Q and A for PARTNER Studies:
Interim analysis results presented at CROI 2014

STATUS: Results embargoed until 4 March 2014, 18:30 Central European Time (CET).

CROI presentation can be found at www.chip.dk

General Q and A's

What is the PARTNER study?
The PARTNER study is an observational study focusing on the risk of sexual HIV transmission when an HIV positive person is on treatment.

The study enrolled couples in which one partner is HIV positive and the other is HIV negative. The participating couples do not use condoms on a regular basis when they enter the study, and some of the couples never use condoms. Though participants are encouraged to use condoms, the study is not aimed at changing their sexual behaviour.

To be eligible for the study, the HIV positive person needs to be on HIV treatment (ART) at time of enrolment.

The study also wants to understand the reasons why couples do not always use condoms. Data is collected via questionnaires completed by study participants every six months.

Why is the PARTNER study being conducted?
The aim of the PARTNER study is to quantify the risk of HIV transmission when an HIV positive person has an undetectable viral load on ART.

It is well documented that treatment reduces the risk of HIV transmission; however, there is little data about how low the risk actually becomes. The limited information currently available on this is from heterosexual studies, providing limited data on anal sex.

Many of the participants in these studies, including the HPTN-052 study, said they regularly used condoms.

Why is quantifying this risk so important?

Quantifying the risk of transmission is important for two main reasons: to help reduce the risk of new infections and to understand the benefit of ART in reducing new HIV infections on a population level.

None of the previous observational studies restricted their analysis to people who reported not using condoms consistently, nor have they provided any substantive data on the risk from anal sex (gay or straight). Only 2% of participants (37 couples) in HPTN 052 were MSM (men who have sex with men) and 96% of the participants reported regular condom use. In MSM, anal intercourse without a condom is the major risk factor for HIV acquisition, especially for the receptive partner.

Currently, only two studies are currently looking at HIV transmission risk in MSM/anal sex: the PARTNER study, covering Europe and Opposites Attract, coordinated from Australia.

Treatment guidelines in many parts of the world already recommend ART initiation at diagnosis to help reduce transmission. Data, such as the PARTNER study provides, is necessary to confirm these assumed benefits.

Can the PARTNER study provide this data?
Yes. The PARTNER study is designed to provide more evidence on this question than all previous studies combined. It will provide data on risks from heterosexual sex, as well as risk from anal sex, both straight and gay.

What are the results so far?
The results presented at CROI 2014 report that no transmissions have occurred from an HIV positive partner who has an undetectable viral load.

Although new HIV transmissions occurred, none of these were linked to the HIV positive partner in the couple enrolled in the PARTNER study. In each case, an analysis of the genetic structure of the virus indicated that it had been acquired from a different partner.

These results are explained in more detail below.

What can the PARTNER study tell about condomless sex outside the main relationship?
Condomless sex outside the main relationship was reported by the HIV negative partner in 3% of heterosexual couples and 34% of gay couples (the HIV positive partners were not asked about this).

Do these results mean it is safe to stop using condoms?
No. The results presented by the PARTNER study report that, so far, no transmissions have occurred, exhibiting a low risk for study participants.

The study needs to continue with the planned follow-up and enrol more gay couples to increase the information about anal sex.

The PARTNER study still recommends using condoms.

Do the results mean that HIV positive people don't have to tell partners about their status?
No. Issues about HIV disclosure are not part of this study.

All HIV negative participants in the study know that their partner is HIV positive and we advise full disclosure of HIV status to all sexual partners.

However, the results from the PARTNER study and other studies will help inform people about the risk of transmission when not using a condom, so they can decide for themselves whether or not to use a condom.

Is the PARTNER study promoting sex without condoms?
No. This study only enrolled people who were already not using condoms. Couples didn't use condoms for an average of two years before entering the study and 25% of couples had not used condoms for more than six years.

The benefits of condom use, including contraceptive purposes and in protecting against other sexually transmitted infections (STIs), is emphasised at every study visit and is an important part of the study.

