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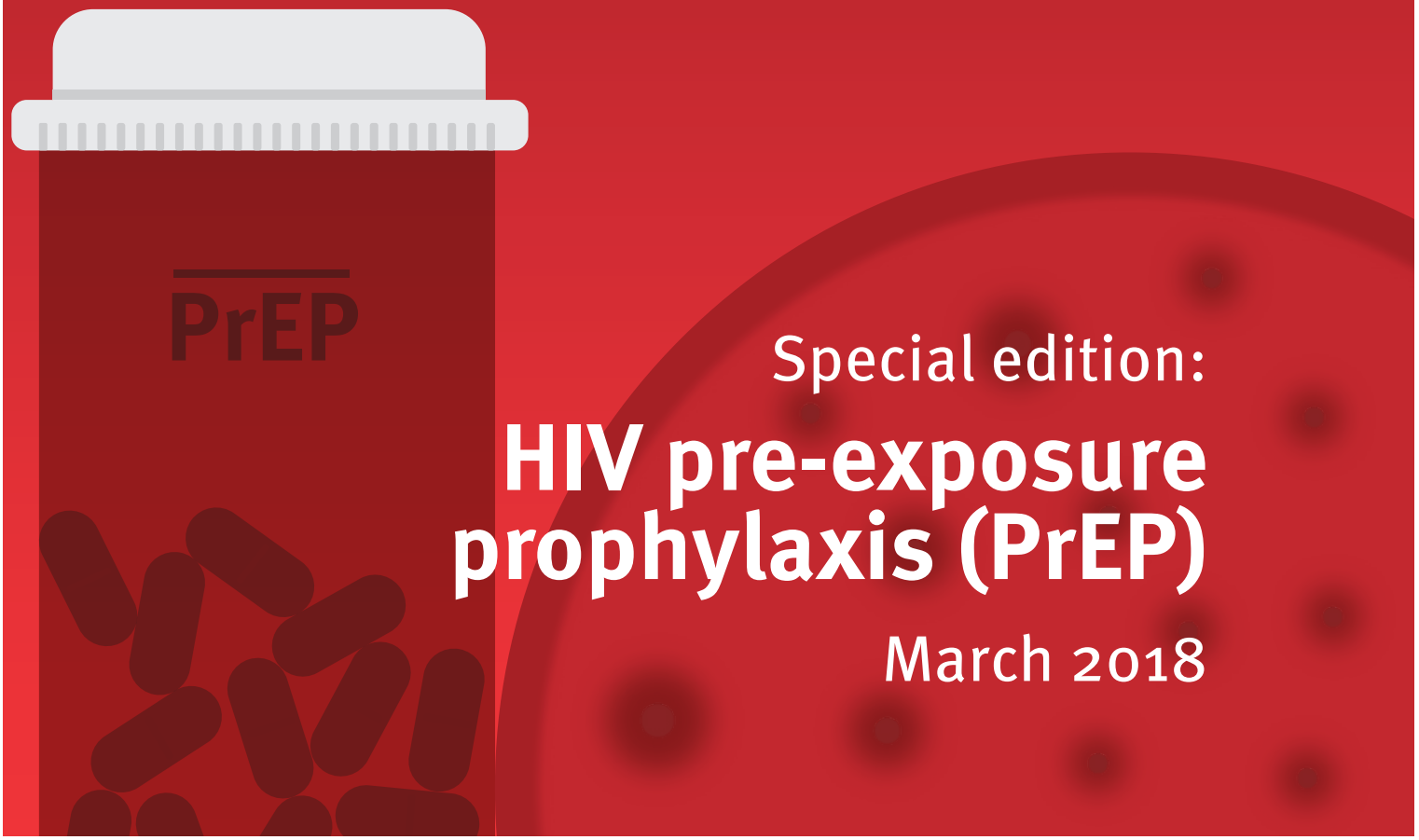

Special edition:

HIV pre-exposure prophylaxis (PrEP)

March 2018

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- **Options for affordable pre-exposure prophylaxis (PrEP) in national HIV prevention programmes in Europe**
- **Economic evaluation of HIV pre-exposure prophylaxis among men-who-have-sex-with-men in England in 2016**
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Options for affordable pre-exposure prophylaxis (PrEP) in national HIV prevention programmes in Europe

Rosalind Coleman[1], Maria Prins[2]
1. PrEP consultant, The Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland
2. Public Health Service of Amsterdam and Academic Medical Center, Amsterdam, The Netherlands

Correspondence: Rosalind Coleman (ColemanR@unaids.org)

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The successful integration of pre-exposure prophylaxis (PrEP) into comprehensive HIV programmes that include increased testing, the offer of early treatment for infected individuals and combination HIV prevention, is showing signs of contributing to a reduction in new HIV infections [1,2]. Such programmes can enable and motivate people with a high risk of HIV infection to come for testing, encourage those who test negative to consider PrEP, support their effective adherence and deliver collateral benefits such as increased screening and treatment of other sexually transmitted infections (STIs) [1,3]. This promising evidence, in the context of stagnant or rising incidence of HIV in many European countries [4], has naturally led to intensifying demand for inexpensive and broader provision of PrEP [5].

The great majority of current PrEP users in Europe and other similar settings are gay and bisexual men and other men who have sex with men (MSM) at high risk of HIV-infection [3,5,6]. They are generally well-informed, motivated and supported by civil society and concerned clinicians. However, even in well-established PrEP programmes that engage with less empowered populations, building up to more extensive distribution and uptake of PrEP remains a challenge [7]. All PrEP programmes need to address persistent barriers and doubts including the need for an estimate of the number of people eligible for PrEP, the price of the PrEP medication, the risk of drug resistance, a potential increase in STI diagnoses via risk compensation and increased testing, achieving effective adherence to PrEP and limited engagement with PrEP by certain members of key populations and certain healthcare providers [6]. Despite some encouraging experience around meeting these concerns [1,2,6] the persistent uncertainty weakens estimates of cost-effectiveness for PrEP and hinders planning for broader implementation. Countries are faced with the dilemma of how to implement and fund effective PrEP programmes at a national scale in a way that addresses need, minimises possible negative impact and remains within the country's means [5,6]. Secure integration with other sexual health and community services has the potential to bring out the collateral benefits of PrEP access [5].

The economic evaluation of PrEP in England by Ong et al., published in this edition of Eurosurveillance [8], explores implications of the first phase of a PrEP programme for MSM at high HIV risk. Despite its limitations, the static decision analytic model that was chosen is attractive due to its simplicity that encourages a broader engagement with cost-effectiveness analyses. The model's short time relevance reflects the difficulties of projecting PrEP costs and effects very far into the future. Limitations also include that effects beyond the benefit to individuals receiving PrEP could not be modelled using this approach, so the total benefits of PrEP might be underestimated.

The results emphasise the high sensitivity of PrEP cost effectiveness to (i) the price of the medicine, (ii) the HIV risk of those taking PrEP and (iii) their level of adherence. This is in line with findings from other modelling studies from high income countries, using various approaches, that indicate that PrEP programmes will become more cost-effective or even cost-saving if PrEP is used by groups (of MSM) who are at the highest risk of HIV infection and when medication costs are reduced, including potential savings through the uptake of on-demand PrEP [5,6,9-13].

PrEP is evaluated as potentially cost effective in England if taken up with good adherence and correspondingly high clinical effectiveness by groups with a ca 3 per 100 person years' risk of HIV infection [8]. The uncertainty around these parameters, and the sensitivity of cost-effectiveness estimates to them, did not allow for stronger conclusions to be drawn.

The budgetary impact of a modest programme was considerable: in a single year, a PrEP service for 5,000 PrEP person years costs €36.6M (£26.9M) at current British National Formulary (BNF) price of the patented drug. Since the price of the PrEP medicine is the main budgetary cost, it is crucial that ways be found to reduce this if PrEP programmes are to go to scale. Different funding models for PrEP have been explored, depending on country health programme frameworks, but the price of the PrEP medicine limits how many people will be offered it whether funding is central, through insurance programmes or private [14].

We take this opportunity to review various strategies to access affordable antiretrovirals for PrEP.

In France, a national programme with subsidised costs has been rolled out since January 2016 [5]. Norway [15] and Scotland [16] have indicated that PrEP will be free to the person using it, and other European countries are taking first steps to roll out PrEP [17]. Otherwise, a number of potential PrEP users find that PrEP programmes have been too slow to come to scale to meet their needs [18]. Different routes to obtain PrEP, have thus been opened through civil society [18] to obtain generic PrEP, mainly via the Internet. Where there is pro-active clinical support, the safety and follow-up of people using PrEP purchased online can be assured. There are, however, Internet sites that require neither a prescription, nor any other proof of a negative HIV test or renal function result in order to pass on the order for PrEP.

Until the end of 2016, the only medicine to be approved and marketed as PrEP in high income countries was the patented version of the fixed-dose oral combination of tenofovir disoproxil fumarate with emtricitabine (TDF/FTC). Beyond negotiating with patent holders, the way for countries to access antiretrovirals for national PrEP programmes at affordable prices may be via market competition between multiple manufacturers, i.e. including generic manufacturers. It is of particular relevance to European PrEP that several generic manufacturers have recently received marketing approval from the European Medicines Agency for tenofovir disoproxil with emtricitabine (TDX/FTC) that is bioequivalent to TDF/FTC [19]. This can now be marketed in countries where it does not infringe a patent. Several generic manufacturers are already supplying their TDX/FTC as PrEP [20]. There are also provisions within the World Trade Organization's *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPS) that countries may apply to access generically manufactured medicines, depending on the necessary national laws being in place [21,22]. Australia, for example, was the first country to use a TRIPS provision to access PrEP at a meaningful scale. The provision allows research with patented medicines in order to understand the medicine more fully [21-23].

The PROUD trial in England [24], showed in 2014 that daily PrEP, introduced through existing sexual health clinics in addition to standard-of-care risk reduction, reduced the HIV incidence by 86%. Questions remained about estimation of PrEP need, cost-effectiveness and the budgetary impact of the available branded drug, so the PrEP Impact trial was proposed to prepare the way for full roll-out [25]. The trial, that started recruiting in October 2017, will involve 10,000 participants in a pragmatic health technology assessment of PrEP implementation, investigating eligibility, uptake and duration of use, as well as impact on HIV and other STIs. The English trial, similarly to the one undertaken in Australia, uses generic TDF/FTC under national legislation [26]. The results will be used to support future clinical and cost-effective PrEP access [25].

Examples of generic PrEP prices in Europe

In England, a generic drug manufacturer won the Impact trial drug supply contract through a competitive tendering process [27], but, the eventual price agreed remains confidential. Given that national and local research costs and the trial drug for 20,000 person years of PrEP use is being paid for out of a total £10 million budget [25], it may be deduced that the price of the trial drug should be considerably cheaper than the current BNF price of the patented drug.

In the Netherlands, different formulations of TDX/FTC are available costing ca 75% of the current Dutch price of the patented drug [28,29]. Although both the patented and generic formulations are currently reimbursed for the treatment of HIV, the level of reimbursement when used as PrEP remains to be determined [30]. The city council of Amsterdam has already committed to pay for healthcare for PrEP users who buy PrEP abroad or obtain it through other means [31]. Meanwhile, the Dutch Health Council is formulating guidance on PrEP use to present to the Minister for Health, Welfare and Sport who decides on PrEP implementation and will be in charge of negotiating PrEP access for a national programme at an affordable price [30].

In parallel to the budgetary impact for governments, the out of pocket costs to the individual users will determine the uptake of PrEP. Internet purchasing prices in Europe are quoted as around €45 (40£) per month which is similar to the recent out-of-pocket cost that has been negotiated in Germany's national PrEP roll-out [32,33].

Internet purchasing, however, is neither a viable or safe long-term substitute for national PrEP programmes, nor legal in all countries. The growth of buyers' clubs demonstrates the demand for PrEP and can act as a stimulus to national programme planners to explore ways of purchasing PrEP medicine and making it available in affordable and safely regulated programmes.

In conclusion, as demonstrated by the paper of Ong and Gill [8], for a PrEP programme to be sustainable

and cost-effective, affordable PrEP needs to be chosen and used appropriately by people at substantial risk of HIV infection. Secure integration with supportive sexual health and community services will have the greatest possibility to bring out the collateral benefits of PrEP access. Since the biggest component of the initial budget impact is the cost of the medicine, active steps are required to enable access to medicine at affordable costs. The European Medicines Agency approval of TDX/FTC represents an opportunity to further advance the roll-out of PrEP although price negotiations and intellectual property legislation review are required on a country-by-country basis.

Conflict of interest

None declared.

Authors' contributions

Rosalind Coleman provided information on the situation in England and PrEP access policies and intellectual property in other European countries. Maria Prins provided the information on the Netherlands and contributed references and background to the cost effectiveness discussion. Both authors have reviewed the final manuscript.

