GUIDELINE

The British HIV Association/British Association for Sexual Health and HIV Position Statement on pre-exposure prophylaxis in the UK

S McCormack MSc FRCP*, **S Fidler** PhD MRCP† **and M Fisher** MBBS FRCP‡

*MRC Clinical Trials Unit, London; †Department of Medicine, Imperial College London, London; ‡Department of HIV/Genitourinary Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK

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PURPOSE OF STATEMENT

The intention of this Position Statement is to inform UK healthcare workers on the role of antiretroviral pre-exposure prophylaxis (PrEP) in the setting of the UK HIV epidemic, so that they can have an informed discussion with their patients. Recent results from clinical trials of PrEP have made it imperative to investigate whether this biomedical tool will have a useful part to play in HIV prevention in the UK. However, 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, postexposure prophylaxis following sexual exposure and early treatment of the positive partner.

We have therefore broadened the scope of the Position Statement to attempt to put the evidence for PrEP in context, both in terms of the characteristics of the UK epidemic and in terms of the evidence for other biomedical interventions. We took note of the current guidelines on the topic of HIV prevention, including those that are out for consultation.

METHODS

Feedback was obtained at the British HIV Association (BHIVA) annual conference, and subsequently through the UK PrEP Working eGroup, to which there is an open invitation to join. Two conference calls were arranged to solicit the opinions of organizations based in the community, and a meeting of stakeholders drawn from the eGroup was held on the 5 May 2011. Comments were solicited on the tables, and then the consensus statements. A further call was held on the 13 July 2011 to discuss the design of a randomized controlled trial (RCT). The tables and statements were updated to reflect new evidence that emerged in July, September and November 2011.

Correspondence to: M Fisher
Email: Martin.Fisher@bsuh.nhs.uk

CONSENSUS STATEMENTS

- HIV remains an infectious disease of major public health importance in the UK with an estimated 91,500 individuals living with HIV at the end of 2010.[1] The epidemic most affects Black African, gay and other men who have sex with men (MSM) communities. In 2010, 3000 new infections were diagnosed in MSM (the highest ever total) and 2440 (81%) of these were judged to have been acquired within the UK;[1]
- The majority of HIV prevention efforts in the UK have focused on behaviour change, mainly the use of condoms and, more recently, testing behaviour. There is limited funding for initiatives to be implemented in accordance with national guidelines, and increasing pressure to make savings. While cross-sectional data-sets of outcomes and impact provide some insight, there has been no systematic approach to the evaluation of behavioural interventions on a national basis;
- Four randomized, placebo-controlled trials have now reported on the use of PrEP, providing evidence for the effectiveness of daily oral Truvada (tenofovir and emtricitabine) in MSM,[2] serodiscordant couples who were predominantly heterosexual,[3] young heterosexual adults[4] and coital tenofovir 1% vaginal gel in women.[5] A fifth trial of daily oral Truvada in women is conducting an orderly closure following an interim analysis which revealed equal numbers of HIV infections in the Truvada and placebo groups.[6] A sixth trial in women is similarly to discontinue daily oral tenofovir (September 2011) and daily tenofovir 1% vaginal gel (November 2011), but will continue daily oral Truvada and their respective placebo.[7] Other trials are underway or planned, one of these in the UK (Table 1), available online only at: http://www.ijsa.rsmjournals.com/cgi/content/full/23/1/1/DC1;
- The momentum following these clinical trials creates the opportunity to re-think our overall strategy for HIV prevention at a time when the NHS is undergoing change. 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;

Table 2 **PrEP in context: summary of the current data on the relative estimates of protection using different prevention strategies for different sex acts**

