminary analysis only included information from couples in which the HIV-positive partner had an undetectable viral load in the blood. However, the blood viral load was tested every 6 months, so it is possible that some of the positive partners may have had temporary blood viral load increases (or “blips”) in-between study visits. Unfortunately, we don’t really know how frequently this may have happened.

We do know that 343 couples in the PARTNER study were excluded from the preliminary analysis. Of particular note, 55 (16%) of these were excluded because their blood viral load was detectable. Some of these individuals may have been experiencing “blips”, but they were not included in the preliminary analysis. This finding also emphasizes the importance of regular viral load testing in order to ensure treatment is working and the viral load is fully suppressed. Also, 243 couples were excluded because they missed a follow-up visit, meaning they were not fully engaged in care and receiving regular viral load tests.

It strikes me, James, that sometimes people look for study results in simple terms where simplification isn’t easy. Would you agree? Let’s take as an example something one of the PARTNER researchers themselves said about transmission risk, I think, of anal sex without a condom where one partner is undetectable: “Our best estimate is it's zero” she said. You don't report that. Tell me why

As with any research study, the PARTNER results are not without uncertainties or limitations and this can make it challenging to translate the findings into simple messages. Front-line service providers need to ensure their messages are nuanced enough to be accurate, yet simple enough to be meaningful. This is hugely challenging and consensus expert consensus statements can play an important role in guiding the development of these messages.

I don’t think the statement “Our best estimate is it’s zero” is a very nuanced response. Say, for example, participants in the PARTNER study only engaged in a total of 10 condomless sex acts and no transmissions occurred. In this scenario, the best estimate, statistically, would also be zero. However, such a statement doesn’t reflect the uncertainty associated with the finding. It also describes the risk as an absolute (zero risk), which I don’t think we should be doing.

Also, this statement was the opinion of only one of the authors of the study and was provided in response to a question from the audience. The conclusion in the conference publication - which was reviewed by all the authors and passed a peer-reviewed process - states that the risk of HIV transmission among the stable serodiscordant couples in the analysis was “extremely low, but uncertainty over risk remains, particularly over receptive anal sex. Additional follow-up is essential…” Although this answer is not as nice and simple as “zero”, it is a more accurate and nuanced response.

I understand. James in your article you said “ART therefore represents an important new HIV prevention tool, which also has the potential to reduce the guilt, blame and anxiety associated with the possibility of transmitting HIV to a partner.” Agree 100%, but why “new”? Some people have been saying this since the Swiss Statement.

The Swiss Statement was released in 2008, but we didn’t have definitive evidence that treatment could prevent HIV transmission until the HPTN 052 results were released in 2011. In addition, we didn’t have definitive evidence that treatment could reduce the risk of HIV transmission through anal sex until this year, when the preliminary analysis
of the PARTNER study was released. I think we can agree that this is relatively “new” information. Regardless, I know we both agree that this information isn’t getting to the people who need it, so for many people this information is new and this is one of the reasons we are doing this interview.

**In retrospect would you say that the Swiss Statement, while put down by many at the time, was highly predictive of actual transmission risk.**

I think the Swiss Statement was challenged by many because, at the time, we didn’t have definitive evidence that treatment could reduce HIV transmission, yet it took a very absolute stance by stating that there is “zero” risk when certain conditions are met. Actually, since the statement was released, one of the authors has come out publicly saying they regret taking this absolute stance. This is summarized in an article on AIDSMAP.

Also, I believe the statement was developed more to influence the criminal justice system, and less to inform public health messaging, similar to the consensus statement released by a group of Canadian scientists last month. That being said, I think the Swiss Statement did have some positive impacts, particularly as it helped improve awareness about the potential lowered risk when the viral load is undetectable and provided the impetus to perform additional studies such as HPTN 052 and the PARTNER study.

**Ok James let’s move on to implications of the PARTNER study. Do you think we should be reacting to it now or waiting until the final results are into adjust our prevention messaging or even suggest to gay men that certain activities may be much safer than was previously established?**

I think we should be reacting now to what we can confidently conclude from the PARTNER study results. For example, our messaging should say that we have definitive evidence that treatment can dramatically reduce the risk of HIV transmission through receptive anal sex and that this reduction seems to be equivalent to the reduction for vaginal sex. However, based on the PARTNER results, I think our messaging should also say that the risk when undetectable may still be higher through receptive anal sex compared to other types of sex. That being said, some experts (such as those at the British HIV Association) think that the risk is reduced to the same levels for both vaginal and anal sex, under certain conditions.

**Anything else in the works then which may confirm - or not - what we have learned so far from PARTNER?**

The PARTNER study stopped following participants in April of this year, so I expect that the full analysis will be published later this year or early next year. This will include information on the gay couples included in this preliminary analysis, but followed up until April 2014 instead of November 2013. Hopefully, no HIV transmissions will have occurred and the upper confidence limit for receptive anal sex will be closer to zero.

It is the PARTNER2 study that is just getting started and won’t conclude until 2017. This study is continuing to follow the gay couples enrolled in the original PARTNER study and is attempting to enroll over 400 more. The main purpose of this study is to collect more data on receptive anal sex in order to drive that upper confidence limit down.

There is also a similar study ongoing in Australia, called the *Opposites Attract study*. Once this and the PARTNER studies are completed, we will have a very large amount of data on this topic, which we will hopefully be able to combine into a single analysis. The estimate from this analysis will allow us to be very confident regarding the “true” risk of HIV transmission when the viral load is undetectable.

**That’s something to look forward to then. One final question. It strikes me, James, that HIV prevention, and in fact the choices that gay men in particular have to make about their sexual risk taking, are having to become increasingly science based – and the science is quite complex. It’s also evolving. How does that increasing complexity affect your job and in fact the role of CATIE as a player in providing evidence to inform gay men’s choices?**

It is challenging, for sure. The science is complex and there are no simple answers that apply to everyone. As I mentioned earlier, when it comes to developing messages on the science, it is about finding a balance between capturing the nuances and keeping it simple and meaningful. It is also important for these messages to be provided in a way that is sex positive, non-judgmental, and non-prescriptive.

It is also important to keep in mind that the science and the numbers are only one part of helping gay men make
informed decisions. There are so many other things that come into play and may need to be discussed, such as context, relationships, trust, intimacy, mental health, alcohol and drug use, stigma, access to care and treatment, and so on. In some cases, the science and numbers may only need to be a small part of the process in helping a person come to a more informed decision.

In the near future, I really hope we see some expert consensus statements and counseling guidelines on this topic coming out of Canada because the guidance is really needed. I hope CATIE, as well as front-line service providers and community members, will be involved in their development.

**Agreed. James, as always thanks for talking to PositiveLite.com. It’s been a real pleasure.**

James: Thanks Bob.

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