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Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)?

AE Brown [1,2], H Mohammed [1,2], D Ogaz [1], PD Kirwan [1], M Yung [1], SG Nash [1], M Furegato [1], G Hughes [1], N Connor [1], VC Delpech [1], ON Gill [1]

1. HIV & STI Department, Centre for Infectious Disease Surveillance and Control (CIDSC), Public Health England, London, United Kingdom
2. These authors contributed equally to this work and share first authorship

Correspondence: Alison Brown (Alison.brown@phe.gov.uk)

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Since October 2015 up to September 2016, HIV diagnoses fell by 32% compared with October 2014–September 2015 among men who have sex with men (MSM) attending selected London sexual health clinics. This coincided with high HIV testing volumes and rapid initiation of treatment on diagnosis. The fall was most apparent in new HIV testers. Intensified testing of high-risk populations, combined with immediately received anti-retroviral therapy and a pre-exposure prophylaxis (PrEP) programme, may make elimination of HIV achievable.

Gay, bisexual and other men who have sex with men (MSM) account for half of all people living with HIV in England and are the group most at risk of acquiring HIV [1]. By end 2015, 94% (34,439/37,590) of MSM diagnosed with HIV in England received anti-retroviral therapy (ART), of whom 95% had supressed viral load (viral load < 200 mL) [1]. An additional 5,000–8,000 MSM were estimated to have undiagnosed infection [1-3].

Since 2012, national guidelines have recommended up to 3-monthly HIV testing for MSM at high risk of acquiring HIV [4,5] and starting ART regardless of CD4 count to prevent onward transmission ('treatment as prevention') [6,7]. Consequently, the number of men starting ART rose from 2,700 in 2013 to 3,600 in 2015 [1]. Beginning in 2013, pre-exposure prophylaxis (PrEP) has been available to some MSM as part of the 'Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD)' trial [8] and more recently through international purchasing online [9,10]. In December 2016, selected London sexual health clinics reported a fall in HIV diagnoses among MSM [11]. A rapid analysis of surveillance and monitoring data was conducted to confirm and explain this fall.

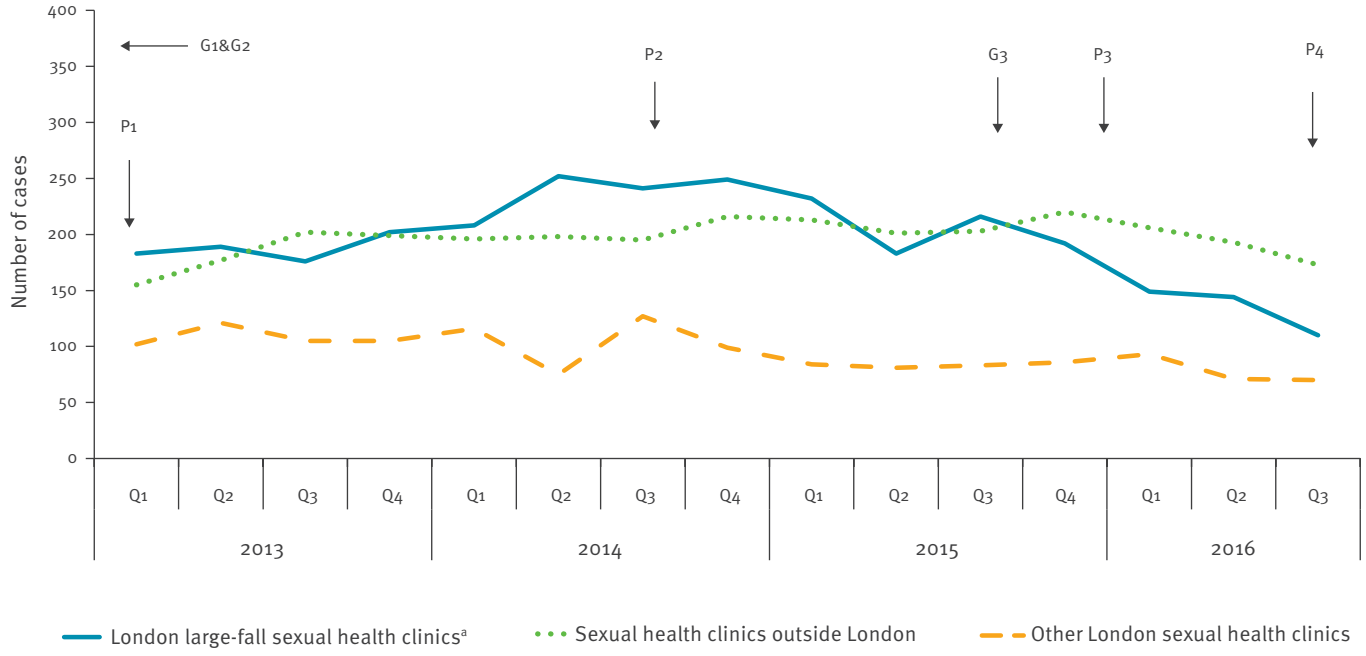
Data sources and analysis

Quarterly data from the genitourinary medicine clinic activity dataset (GUMCADv2) for January 2013–September 2016 [12] were used to examine HIV diagnoses and testing patterns among MSM attending one of the over 200 free, confidential, open-access sexual health clinics in England. Clinics that reported a large fall in diagnoses in the most recent year for which data were available, i.e. clinics with a > 20% decline and > 40 cumulative new HIV diagnoses between October 2014–September 2015 and October 2015–September 2016, were compared with other clinics in London and outside London. The number of HIV-negative MSM attending with a history of an HIV test and a bacterial sexually transmitted infection (STI) (> 90% were genital or rectal infections) was used as an indicator for those at high risk of HIV acquisition.

The HIV and AIDS Reporting System (HARS) [13] data, geographically aligned for clinics, for the most recent years (2013–2015) were used to examine: (i) trends in CD4 count within 91 days of HIV diagnosis; (ii) the number of MSM diagnosed with HIV who are untreated or treated but whose viral load is not suppressed; and (iii) time from HIV diagnosis to ART initiation. National estimates of HIV prevalence were stratified by the proportion of diagnosed and undiagnosed infection [3]. Estimates of the proportion of MSM with undiagnosed HIV infection [1] were calculated using the number of MSM with diagnosed infection to estimate the number of those undiagnosed in the catchment area of each clinic group.

Figure 1

New HIV diagnoses among men who have sex with men attending sexual health clinics by year and quarter, England, 2013–2016 (n = 7,291 HIV diagnoses)



BASHH: British Association for Sexual Health and HIV; BHIVA: British HIV Association; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; PROUD: Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection; Q = quarter.

[a] Defined as clinics with at least a 20% decrease in HIV diagnoses and over 40 cumulative diagnoses between October 2014–September 2015 and October 2015–September 2016.

P1: Recruitment to the PROUD trial began with 50% of participants allocated to the deferred arm (12 months after trial commenced) [8]. P2: All deferred participants offered PrEP. P3: Online purchasing of PrEP began in late 2015. P4: Online purchasing of PrEP routine. Interpolating from the trial enrolment figures over time [5], an estimated 200 MSM were taking PrEP by end 2013, 500 by end 2014, and it is likely an additional few hundred by end 2016 with the majority of the latter via online purchase [9,10,14,15].

G1: In May 2012 BHIVA/ BASHH and in November 2012, Public Health England (at the time, the Health Protection Agency) recommended that high-risk MSM have an HIV test annually and up to every 3 months if having condomless sex with new or casual partners.

G2: In May 2012, BHIVA guidelines advised people could start ART with a CD4 count › 350 cells after discussion with the clinician should the patient wish to protect partners from sexual HIV transmission.

G3: In September 2015, BHIVA guidelines were strengthened to recommend treatment for all individuals regardless of CD4 count for the purpose of treatment as prevention.

Fall in HIV diagnoses among men who have sex with men

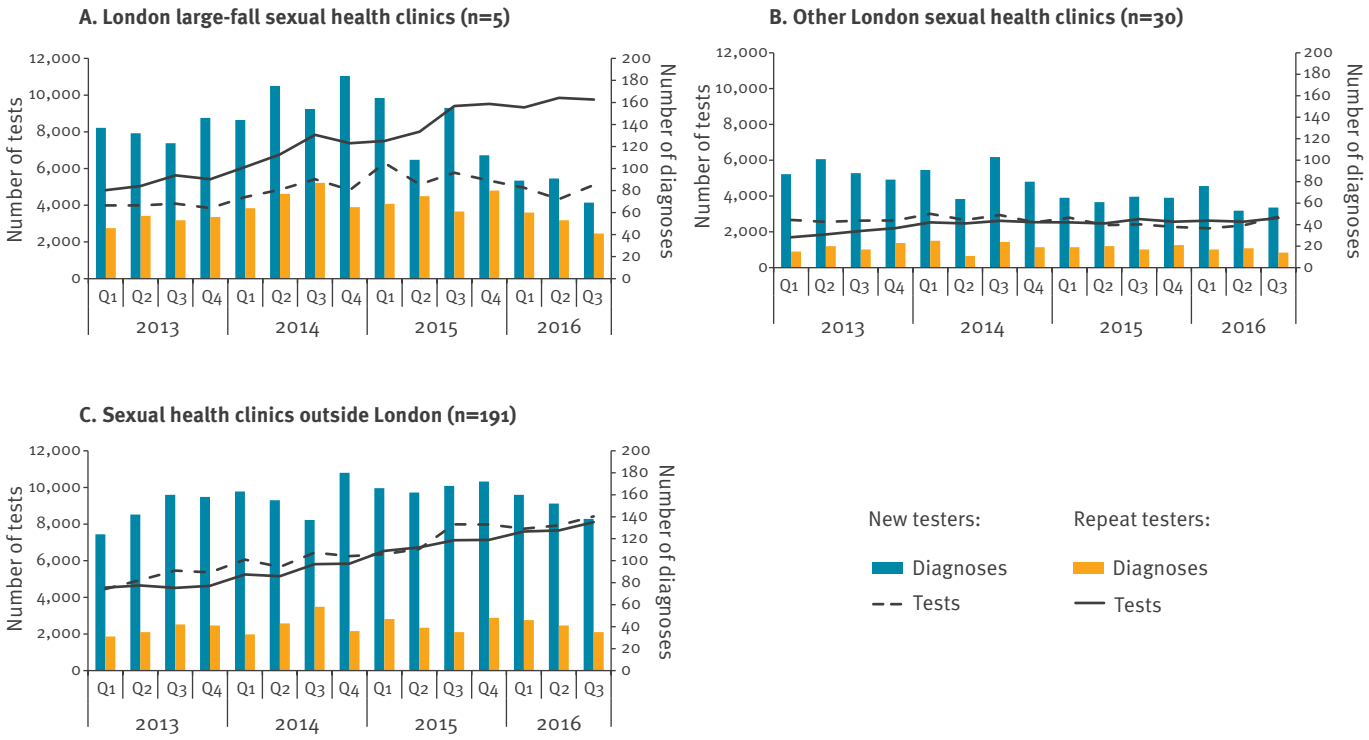
Between October 2014–September 2015 and October 2015–September 2016, reported new HIV diagnoses among MSM fell by 17% (from 2,060 to 1,707) in England and by 25% (from 1,227 to 915) in London. Nationally, diagnoses among heterosexuals remained stable at 1,500 in both periods. A 32% decline was observed among five London large-fall clinics (from 880 to 595; p = 0.014 for test of linear trend in diagnoses by quarter) compared with 8% at 30 other London clinics (from 347 to 320, p = 0.115) and 5% (from 833 to 792, p = 0.101) in 191 clinics in the rest of England (Figure 1,2).

Changing patterns of HIV testing

Testing patterns were analysed from January 2013–September 2016. Among the large-fall clinics (Figure 2a), the number of HIV tests in MSM increased by 50% (from 8,820 in January–March 2013 to 14,820 in July–September 2016); the number of new testers, i.e. those not tested in the previous 2 years, was stable at around 5,000 per quarter, whereas the number of repeat testers i.e. those who had an HIV test within the previous 2 years increased by 60%, from 4,800 to 9,760. The 3-year rise in testing in the large-fall clinics coincided with an initial increase in HIV diagnoses through 2014 in both new and repeat testers and in early 2015 the decline was observed, predominantly in new testers. In other London clinics, the number of new and repeat

Figure 2

Number of HIV tests and diagnoses in men who have sex with men at sexual health clinics by new and repeat tests and clinic group, England, 2013–2016



Q: quarter.

testers remained stable, and outside London, new and repeat testers increased equally, although there was no discernible effect on HIV diagnoses in either setting (Figure 2b and c).