Route of exposure	Intervention	Estimated size of effect	Strength of evidence
HIV-negative men having insertive vaginal sex with women	Condoms	Large: 94.2% or greater	High: Cochrane meta-analysis of cohort studies[10] 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[13]	High: Summary estimates for 3 RCTs 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[14]
	PrEP		High: Two RCTs demonstrated benefit for Truvada in HIV-negative men and women[3,4] with large estimates of effect for heterosexual men. Partners in PrEP also demonstrated significant benefit with tenofovir alone, although this was modest[3]
	Truvada oral daily	Large for Truvada: 80–83% overall	
	Tenofovir oral daily	Modest for tenofovir: 55% (4–79%)	
	ART for HIV-positive female partner	Large: 92[12]–96% if monogamous[11]	High: 96% (95% CI 82–99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)[11] and meta-analysis of cohort studies[12] At least 7/11 remaining were not linked, suggesting 30% acquisition is outside main partnership, similar to a previous RCT[15]
HIV-negative women having receptive vaginal sex with men	Condoms	Large: 94.2% or greater	High: Cochrane meta-analysis of cohort studies[10] 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-positive male partner	Modest: 46% reduction in HIV incidence, *24 months after procedure*[16]	Moderate: Recent meta-analysis of two cohort studies suggests effect was previously missed because no benefit in the first 24 months 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 without PEPSE[14]
	PrEP		High: One of 3 RCTs,[3] observed significant benefit for women using Truvada, a second was supportive (49%),[4] and a third observed no difference.[6] Partners in PrEP demonstrated modest protection for oral tenofovir,[3] but this drug is to be discontinued in the VOICE trial due to futility.[7] Oral dosing with tenofovir leads to lower levels of active metabolites in vaginal tissue compared with rectal tissue, and when compared with vaginal dosing.[18] This could go some way to explain the differences in the clinical trial results, as could adherence. Only vaginal dosing significantly reduced HSV-2, which may be explained by the higher level of drug
	Tenofovir 1% vaginal gel before and after sex	Modest: 39% (6–60%) reduction in HIV incidence[5]	
	Tenofovir 1% vaginal gel daily	None	
	Tenofovir oral daily	(None) – Modest: 68% (29–85%)[3,7]	
	Truvada oral daily	(None)– Modest: 62% (19–82%)[3,4,6]	
	ART for HIV-positive male partner	Large: 92[12]–96% *if monogamous*[11]	High: 96% (95% CI 82–99%) effect based on 28/39 seroconversions that were genetically linked (HPTN052)[11] and meta-analysis of cohort studies[12] At least 7/11 remaining in 052 were not linked
HIV-negative men having insertive anal intercourse with either men or women	Condoms	Large: 94.2% or greater	Moderate: Cochrane analysis excluded MSM couples, and proportion of anal sex acts in heterosexuals not recorded.[10] 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.[19] More research needed as biological rationale for protection, although methodological challenges are noted
	PEPSE	Not established	Low: quality of single observational study was weak[20] 10/11 seroconverters did not use PEPSE, but no population benefit compared with historical control
	PrEP	Not demonstrated for MSM: HR 1.59 (0.66–3.84) if no URAI[2]	High for MSM: iPREX benefit only seen in those reporting URAI at baseline[2]
	Truvada oral daily	Not assessed for heterosexuals	Partners in PrEP[3] and CDC TDF2[4] have not specifically addressed this question, but may be able to do so
	ART for HIV-positive partner	Large: 92[11]–96%[12]	Moderate for MSM – High for heterosexuals: one RCT (HPTN052)[11] with 3% MSM couples, and meta-analysis of heterosexual cohorts,[12] so anal sex with men infrequent. However, many ARVs concentrate in the rectal tissue, so viral shedding should be controlled
HIV-negative 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.[10] Biological efficacy still likely to approach 100% with correct use, but condom breakage more likely with anal intercourse

(Continued)

Table 2 **Continued**

Route of exposure	Intervention	Estimated size of effect	Strength of evidence
	Male circumcision of HIV-positive 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.[20] 10/11 seroconverters did not use PEPSE, but no population benefit compared with historical control
	PrEP		
	Truvada oral daily	Modest: 44% (15–63%)	High: good internal consistency with increasing effect up to 73% (41–88%) at visits associated with self-report of 90% pill use. Case control analysis using PK data suggests efficacy even higher (estimate 92%), but subject to bias from confounding. Greater protection seen in those reporting URAI at baseline 58% (32–74%). No protection against HSV-2 as seen in CAPRISA 004, but could be because of lower levels of drug with oral dosing
	Tenofovir 1% rectal gel	Not assessed (clinically)	Rectal microbicides in development but PK/PD data after topical dosing and *ex vivo* challenge encouraging[21]
	ART for HIV-positive partner	Large: 92[11]–96%[10]	Moderate: one RCT (HPTN052)[11] with 3% MSM couples, and meta-analysis of heterosexual cohorts,[12] so anal sex with men infrequent. However, viral shedding in ejaculate should be controlled by ART

RCT = randomized controlled trial; PEPSE = post-exposure prophylaxis following sexual exposure; PrEP = pre-exposure prophylaxis; ART = antiretroviral therapy; MSM = men who have sex with men; HSV-2 = herpes simplex virus type 2; URAI = unprotected receptive anal intercourse; ARV = antiretroviral drug; PK = pharmacokinetics; PD = pharmacodynamics; CI = confidence interval

- Of note, Truvada and tenofovir vaginal gels are not licensed for prevention anywhere in the world; Truvada is licensed for HIV treatment in the UK. Nonetheless, the USA Centers for Disease Control and Prevention (CDC) has issued interim guidance to support clinicians in offering daily oral Truvada in high-risk MSM;[8]
- A number of concerns have been expressed about the widespread use of PrEP in the UK by the gay communities, the sexual health-care commissioners, the regulatory authorities, clinicians and the research community. These concerns are common to other countries, and include cost, not only of drug but the feasibility of delivering it, the emergence of drug resistance, toxicity, and the possibility that people will drift away from consistent condom use or be pressured to do so by their partners and peers, outweighing any protection offered by PrEP.

