

BHIVA–BASHH Position Statement on PrEP in UK

Second Update May 2016

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Purpose of the update

This update follows the NHS England update on the commissioning and provision of pre-exposure prophylaxis (PrEP) for HIV prevention (<https://www.england.nhs.uk/2016/03/prep>)

Introduction

The General Medical Council advice on ‘Consent and Decision making’ is clear that a doctor’s duty is to give patients the information they want and need about options for treating and managing their condition, the potential benefits, burdens and risks for each option, and any treatments that they think have greater potential benefit for the patient than they or their organisation can offer [1].

Recent results from clinical trials of pre-exposure prophylaxis (PrEP) have made it clear that this biomedical prevention tool could have a major impact on the HIV epidemic in the UK [2-4]. The intention of this updated Position Statement is to inform the UK healthcare workers on the role and availability of oral antiretroviral pre-exposure prophylaxis (PrEP) in the setting of the UK epidemic, so that they can comply with their duty of care by having an informed discussion with their patients.

Fragmentation of commissioning for sexual health services and HIV is already threatening provision of a comprehensive prevention package that should include open access to free HIV and STI screening, treatment, partner notification, condoms, behavioural interventions and post-exposure prophylaxis. On 21st March 2016, after 18 months of work on a policy proposal for NHS England to commission the drug for PrEP to be included in this package, NHS England announced that Local Authorities are the responsible commissioner for HIV prevention services within the current legal framework and the policy will not be progressed further for consideration by NHS England specialist services [5]. Following a legal challenge by the National AIDS Trust, NHS England is reconsidering this decision [6]. Consequently there is no mechanism for PrEP to be provided free of charge in England and Wales. In Scotland and Northern Ireland there have been no announcements regarding PrEP provision.

Healthcare providers see people who are at imminent risk of acquiring HIV every day. These individuals have two options for purchasing PrEP within the current legal framework: either from pharmacies outside the European Union selling generic products, or from pharmacies within the UK with a private prescription.

Advocacy for commissioning policies for all the UK nations to ensure equity of access to PrEP must continue, as many vulnerable individuals will not be able to afford their own PrEP, and to maximise the public health impact of PrEP in each nation in the UK.

History of updates

In September 2015 we updated the 2012 Position Statement [7] to put the evidence for PrEP in context. The September 2015 update [8] incorporated the results of the PROUD trial which was conducted in 13 sexual health clinics in England [2], the IPERGAY trial conducted in France [3], and the Partners PrEP Demonstration Project [4]. It also included some practical guidance on the regimen of choice and safety monitoring for patients purchasing Truvada online at the request of healthcare providers.

This 2016 update captures the latest information on regulatory submissions, approvals and the lack of commissioning process. It also takes into account new European guidelines on PrEP and expands the practical advice as several clinics are facing enquiries from patients who are seeking PrEP or already sourcing their own PrEP medication.

Consensus statements

The context of the UK epidemic

- HIV remains an infectious disease of major clinical and public health importance in the UK with an estimated 103,700 infected individuals, 17,500 (17%) of whom are not aware of their HIV status in 2014 [9]. The UK HIV epidemic most affects gay and other men who have sex with men (MSM) and Black African communities. In 2014, 3,360 new infections were diagnosed in MSM (the highest ever number) and 2,550 (76%) of these were probably acquired within the UK [9]. 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 behaviours. Since 2012 provision of antiretroviral therapy to HIV positive individuals to reduce the risk of onward transmission has been recommended as an effective prevention method in the BHIVA HIV treatment guidelines; NHS England commissioned this in July 2015. Funding for motivational interviewing (recommended in national guidelines) is limited which restricts access. 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.