Over the period, the number of MSM attending clinics increased by 4% for both groups of London clinics, and by 16% outside of London. Importantly, the volume of testing at the large-fall clinics was such that 41% (58,180/140,980) of HIV tests in MSM attending clinics in England during October 2015–September 2016 occurred at one of these five clinics. Exceptionally, the median CD4 count at HIV diagnosis of men diagnosed at large-fall clinics increased substantially (from 469 in 2013 to 548 in 2015). In contrast, the median CD4 count rose only from 442 to 489 in other London clinics, and remained around 430 outside London, over the same period. This indicates that the testing volumes and frequency of testing carried out in these settings were still insufficient to substantially reduce the average time from infection to diagnosis compared with large-fall clinics.

Prompt treatment following HIV diagnosis

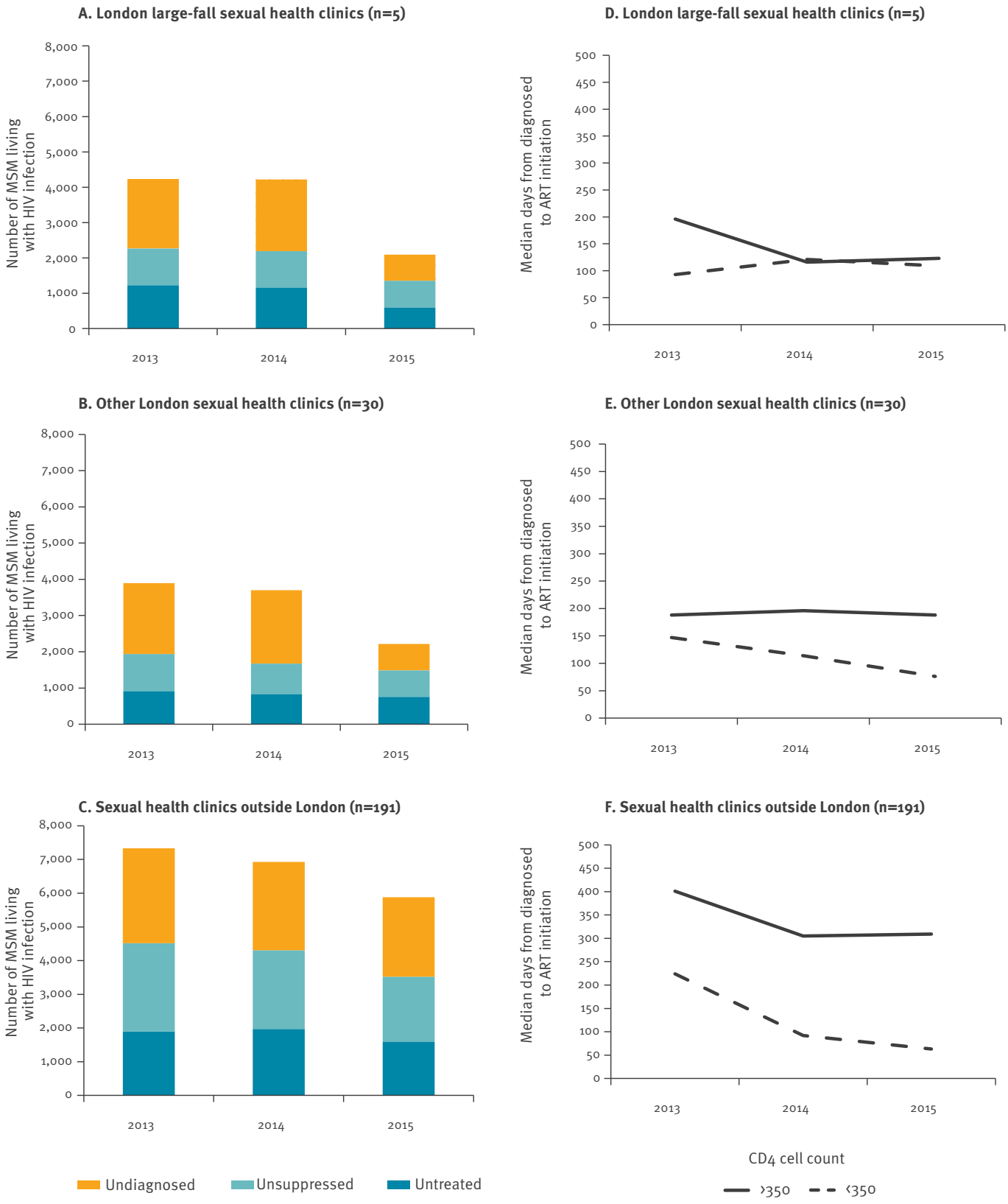
Although the number of MSM living with diagnosed HIV infection who were untreated declined by 27% in England (from 4,025 in 2013 to 2,950 in 2015), this decline was greatest at large-fall clinics (51%; from 1,224 to 601) compared with other London clinics (17%; from 906 to 754) and clinics outside London (16%; from 1,895 to 1,595) (Figures 3a-c). Moreover, while there has been a general reduction in the time to starting ART in those with a CD4 count›350 at onset of ART, the median time from diagnosis to treatment in 2015 was substantially shorter at large-fall clinics (120 days) compared with other London clinics (190 days) and clinics outside London (260 days) (Figures 3d-f).

Men who have sex with men with transmissible levels of virus

MSM with transmissible levels of virus include those diagnosed who are untreated or treated with a viral load›200 copies/mL, as well as those with an undiagnosed infection (Figure 3a-c). In 2015, there were an estimated 10,190 MSM with transmissible levels of virus in England: 29% (n=2,950) untreated, 34% (n=3,420) unsuppressed and 37% (n=3,820) undiagnosed. In the same year, among clinic attendees, the ratio of MSM with transmissible levels of virus to MSM at high-risk of HIV acquisition was 0.6 (2,088/3,596) at large-fall clinics, 2.6 (2,219/868) at other London clinics and 2 (5,877/2,933) at clinics outside London. Assuming that sexual networks broadly correspond with clinic attendance patterns, the documented ratio differences suggest that MSM at high risk of HIV acquisition who attended one of the large-fall clinics have a

Figure 3

Numbers of men who have sex with men living with HIV infection who are undiagnosed, diagnosed and untreated or treated and non-supressed viral load (A-C) and median time (days) from HIV diagnosis to ART initiation, by CD4 count at ART start (D-F) by clinic group, England, 2013–2015



ART: anti-retroviral therapy; MSM: men who have sex with men.

Treatment data and viral load data are adjusted for missing information (99% and 84% respectively): CD4 cell count taken within 91 days of diagnosis, available for 91% (7,519/8,297) of records; CD4 count at ART initiation, available for 76% (6,960/9,150) of records. Year-specific estimates of proportion of all MSM with HIV who are undiagnosed were obtained using Multi-Parameter Evidence Synthesis [1,3].

much lower likelihood of exposure to a man with transmissible levels of virus.

Availability of pre-exposure prophylaxis

Available data suggest the number of MSM who began PrEP in England either as trial participants or via online purchase has been limited to date. Although all five large-fall clinics participated in the PROUD trial, three other clinics in London and five clinics outside London did so as well. An estimated 200 MSM were taking PrEP by end 2013, 500 by end 2014 [8,14] and it is likely an additional few hundred by end 2016 [9,10,15].

Assuming a best prevention case scenario of a 9% annual HIV incidence, the very high-risk level as observed in the PROUD trial [8], by end 2015, the cumulative number of HIV infections directly prevented by PrEP would have been 90 at most. Not all of them would have attended large-fall clinics and of those who did, the decline in directly prevented infections would have been most apparent in repeat HIV testers.

Limitations

Though powerful, the surveillance and monitoring data needs cautious interpretation, especially given the post-hoc nature of the analysis. Conclusions could be affected by reporting delay (albeit minimal), incomplete data in relation to ART coverage, ART start date and CD4 count at HIV diagnosis, and neither the impact of partner notification nor the movement between clinics for HIV testing is measured. The assumption that attendees of the same clinics are more likely to form part of the same sexual network compared with random sexual mixing is plausible but unsubstantiated. Finally, while numbers of HIV diagnoses are not synonymous with HIV incidence, the rise in median CD4 count at HIV diagnosis suggests that the fall in diagnoses reflects a fall in incidence.

Conclusions

The 17% fall in new HIV diagnoses in MSM in England between October 2014–September 2015 and October 2015–September 2016 was focussed in five clinics which experienced a 32% decline. The fall seen at these five clinics coincided with accelerated treatment at diagnosis and a substantial increase in HIV testing, particularly repeat testing.

The volume of HIV tests across London combined with rapid treatment following diagnosis at the five large-fall clinics is now likely to have reached a level that decreases the number of men with transmissible levels of virus thereby reducing transmission. The use of PrEP among high-risk MSM, although limited at this stage, will also have contributed to the fall in new diagnoses. If HIV testing of MSM at high risk of HIV is intensified, and wide-scale immediate ART, as observed within the London large-fall clinics, is replicated elsewhere, it is probable that a substantial reduction in HIV transmission among MSM could be achieved nationally. Should the promise of the 'PrEP Impact Trial' proposed in England [16] be realised promptly, then a very large reduction in HIV transmission in MSM may be attained. The similarity of the MSM HIV epidemic in England to elsewhere in western Europe [17] suggests a similar approach in these countries might be equally successful.

Conflict of interest

None declared.

Authors' contributions

The analysis was performed by: AB, HM, DO, PK, MY, SN, MF. AB, HM, NC, GH, VD and ON were responsible for conceiving, developing and interpreting the analyses. AB and HM led the writing jointly with significant input from VD and ON.

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Using data from a behavioural survey of men who have sex with men (MSM) to estimate the number likely to present for HIV pre-exposure prophylaxis (PrEP) in Ireland, 2017

Laura Nic Lochlainn[1], Kate O'Donnell[1], Caroline Hurley[2], Fiona Lyons[2], Derval Igoe[1]
1. Health Service Executive Health Protection Surveillance Centre, Dublin, Ireland
2. Health Service Executive Sexual Health and Crisis Pregnancy Programme, Dublin, Ireland

Correspondence: Derval Igoe (derval.igoe@hse.ie)

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In Ireland, men who have sex with men (MSM) have increased HIV risk. Pre-exposure prophylaxis (PrEP), combined with safe sex practices, can reduce HIV acquisition. We estimated MSM numbers likely to present for PrEP by applying French PrEP criteria to Irish MSM behavioural survey data. We adjusted for survey bias, calculated proportions accessing testing services and those likely to take PrEP. We estimated 1–3% of MSM in Ireland were likely to present for PrEP.

In Ireland, men who have sex with men (MSM) are at increased risk of sexually acquired HIV infection [1]. A priority action in Europe is to reduce new HIV infections among MSM by improving HIV combination prevention programmes, potentially in part through provision of pre-exposure prophylaxis (PrEP) [2,3]. Across Europe, many countries are working towards implementation of PrEP [4].

Estimating the number likely to present for PrEP is important for informing decision making about PrEP introduction. As recent behavioural data in MSM were available from an online convenience survey, MSM Internet Survey Ireland (MISI) [5], this allowed us to estimate the number of MSM likely to present for PrEP in Ireland.

Determining PrEP estimates for Ireland

We researched PrEP criteria from Australia [6], England [7], France [8,9], and the United States [10,11], and preliminarily applied those criteria to MISI data to estimate MISI respondents eligible for PrEP. We presented and discussed our estimates and underlying criteria during consultation meetings with clinicians, public health experts and the national PrEP working group, which is a multi-sectoral group, comprised of clinicians, pharmacists, community leaders and public health experts. We obtained consensus that French PrEP criteria were most suited for the purpose of PrEP estimates for Ireland. In this study, we therefore chose variables which were the same as, or the closest fit to French PrEP criteria but restricted our analysis to MISI respondents aged 18–64 years.

PrEP is available in France for men and transgender people over the age of 18 years who have had sex with men and who reported one or more of the following: condomless anal intercourse (CAI) with at least two different sexual partners in the last 6 months; episodes of sexually transmitted infections (STIs) in the past 12 months; multiple post-exposure prophylaxis (PEP) treatments in the last 12 months; or used drugs during sex [8,9].

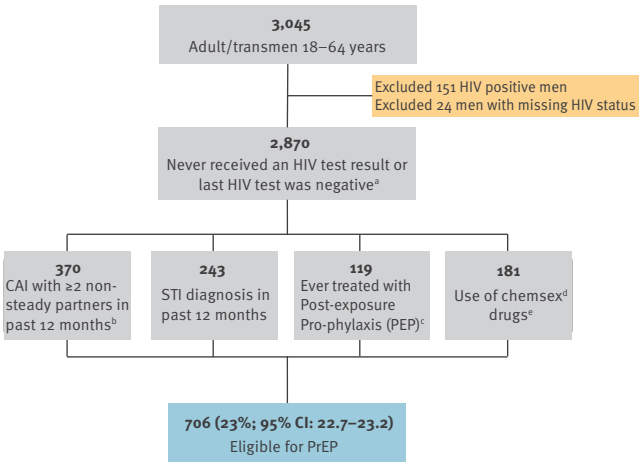
Stepwise approach to estimate the number of MSM likely to present for PrEP

After estimating the proportion of MISI respondents eligible for PrEP (Figure 1), we developed a stepwise approach to estimate the MSM population in Ireland likely to present for PrEP in the first year of a PrEP programme, should this be introduced (Figure 2). Using the 2015 Healthy Ireland Survey, which found 6% of men in Ireland reporting that their last sex was with a man [5], we applied this estimate to the Irish male population aged 18–64 years from the 2011 census (n = 1,441,603) [12]. This gave us the estimated number of MSM in Ireland to be 86,498.