CONCLUSION

It is imperative to gather evidence for the value of PrEP in the UK, in order to achieve universal access should it prove cost-effective as part of a combination prevention package. There are important concerns, and we recommend that *ad hoc* prescribing is avoided, and that PrEP is only prescribed in the context of a clinical research study in the UK. Ideally, this would be a RCT, which is embedded in a broader concerted effort to intensify HIV prevention and implement the existing guidelines.[9]

Health-care workers should note that PrEP is one of several prevention tools and use the information in Table 2 to aid discussion of the options available to their service users. The data in support of condoms[10] and treatment of positive partners[11,12] are too compelling to be ignored. While further evidence relevant to the UK setting is being gathered, validated behavioural interventions, regular HIV testing, the diagnosis and treatment of other sexually transmitted infections, and intensive health-promotion activities according to current BASHH-BHIVA guidelines should be implemented in preference to PrEP.[9]

GUIDE TO INTERPRETING TABLE 2

Size of effect*	Strength of evidence
Estimate (95% confidence interval [CI])	Takes account of circumstances where randomized controlled trial (RCT) is not possible (e.g. to evaluate condoms).
Large	High
~80% or greater	Supported by a meta-analysis of RCTs or at least one RCT of high quality with evidence specific to the recommendation or in circumstances where RCT not possible, effect size well characterized through meta-analysis of cohorts and estimate very unlikely to change
Modest	Moderate
~50%	Supported by well-conducted clinical studies on the topic of recommendation, with a prospective control group or other control used to minimize bias or well-designed descriptive studies in which the comparative group is clearly defined in the analysis, even though bias from selection and confounding cannot be completely excluded, e.g. case-control study
Small	Low
~35% or less	Supported mainly by expert committee reports or opinion. 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% CIs are provided where there is a single study/trial/analysis. Where there are several the range of estimates is quoted

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REFERENCES

1 Health Protection Agency. *HIV in the United Kingdom*. London: Health Protection Agency, 2011. See http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131685847 (last accessed 8 February 2012)
2 Grant RM, Lama JR, Anderson PL, *et al.* Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;**363**:2587–99
3 http://depts.washington.edu/uwicrc/research/studies/files/PrEP_PressRelease-UW_13Jul2011.pdf (last accessed 16 January 2012)
4 http://www.cdc.gov/nchhstp/newsroom/PrEPHeterosexuals.html (last accessed 16 January 2012)
5 Abdool Karim Q, Abdool Karim SS, *et al.* Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010;**329**:1168–74
6 http://www.fhi360.org/en/Research/Projects/FEM-PrEP.htm (last accessed 8 February 2012)
7 VOICE: http://www.mtnstopshiv.org/node/3619 (last accessed 16 January 2012)
8 http://www.cdc.gov/nchhstp/newsroom/PrEPMSMGuidanceGraphic.html (last accessed 16 January 2012)
9 http://www.bashh.org/guidelines; http://www.bhiva.org/ClinicalGuidelines.aspx (last accessed 16 January 2012)
10 Weller S, David K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev* 2002;**1**:CD003255
11 Cohen MS, Chen YQ, McCauley M, *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;**365**:493–505
12 Attia S, Egger M, Müller M, *et al.* Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* 2009;**23**:1397–404
13 Weiss HA, Halperin D, Bailey RC, *et al.* Male circumcision for HIV prevention: from evidence to action? *AIDS* 2008;**22**:567–74
14 Cardo DM, Culver DH, Ciesielski CA, *et al.* A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med* 1997;**337**:1485–90
15 Celum C, Wald A, Lingappa JR, *et al.* Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Eng J Med* 2010;**362**:427–39
16 Hallett TB, Alsallaq RA, Baeten JM, *et al.* Will circumcision provide even more protection from HIV to women and men? New estimates of the population impact of circumcision interventions. *Sex Transm Infect* 2011;**87**:88–93
17 Drezett J. Post-exposure prophylaxis in raped women. IV International Conference on HIV Infection in Women and Children, Livro De Resumos, Universidade, Federal do Rio De Janeiro e Institute of Virology of Maryland, Rio de Janeiro, Brazil, 2002
18 Hendrix C, Minnis A, Guddera V, *et al.* A Phase II cross-over study of daily oral and vaginal tenofovir in healthy sexually active women results in significantly different product acceptability and vaginal tissue drug concentrations. Abs 35LB. 18th Conference on Retroviruses and Opportunistic Infections, Boston, 2011
19 Sánchez J, Sal Y, Rosas VG, Hughes JP, *et al.* Male circumcision and risk of HIV acquisition among MSM. *AIDS* 2011;**25**:519–23
20 Schecter M, do Lago RF, Mendelsohn AB, *et al.* Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV. *J Acquir Immune Defic Syndr* 2004;**35**:519–25
21 Anton P, Cranston R, Carbello-Dieguez A, *et al.* RMP-02/MTN006 A phase I placebo controlled trial of rectally applied 1% vaginal tenofovir gel, with comparison to oral tenofovir. Abs 34LB. 18th Conference on Retroviruses and Opportunistic Infections, Boston, 2011

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