If a transmission occurs can the HIV positive person participating in the PARTNER study be prosecuted?
No. The study is only being run in countries in which disclosure of HIV positive status provides protection against legal action or where such legal action is judged unlikely to occur.

By signing the informed consent form, HIV negative partners state that they know their partner is HIV positive and that they understand there is a risk of transmission from not using condoms.

If a negative partner becomes positive, the data from both partners is anonymized so their individual samples cannot be identified through the central study database.

Why don't people just use condoms?
This is a good question and it is part of the PARTNER research.

More than 30 years into the HIV epidemic, many people, even in high risk groups, do not report consistent and continuous condom use. The reasons

behind this are likely to be complex, but most Western countries continue to report high rates of new infections.

If the PARTNER study can help quantify the level of protection from HIV treatment, this will highlight that most new infections are likely to come from people who are not on treatment, including because they are undiagnosed.

This information will be invaluable in supporting programming for earlier testing and for the choice of earlier treatment if transmission risk is a concern.

The results will be just as important for HIV sero-different couples who continue to use condoms. Knowing that the risk is dramatically reduced even if a condom breaks or slips off is likely to have a significant psychological benefit in reducing residual anxiety that either partner might have about even a low risk of transmission.

Who is taking part?
By February 2014, the PARTNER study had enrolled 1145 sero-different couples, of which 458 couples are gay male couples and 687 are heterosexual couples.

Most of the HIV positive partners have been on treatment for many years, with a median (average) of 7 years. However, 25% of participants have been on treatment for less than 3 years and 25% for more than 14 years.

Couples reported having sex without a condom about once a week (average of 50 times a year). For 25% of couples this was less than 15 times a year and for another 25% it was more than 76 times a year.

Where is the study taking place?
The PARTNER study has enrolled participants in 14 European countries: Finland, Sweden, Denmark, UK, Ireland, Belgium, Germany, The Netherlands, France, Austria, Switzerland, Italy, Spain and Portugal.

In total, 75 clinics and hospitals participate in the PARTNER study.

How is the PARTNER study funded?
The first stage of the PARTNER study is funded by the National Institute of Health Research in the UK.

Who is running this study?
The PARTNER study is a collaboration involving independent researchers and scientists from Europe.

The study Steering Committee includes doctors, researchers and community advocates.

The PARTNER study Executive Committee is:
Prof Andrew Phillips, University College London (UCL)
Prof Jens Lundgren, University of Copenhagen and Rigshospitalet, Copenhagen, Denmark
Dr Alison Rodger, UCL
Tina Bruun, Copenhagen HIV Programme (CHIP)
Simon Collins, HIV i-Base, London
Prof. Pietro Vernazza, Switzerland
Dr. Vicente Estrada, Spain
Prof Jan Van Lunzen, Germany
Giulio Maria Corbelli, EATG, Italy

Q and A's about the interim results from PARTNER

What was presented at CROI?
The results presented at CROI are part of a planned interim analysis. Since this is an observational study and all partners are encouraged to use condoms in any case it was decided to present interim results irrespective of what results were observed.

The interim results are based on nearly 1000 couple-years of condomless sex in sero-different couples where the positive person is on ART.

The analysis showed that so far no transmissions have occurred within a couple in which the positive person was on ART. This is only from eligible couple years – which mean it is based on data where the HIV positive partner had an undetectable viral load on the most recent test (at most 12 months before).

By 1st November 2013, 1,110 couples were recruited and followed for a total of 1151 years of follow-up. The interim results are from 767 couples who contributed 894 eligible couple years of follow-up (586 in heterosexual couples and 308 in gay male couples).

How will the results be communicated to the participating couples?
A few weeks before the conference, the study sites were informed about these results. This was to allow the study sites that experienced a sero-conversion time to discuss the results with involved study participants in advance.

Although these results remain confidential until the presentation, it is important that participants hear the results from their study team rather than in a news report.

What do these results mean?
Because no transmission has so far occurred between partners, the results support that treatment dramatically reduces the risk of transmission.

This is an early analysis and the study needs to continue to collect data with a longer follow-up.