Previous research found that high-risk MSM were twice as likely to respond to convenience surveys and report more risk behaviours, STI outcomes and HIV testing compared with probability based surveys [13-15].

Figure 1

Using data from the MSM Internet Survey Ireland (MISI) and French pre-exposure prophylaxis (PrEP) criteria to estimate the proportion of MISI respondents eligible for HIV PrEP, Ireland, 2017 (n = 3,045 survey respondents)



CAI: condomless anal intercourse; PrEP: pre-exposure prophylaxis; STI: sexually transmissible infection; MISI: Men who have sex with men Internet Survey Ireland (MISI).

Criteria for receiving PrEP in France have been previously described [8,9].

[a] Number of men who reported to be HIV negative or did not know their HIV status.

[b] This criterion is the closest fit in the MISI survey to the French PrEP eligibility criterion 'CAI with two or more partners in the past six months'.

[c] This criterion is the closest fit in the MISI survey to the French PrEP eligibility criterion 'multiple post-exposure prophylaxis (PEP) in the past 12 months'.

[d] Crystal methamphetamine, gammahydroxybutrate (GHB) or gamma-butyrolactone (GBL), mephedrone, ketamine.

[e] This criterion is the closest fit in the MISI survey to the French PrEP eligibility criterion 'use of drugs during sexual intercourse'.

Therefore, subsequent to estimating the proportion of MSM eligible for PrEP using MISI data, we applied a 50% correction factor to our estimate (Figure 2).

The proportion of MSM accessing STI and HIV testing services in Ireland is not available. However, based on previous study findings [5,16], we applied a range of estimates (15%, 30%, 45%) for the proportion of MSM accessing services.

We applied a rate of 58% for the proportion of MSM likely to take PrEP based on results from an online survey of PrEP awareness and acceptability among MSM in Scotland, Wales, Northern Ireland and the Republic of Ireland [17]. This survey targeted HIV-negative/status unknown MSM who reported CAI with two or more men in the last year, whereby respondents had similar characteristics to the MISI respondents considered in the PrEP eligible group.

Results of PrEP estimates

Applying French PrEP criteria to MISI data, we estimated that 23% (95% confidence interval (CI): 22.7–23.3) of the MISI respondents (n = 3,045) would be eligible to receive PrEP (Figure 1).

In order to adjust for over-reporting, we applied a 50% correction factor to the proportion of MISI respondents eligible for PrEP. Applying the adjusted estimate of 11.5% to the MSM population in Ireland, we estimated that 9,947 MSM (95% CI: 9,765–10,129) in Ireland would be eligible for PrEP (Figure 2).

The application of estimate ranges (15%, 30% and 45%) to account for the proportion of MSM accessing HIV and STI services, further adjusted the estimated number of MSM likely to present for or be offered PrEP to between 1,492 and 4,476 (95% CI: 1,423–4,574) (Figure 2).

Applying 58% for the proportion of MSM likely to take PrEP if requested or offered while accessing HIV and STI services, we estimated that 865–2,596 (95% CI: 811–2,683) MSM would likely present and take PrEP (Figure 2).

This estimate of 865–2,596 MSM (95% CI: 811–2,683) likely to present and take PrEP equates to 1–3% of the MSM population in Ireland aged 18–64 years.

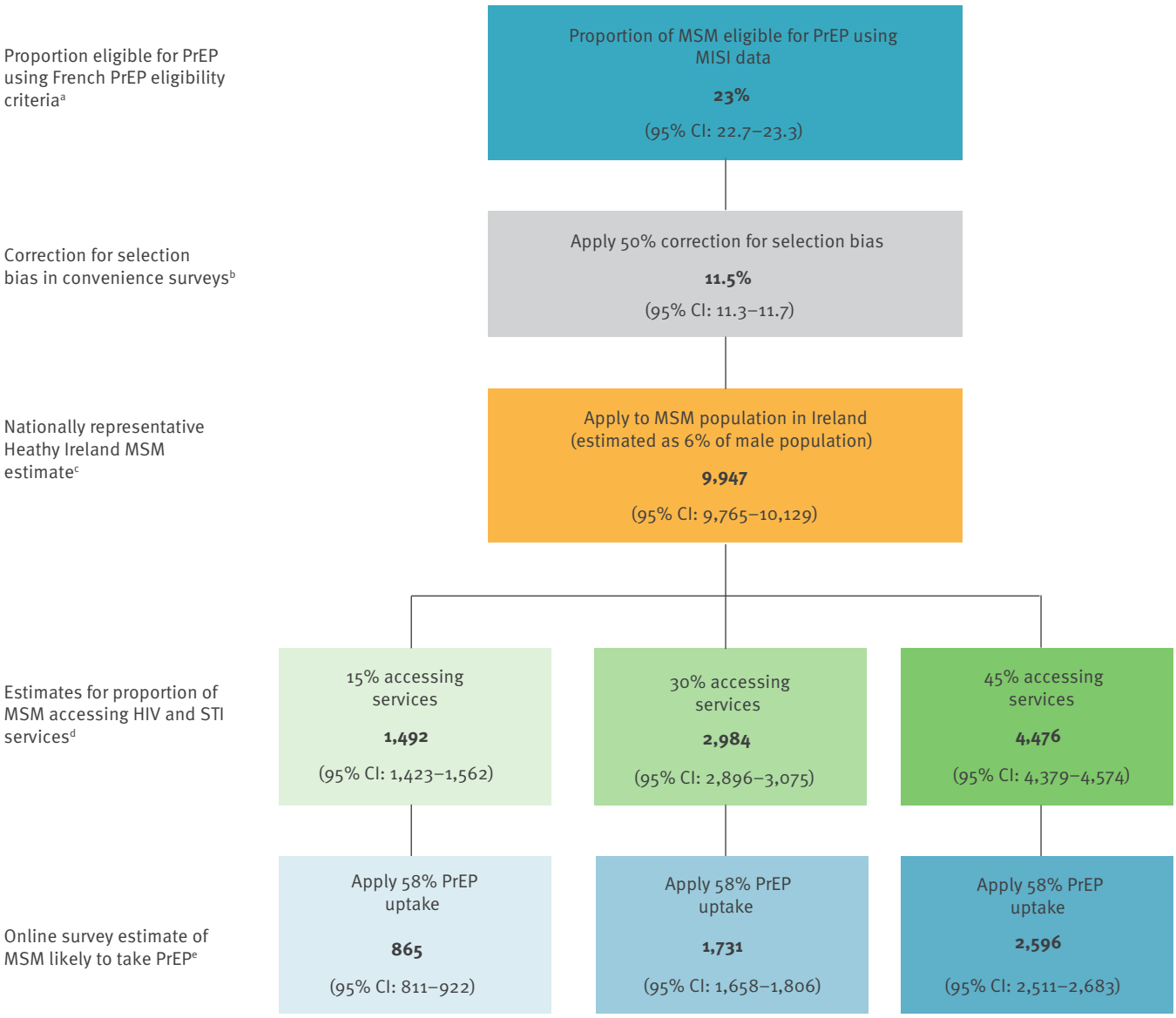
Discussion and conclusion

Through consultation with experts and community leaders, we were able to establish suitable criteria, data sources and a stepwise approach for estimation of the likely number of MSM to present for PrEP in Ireland. We estimated that 1–3% of the MSM population accessing services in Ireland aged 18–64 years would be likely to present and take PrEP. These estimates are currently being used to inform the pharmacoeconomic evaluation of Truvada for PrEP in line with the reimbursement process for medicines in Ireland.

Our findings are subject to some limitations. These estimates are limited to men aged 18–64 years due to the age distribution of MISI respondents. However, if made available, PrEP would not have an upper age limit for eligibility. Also, these estimates are based on the proportion of MSM accessing services. However, if MSM who are not currently accessing services come forward for PrEP, this will increase the number presenting for PrEP. We were unable to apply the exact French PrEP criteria to some MISI variables, which might have under- or over-estimated our findings. The estimate for the proportion of MSM likely to take PrEP is based on findings from an online survey [17] which may not reflect actual uptake when an individual is presented with the option of taking PrEP. Although the MISI survey was large (3,090 respondents), and corrected for over-reporting, responses may still not be representative of the MSM population in Ireland. Finally, the proportion of males in Ireland who are MSM is based on a national probability based survey [5], which may be

Figure 2

Stepwise approach to estimating the number of men who have sex with men (MSM) who would likely present for HIV pre-exposure prophylaxis (PrEP)[a] in Ireland, 2017



CI: confidence interval; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

[a] Estimated proportion of respondents to a behavioural survey, who might present for HIV pre-exposure prophylaxis based on French PrEP eligibility criteria [8,9].

[b] Based on findings that high-risk MSM were twice as likely to respond to convenience surveys and report more risk behaviours, STI outcomes and HIV testing, compared with probability based surveys [13-15].

[c] 6% estimate based on [5].

[d] Applied proportions of MSM accessing STI and HIV testing services in Ireland based on [5,16].

[e] 58% PrEP uptake rate based on [17].

an over- or under-estimate of the proportion of MSM in Ireland.

These estimates should be reviewed one year post-implementation of PrEP to calculate future projections. It is also important to monitor PrEP uptake to assess its utilisation and to support the development of targeted implementation programmes and policies to increase access for populations most at risk of HIV acquisition.

Given the priority actions within Europe to reduce new HIV infections and improve HIV combination prevention

programmes for MSM, other countries may consider replicating the approach we took to estimate the number likely to present for PrEP.

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Conflict of interest

None declared.

Authors' contributions

LN, KOD, CH, FL and DI were responsible for conceiving, developing and interpreting the PrEP estimates. LN analysed the data and prepared the first draft of the manuscript. All co-authors contributed towards revising the manuscript and approved the final version.

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Research article

Economic evaluation of HIV pre-exposure prophylaxis among men-who-have-sex-with-men in England in 2016

Koh Jun Ong[1], Sarika Desai[1], Nigel Field[2], Monica Desai[1], Anthony Nardone[1], Albert Jan van Hoek[3], Owen Noel Gill[1]
1. HIV & STI Department, National Centre for Infectious Disease Surveillance and Control (CIDSC), Public Health England, London, United Kingdom
2. Research Department of Infection & Population Health, University College London, London, United Kingdom
3. London School of Hygiene & Tropical Medicine, London, United Kingdom

Correspondence: Koh Jun Ong (kohjun.ong@phe.gov.uk)

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Clinical effectiveness of pre-exposure prophylaxis (PrEP) for preventing HIV acquisition in men who have sex with men (MSM) at high HIV risk is established. A static decision analytical model was constructed to inform policy prioritisation in England around cost-effectiveness and budgetary impact of a PrEP programme covering 5,000 MSM during an initial high-risk period. National genitourinary medicine clinic surveillance data informed key HIV risk assumptions. Pragmatic large-scale implementation scenarios were explored. At 86% effectiveness, PrEP given to 5,000 MSM at 3.3 per 100 person-years annual HIV incidence, assuming risk compensation (20% HIV incidence increase), averted 118 HIV infections over remaining lifetimes and was cost saving. Lower effectiveness (64%) gave an incremental cost-effectiveness ratio of + GBP 23,500 (EUR 32,000) per quality-adjusted life year (QALY) gained. Investment of GBP 26.9 million (EUR 36.6 million) in year-1 breaks even anywhere from year-23 (86% effectiveness) to year-33 (64% effectiveness). PrEP cost-effectiveness was highly sensitive to year-1 HIV incidence, PrEP adherence/effectiveness, and antiretroviral drug costs. There is much uncertainty around HIV incidence in those given PrEP and adherence/effectiveness, especially under programme scale-up. Substantially reduced PrEP drug costs are needed to give the necessary assurance of cost-effectiveness, and for an affordable public health programme of sufficient size.