Evidence for PrEP

- Ten randomised controlled trials have reported on the use of pre-exposure prophylaxis, five providing evidence for the effectiveness of daily oral tenofovir [10,11] or Truvada [2,12,13] and one for Truvada taken before and after sex [3]. Effectiveness for oral tenofovir-based regimens has been demonstrated in MSM [2,3,12], heterosexual serodifferent couples [10], young heterosexual adults [13] and injecting drug users [11]. 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 [14] but this was not confirmed in the subsequent trial conducted in South Africa [15] (Table 1). Two randomised placebo-controlled trials conducted in women in Sub-Saharan Africa observed no benefit for daily oral tenofovir or Truvada or daily tenofovir 1% vaginal gel [16,17]; the discrepant results for these trials are explained by low levels of adherence – 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 [15,17]. Two trials of the dapivirine intravaginal ring recently reported a small reduction in HIV acquisition. This was higher in women aged over 25, as there was no benefit in women younger than this due to lower adherence [18,19].
- Two of the randomised trials were conducted in European MSM populations and reported in 2015. PROUD was an open-label design in which half the participants had access to daily Truvada in the first year and half did not [2]. IPERGAY was a placebo-controlled design evaluating an event based regimen of Truvada (two tablets before sex, and one a day for 2 days after the last condomless anal sex act)[3]. In both trials the HIV incidence in the control group was much higher than anticipated, 9.0/100 person years in PROUD and 6.6/100 person years in IPERGAY. The incidence in PROUD is eighteen fold higher than the estimated incidence based on the overall MSM populations in England, and seven fold higher than MSM attending sexual health clinics. The reduction in HIV was also the highest seen to date (86% in both trials by ITT analysis). 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-based regimen, which required half as much drug as a daily regimen, was just as effective.

- 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. 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 were no significant differences between the group on PrEP and the group not on PrEP in terms of sexually transmitted infections.
- 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 [20]. A second analysis using a different model has been conducted by Public Health England. Even at current drug prices, PrEP would be cost-saving if given to people with a background HIV incidence of over 5.2% a year (similar to HIV incidence in MSM diagnosed with a rectal STI in the previous year)[21]. The usage and cost of drug should be substantially reduced with an event-based regimen (it was approximately halved in the IPERGAY trial). This is a key driver of the cost-effectiveness, as is the background incidence in the population seeking PrEP. The cost of drug will also reduce when tenofovir comes off patent in Europe in December 2017, as emtricitabine does not have a patent in Europe (provided a two tablet regimen is acceptable).
- The very high HIV incidence seen in MSM in both these trials, coupled with the continued increase in new infections identified in MSM, acquired within the UK, each year underscores the urgent need for clinicians to act. Central to our response is full engagement of the most affected communities.

Policy

- The results of the two European trials accelerated implementation in the US where Truvada was licensed for use as PrEP [22], informed the inclusion of PrEP in the European AIDS Clinical Society (EACS) guidelines [23], informed the World Health Organization (WHO) recommendation [24] and increased the pressure globally to submit to regulatory authorities and include PrEP in national policies. EACS guidelines advise tenofovir or Truvada daily as PrEP for heterosexuals at risk, and Truvada daily or on-demand for MSM. In contrast, WHO guidelines only advise daily tenofovir or Truvada for populations at substantial risk of acquiring HIV.
- The European Centre for Disease Control revised their previous statement that expressed concern about risk compensation, to recommend ‘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.’ The European Medicines Agency is currently reviewing a submission from Gilead for an

extension to their application for Truvada and a decision is expected in the autumn of 2016. However, Truvada is already used off label throughout Europe for prevention as PEP, so it is difficult to determine how necessary regulatory approval is for implementation.

