June 2013

Project Description - The PARTNER Study – stage 2 (2014-2017):

Estimating the risk of HIV transmission irrespective of sexual practice

Content

1. Executive summary

There is increasingly strong evidence that virally suppressive ART reduces infectiousness of people with HIV through sex. However, precise estimates of the risk of transmission from unprotected intercourse when the infected person is on ART with a most recent plasma viral load < 50 copies/mL are not available, particularly for men who have sex with men. Stage 2 of the PARTNER Study aims to define the risk of HIV transmission in such sero-discordant couples who do not use condoms. The study comprises 75 clinics in 14 European countries, and is projected to run until March 2017. Approximately 950 gay couples will be enrolled.

2. Introduction

A critical yet still unresolved public health question related to HIV is, whether HIV positive persons on antiretroviral treatment (ART) are still able to transmit HIV to their HIV seronegative sexual partner. The HPTN 052 study gave indications towards the answer to this, but without conclusive evidence for sexual partnerships having condom-less sex, due to the high reported (but unknown actual) levels of condom use. Additionally, HPTN 052 provided essentially no information on risk through anal intercourse irrespective of use of condoms. The PARTNER study is the only ongoing study worldwide able to comprehensively address the risk of HIV transmission in situations of sexual intercourse without condoms in general, and in particular in situations where a couple have anal intercourse.

2.1 Background – beyond HPTN 052 results

In men-having-sex-with-men (MSM), receptive and, to a lesser extent, insertive condom-less anal intercourse is the major risk factor for HIV acquisition. There have been studies documenting per act estimates of HIV transmissibility for anal intercourse, but to date no data are available from observational cohorts or RCTs to determine HIV transmission rates for anal sex in MSM when the HIV positive partner is on ART. As the risk of HIV transmission in the absence of ART is greater for anal sex than for vaginal sex, the degree to which the HPTN 052 results in heterosexual couples can be extrapolated to MSM or to heterosexuals having anal sex is unknown. Only 37 couples (2%) enrolled in HPTN 052 were MSM and 96% of the participants reported regular condom use. Conversely, in the PARTNER study, to be eligible the participating couples have to report condom-less sex in the past month prior to enrolment into the study and only the couples continuing to report having sex without condom (despite advice to use a condom) will be included in the final risk analysis. As such, PARTNER is testing the most risky situations for potential transmission through vaginal or anal intercourse.

It remains debated how to define the threshold of risk of HIV transmission which is both tolerable and acceptable. In addition, this level is largely an individual opinion. Even after HPTN 052, the upper confidence limit of the risk of having sex without a condom is higher than some individuals would consider acceptable. The only route to reduce confidence limits (and increase the precision of the risk estimate) is by increasing the amount of observation time on serodifferent couples. To reach acceptable certainty that the risk of transmission approaches zero in defined circumstances (i.e. anal condom-less intercourse), a larger number of couple years of condomless sex (and particularly anal sex) than were observed in HPTN 052 will have to be studied (Fidler et al 2013).

It is likely that an acceptable risk will be one that is at least twice an individual's life span i.e. 1 transmission per 200 years (meaning approximately four times an individual's sexually active life). In order to be able to show that the risk is very likely to be at this level or lower, 2000 person years are needed (see table 1 and 2).

The PARTNER study is set out to define whether such an acceptable risk exists for sexual relationships that do not use condoms regularly or not at all. Table 2 summarizes the results of HPTN 052, the first stage of PARTNER that is funded and will continue until March 2014, and the second stage of PARTNER which remains unfunded but intends to define the risk of transmission via condom-less anal sex.

2.2 Implications from the PARTNER study for treatment as prevention in MSM

In 2011, a WHO/NIH working group reviewed what further evidence is required in order to recommend a policy of ART for prevention of HIV transmission in MSM couples[4]. Concern was raised about the external validity of the results of HPTN 052 in MSM and others who engage in anal sex, given that only 2% of the pairs were MSM. Further, new diagnoses are continuing to rise in these populations (WHO 2008). A recent position statement on the use of ART to reduce HIV transmission from the British HIV Association (BHIVA) and the UK government's Expert Advisory Group on AIDS (EAGA) (January 2013)[3] also concludes that there are insufficient data to definitively conclude that successful ART use can provide similar levels of protection in relation to other sexual practices, including unprotected anal intercourse.

WHO, NIH and BHIVA refer to the PARTNER study as the only established study that can provide precise estimates of the rate of transmission of HIV in serodifferent MSM couples, where the positive partner is on ART. Hence, the PARTNER study aimed to be able to conclude on any difference in the magnitude of the effect of ART for HIV prevention between vaginal sex and anal sex.