Introduction

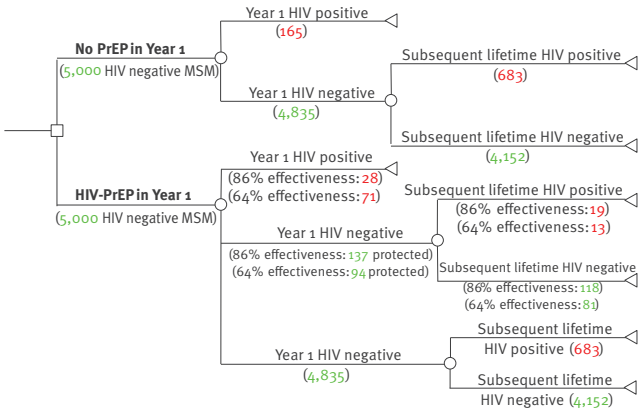
In the United Kingdom (UK) new prevention initiatives are needed to reduce the estimated 2,800 incident HIV infections occurring annually in men who have sex with men (MSM) [1]. The UK PROUD study demonstrated that HIV pre-exposure prophylaxis (PrEP) with daily oral antiretroviral (ARV) drug combination tenofovir disoproxil and emtricitabine in addition to standard-of-care risk reduction for MSM at high HIV risk, reduced HIV incidence over the participant follow-up period by 86% (90% confidence interval (CI): 64–96%) [2]. The PROUD data on PrEP effectiveness, supported by the placebo-controlled efficacy data from iPrEX and IPERGAY, showed that PrEP offers a major opportunity to reduce HIV incidence in MSM [3,4]. A PrEP policy was proposed by National Health Service (NHS) England for high HIV risk attendees of the 215 genitourinary medicine (GUM) clinics in England that provide free, confidential, open-access sexual health services [5].

In England, new clinical commissioning policies are prioritised on their effectiveness and value for money [6]. Cost-effectiveness evidence is reviewed, with incremental value for money of competing services scored and compared on the basis of their incremental costs and incremental benefits. In other areas of publically funded public health prevention programmes (e.g. immunisation), one decision criterion used is a high certainty that the incremental cost-effectiveness ratio (ICER) falls below a recommended threshold, currently GBP 20,000 (EUR 27,210) per quality-adjusted life year (QALY) gained [7,8]. In addition, the affordability of any new service must be ensured based on practical eligibility criteria that are developed to guarantee the service reaches those with greatest need [6].

A static decision analytical model was used to explore the economic implications of a first phase scale-up of a PrEP programme for MSM GUM clinic attendees at high HIV risk, beginning in 2016. The method is valid for a modest scale initial PrEP programme with limited indirect (herd) effect [9], and was chosen for the relatively limited assumptions required, its transparency and ease of interpretation for decision makers, and because of the increasing uncertainties when estimating costs and effects after 5 to 10 years. Moreover, the technique was suitable because the impact on population disease dynamics is likely to be limited in the early years of a PrEP policy given the small numbers protected relative to the total at risk [9].

Figure 1

Decision analytical model structure comparing no-PrEP with PrEP in 5,000 men who have sex with men at high HIV risk[a], England, 2016



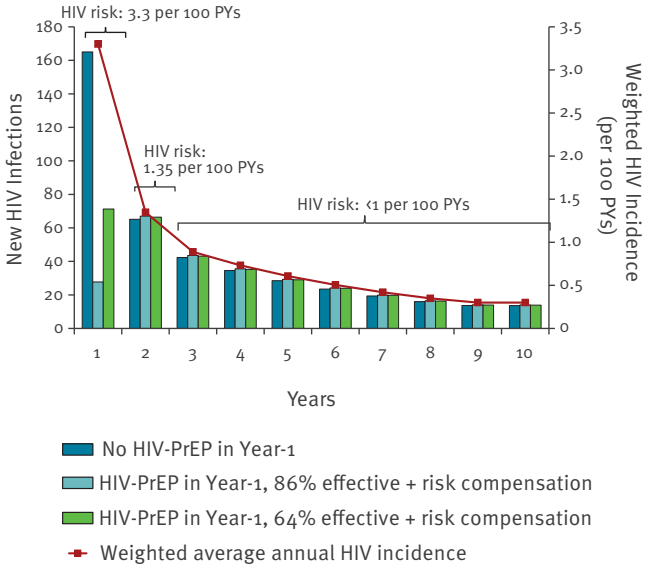
MSM: men who have sex with men; PrEP: pre-exposure prophylaxis.

Red and green colours are used to indicate the estimated numbers of HIV-positive or negative MSM respectively, after a defined period (i.e. after the first year of PrEP (year-1) or, for the control group, after year-1 without PrEP, and for the remaining lifetime in both groups).

[a] HIV incidence in Year-1 is 3.3 per 100 person-years and cumulative lifetime incidence without PrEP is 16.96%.

Figure 2

Impact of year-1 PrEP[a] on HIV incidence over 10 years for 5,000 MSM at initial high HIV risk, England, 2016–2025



PrEP: pre-exposure prophylaxis; PYs: person-years.

The bars on this chart represent the number of new HIV infections by year: (i) In the absence of PrEP (blue bars); (ii) If PrEP is given in year-1 and assuming 86% effectiveness + risk compensation (turquoise bars); (iii) and if PrEP is given in year-1 and assuming 64% effectiveness + risk compensation (green bars).

Up to age 75 years, there were 848 HIV infections without PrEP, and 730 with PrEP at 86% effectiveness and 767 with PrEP at 64% effectiveness. Slightly more later-HIV infections occur in those given PrEP during year-1 as the MSM protected by PrEP become susceptible on stopping PrEP, albeit at a much lower risk level.

[a] PrEP effectiveness at either 86% or 64%, both with risk compensation adjustment (see text).

Methods

The perspective of a healthcare provider was taken. A 5,000 person-years PrEP coverage level was judged to be reasonable for this initial scale-up period, based on the range suggested by a multidisciplinary, multi-stakeholder group of clinicians, patients, commissioners (budget holders) and public health practitioners [5]. The 4,500–6,500 range was generated after considering the evidence around likely programme roll-out scenarios, the GUM clinic activity dataset (GUMCAD) estimated need, patient-level uptake as informed by community surveys about willingness to take PrEP, and considered potential organisational challenges of delivery across many GUM clinics as well as evidence of PrEP scale-up in other countries [10].

The lifetime HIV risk of 5,000 MSM who began an initial high HIV risk period of one year on PrEP was compared with the lifetime risk of the same group in the absence of PrEP (Figure 1). This required age distribution of MSM at high behavioural risk and estimates of HIV acquisition during the high-risk period of PrEP eligibility, as well as estimates of lifetime HIV acquisition, to account for the residual HIV risk after the high-risk period had passed. PrEP provision to a single high-risk year was modelled at the cohort-level. At the individual-level, should high risk continue beyond the first year, then that individual will form part of a new high-risk cohort in the second year. The ICER for PrEP remains the same for the second cohort as for the previous year's high-risk cohort.

Data were extracted from GUMCAD [11], a comprehensive, pseudo-anonymised digital download of patient-level data on all sexually transmitted infection (STI) services and diagnoses provided in GUM clinics in England. Each pseudo-anonymised record contains a clinic identifier as well as a local patient number, so data from the same individual attending the same clinic can be linked longitudinally. Estimates of lifetime HIV risk were adjusted to the age-distribution of MSM GUM clinic attendees, using averages for years 2013–14 (see supplementary material [12]).

In the principal scenarios, MSM receiving PrEP were assumed to be prescribed daily tenofovir disoproxil and emtricitabine combined tablet, in accordance with the European Medicines Agency licensed prevention indication [13]. Event-based dosing (i.e. PrEP given before and after sexual exposure) for an average of four tablets used per 7-day period, was explored in sensitivity analyses [4].

Figure 3

Multivariate sensitivity of incremental cost-effectiveness ratio (ICER) for different levels of pre-exposure prophylaxis (PrEP) effectiveness, England, 2014/15 cost values

Parameter combinations[a]		PrEP effectiveness[b]			
		44%	64%	86%	96%
1. Year-1 HIV incidence (no risk compensation)	9.0 per 100 person-years[c]	-GBP 23,010 (-EUR 31,305)	-GBP 36,764 (-EUR 50,017)	-GBP 44,504 (-EUR 60,548)	-GBP 46,850 (-EUR 63,739)
	5.2 per 100 person-years[d]	GBP 7,786 (EUR 10,593)	-GBP 15,572 (-EUR 21,186)	-GBP 28,717 (-EUR 39,069)	-GBP 32,701 (-EUR 44,490)
	3.3 per 100 person-years	GBP 49,762 (EUR 67,701)	**GBP 13,296 (EUR 18,089)**	**-GBP 7,227 (EUR 9,832)**	**-GBP 13,446 (EUR 18,293)**
	2.0 per 100 person-years[e]	GBP 124,421 (EUR 169,275)	GBP 64,630 (EUR 87,929)	GBP 30,980 (EUR 42,148)	GBP 20,783 (EUR 28,275)
2. Risk compensation in those given PrEP, as percentage increase in HIV incidence **(Year-1 HIV incidence: 3.3 per 100 person-years)**	0%	GBP 49,762 (EUR 67,701)	GBP 13,296 (EUR 18,089)	-GBP 7,227 (-EUR 9,832)	-GBP 13,446 (-EUR 18,293)
	10%	GBP 66,780 (EUR 90,854)	GBP 18,078 (EUR 24,595)	-GBP 6,239 (-EUR 8,488)	-GBP 13,222 (-EUR 17,989)
	20%	GBP 89,608 (EUR 121,912)	**GBP 23,465 (EUR 31,924)**	**-GBP 5,218 (-EUR 7,099)**	-GBP 12,997 (-EUR 17,682)
	30%	GBP 121,837 (EUR 165,759)	GBP 29,582 (EUR 40,246)	-GBP 4,161 (-EUR 5,661)	-GBP 12,769 (-EUR 17,372)
3. Percentage reduction in ARV treatment cost from 2019 **(Year-1 HIV incidence: 3.3 per 100 person-years; risk compensation in those given PrEP of 20% HIV incidence increase)**	0% GBP 4,741 (EUR 6,450)	GBP 89,608 (EUR 121,912)	GBP 23,465 (EUR 31,924)	-GBP 5,218 (-EUR 7,099)	-GBP 12,997 (-EUR 17,682)
	30% GBP 3,032 (EUR 4,125)	GBP 98,864 (EUR 134,504)	**GBP 32,721 (EUR 44,517)**	**GBP 4,038 (EUR 5,494)**	-GBP 3,741 (-EUR 5,090)
	50% GBP 2,371 (EUR 3,226)	GBP 105,034 (EUR 142,899)	GBP 38,891 (EUR 52,911)	GBP 10,208 (EUR 13,888)	GBP 2,429 (EUR 3,305)
	80% GBP 948 (EUR 1,290)	GBP 114,289 (EUR 155,490)	GBP 48,146 (EUR 65,503)	GBP 19,463 (EUR 26,479)	GBP 11,684 (EUR 15,896)
4. Percentage reduction in PrEP BNF annual drug price **(Year-1 HIV incidence: 3.3 per 100 person-years; risk compensation in those given PrEP – 20% HIV incidence increase; 30% reduction in ARV treatment cost after 2019)**	0% GBP 4,331 (EUR 5,892)	GBP 98,864 (EUR 134,504)	**GBP 32,721 (EUR 44,517)**	**GBP 4,038 (EUR 5,494)**	-GBP 3,741 (-EUR 5,090)
	21% GBP 3,403[f] (EUR 4,630)	GBP 66,260 (EUR 90,147)	**GBP 13,893 (EUR 18,901)**	**-GBP 8,816 (-EUR 11,994)**	-GBP 14,974 (-EUR 20,372)
	43% GBP 2,475[g] (EUR 3,367)	GBP 33,656 (EUR 45,789)	**-GBP 4,934 (-EUR 6,713)**	**-GBP 21,669 (-EUR 29,481)**	-GBP 26,208 (-EUR 35,656)
	90% GBP 431[h] (EUR 586)	-GBP 38,072 (-EUR 51,797)	**-GBP 46,355 (-EUR 63,066)**	**-GBP 49,947 (-EUR 67,953)**	-GBP 50,921 (-EUR 69,278)

Colour coding

Cost saving

GBP 0 < ICER < GBP 20,000 (EUR 0 < ICER < EUR 27,210)

GBP 20,000 < ICER < GBP 30,000 (EUR 27,210 < ICER < EUR 40,815)

ICER > GBP 30,000 (ICER > EUR 40,815)

BNF: British National Formulary; GUM: genitourinary medicine; GUMCAD: GUM clinic activity dataset; MSM: men who have sex with men; STI: sexually transmitted infection; UK: United Kingdom.

[a] First parameter combination (i.e. Year-1 HIV incidence of 3.3 per 100 person-years) assumed within second combination, first and second within third, etc.

[b] 44% was the efficacy level reported in the iPrEx trial; 86% was the UK PROUD trial observed clinical effectiveness level, while 64% and 96% were the lower- and upper-bound 90% confidence intervals reported in this latter trial [2,3].

[c] Reported HIV incidence in the deferred part (no PrEP, n=267 MSM) of the PROUD trial [2].

