Updated BHIVA-BASHH Position Statement on PrEP in the UK

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Purpose of statement

Recent results from clinical trials of PrEP have made it clear that this biomedical prevention tool could have a major impact on the HIV epidemic in the UK(1, 2). The intention of this updated Position Statement is to inform the UK healthcare workers on the role of antiretroviral pre-exposure prophylaxis (PrEP) in the setting of the UK epidemic, so that they can have an informed discussion with their patients.

Commissioning policies placing PrEP within a combination prevention package will be central to the delivery of high quality HIV prevention services, and should be developed as soon as possible. This work is in progress in England, but as yet a commissioning policy is not yet in place in any of the UK nations. It is true that clinicians can prescribe medicines for non-licensed indications (as is the case for post-exposure prophylaxis [PEP]), but their freedom to do so is constrained by cost pressures, and a coordinated national response is required to ensure equity of access and to maximise the public health impact of PrEP in each nation in the UK.

It is not possible to review the evidence for this biomedical intervention in isolation, as PrEP (systemic and topical) is one of several methods in the prevention package, and one of four biomedical tools available, the other three being medical male circumcision, PEPSE and treatment of an HIV positive individual to reduce the risk of viral transmission.

We therefore broadened the scope of the Position Statement published in the International Journal of STDs and AIDS in 2013 to attempt to put the evidence for PrEP in context, both in terms of the characteristics of the UK epidemic and the evidence for other biomedical interventions. This update takes account of new evidence collected in Europe, and the policy activities in England. We took note of the updates to other guidelines around the topic of prevention, including those that are in development and out for consultation.

Methods

The previous statement was amended to incorporate the most recent evidence, including the results of the PROUD trial which was conducted in 13 sexual health clinics in England(1). The draft was circulated for comment to the original writing group on the 26th March 2015. The writing group requested that two further topics be included, one outlining how to support patients who

are purchasing Truvada online, and a second commenting on the dosing schedule to recommend – daily or on-demand(2). A further amendment was circulated on 5th May before posting the consensus statement for public consultation on the association websites.

Consensus statements

- HIV remains an infectious disease of major public health importance in the UK with an estimated 107,800 infected individuals, a quarter of whom are not aware of their HIV status (3). The UK HIV epidemic most affects Black African, gay and other men who have sex with men (MSM) communities. In 2013, 3,250 new infections were diagnosed in MSM (the highest ever number) and 2,470 (76%) of these were probably acquired within the UK(3). The number of MSM estimated to have acquired HIV in the UK each year has not decreased in the last decade.

- The majority of HIV prevention efforts in the UK have focused on behaviour change, mainly the use of condoms and testing behaviour. Since 2011 provision of antiretroviral therapy to reduce the risk of onward transmission has been formally included as an effective prevention method in the BHIVA HIV treatment guidelines, although the commissioning policy to support this is still under review. There was limited new funding for motivational interviewing to be implemented in accordance with national guidelines, and clinics have been under increasing pressure to make savings which has restricted access to this as well as to treatment for prevention. Whilst cross-sectional datasets of outcomes and impact provide some insight, there has been no systematic approach to the evaluation of behavioural interventions on a national basis.

- Ten randomised controlled trials have reported on the use of pre-exposure prophylaxis, five providing evidence for the effectiveness of daily oral tenofovir(4, 5) or Truvada(1, 4, 6, 7) and one for Truvada taken before and after sex(2). Effectiveness for oral tenofovir based regimens has been demonstrated in three of three trials in MSM(1, 2, 6), one of one trial in predominantly heterosexual serodiscordant couples(4), one of one trials in young heterosexual adults(7) and one of one trials in injecting drug users(5). A seventh trial assessing tenofovir 1% vaginal gel applied before and after sex observed a modest reduction in HIV incidence in women in Kwazulu-Natal(8) but this was not confirmed in the subsequent trial conducted in South Africa(9) (Table 1). Two randomised placebo controlled trials conducted in women in Sub-Saharan Africa observed no benefit in the modified intent to treat analysis for daily oral tenofovir or Truvada or daily tenofovir 1% vaginal gel(10, 11). The discrepant results are explained by low levels of adherence observed in the trials that did not see a reduction in HIV incidence - less than a third of women on the active arms had detectable drug at the first study visit. Biological efficacy is supported by subset analyses conducted in women using gel who had detectable drug(9, 11).