More precise knowledge of transmissibility among sero-different MSM couples practicing condom-less intercourse will have major public health consequences in areas of the world where anal sex is a major route of forward transmission. Additionally, it will be important for the test and treat concept of reducing ongoing transmission to be able to provide concrete and direct evidence as part of informing MSM couples as well as heterosexual couples of the risks of infecting persons they have anal sex with.

PARTNER stage 2 can provide the necessary additional evidence required to inform potential scale up of ART for prevention in MSM, transgender women and others who have anal sex.

3. Methods

This is an observational study in which HIV MSM sero-different partnerships will be followed over time, with 3-6 monthly reporting of transmission risk behaviour and HIV testing for the HIV negative partner.

Inclusion/exclusion criteria:

Inclusion criteria

- Confirmed HIV positive

- On ART (regardless of viral load)

- Age > 18

- Expected to remain under care at the clinic for as long as the participate in the study

- Has a partner not known to be HIV infected and the following criteria are met:

The partners have had unprotected penetrative anal together in the past month (during which period the HIV negative partner was aware of the HIV status of the HIV positive partner)

Both partners consent to attend clinic to complete a risk behaviour questionnaire every 3-6 months for as long as they participate in the study and the HIV negative partner consents to testing for HIV at these visits.

Both partners consent to provide a separate blood sample if the HIV negative partner should become infected with HIV (this is for an anonymous comparison of viruses – results will not be linked to the partnership)

4. The PARTNER Study – what will be the results of stage 1 (2011-2014) and stage 2 (2014-2017) and why is stage 2 important to complete?

Stage 1: Hypothesis to be addressed mid 2014:

*The risk of HIV transmission with condom-less penetrative sex is very low when the HIV positive partner has an undetectable viral load.**

In other words, the study will at the completion of the first stage be able to establish the average risk of transmission for couples having condom-less sex, amongst which around 40% are practising condom-less penetrative anal sex.*

Stage 2: Hypothesis to be addressed by 2017:

The risk of HIV transmission with condom-less penetrative sex is very low when the HIV positive partner has an undetectable viral load ***regardless of sexual practice**.***

In other words, the study will at the completion of the second stage be able to establish the risk of transmission for couples practising condom-less penetrative anal sex as well as the risk for couples practising only vaginal sex.

* since the proportion of couples followed having anal sex is only around 40%, there will be less certainty over whether the rate is low specifically for anal sex.

** ie including anal sex

The first stage of the PARTNER study is funded by the National Institute of Health Research in the UK. The estimated accrual of couple years of follow-up in the PARTNER by March 2014 is 1753 couple years. If there are no transmissions observed in couples where the plasma viral load is undetectable, the upper 95% confidence limit on the estimated transmission rate is 3.689/1753 per couple year of condom-less sex, which is 1 transmission per 474 couple years. This is the risk for vaginal and anal practices combined. The couple years of follow up for MSM couples and for heterosexual couples having condomless anal sex in PARTNER will have reached 879 couple years by March 2014 (650 amongst MSM couples). If there are no transmissions observed the upper limit of the upper 95% confidence limit on the estimated transmission rate will be 3.689/879, which is 1 transmission per 238 couple years.

Table 1: Upper 95% confidence limit for risk of transmission (cy – couple years)

cy condom-less sex observed	Transmissions observed in the study		
	0 transmission	1 transmission	2 transmissions
500	1/136 cy	1/90 cy	1/69 cy
1000	1/271 cy	1/179 cy	1/138 cy
1500	1/407 cy	1/269 cy	1/208 cy
2000	1/542 cy	1/359 cy	1/277 cy

The rate of transmission through anal sex will be reported by the end of stage 1, but the upper 95% CI will be too high to finally resolve the question, even if there are no transmissions observed.

In order to increase the precision of the risk assessment for anal sex the second stage of the PARTNER study will cease the follow-up of couples not practicing anal sex in the spring 2014 and continue follow-up of anal sex couples for an additional three years, as well as continuing to recruit new MSM couples.

It is crucial to continue to recruit and follow MSM couples as part of the 2nd stage of the PARTNER study. If recruitment and follow-up of MSM (beyond the 650 couple years) is not continued, the upper limit of the upper 95% confidence limit on the estimated transmission rate, if there are no transmissions will be 3.689/650, 1 transmission per 176 couple-years, which is not considered a sufficiently precise estimate, considering the critical significance of the information. Clearly, this will be even more imperative if one or perhaps even two linked transmissions are observed,

Support for PARTNER stage 2 will allow obtaining an estimate of the transmission rate with the same level of precision for anal intercourse as for vaginal intercourse.