[d] Estimated HIV incidence in HIV-negative MSM with documented rectal bacterial STI diagnosis in 2012, GUMCAD analysis.

[e] Estimated HIV incidence in all HIV-negative MSM GUM attendees in 2012, GUMCAD analysis.

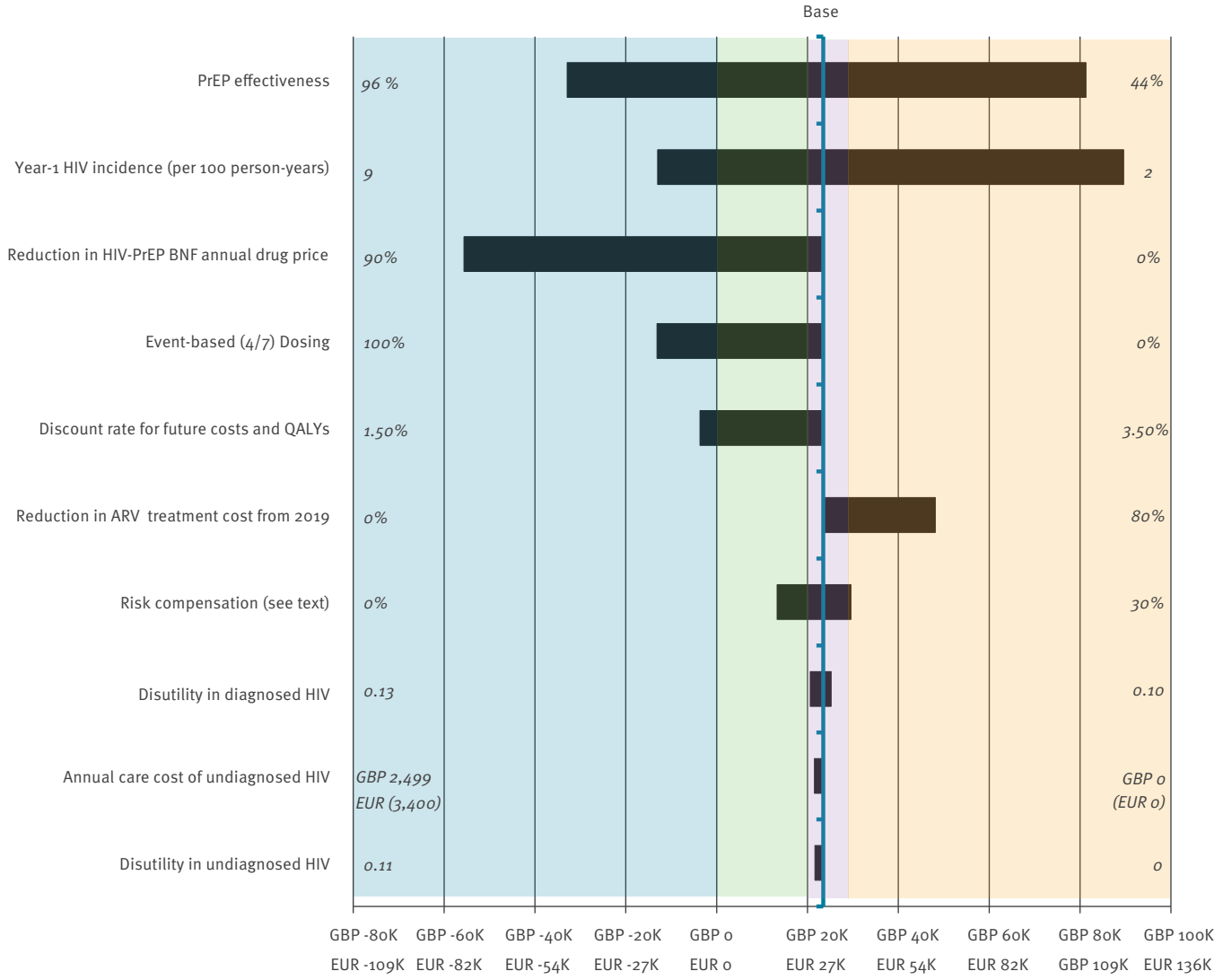
[f] 21% reduction in PrEP drug price due to 50% event-based dosing i.e. prorated 5.5 tablets per 7-day. This assumed that if an MSM was prescribed event-based dosing, then only four tablets would be dispensed for every 7-day i.e. 4/7 of the drug cost. Event-based dosing frequency based on the findings reported in the IPERGAY trial [4]. Service provision through GUM clinics remained the same, as frequency of monitoring remained the same.

[g] 43% reduction in PrEP drug price due to 100% event-based dosing (four tablets per 7-day).

[h] 90% reduction in PrEP drug price due to fall in current tenofovir disoproxil/emtricitabine price following patent expiry of the PrEP drug used. This is an arbitrary assumption. The future price is dependent on market competition. The exact timing of when this will happen, however, is uncertain. The patents for tenofovir disoproxil and emtricitabine expired in 2016 and July 2017, respectively. However, Truvada as a combination tablet containing both tenofovir disoproxil/emtricitabine has a supplementary protection certificate (SPC) providing market exclusivity protection until February 2020, although this SPC is being challenged [39].

Figure 4

Univariate sensitivity of pre-exposure prophylaxis (PrEP) incremental cost-effectiveness ratio (ICER) around base case[a] for plausible ranges[b] of key parameters, 2014/15 cost values



ARV: antiretroviral; BNF: British National Formulary; QALY: quality-adjusted life year.

[a] Base case ICER + GBP 23,500 (EUR 31,900) per QALY gained, set at 64% PrEP effectiveness and a 20% increase in HIV incidence in those given PrEP due to risk compensation (see text).

[b] Extremes of parameter ranges shown at either end of horizontal bars.

Individuals given PrEP will be managed via GUM clinics; for a one year programme, each individual will have five visits to the clinic, at month 0, 1, 3, 6, and 9. The first visit includes assessment of clinical need for PrEP, confirmation of HIV and STI status, and measurement of renal function. Subsequent visits are for monitoring of drug adherence, tolerability, and safety, together with quarterly checking of HIV and STI status [2]. The additional elements of GUM clinic care directly attributable to PrEP were micro-costed (see supplementary material [12]).

Estimating HIV incidence

GUMCAD data on HIV-negative clinic attending MSM for 2009 to 2013 were extracted. Diagnosis or not of any bacterial STI in the previous year was used to indicate recent condomless anal intercourse and to stratify the future risk of being diagnosed with HIV. Those with a bacterial STI in the previous year were labelled 'high-risk' and eligible for PrEP, and those without as having 'medium-risk' for HIV acquisition [14]. To estimate current HIV incidence in these strata, records were used of MSM with at least one additional documented HIV test between 43 to 365 days after the first HIV test

Table 1

Economic parameter estimates used in the two principal scenarios (providing PrEP or not), and value or range explored in sensitivity analyses, England, 2014/15 cost values

Parameter	Value	Sensitivity analyses range (min. to max. value of scenarios considered)	Explanatory notes and data source
Discount rate (cost)	3.5%	1.5% – 3.5%	[7]
Discount rate (QALYs)	3.5%	1.5% – 3.5%	[7]
Costs			
Annual cost of PrEP drug	GBP 4,331 (EUR 5,892)	GBP 433 – GBP 4,331 (EUR 589 – EUR 5,892) Discount range: 20% to 90%	[32] (last accessed 5 August 2016); price excludes VAT and was directly applied to the cost-effectiveness analysis
Annual cost of PrEP-related GUM tariffs	GBP 176 (EUR 239)	ND	[2,33], see also supplementary material [12]
PEPSE drug cost[a] (averted in those taking PrEP)	GBP 772[a] (EUR 1,050) per PEPSE course	NA	[32] (BNF last accessed 5 August 2016); price excludes VAT and was directly applied to the cost-effectiveness analysis
PEPSE GUM clinic costs (averted in those taking PrEP)	GBP 250 (EUR 340) per PEPSE course	NA	[33] (adapted to the current study)
Annual cost of an undiagnosed HIV infection	GBP 0 (EUR 0)	GBP 0 – GBP 2,499 (EUR 0 – EUR 3,400)	Assumption; GBP 2,499 based on HIV care costs for individuals diagnosed at CD4+ › 200 cells per mm3 not on ARV treatmentb [17,21]
Annual cost of ARV treatment per HIV-positive individual	GBP 4,741 (EUR 6,450)	Price reductions from 2019: range 0% to 80%	[20]c
Annual care cost of HIV + CD4 › 200 cells per mm^3	GBP 4,734 (EUR 6,441)	ND	[17,21]
Annual care cost of HIV + CD4 ‹ 200 cells per mm^3	GBP 7,479 (EUR 10,175)	ND	[17,21]
Time to CD4+ recovery from ‹ 200 cells per mm^3	3 months	NA	Based on analysis of HIV data [18]
QALY values			
Disutility between HIV infection and diagnosis	0	0 – 0.11	Assumption [34]
Disutility associated with HIV infection – per annum	0.11	0.10 – 0.13	[34]
Utility values in UK men aged over 75 years[d]	0.75	NA	[35]

ARV: antiretroviral; BNF: British National Formulary; GUM: genitourinary medicine; max: maximum; min: minimum; NA: not applicable; ND: not done; NHS: National Health Service; NICE: The National Institute for Health and Care Excellence; PEPSE: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; QALY: quality-adjusted life year; VAT: value added tax; UK: United Kingdom.

[a] This price represents the highest possible cost of current PEPSE drug recommended for use by NHS England (tenofovir disoproxil/emtricitabine/raltegravir) based on BNF list price, excluding VAT for the cost-effectiveness analysis in accordance with NICE Methods Guide.

[b] Cost excludes specific HIV-related costs such as CD4+ and viral load measurements, and resistance testing (personal communication, V Cambiano, December 2015).

[c] Principal scenario used NHS England reported spend on ARV treatment. In sensitivity analyses, although actual timing of availability of generic ARVs for treatment is unknown, sensitivity analyses explored potential availability from 2019. This was based on the estimated patent expiration of individual compounds of the combination ARV treatment tenofovir disoproxil/emtricitabine/efavirenz (proprietary name: Atripla) by 2018 [36]. Combination tenofovir disoproxil/emtricitabine/efavirenz is one of the British HIV Association preferred choice of ARV treatment to begin with in therapy-naïve patients [37].

[d] We assumed that an HIV-positive individual has a life-expectancy of 75 years [38]. Given that the life-expectancy at birth for males in England (2010 to 2012 Office for National Statistics estimates) was 79 years, this meant that an HIV-positive individual who dies at age 75 years would have lost four years of quality of life [16]. We combined this last four years with the utility values among UK men aged above 75 years (0.75 per year), which was obtained from the EQ-5D utility values for UK male population, to obtain the QALY losses during these final four years of life lost consequent to earlier deaths related to HIV [35].

Table 2

Population size and HIV incidence in men having sex with men (MSM), England, 2012

HIV-negative MSM by risk stratum	MSM numbers[a]	Annual HIV incidence, per 100 person-years (95% CI)	Annual HIV infections[a]
a. HIV incidence in GUM clinic attendees (directly estimated[b])			
High-risk – GUM clinic attendees with bacterial STI in previous year and/or at first attendance of year	17,400	3.3 (2.8–4.9)[c]	570[d]
Medium-risk – GUM clinic attendees with no recorded bacterial STI in previous year or at first attendance of year	68,100	1.5 (1.3–1.8)[c]	1,020[d]
b. Overall HIV incidence, England			
PHE back-calculation[e]			2,790
c. HIV incidence in non-GUM clinic attendees (indirectly estimated[f])			
Low-risk – HIV-negative non-GUM clinic attendees	395,000	0.3	1,200

CI: confidence interval; GUM: genitourinary medicine; ONS: Office for National Statistics; MPES: multi-parameter evidence synthesis; Natsal: National Survey on Sexual Attitudes and Lifestyles; PHE: Public Health England; STI: sexually transmitted infection.

[a] Numbers rounded to three significant figures or nearest 10.

[b] Estimated using 2013 Genitourinary Medicine Clinical Activity Dataset – GUMCAD [11].

[c] As observed in re-attending sub-group.

[d] Applying observed incidence to whole group and rounded to three significant figures or nearest 10.

[e] Year 2012 estimated numbers, using methodology as described in Birrell et al., 2013 [30].

[f] Estimated 1,200 annual infections calculated by deducting number of infections among GUM clinic attendees (high-risk and medium-risk; 1,595) from overall annual HIV incidence (2,790) [30]. Low-risk population size of 395,000 (i.e. non-GUM attending MSM) estimated using a combination of MPES (England and Wales, aged 15–44 years), ONS (England and Wales population estimates for mid-2012), and Natsal-3 (proportion of MSM by age group), to obtain an estimate of the non-GUM attending MSM population in England for ages 15–74 years [1,15,16]. HIV incidence in this low-risk group (1,200 annual infections per 395,000 population) rounded to 0.3 per 100 person-years.

documented in 2012, the most recent year with sufficient data (followed-up to end 2013) for analysis [14]. HIV incidence estimation methodology follows that used in Desai et al. [14].