- Two of the randomised trials were conducted in European MSM populations and reported early this year. PROUD was an open-label design in which half the participants had access

to daily Truvada in the first year and half did not(1). IPERGAY was a placebo-controlled design evaluating an event driven regimen of Truvada (two tablets before sex, and one a day for two days after the last condomless anal sex act)(2). In both trials the incidence in the control group was much higher than anticipated, 8.9/100 person years in PROUD and 6.6/100 person years in IPERGAY. The incidence seen in PROUD is eighteen fold higher than the estimated incidence based on the overall MSM populations in England. The reduction in HIV was also the highest seen to date in intent to treat analyses (86% in both trials). PROUD also demonstrated the feasibility of delivering PrEP through sexual health clinics using simple and easy to apply inclusion criteria. IPERGAY demonstrated that an event driven regimen, which required half as much drug as a daily regimen overall, was also highly effective at reducing acquisition of HIV.

- The momentum following these two European trials reinforces the need to rethink our overall strategy for HIV prevention. The continued increase in infections being identified in MSM, acquired within the UK, underscores the urgent need to do so. Central to the prevention strategy is full engagement of the most affected communities.

- As a consequence of the high HIV incidence in the non-PrEP and placebo groups and the large effect size in both trials, the numbers that need to be treated in populations similar to those enrolled in the PROUD and IPERGAY studies to avert one infection in a year are very low, 13 and 18 respectively. A preliminary cost-effectiveness evaluation using the eligibility criteria for these two trials and the 86% reduction in HIV incidence, suggests that daily PrEP for MSM will be cost-effective if HIV testing continues at the current rate and there is no substantial change in the proportion of MSM who manage their risk with condoms(12). The cost of drug, which is approximately half using the IPERGAYdosing schedule, is a key driver of the cost-effectiveness, as is the background incidence in the population seeking PrEP.

- It is helpful for health care workers to be aware of the international response to the evidence. Tenofovir vaginal gel is not licensed for prevention anywhere; Truvada is licensed for prevention in the US(13), and submissions are under review in Australia, Brazil, South Africa and Thailand, and on a named patient basis in France. Truvada is licensed for treatment in the UK and Europe and used off label for prevention as PEP. The drug comes off patent in Europe in 2018 and this is relevant for the cost-effectiveness analyses. The Centre for Disease Control and Prevention has issued guidance for US clinicians to support daily oral Truvada in anyone at sexual risk of acquiring HIV, and the World Health Organisation issued a new recommendation in July 2014 that PrEP is an additional HIV prevention choice in a comprehensive HIV prevention package among MSM(14, 15).

- At the time the iPrEx trial reported, a number of concerns were expressed about the widespread use of PrEP by a range of stakeholders, including the gay communities, sexual health and HIV commissioners, the European regulatory authorities, clinicians and the research community. These concerns included cost, not only of drug but the feasibility of delivering it, the emergence of drug resistance and toxicity. A major concern was the

possibility that people would drift away from consistent condom use or be pressurised to do so by their partners and peers, and that this would outweigh the protective effect of PrEP as this was expected to be modest based on iPrEx (~50% reduction in HIV). PROUD was designed to address this major concern and to obtain a measure of 'real-world' effectiveness. The benefit observed in PROUD was high, and there was no difference between the group on PrEP and the group not on PrEP in terms of sexually transmitted infections. The European Centre for Disease Control has revised their previous statement which expressed concern about risk compensation, and now recommends that "EU Member States should give consideration to integrating PrEP into their existing HIV prevention package for those most at-risk of HIV infection, starting with MSM."

- A PrEP sub-group of the National Clinical Reference Group was established in September 2014 to scope the work to be done for a commissioning policy in England. The aim of the sub-group is to assemble the necessary information including the cost-effectiveness analysis of a PrEP programme in England, to enable a decision to be taken in time for the 2016/17 financial year.