Risk of transmission is likely to be highest for couples for which the positive partner is insertive and ejaculates. If PARTNER stage 2 can be completed, couple years for this are projected to grow from 282 to 726.

3.1 Comparison HPTN 052, PARTNER stage 1 and 2

Table 2: Comparison of results generated by HPTN 052, and projected for PARTNER stage 1 and 2

	HPTN 052	**PARTNER stage 1 (by March 2014)**	**PARTNER stage 2 (by March 2017)**
Number of serodiscordant couples	1763	App 1350	App. 1780
Number MSM couples	37	App. 500	App .950
Condom-less sex	96% reported regular condom use 5-6% reported having unprotected sex prior to	Only couples reporting having sex without condom will be included in the final analyses.	Only couples reporting having (anal) sex without condom will be included in the final analyses.

	enrolment		
PYFU overall	1585	2015	3590
PYFU eligible	1145 **	1753*	3124*
PYFU of condomless sex	Estimated <200 PYFU	1753*	3124*
MSM/Anal sex	2%	48%	100%
PYFU from anal sex couples	Unknown < 50	879	2250
PYFU receptive anal sex with ejaculation	Unknown	282	726
upper 95% confidence limit for Risk of transmission – overall	**If no transmissions occur in the study:** 1/54 couple years combined	**If no transmissions occur in the study(**):** 1/474 couple years combined	**If no transmissions occur in the study (**):** 1/847 couple years combined
upper 95% confidence limit for Risk of transmission – anal sex	**If no transmissions occur in the study:** 1/14 couple years anal sex	**If no transmissions occur in the study (**):** 1/238 couple years anal sex	**If no transmissions occur in the study (**):** 1/610 couple years anal sex

* Eligibility criteria: HIV negative reporting condom-less sex; HIV+ VL<200 in the last year

** These numbers will be lower if one or more linked transmissions are observed (see table 1 above for details)

5. Funding

5.1 Budget – PARTNER stage 1 and 2

The cost for stage 1 and the supplementary cost to also complete stage 2 are detailed below (in Euro).

Table 2: Budget Stage 1 and 2

		Cost stage 1		Cost stage 2
Central Coordination		549.000		368.000
Site establishment (bonus)		50.000		-
Site MA and IEC approvals		39.000		4.500
Site payment		472.000		269.000
Closeout		-		11.500
TOTAL	**€**	**1.110.000**	**€**	**653.000**

5.2 Sponsorship requests to complete stage 2

Funding is already secured for stage 1. The total pending funding required to complete Stage 2 of PARTNER is 653.000 €. We therefore seek sponsor partnerships at the below levels.

Platinum partners

40% of stage 2 budget (260.000 €) providing an additional 560 CYFU of anal sex

Gold partners

25% of stage 2 budget (160.000 €) providing an additional 350 CYFU of anal sex

Silver partners

10% of stage 2 budget (65.000 €) providing an additional 140 CYFU of anal sex

Stage 2 will allow increasing the amount of observation time for condom-less sex, and the scientific rationale for why this is important, relevant and innovative is explained in section 3 above.

Investing in stage 2 of PARTNER is cost-efficient. Since PARTNER stage 2 is a second phase of the PARTNER study, the existing and already funded study infrastructure will be maintained, with a low cost for coordination and payment for the sites, and without large expenses for site establishment and IEC approvals etc.

A total of 75 sites from the following European countries collaborate in the PARTNER study: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, and the UK.

5.3 Funding the PARTNER Study – stage 2: what are the advantages to the sponsor?

Funders of the PARTNER Study – stage 2 will have a unique opportunity to contribute to finally closing the discussion on transmission risk on ART with a definitive study on anal sex – and thereby support clarifying an essential public health problem and potential benefit of ART. The existing study structure developed through stage 1 of PARTNER provides a unique and cost-effective opportunity to generate definitive evidence within a limited time-period.

All funders will be appropriately acknowledged on all study materials, and will be invited to quarterly update teleconference as well as to all investigator meetings held at international conferences during the study period.

6. References

1. Rodger, A et al. Partners of people on ART - a New Evaluation of the Risks (The PARTNER study): design and methods; BMC Public Health 2012, 12:296 doi:10.1186/1471-2458-12-296.
2. Cohen, M.S. et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy: NEJM 2011;365:493-505.
3. Position statement on the use of antiretroviral therapy to reduce HIV transmission, January 2013, The British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA)
4. WHO and NIH Working Group Meeting on Treatment for HIV Prevention among MSM: What additional Evidence is Required? Geneva, 26-27 October 2011.
5. Meeting report and background paper to inform global WHO Consultation on Strategic Use of Antiretrovirals for Prevention and Treatment, 14-16 November 2011.