MSM who did not attend a GUM clinic were assumed to be at 'low-risk' [14] (see also supplementary material [12]). To estimate HIV incidence in this stratum, total MSM numbers were calculated by combining the male proportion reporting same-sex partnerships in a 2010–12 national survey with 2012 male population estimates [15,16]. Estimated MSM living with HIV (diagnosed and undiagnosed) and GUM attending HIV-negative MSM were subtracted to get the denominator of those at low-risk [1]. Estimated HIV infections that occur in high- and medium-risk MSM were subtracted from the back-calculation estimate of all 2012 HIV infections in MSM to give the numerator for those at low-risk.

MSM eligible for PrEP begin at high-risk and move to medium- or low-risk at a changing probability. Lifetime HIV incidence combined movement between risk strata with estimated stratum-specific HIV incidence. Follow-up of high-risk MSM clinic attendees informed the proportions that stayed high-risk with bacterial STI diagnoses each year, those that became medium-risk who attended a clinic annually without bacterial STI diagnosis, and those without clinic attendance who became low-risk. Allowance was made for any transition from low- or medium-risk back to medium- or high-risk. If in 2013, x% of MSM who began as high-risk in 2009 remained high-risk, y% had become medium-risk, and z% low-risk, and HIV incidence was H, M, and Λ for high, medium, and low-risk respectively, then the weighted average HIV incidence in 2013 was $(x\%*H) + (y\%*M) + (z\%*\Lambda)$. Similarly calculated weighted HIV incidence averages were used for years 2010, 2011 and 2012. By assuming the same rate of change in risk from 2009 through 2013 and the same HIV incidence by risk stratum, future HIV incidence in 2017 through 2020 was estimated for MSM who began as high-risk in 2016 (PrEP programme year-1). After year-5 in 2020, future annual HIV incidence was interpolated using a constant rate of reduction until it reached Λ, and subsequently kept at Λ until age 75 years, after which risk of HIV acquisition was assumed to be zero. This approach created a declining HIV incidence over time. A slightly higher number remained susceptible in the PrEP group due to their PrEP protection during the first year. Therefore, over the subsequent lifetime to age 75 years, the absolute number of HIV infections each year was slightly greater in the PrEP group compared with the non-PrEP group (Figure 2).

Economic evaluation

A national guide for technology appraisals was followed [7]. PrEP users were assumed not to require HIV post-exposure prophylaxis following sexual exposure (PEPSE). Lifetime HIV infection care cost (excluding ARV costs) were stratified by CD4+ status at diagnosis [7,17]. HIV surveillance data were used to estimate average time to diagnosis once infected, CD4+ count at diagnosis, and rate of CD4+ recovery upon ARV commencement [18] (see also supplementary material [12]). Prompt initiation of ARV treatment following diagnosis was assumed [19].

Drug treatment costs used average 2013–15 NHS England ARV cost [20]. Future costs and QALYs were discounted annually by 3.5% and adjusted to 2014/15 GBP values (EUR values presented in parentheses, using year end 31 December 2015 historical exchange rates of GBP 1 equals EUR 1.3605) [7,21]. Economic parameters are presented in Table 1.

Model outputs included number of new HIV infections and the ICER, as cost per QALY gained, of PrEP compared with no PrEP. Budget impact analyses were presented in present 2014/15 values and included value added tax (VAT: + 20%) on PrEP drug costs [7]. PrEP service investment time to break-even was calculated as the years to when the cumulative savings from HIV infections averted in year-1 began to exceed PrEP costs in year-1.

Risk compensation

Published evidence suggests increased frequency of condomless anal sex subsequent to PrEP use and increased STI diagnoses [2,22]. Risk compensation would also lead to an increase in HIV exposure. With PrEP scale-up, adherence may reduce and thereby increase HIV transmission. To explore risk compensation, an arbitrary increase of HIV incidence by 20% in those given PrEP was assumed in the principal scenarios. At 64% PrEP effectiveness, for example, annual HIV incidence is (100% – 64%) * H = 36% * H, where, H = HIV incidence in high-risk MSM. If H is increased by 20% due to risk compensation, then annual HIV incidence becomes (100 – 64%)*(100% + 20%) *H = 43.2% * H.

Sensitivity analyses

Sensitivity analyses explored plausible ranges of key parameter values (Table 1). Univariate sensitivity analyses were based on cautious choices considered more plausible with substantial scale-up. The scenario with 64% PrEP effectiveness and risk compensation was the preferred benchmark and corresponding ICERs were plotted on a tornado diagram.

Multivariate sensitivity analyses were conducted to illustrate the margin of certainty around whether or not PrEP would remain cost-effective, at different PrEP effectiveness level (Figure 3). Due to the nature of the uncertainties, full probabilistic sensitivity analysis was not possible.

Results

An estimated 466,000 HIV-negative MSM aged between 15 to 75 years-old live in England in 2012, 85,500 (23%) of whom attended GUM clinics during that year. A fifth of the 85,500 (17,400 MSM) had a documented bacterial STI diagnosis i.e. proxy for high risk. Over time, GUMCAD data have shown an increase in the number of HIV-negative MSM GUM attendees, as well as the subset diagnosed with bacterial STI. Thus, the 5,000 person-years PrEP covered 29% of the GUMCAD identified high-risk cohort (who may not represent all high-risk MSM as not all attended GUM clinics [23]), 6% of all HIV-negative MSM GUM attendees, and just 1% of the estimated HIV-negative MSM population in England.

The HIV incidence observed in the high-risk PrEP-eligible stratum was 3.3 per 100 person-years (95% CI: 2.8–4.9 per 100 person-years), and 1.5 per 100 person-years (95% CI: 1.3–1.8 per 100 person-years) in the medium-risk stratum. In the low-risk MSM stratum the indirectly estimated HIV incidence was 0.3 per 100 person-years (Table 2). The HIV incidence estimates showed that GUM attending MSM had higher HIV risk than non-GUM attending MSM.

Of the 11,742 MSM without diagnosed HIV and with a recent bacterial STI (proxy for high HIV risk), who attended clinic in 2009 (the first of a five year, 2009–2013, longitudinal analysis), only 26% were categorised as high-risk in 2010. This decrease in the proportion of the initial 2009 attendees categorised as high-risk in subsequent years continued through 2011, 2012 and 2013, to 10%, 7% and 5% (see supplementary material [12]). Consequently, there was a large reduction in the weighted average annual HIV incidence for year-2 to year-5 (Figure 2). Interpolating the declining risk behaviour in the cohort and subsequent HIV acquisition forward, the annual HIV incidence reached the lower risk tier of 0.3 per 100 person-years annually by year-9, after which it was kept constant until age 75 years.

Combining the weighted average annual HIV incidence for MSM and the age distribution of MSM clinic attendees in 2013 and 2014, the estimated lifetime HIV incidence to age 75 years in an MSM clinic attendee who began year-1 at high-risk, was 16.96%.

Applying a 20% HIV incidence increase to those given PrEP in year-1, as a risk compensation adjustment, the estimated cumulative HIV incidence to age 75 years was reduced from 16.96% (no PrEP) to 15.4% at 64% PrEP effectiveness, while at 86% effectiveness, it fell to 14.6%.

After the year-1 high-risk period, HIV incidence reduced to 1.35 per 100 person-years and PrEP was no longer indicated. Moreover, a small fraction of those who were protected by PrEP during the first year became infected later in life. The contribution of PrEP, given only during the year-1 high-risk period, to reducing lifetime HIV risk was modest, impacting on close to 20% of lifetime risk, because of the relatively short period that MSM remained at high risk (see supplementary material [12]).

Economic evaluation

Without PrEP in year-1, an estimated 848 HIV infections occurred, producing future discounted HIV care costs of GBP 84.3 million (EUR 115 million), and a loss of 1,830 QALYs (discounted). Almost half of these infections occurred within the first 10 years (see supplementary material [12]).

Assuming daily PrEP at 86% effectiveness (with risk compensation), an estimated 730 lifetime HIV infections occurred. Year-1 PrEP cost (drug and GUM clinic) of GBP 22.5 million (EUR 30.7 million) prevented GBP 24.1 million (EUR 32.9 million) HIV care costs (discounted) and GBP 256,000 (EUR 348,000) PEPSE-related costs, saved 361 QALYs (discounted), and over a lifetime was cost-saving (i.e. ICER is negative), compared with no PrEP. Delivering PrEP to 5,000 high-risk MSM resulted in 137 less year-1 HIV infections. However, 19 of these 137 acquired HIV while at medium- or low-risk later in life, reducing the total infections prevented to 118. Nevertheless, these 19 infections were delayed with corresponding reductions in costs and QALY losses.

At 64% PrEP effectiveness (with risk compensation), the lifetime HIV infections were 767. Year-1 PrEP service cost of GBP 22.5 million (EUR 30.7 million) prevented GBP 16.5 million (EUR 22.4 million) HIV care costs (discounted) and GBP 256,000 (EUR 348,000) PEPSE-related costs, and saved 247 QALYs (discounted). Under this scenario, the ICER increased to + GBP 23,500 (EUR 31,900), just above the current cost-effectiveness threshold for England [7]. The reduced effectiveness gave 94 less year-1 HIV infections, although 13 of the 94 acquired HIV in later years.

The ICER was very sensitive to assumptions about HIV incidence in the PrEP eligible group, PrEP effectiveness when scaled-up, PrEP drug costs, and future reductions in the cost of ARV treatment (Figure 4).

PrEP was much less cost-effective if HIV incidence was 2 per 100 person-years (the estimated overall HIV incidence in MSM GUM clinic attendees), or if PrEP effectiveness dropped to 44%. Similarly, albeit to a lesser extent, reduced future treatment costs produced a less favourable ICER for PrEP. However, a more favourable ICER resulted through reducing PrEP drug costs, either through price reduction or reduced dosing frequency from daily to event-based.

If, under scale-up, PrEP stayed 86% effective with 20% HIV risk increase (risk compensation adjustment), then for most parameter combinations a PrEP policy stays cost-effective, unless the eligible group HIV incidence was 2 per 100 person-years or less (Figure 3). If, however, effectiveness was 64% with the same degree of risk compensation, then a PrEP service will only be cost-effective if year-1 incidence is over 3.3 per 100 person-years and there is no change in future HIV treatment costs (i.e. ignoring availability for treatment of generic ARVs by 2019, see notes for Table 1), or if PrEP drug cost is reduced.

Budgetary implications

In a single year, a PrEP service of 5,000 person years cost GBP 26.9 million (EUR 36.6 million), at current British National Formulary (BNF) list price (inclusive of 20% VAT). As HIV care costs accrued over time, it took many years before investment in the first year was recovered. At 86% PrEP effectiveness, it took 23 years of cumulative savings from HIV care cost averted for the year-1 investment to break even and 33 years if PrEP was only 64% effective, both assuming risk compensation.

If there was a substantial reduction in PrEP drug price (e.g. by 90%), the budget to cover 5,000 person years became GBP 3.48 million (EUR 4.73 million). Break-even of year-1 investment happened by the fifth year at 86% effectiveness or by the sixth year at 64% effectiveness, again assuming risk compensation.

Time to break-even of the initial year of PrEP was extended should future HIV treatment costs reduce. At current BNF list price, a 30% reduction in future ARV treatment costs from 2019 onwards increased the time to break-even of the one-year investment in PrEP in 2016 to 38 years, assuming 64% PrEP effectiveness with risk compensation.

Discussion

Oral PrEP given to MSM at high HIV risk, assuming good adherence and correspondingly high clinical effectiveness, was potentially cost-effective in England. The ICERs, however, were very sensitive to key parameters such as the risk of HIV for PrEP recipients and adherence (effectiveness). When PrEP is scaled-up to service provision level there is doubt that the values for these parameters observed in clinical trial settings will apply. Moreover, at the current BNF price the budgetary impact of a modest annual programme of 5,000 PrEP person years was considerable.