- The French Minister of Health has agreed that the costs for drug and monitoring of PrEP will be reimbursed through the social security system from January 2016, following approval of an expanded access programme providing Truvada as PrEP by the French Regulatory Authority.
- A PrEP working group of the National Clinical Reference Group of NHS England was established in September 2014 to scope the work to be done for a commissioning policy to be considered in England. The working group assembled the necessary information including the evidence review, two cost-effectiveness analyses of a PrEP programme in MSM in England, the impact assessment and stakeholder consultation to enable a decision by the Clinical Priorities Advisory Group that could be implemented within the 2016/17 financial year. At the point of public consultation, NHS England announced that they were not the responsible commissioner for PrEP as this was HIV prevention [5]. This leaves a vacuum as they are the only commissioner with experience of purchasing the antiretroviral drugs needed for PrEP. Following a legal challenge by the National AIDS Trust, NHS England is reconsidering their decision and role [6].

Practice and professional guidance

- Clinicians have a duty of care to individuals at risk of acquiring HIV. In paragraph 9 of the General Medical Council's 'Consent and decision making' ([http://www.gmc-uk.org/static/documents/content/Consent - English 1015.pdf](http://www.gmc-uk.org/static/documents/content/Consent_-_English_1015.pdf)) the GMC says that doctors should give patients the information they want and need about options for treating and managing their condition, the potential benefits, burdens and risks for each option, and any treatments that they think have greater potential benefit for the patient than they or their organisation can offer. One of these options is PrEP, and practical guidance to aid the discussion on risk and benefits is provided in the Appendix to this statement and Table 2, respectively. Individuals need to be informed about their risk of acquiring HIV, the risks from Truvada including risks associated with the source of the drug, the available options to reduce their risks, and the benefits of including PrEP as one of these options. Individuals obtaining their own PrEP medications should be provided with monitoring to help them take PrEP safely.
- Clinicians who wish to prescribe Truvada for use as PrEP should read the guidance on prescribing unlicensed medicines (www.gmc-uk.org/guidance/ethical_guidance/14327.asp) and seek advice from their Trusts and defence unions.
- HIV testing guidelines recommend the use of 4th generation antigen/antibody test. For individuals at high imminent risk of HIV infection it is preferable to start PrEP promptly after confirming that a point of care antibody test is negative and that there is no clinical suspicion of acute HIV infection. In PROUD, a more sensitive 4th generation test was also performed on sample collected on the day PrEP started and patients recalled to clinic in the event of a positive result. Patients who are taking Truvada as PrEP need to know they are HIV negative and should be tested every quarter by a 4th generation test. They are also very likely to meet the criteria for quarterly STI screening.

- In the event of a reactive HIV result during PrEP, the risks and benefits of immediate triple antiretroviral therapy whilst awaiting confirmation and the results of resistance testing should be discussed with a HIV specialist [25]. As much information as the patient is willing and able to give about adherence should be recorded in the notes in order to understand whether the event is a biological failure of PrEP. If the evidence suggests this is the case, it is important for the clinician to report this in the literature as PrEP failures are rare [26].
- In the absence of a measurement within the preceding year, serum creatinine is ideally collected at the time that PrEP is started. Placebo-controlled trials have revealed statistically significant but clinically unimportant differences in creatinine clearance between those on tenofovir compared to placebo [27–29]. Creatinine was checked annually in PROUD with additional checks if there was 1+ or more of protein in the urinalysis at the quarterly visits. More frequent monitoring may be required in patients aged over 50 and those taking other medications. Clinicians should explain the purpose of the recommended investigations, in line with GMC guidance (www.gmc-uk.org/guidance/ethical_guidance/consent_guidance_part2_making_decisions_about_investigations_and_treatment.asp).
- PrEP can start the day of the other tests, provided the point of care antibody test is negative and there is no clinical suspicion of acute HIV infection. PrEP should be started promptly when risk is ongoing and there is little chance of establishing that the individual is HIV negative.
- An early check within the first month of starting PrEP is useful to see if PrEP was initiated, which regimen is being used, if adherence is adequate, and whether there are any adverse effects. This can be done over the phone, unless an additional 4th generation HIV test is indicated.
- In all situations, it is important to document the discussion of risks and benefits and the decisions taken in the clinic notes.