- Clinicians need to know how to respond to patients who are seeking PrEP, including patients who have or plan to purchase Truvada online. The first thing to assess is why they think they need PrEP. It may be helpful to see them with their regular partner if they are in a monogamous serodiscordant relationship in which the positive partner has undetectable viral load, to discuss the evidence that treatment prevents transmission and to encourage them to enrol in the PARTNER study(16). If the positive partner is not on treatment or is not yet virally suppressed, then there may be a role for PrEP for the negative partner. MSM and transgender women who are having condomless anal sex with casual male partners would clearly benefit from PrEP as this was the eligibility for PROUD and IPERGAY. It is important to have access to a 4th generation HIV test and serum creatinine with timely return of the results (within one week) and it may be appropriate to wait for the result before taking the first tablet when starting PrEP. However, PrEP can start the day of the tests, provided the point of care antibody test is negative and there is no suspicion of acute HIV infection, and should be started promptly when risk is a continuum. An early check within the first month of starting PrEP is useful and this is an opportunity for an additional 4th generation HIV test if indicated. Otherwise screening for HIV and STIs whilst on PrEP should continue according to the current recommendations (3 monthly). Renal safety can be checked at these visits through urinalysis with additional tests according to clinic practice if there is 1+ of protein and no other explanation for this, such as infection. If there is sufficient concern that the Truvada is counterfeit, a sample could be collected for tenofovir levels.

- Discussing the event driven regimen followed in IPERGAY will facilitate full disclosure about the nature and frequency of sexual risk, and provide an opportunity to ensure the patient understands the timing of HIV transmission. The event driven regimen will be more naturally interrupted during periods of no risk, thereby lowering the pill burden. The

estimated time to complete a cycle from virion to virion *in vivo* in productively infected CD4+ cells takes 52 hours, 33 hours of which is reverse transcriptase activity(17). Clinical research suggests that virus escapes the genital compartment after a very short period (3-6 days after exposure)(18). Therefore the time in which a reverse transcriptase inhibitor is most likely to prevent an established infection is within this very short period. The IPERGAY regimen advised two tablets 2-24 hours before sex, which allows both drugs to be active in the genital tissue at the time of sex or 22 hours afterwards. If patients have not managed to take a dose beforehand (because sex without a condom cannot always be predicted), taking two tablets within 12 hours of sex will still ensure active drug is present during the reverse transcriptase phase. Drug should be continued daily such that the last dose following the last condomless anal sex act is at least 48 hours later, which could mean daily through to and including Monday morning if sex continued through Saturday. It is important to be practical about the timing of the doses and opt for times when the patient is likely to be awake. An event driven regimen will not suit patients who have condomless anal sex with casual partners more frequently than once a week. Other factors for the clinician to discuss with patients with regard to choosing a regimen include adherence, as missing pills in the event driven regimen will matter far more than missing pills in a daily regimen.

- Just under half the new diagnoses in the UK arise in heterosexuals. This group is more likely to be diagnosed outside the GUM clinic network. Nonetheless, heterosexuals at risk of acquiring HIV from sexual partners may also present for advice. As with MSM, the discussion should start with the reason they consider themselves at risk, the pattern of risk, and the offer to see them with their regular partner, if appropriate. The Partners PrEP demonstration project used data from the demonstration project in which there were 2 seroconversions amongst 1013 couples when PrEP was used by the negative partner for a 6 month period, allowing time for the positive partner to become undetectable with treatment(19). They modelled the expected incidence in the population in the absence of PrEP and concluded that the reduction in HIV with PrEP was 96% (95% CI: 81-99%).

Conclusion

We have gathered evidence on the effectivenesss of PrEP in England, which can be extrapolated to MSM throughout the UK in support of access. The concern that access to PrEP would change condom behaviour to the extent that this would impact on sexually transmitted infections and PrEP effectiveness, were not substantiated in the PROUD trial.

There are outstanding research questions regarding the broader heterosexual community, new drugs and formulations, and the need for greater precision around the effectiveness of event-driven Truvada, and we encourage clinical research in these areas. However, PROUD and IPERGAY have provided robust evidence for a large reduction in HIV incidence when PrEP is offered to MSM having condomless anal sex, and revealed a sub-group of MSM who are at imminent risk of HIV

and who need additional risk reduction support over and above the standard of prevention care outlined in the BASHH-BHIVA guidelines. Therefore BASHH and BHIVA strongly recommend that PrEP be made available within a comprehensive HIV prevention package to MSM who are engaging in condomless anal sex, and to HIV negative partners who are in serodiscordant heterosexual and same sex relationships with a HIV positive partner whose viral replication is not suppressed.