No study can prove that something is 100% safe. Research can only try to quantify levels of risk. If the risk is shown to be very low, this is generally interpreted as being safe. However, these interpretations may vary depending on individual decisions about risk.

How many HIV transmissions would we have observed had HIV positive partners not been on ART, but had the same sexual behaviour?
We estimated that we would have observed approximately 15 infections in heterosexual couples and 86 in homosexual couples.

These estimations are based on assumptions regarding the probability of HIV transmission per sex act from two meta-analyses:
Boily (2009) estimated the rate of transmission per heterosexual sex act in high income countries: Male to female to be 0.0008 (95% CI: 0.0006-0.0011) and female to male to be 0.0004 (95% CI:0.0001-0.0014).

Baggaley (2010) estimated the probability of transmission per receptive anal sex act to be 0.014 (95%CI: 0.002-0.025).

Why does the study refer to confidence intervals? What do these mean?
When estimating risk, scientists have to allow for the fact that results may occur by chance. This involves calculating an upper or lower range of possible values called the confidence interval (CI). The 95% CI is the range of results that could be observed given the possible effects of chance.

In general, the larger the study, the more confident we can be that the results are genuine and not due to chance. In this type of study, the size of the study is measured by the total number of years people are followed for rather than just the number of participants. This is why the continued follow-up time is essential in the PARTNER study.

In the interim results, the upper 95% confidence limit for the risk of overall transmission over a 10-year period, of a couple having condomless sex with undetectable viral load is 3.9%.

This essentially means that there is a 2.5% chance that the 10-year transmission risk is higher than 3.9%.

Compared with other risks of daily life, this maximum estimate could be considered as relatively low. However, it will also be a personal decision for deciding whether individual health risks are considered high or low, and whether the benefits outweigh the risks.

The upper limit of the 95%CI varies depending on the type of sex.

What do the results tell us about risk for anal sex?
The detailed questionnaires completed by study participants enable the PARTNER study to estimate risk of transmission via different types of sex.

Already, PARTNER has more data than any other study on the risk of HIV transmission by anal sex (straight or gay) when the positive partner has an undetectable viral load.

However, since the number of couples reporting anal sex was relatively low, the calculated maximum risk estimate for anal sex is higher.

The upper 95%CI for anal sex is 9.2% over 10 years.

This does not mean that PARTNER found any evidence that risk through anal sex is higher than risk through vaginal sex. This is a factor of the amount of data we have. With less data, there is more uncertainty due to the smaller number of couples reporting anal sex.

An extension of the PARTNER study, called PARTNER 2, is planned to increase the level of certainty of the risk from anal sex.

This is especially important for receptive anal sex with ejaculation.

What is a linked transmission?
A linked transmission is when a negative partner's new HIV infection is with a type of HIV that is similar to that of their HIV positive partner.

This uses a specialized genetic analysis called phylogenetic analysis.

Although this test cannot be used to prove the route of infection, it is very useful in being able to identify if the viruses in the two infections are related.

This is essential when looking at HIV risk because many previous studies reporting transmission between sero-different couples found that 25%-50% of those cases of new infection were from people outside the main relationship.

When the person with recent infection has an HIV viral strain that is genetically very close to that of their partner, it suggests that the virus might have been acquired from that partner. However, it is important to note that it does not necessarily prove this is the case.

If the negative partner becomes infected but their virus is genetically very different from the positive partner, this suggests that the infection was from a different sexual partner.

The genetic analysis is an essential part of the PARTNER study.

So far, the study has been able to show that although some HIV negative people in the study have become HIV positive, none of the new infections is with HIV similar to that of their positive partner in the PARTNER study. It was thus concluded that it is likely that these new infections were not from their respective partner in the PARTNER study.

Does this mean that people who became positive now know that they acquired HIV from someone else?
The PARTNER study can only report that we found no linked transmissions within the partners enrolled in the study.
There may be other reasons why a transmission may not be included in these results, for example, if the viral load was detectable or if the last value recorded was over 1 year before.