Advising MSM on regimen

- MSM have the option to use the event based (on-demand) regimen evaluated in the IPERGAY trial or daily, unless they have active hepatitis B infection in which case a daily regimen is preferred to avoid hepatic flares when drug is interrupted and emergence of resistance. Discussing the two dosing options will facilitate a helpful discussion about the nature and frequency of sexual risk, and provide an opportunity to ensure the patient understands the timing of HIV transmission. The event-based regimen will be more naturally interrupted during periods of no risk, thereby reducing potential drug toxicity. 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 [30]. Clinical research suggests that virus escapes the genital compartment after a very short period (3–6 days after exposure)[31]. 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. Drug should be continued daily whilst sex continues and then for 2 days after the last condomless anal sex act. 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-based 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 the risks of non-adherence, as missing pills in the event based regimen will matter far more than missing pills in a daily regimen. However, if the dose before sex is missed (because sex without a condom cannot always be predicted), it is better to take two tablets as soon as possible after sex and seek advice regarding PEP, than to do nothing. The sooner active drug reaches the genital tissue, the better.

- Almost half the new diagnoses in the UK arise in heterosexuals. Evidence has also been collected in this group, but only for a daily regimen. However, tenofovir alone appears to have similar clinical effectiveness to Truvada even in women who are recognised to have lower levels of active drug in the cervico-vaginal tissue compared to rectal tissue after oral dosing [32].

Conclusion and recommendation

We have gathered robust evidence on the effectiveness of PrEP in England that informs our duty of care in support of access to PrEP. PROUD and IPERGAY have provided strong 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. The concern that PrEP would change condom behaviour to the extent that this would impact on sexually transmitted infections and PrEP effectiveness was not substantiated in the PROUD trial. Other groups have collected similar strong evidence for the benefits of PrEP in heterosexuals at risk of acquiring HIV. Therefore BASHH and BHIVA strongly recommend that PrEP be made available within a comprehensive HIV prevention package to

- MSM, trans men and trans women who are engaging in condomless anal sex
- HIV-negative partners who are in serodifferent heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not suppressed
- Other heterosexuals considered to be at high risk.

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 in women particularly, and we encourage clinical research in these areas.

However, PrEP is one of several prevention tools and healthcare workers should use the information in the Appendix and Table 2 to aid the discussion of the options available, and the risks and benefits, to their service users. There is robust evidence that demonstrates consistent condom use [33] and effective treatment of people living with HIV are highly effective interventions [34,35].

The evidence gathered in our own epidemic setting for the benefits of PrEP for the individual, for clinical services and for the wider public health, 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.

Guide to interpreting Table 2

Size of Effect [†] Point estimate	Strength of evidence Takes account of circumstances where RCT is not possible (e.g. 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 e.g. 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 e.g. 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[14]	iPrEx [12]	FEM-PREP [16]	Partners in PrEP [10]	CDC-TDF2 [13]	HPTN 052 [34]	CDC 370 [11]	VOICE [17]	FACTS-001 [15]	IPERGAY [3]	PROUD [2]	IPM 027/ The Ring Study [18]	MTN020/ Aspire [19]
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,	414 MSM in France and Canada	544 MSM in England	1959 Women from urban and rural settings in South Africa, Uganda	2629 Women from urban and rural settings in Malawi South Africa, 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 enrolls 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	Daily Oral Truvada	Continuous (30-day) Dapivirine, released from a vaginal ring	Continuous (30-day) 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	Reported Feb 2016	Reported Feb 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 [33] 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 [36]	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[37]
	PrEP Truvada oral daily Tenofovir oral daily	LARGE for Truvada: 80–83% in MITT[10]; 96% (81–99%) in models [4] MODEST for tenofovir: 55% (4–79%)[10]	HIGH: Two RCT demonstrated benefit for Truvada in HIV negative men and women [10,13] with large estimates of effect for heterosexual men. Partners in PrEP also demonstrated significant benefit with tenofovir alone, although this was modest [10]. 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% [35] to 96% if <u>monogamous</u> [34]	HIGH: 96% (95% CI 82–99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)[34] and metanalysis of cohort studies [35] At least 7/11 remaining were not linked, suggesting 30% acquisition is outside main partnership, similar to a previous RCT [38]. 0 transmissions in 272 couple years of condomless insertive vaginal sex in serodiscordant couple in PARTNER (upper 95% CI for transmission rate is 1.3/100 couple years)[39]