PrEP is one of several prevention tools and Healthcare workers should use the information in Table 2 to aid discussion of the options available to their service users. The data in support of condoms(20) and treatment of positive partners(21, 22) are also robust.

The evidence gathered in our own epidemic setting for the benefits of PrEP for the individual, and for the health service, is compelling. Further, it offers an opportunity to engage with those most at risk of HIV, buying time for a sustainable change in behaviour and averting a condition that requires life-long therapy. The HIV incidence observed in PROUD and IPERGAY is unacceptably high, and existing prevention strategies are clearly insufficient. Our recommendation is that PrEP should be made available to the most at-risk populations.

Guide to interpreting Table 2

Size of Effect[†] Point estimate	Strength of evidence Takes account of circumstances where RCT is not possible (eg to evaluate condoms)
LARGE ~80% or greater	HIGH Supported by a meta-analysis of RCTs (Ia) or at least one RCT (Ib) of high quality with evidence specific to the recommendation or in circumstances where RCT not possible, effect size well characterised through meta-analysis of cohorts (III) and estimate very unlikely to change
MODEST ~50%	MODERATE Supported by well conducted clinical studies on the topic of recommendation, with a prospective control group (IIa) or other control used to minimise bias (IIb) or well designed descriptive studies in which the comparative group is clearly defined in the analysis, but bias from selection and confounding cannot be completely excluded eg case-control,
SMALL ~35% or less	LOW Supported mainly by expert committee reports or opinion (IV). Indicates the absence of directly applicable studies of good quality eg when treatment for comparative group selected by individuals/physicians.

†

Not assessed	no study, trial or analysis of note has been conducted
Not established	there has been an attempt to estimate the effect, but this was not possible
Not demonstrated	the result implies there is no effect

95% Confidence intervals (CI) are provided where there is a single study/trial/analysis. Where there are several publications, the range of estimates is quoted

Table 1 PrEp and ART evidence to come: Summary of status of relevant PrEP and ART effectiveness trials including those underway

	CAPRISA 004(8)	iPrEx(6)	FEM-PREP(10)	Partners in PrEP(4)	CDC-TDF2(7)	HPTN 052(21)	CDC 370(5)	VOICE(11)	FACTS-001(9)	IPERGAY(2)	PROUD(1)	IPM 027/ The Ring Study	MTN20/ Aspire
Population	889 women from urban and rural settings in Kwazulu Natal, South Africa	2499 MSM or transgender men in South America, the US and South Africa	1,950 Women at high risk in Kenya, South Africa and Tanzania	4,758 Sero-discordant couples in Kenya, Uganda,	1,219 young adults in Botswana	1,750 Sero-discordant couples in Uganda, Kenya, , Brazil, India, Thailand	2, 413 male and female Injecting drug users in Bangkok, Thailand	5,000 Women from urban and rural settings in South Africa, Uganda, Zimbabwe	2059 women from urban and rural settings in South Africa,	413 MSM in France and Canada	545 MSM in England	1950 Women from urban and rural settings in South Africa, Uganda	3476 Women from urban and rural settings in Malawi South Afria, Uganda, Zimbabwe
Intervention	Before and after sex 1% tenofovir vaginal gel applied	Daily Oral Truvada	Daily Oral Truvada	Daily Oral tenofovir or Truvada	Daily Oral Truvada	ART for positive partner when enrols vs standard	Daily Oral tenofovir	Daily Oral tenofovir or Truvada or 1% tenofovir vaginal gel	Before and after sex 1% tenofovir vaginal gel applied	Before and after sex Oral Truvada	Dailu Oral Truvada	Continuous Dapivirine, released from a vaginal ring	Continuous Dapivirine, released from a vaginal ring
Trial status	Reported Jul 2010	Reported Nov 2010	Reported Apr 2011	Reported Jul 2011	Reported Jul 2011	Reported Aug 2011	Reported Jul 2013	Reported Feb 2015	Reported Feb 2015	Reported Feb 2015	Reported Feb 2015	In follow-up to report 2016	In follow-up to report 2016

Adapted from AVAC table **www.avac.org/: click on the Quick link 'Prevention research timeline' and on individual trials for more details.**

Table 2 PrEP in context: Summary of the current data on the relative estimates of protection using different prevention strategies for different sex acts (95% CI)