However, the phylogenetic analysis shows that it is highly likely that these partners were infected by another source.

How many transmissions have occurred so far?
The total number of HIV negative people in the study who became HIV positive was not included in the interim analysis, as the study is only focused on linked transmissions.

What else will the PARTNER study report?
As well as the risk of transmission, the study includes questionnaires about behaviour and risk.

These results will be important to understand the motivations and beliefs behind not using condoms.

Does this mean a HIV negative person does not need a condom if their partner has an undetectable viral load?
No. The results only show that based on the available follow-up data, no linked transmission has occurred.

This information needs to be interpreted together with the 95% confidence limits. This is related to the size of the study and the amount of follow up.

The upper 95% confidence limit for the estimated transmission rates are not zero, so transmission is still possible.

Other factors may also be important.

STIs can make transmission more likely even if a person has an undetectable viral load. Condoms reduce the risk of some other infections.

Genetics may also be important. Some people are genetically more likely to become infected and others genetically more resistant. Genetic testing for this is not readily available or able to produce accurate results on individual risk.

It is also important to point out that we only studied couples who had previously had sex without a condom and transmission had not occurred. It could be that when having sex for the first time the risk is higher, for example, due to the negative partner being particularly susceptible to HIV in ways that we do not yet understand.

How does the PARTNER study define 'undetectable viral load'?
In the PARTNER study, an undetectable viral load was defined as being less than 200 copies/mL.

Different hospitals use viral load test that have different low-level cut-off values. For example, this can be at 20 or 50 or 200 copies/mL depending on the study site.

How long does viral load remain undetectable after a viral load test?
Viral load results only given information about the viral load at the time the blood was taken. So long as someone continues to take treatment on time, viral load is very likely to remain undetectable.

Approximately 5% of patients each year who are on stable treatment see their viral load rebound. This is largely thought to be related to difficulties with adherence. Viral load rebound in the context of good adherence to meds is unusual.

If someone stops treatment or misses medication for several days, it is likely that viral load will quickly become detectable.

Q and A's about PARTNER 2 in general

What is PARTNER 2?
PARTNER 2 is a continuation of the main PARTNER study, but it will only enroll gay (MSM) couples.

Why is PARTNER 2 important?
PARTNER 2 will provide the additional evidence required to have better confidence in the risks from anal sex.

This data is essential to inform potential scale up of ART for prevention in MSM, transgender women and others who have anal sex.

How many MSM couples are needed?
We need to enrol another 450couples. As 450 MSM couples are enrolled, this will take the total to approximately 950.

Who can participate in PARTNER 2?
Men living with HIV who are on antiretroviral treatment and had condomless sex at least once in the last six months with an HIV negative man can participate with their partners if they are supposed to have sex again in the future.

How many follow up years are needed to estimate transmission risk in anal sex?
To get the same level of confidence as the data on vaginal sex, we need to reach 2082 person years of follow up with anal sex.

Why is the MSM couple data so important?
More precise knowledge of the actual risk will enable people to make decisions about risk based on accurate data.

Gay men need to have data on the actual risk from anal sex, not just have a risk assumed to be similar to vaginal sex.

It will also have major public health consequences. This is especially important in areas of the world where anal sex is a major route of forward transmission.

Additionally, it will be important for programmes based on the wider use of treatment to reduce transmission.

Who will fund PARTNER 2?
Funding for PARTNER 2 will include pharmaceutical companies, national funds and charitable foundations.

So far ViiV, Augustinus Fonden (a Danish foundation) and A.P Møller Fonden (a Danish foundation) have sponsored PARTNER 2.

We are still actively looking for financial support to complete PARTNER 2.

If you are interested in supporting this important research please contact or need more information please contact:

Tina Bruun, Nurse MSA
Projector coordinator for PARTNER

Direct: + 45 35 45 57 93
Mail: tbr@cphiv.dk

Rigshospitalet, University of Copenhagen
CHIP, Department of Infectious Diseases and Rheumatology, Section 2100
Finsencentret
Blegdamsvej 9
DK-2100 Copenhagen Ø, Denmark