Table 2 (continued). 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 WOMEN having receptive VAGINAL sex with men	Condoms	LARGE: 94.2% or greater [33]	HIGH: Cochrane meta-analysis of cohort studies [33] 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, <u>24m after procedure</u> [40]	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 [41]
	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 [14,15,17] (NONE)–MODEST: 71% (47–87%)[10,17] (NONE)–MODEST: 66% (28–84%)[10,13,16] 96% (81–99%) in models [4]	HIGH: An event-based 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. Partners in PrEP demonstrated modest protection for oral tenofovir [10], but there was no benefit in VOICE[17]. One of three RCT [10] observed significant benefit for women using Truvada, a second was supportive (49%)[13], and two others observed no difference [16,17]. 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[4]. Of note the two seroconversions occurred in two women who were not taking their PrEP at the time.
	Dapivirine intravaginal ring	SMALL: 31%(0.9–51%) [18] 27% (1–46%)[19];	Two RCT of dapivirine intravaginal ring reported consistent results. Although the ITT benefit was small, post hoc analyses excluding younger women who were less likely to have detectable drug revealed modest benefit (61% (32–77) in ASPIRE in women ≥25)[19].
ART for HIV+ve male partner	LARGE: 92% [35] to 96% if <u>monogamous</u> [34]	HIGH: 96% (95% CI 82–99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)[34] and meta-analysis of cohort studies[35] At least 7/11 remaining in 052 were not linked. 0 transmissions in 192 couple years of condomless sex with ejaculation in serodiscordant couple in PARTNER (upper 95% CI for transmission rate is 1.9/100 couple years)[39]	

Table 2 (continued). 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 ANAL intercourse with either men or women	Condoms	LARGE: 94.2% or greater [33]	MODERATE: Cochrane analysis excluded MSM couples, and proportion of anal sex acts in heterosexuals not recorded [33]. 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 [42]. More research needed as biological rationale for protection, although methodological challenges are noted.
	PEPSE	NOT ESTABLISHED	LOW: quality of single observational study was weak [43] 10/11 seroconverters 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[12] NOT ASSESSED for heterosexuals	HIGH for MSM: iPREX benefit only seen in those reporting URAI at baseline [12]. 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[2,3]. Partners in PrEP[10] and CDC TDF2[13] have not specifically addressed this question, but may be able to do so.
	ART for HIV+ve partner	LARGE: 92%[34] to 96%[35]	MODERATE for MSM-HIGH for heterosexuals: one RCT (HPTN052)[34] with 3% MSM couples, and meta-analysis of heterosexual cohorts[35], 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 serodiscordant couple in PARTNER (upper 95% CI for transmission rate is 1.4/100 couple years)[39]

Table 2 (continued). 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 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 [33]. 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 [43] 10/11 seroconverters 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% [2,3,12]	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%; 40–98%) of event based Truvada compared to placebo (two tablets before sex and one a day for 2 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 <i>ex vivo</i> challenge encouraging [44].
ART for HIV+ve partner	LARGE: 92% [34] to 96% [33]	MODERATE: One RCT (HPTN052)[34] with 3% MSM couples, and meta-analysis of heterosexual cohorts [35], 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) and 0 transmissions between MSM having condomless receptive anal sex without ejaculation in 157 discordant couple years in PARTNER [39]	

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