Route of exposure	Intervention	Estimated SIZE OF EFFECT	STRENGTH OF EVIDENCE
HIV-ve MEN having insertive VAGINAL sex with women	Condoms	LARGE: 94.2% or greater	HIGH: Cochrane meta-analysis of cohort studies(20) suggests best case population benefit 94.2%. True biological efficacy close to 100% as cohort studies did not account for incorrect use or over-reporting of condom use due to social desirability
	Male circumcision	MODEST: 58% reduction in HIV incidence(23)	HIGH: Summary estimates for 3 RCT and observational studies identical 58% reduction in HIV acquisition risk following healed male circumcision, greater in men with 2 or more partners. True benefit probably larger as suggested by the as-treated estimate of 65%.
	PEPSE	NOT ASSESSED	LOW: Estimate from occupational exposure is 81% (48-94%) reduction(24)
	PrEP Truvada oral daily Tenofovir oral daily	LARGE for Truvada: 80-83% in MITT(4); 96% (81-99%) in models(19) MODEST for tenofovir: 55% (4-79%)(4)	HIGH: Two RCT demonstrated benefit for Truvada in HIV negative men and women(4, 7) with large estimates of effect for heterosexual men. Partners in PrEP also demonstrated significant benefit with tenofovir alone, although this was modest(4). Modelling using HIV incidence data collected in the open-label extension study and validated risk categories to predict expected incidence without PrEP suggests a 96% reduction (95% CI 81-99%) with Truvada.
	ART for HIV+ female partner	LARGE: 92%(22) -96% if monogamous(21)	HIGH: 96% (95% CI 82-99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)(21) and metanalysis of cohort studies(22) At least 7/11 remaining were not linked, suggesting 30% acquisition is outside main partnership, similar to a previous RCT(25). 0 transmissions in 272 couple years of condomless insertive vaginal sex in serodiscrodant couple in PARTNER (upper 95% CI for transmission rate is 1.3/100 couple years)(16)

Route of exposure	Intervention	Estimated SIZE OF EFFECT	STRENGTH OF EVIDENCE
HIV-ve WOMEN having receptive VAGINAL sex with men	Condoms	LARGE: 94.2% or greater(20)	HIGH: Cochrane meta-analysis of cohort studies(20) suggests best case population benefit 94.2% .True biological efficacy close to 100% as cohort studies did not account for incorrect use or over-reporting of condom use due to social desirability
	Male circumcision of HIV+ve male partner	MODEST: 46% reduction in HIV incidence, 24m after procedure(26)	MODERATE: Recent meta-analysis of two cohort studies suggests effect was previously missed because no benefit in the first 24m demonstrated in one RCT, probably because sex was resumed before healing was complete.
	PEPSE	NOT ESTABLISHED	LOW: Single observational study in sexual assault 0/182 with PEPSE 4/145(27)
	PrEP Tenofovir 1% vaginal gel Before+After Sex, or Daily Tenofovir oral daily Truvada oral daily	(NONE)-MODEST: 39% (6-60%) reduction in HIV incidence(8, 9, 11) (NONE)-MODEST: 71% (47-87%)(4, 11) (NONE)-MODEST: 66% (28-84%)(4, 7, 10) 96% (81-99%) in models(19)	HIGH: One of 3 RCT(4) observed significant benefit for women using Truvada, a second was supportive (49%)(7)', and two others observed no difference(10, 11). Partners in PrEP demonstrated modest protection for oral tenofovir(4), but there was no benefit in VOICE(11). An event driven regimen of vaginal gel reduced HIV in one trial, but this was not confirmed in a second trial. The inconsistency between the trials is explained by the differences in adherence. Vaginal dosing significantly reduced HSV2 in CAPRISA 004, and in a subset of women in the gel group in VOICE who had detectable drug. Modelling using HIV incidence data collected in the Partners PrEP open-label extension study and validated risk categories to predict expected incidence without PrEP suggests a 96% reduction (95% CI 81-99%) with Truvada(19). Of note the two seroconversion occurred in two women who were not taking their PrEP at the time.
	ART for HIV+ve male partner	LARGE: 92%(22) -96% if monogamous(21)	HIGH: 96% (95% CI 82-99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)(21) and meta-analysis of cohort studies(22) At least 7/11 remaining in 052 were not linked. 0 transmissions in 192 couple years of condomless sex with ejaculation in serodiscrodant couple in PARTNER (upper 95% CI for transmission rate is 1.9/100 couple years)(16)

Route of exposure	Intervention	Estimated SIZE OF EFFECT	STRENGTH OF EVIDENCE
HIV-ve MEN having insertive ANAL intercourse with either men or women	Condoms	LARGE: 94.2% or greater(20)	MODERATE: Cochrane analysis excluded MSM couples, and proportion of anal sex acts in heterosexuals not recorded(20). Biological efficacy still likely to approach 100% with correct use, but condom breakage more likely with anal intercourse.
	Male circumcision	NOT ESTABLISHED	LOW-MODERATE: well conducted analysis using prospective MSM cohort data suggests likely protection if >60% acts insertive(28). More research needed as biological rationale for protection, although methodological challenges are noted.
	PEPSE	NOT ESTABLISHED	LOW: quality of single observational study was weak(29) 10/11 seroconvertors did not use PEPSE, but no population benefit compared to historical control
	PrEP Truvada oral daily	NOT DEMONSTRATED for MSM: HR 1.59 (0.66-3.84) if no URAI(6) NOT ASSESSED for heterosexuals	HIGH for MSM: iPREX benefit only seen in those reporting URAI at baseline(6). In spite of this, MSM who only reported insertive anal sex were considered eligible for PROUD and IPERGAY, and these trials observed a large benefit(1, 2). Partners in PrEP(4) and CDC TDF2(7) have not specifically addressed this question, but may be able to do so.
	ART for HIV+ve partner	LARGE: 92%(21) -96%(22)	MODERATE for MSM-HIGH for heterosexuals: one RCT (HPTN052)(21) with 3% MSM couples, and meta-analysis of heterosexual cohorts(22), so anal sex with men infrequent. However, many ARV concentrate in the rectal tissue, so viral shedding should be controlled. 0 transmissions in 262 couple years of condomless insertive anal sex in serodiscrodant couple in PARTNER (upper 95% CI for transmission rate is 1.4/100 couple years)(16)

Route of exposure	Intervention	Estimated SIZE OF EFFECT	STRENGTH OF EVIDENCE
HIV-ve MEN having receptive ANAL intercourse	Condoms	LARGE: 94.2% or greater	MODERATE: Cochrane analysis excluded MSM couples, and proportion of anal sex acts in heterosexuals not recorded(20). Biological efficacy still likely to approach 100% with correct use, but condom breakage more likely with anal intercourse.
	Male circumcision of HIV+ve male partner	NOT ASSESSED	LOW: No evidence, but plausibly some benefit if insertive partner is circumcised.
	PEPSE	NOT ESTABLISHED	LOW: quality of single observational study was weak(29) 10/11 seroconvertors did not use PEPSE, but no population benefit compared to historical control
	PrEP Truvada oral daily or event-driven	MODEST-LARGE: 44% (15-63%) to 86% (1, 2, 6)	HIGH: Case control analysis in iPrEX using PK suggested efficacy was higher (estimate 92%), and this is supported by the open-label extension in which no seroconversions were observed when drug levels were compatible with 4 or more tablets a week. Large reductions were observed in the PROUD open-label trial (86%: 52-97%) of Truvada compared to no Truvada, and in the IPERGAY trial (86%; 40-99%) of event driven Truvada compared to placebo (two tablets before sex and one a day for two days after the last condomless anal sex act). The only infections acquired in these two trials were in participants who were unlikely to be taking Truvada at the time of exposure.
	Tenofovir 1% rectal microbicide gel	NOT ASSESSED (clinically)	Rectal microbicides in development but PK/PD after topical dosing, and ex vivo challenge encouraging(30).
	ART for HIV+ve partner	LARGE: 92%(21) -96%(20)	MODERATE: One RCT (HPTN052)(21) with 3% MSM couples, and meta-analysis of heterosexual cohorts(22), so anal sex with men infrequent. However, viral shedding in ejaculate should be controlled by ART. 0 transmissions between MSM having condomless receptive anal sex with ejaculation in over 93 discordant couple years in PARTNER (upper 95% CI for transmission rate is 3.94/100 couple years)(16)

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