The cost-effectiveness of PrEP scale-up depends first on reaching those at high risk of HIV, who need to be identified, offered and to accept PrEP; if many at medium-risk take PrEP, HIV incidence in those taking PrEP will be overestimated. Second, PrEP adherence may be lower with scale-up than in smaller clinical trials; results from 'real-world' effectiveness trials, which generally recruit committed early adopters who may be at exceptionally high-risk, may not be repeated in programmes for all at high-risk [24]. Third, there is uncertainty about whether or not condomless anal intercourse frequency will increase in those given PrEP (risk compensation), leading to more exposures and increased HIV in those with poor PrEP adherence as well as increased bacterial STIs and hepatitis C, thus blunting PrEP benefit; so far a possible HIV incidence increase mediated through diminished adherence during scale-up has not been observed, but there is emerging evidence suggesting risk compensation and bacterial STI increase in those on PrEP [25]. Sensitivity analyses of plausible combinations of these factors did not give a high degree of certainty that the ICER for PrEP would be below GBP 20,000 (EUR 27,210) per QALY gained [7]. Moreover, despite differences in model structure and input assumptions that were appropriate for England, these findings were broadly in agreement with economic evaluations from other

high income countries [26-29], which found ICERs to be highly dependent on HIV incidence, costs of the PrEP drug and adherence-related effectiveness. This analysis highlights critical considerations for PrEP implementation in other European countries, even if their HIV epidemic is different, as the problems arising around implementation, financial considerations, and programme sustainability are common.

A key strength of this study was the use of empirical data on many thousands of MSM attending GUM clinics in England over a contemporary period to measure HIV incidence and risk turnover. A critical assumption was that future HIV incidence in MSM GUM clinic attendees will replicate that observed between 2009 and 2013, and further consequences of any recent changes in sexual behaviour were not captured. However, it was reasonable to extrapolate forward current HIV incidence estimates given the scale and timeliness of the source GUMCAD data and the recent back-calculation estimates that showed no change in overall HIV incidence in MSM [1,30].

A major limitation of our analysis was the use of a static decision analysis approach instead of a dynamic transmission model, as it did not quantify the benefit of PrEP on the wider HIV epidemic in England, including the benefits for those not given PrEP. Therefore, there was an underestimation of the total benefit. Nevertheless, since our cohort of 5,000 MSM was very small (1%) compared with the overall HIV-negative MSM population in England, and modest compared with the higher risk group of GUM attendees (29%), the likely indirect impact of the PrEP programme would be limited. Recently, Nichols et al. quantified this indirect effect of a similarly modest PrEP intervention (average 4,500 MSM annually) delivered to a Dutch MSM population using a dynamic model and showed only a 13–16% change in the ICER when indirect effects were included [26]. Therefore, with a modest programme, the majority of benefits fall on those given PrEP. Should a very large PrEP programme be implemented, the long-term indirect effects would increase in dominance and a static modelling approach would be inappropriate.

In conclusion, whether or not PrEP drug is priced at a level that guarantees favourable cost effectiveness, reduced budgetary impact, and a shorter return on investment period, the analysis highlights other questions about PrEP scale-up that directly affect the financial considerations and the sustainability of any future programme. When proposed high-risk eligibility criteria are implemented, who and how many will access and take up PrEP? Will PrEP be taken up by those in whom PrEP is clinically recommended? What will be their level of adherence? What will be the effectiveness of regular clinical risk assessment at assuring that only those at continuing high-risk stay on PrEP to maintain cost-effectiveness and equitable access based on clinical need? These questions should be answered before embarking on a long-term PrEP-based intervention. A further clinical trial is proposed as a means to do this [31].

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Conflict of interest

None declared.

Authors' contributionsKJO, AJvH, and ONG designed the analysis and developed the methodology. SD performed analysis of genitourinary medicine clinic activity data and provided HIV incidence estimates. KJO, AJvH, and ONG analysed key data sources. KJO performed the cost-effectiveness and budget impact analysis, which was appraised by AJvH. KJO, AJvH, and ONG wrote the first draft of the manuscript and subsequent versions, with comments from SD, NF, MD, and AN. All authors approved the final version of the manuscript.

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Meeting report: Pre-exposure Human Immunodeficiency Virus Prophylaxis in the EU/EEA: Challenges and Opportunities, Stockholm April 2016

T Noori [1] , A Pharris [1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Correspondence: Teymur Noori (teymur.noori@ecdc.europa.eu)

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The ECDC held an expert meeting in Stockholm on 27–28 April 2016 to discuss practical considerations for pre-exposure prophylaxis (PrEP) implementation in Europe. The meeting focused on four key areas: (i) eligibility criteria for PrEP in Europe; (ii) appropriate models of service delivery; (iii) cost-effectiveness of PrEP, and (iv) routine monitoring of people on PrEP.

PrEP is the regular use of an antiretroviral medication by people who are uninfected to prevent the acquisition of HIV infection. Currently Emtricitabine/Tenofovir Disoproxil Fumarate (TDF/FTC) or tenofovir alone is used. Since 2010, the efficacy of oral PrEP has been shown in four randomised controlled trials [1-4]. In 2015, the World Health Organization (WHO) recommended that PrEP should be offered as an additional prevention option for people at substantial risk of HIV infection as part of combination prevention approaches [5].

In the European Union/European Economic Area (EU/EEA), men who have sex with men (MSM) are disproportionately affected by human immunodeficiency virus (HIV) and other sexually transmitted infections (STI) [6,7]. Consequently, strengthening efforts to reduce the incidence of HIV and STI among MSM is a priority for the European Centre for Disease Prevention and Control (ECDC), which recently published comprehensive guidance on HIV and STI prevention among MSM [8] and an opinion encouraging countries to consider integrating PrEP into their existing HIV prevention packages for those most at-risk of HIV infection, starting with MSM.

Eligibility criteria for pre-exposure prophylaxis in Europe

Elske Hoornenborg from the AMPrEP project in Amsterdam, the Netherlands, provided an overview of eligibility criteria for PrEP. Review of PrEP studies, demonstration projects and existing guidelines show that eligibility criteria are very similar. WHO guidelines recommend PrEP for population groups with HIV incidence › 3%; United States (US) Centers for Disease Control and Prevention guidelines recommend PrEP for MSM at substantial risk of HIV, and European AIDS Clinical Society (EACS) guidelines recommend PrEP for MSM or transgender people with inconsistent condom use with casual partners or an HIV positive partner not on treatment, with recent STI or use of post-exposure prophylaxis (PEP) [5,9,10].

Key issues emerging from the presentation and following discussion include:

- Eligibility criteria may need to be adapted to reflect the epidemiological context, since population groups at high risk of HIV differ between countries in Europe. MSM at high risk for HIV acquisition are a key group for which PrEP is being considered in many EU/EEA countries.

- The need (i.e. those at high risk of HIV) and demand (i.e. those coming forward for PrEP or accepting if offered) of PrEP should be considered separately when formulating eligibility criteria.

- Eligibility criteria should ensure that PrEP use maximises public health benefit and cost- effectiveness.

- Some country representatives expressed concerns about people who do not meet eligibility criteria but are still obtaining PrEP. However, the evidence to-date suggests that most MSM seeking PrEP self-select, i.e. they are at high risk of HIV.

Appropriate models of service delivery

Sheena McCormack, from University College London (UCL), United Kingdom (UK), presented an overview of options for delivering PrEP, including delivery in clinic-based services, community-based services, by HIV

specialists, primary care physicians, peers and online. She pointed out that whichever model is chosen, consideration must be given to suitable systems for purchasing drugs, additional resource requirements and how best to integrate PrEP into existing services. Integrating PrEP should be relatively straightforward for countries with services offering HIV and STI diagnosis and treatment and PEP, as PrEP is relatively simple to prescribe as there are limited drug choices and few side effects or drug interactions.

Key issues emerging from the presentation and following discussion include:

- Feasible options will depend on the country context and the way in which the health system is organised. In some countries, primary care physicians provide HIV and STI treatment and care and could deliver PrEP, but, in others, HIV care and follow up is provided by HIV or infectious diseases specialists.

- Given differences in country contexts, it is not feasible to make Europe-wide recommendations. Each country will need to consider where HIV/STI testing and treatment are best delivered. However, European guidance on general principles and minimum standards, e.g. for safe prescribing, quality of care and monitoring, and maximising the benefits of PrEP as a prevention tool, would be helpful.

- Encouraging people who are at risk but who are HIV negative to engage with health services is critical, and MSM-friendly services can facilitate this.

- Community-based services should have appropriate referral links and pathways in place to ensure that people on PrEP receive follow-up care and routine monitoring. Specific concerns about online delivery of PrEP include how to promote adherence and provide follow-up care, as well as how to ensure that people are purchasing genuine drugs and reduce the risks associated with stock outs of drugs.

Cost and cost-effectiveness of PrEP

Valentina Cambiano (UCL) and Nigel Field (UCL and Public Health England, UK) presented work on the cost-effectiveness of PrEP among MSM in the UK, using two different models, and the work by Brooke Nichols and colleagues (Erasmus Medical Center, Rotterdam) in the Netherlands.

Available evidence suggests that significant reductions in drug prices will be needed for PrEP to be considered cost-effective (now) if the time horizon under consideration is only short-medium term. However, each infection averted now is averting health service antiretroviral therapy costs for many decades to come and so it is appropriate to consider a long-term time scale (e.g. 80 years). Based on the modelling conducted by Cambiano and colleagues and by Nichols and colleagues, PrEP is likely to prove to be cost effective, although in the Netherlands only if PrEP is taken on demand considering a long time horizon. Presenters pointed out that making the public health case for an intervention such as PrEP, which has a substantial short-term budget impact but potential for substantial longer-term savings in cost and public health benefit, is challenging.

Key issues emerging from the presentation and following discussion include:

- Demonstrating the impact of PrEP on new HIV infections outside of clinical trials will be critical. Positive results from France, where PrEP is currently implemented, and from demonstration projects showing a reduction in new infections will be important evidence to aid decision makers considering PrEP.

- As individual countries might need to conduct their own cost-effectiveness studies, some guidance to standardise these cost-effectiveness studies would be useful. Some participants in the meeting were doubtful whether the cost-effectiveness arguments would be of value in convincing policymakers, as decisions are more strongly influenced by the short-term budget impact.

- The cost of the drugs is the key barrier to free provision of PrEP by public health services. Costs are expected to drop once generic drugs become available in Europe.

Monitoring of people on PrEP

The key points related to routine clinical and public health monitoring of people on PrEP such as adherence, drug resistance and regular STI screening were covered in three presentations.

Pep Coll (Barcelona Checkpoint, Spain) provided an overview of the evidence about adherence to PrEP. Studies have shown that PrEP is efficacious if it is taken as prescribed (in the range of 90%). Ensuring adherence to the dosing regimen is crucial whether PrEP is taken daily or on demand. The barriers to adherence include stigma, lack of community acceptance of PrEP, the need to conceal PrEP use, chemsex, mental health problems, social factors, and mobility.

Robert Grant (University of California, San Francisco, US) discussed the issue of drug resistance in the context of PrEP. Concerns have been raised that generalised or inappropriate PrEP use could result in the development and transmission of drug-resistant strains of HIV. Drug resistance during PrEP use and PrEP trials has been low. A systematic review of drug resistance in PrEP trials found that there were five cases of incident drug resistance in 9,222 people in the active PrEP arms, i.e. the overall risk of resistance was 0.5%. The risk of drug resistance is higher in people with acute HIV infection when they start PrEP, i.e. in the window period, but is low in those who seroconvert while taking PrEP. There

is a case report of oral FTC/TDF PrEP failure to prevent HIV infection despite good adherence. This was a very particular case involving the acquisition of an extensively resistant virus mutated strain. One strategy to mitigate the risk of drug resistance could be the use of more sensitive assays to detect acute HIV infection in the window period.

In her second talk, Sheena McCormack discussed the impact on other STIs following the introduction of PrEP. Both overall European Union/European Economic Area (EU/EEA) and UK data show that bacterial STIs were increasing among MSM before PrEP, particularly among high risk MSM. Data from the UK PROUD study, which was conducted among HIV-negative MSM with a high burden of self-reported STI, show that there was no difference in the proportion with an STI between those on PrEP and those not on PrEP after 12 months, with both groups followed up for HIV and STI every 3 months. The incidence of STIs among MSM is increasing and is likely to continue to increase in Europe with or without PrEP. PrEP can contribute positively to STI control by increasing regular asymptomatic screening, prompt treatment and partner notification, at the same time as providing support to MSM who want to reduce risk behaviour.

Key issues emerging from the presentations and following discussions include:

- Lack of access to PrEP through health services will contribute to adherence problems, because if users are purchasing PrEP online they might not receive quality products, or find it hard to continue to pay or the supplies will not be reliable.

- The rise in practicing condomless sex resulting in greater exposure to STIs by those on PrEP is of concern to some stakeholders. In particular there are concerns that widespread PrEP use could lead to an increase in the incidence of MDR gonorrhoea, although this has not been seen in the US or in France so far. In France, rates of gonorrhoea among PrEP users have actually dropped even though rates of testing have increased in this risk group. In the UK, data from the PROUD study indicates that there is still a good level of condom use in this risk group.

- Clear evidence and messages to various stakeholders (policymakers, public health experts, clinicians, community representatives, etc.) about PrEP and STIs (e.g. that STI rates are already high in those MSM who would benefit most from PrEP, or that rates of STI are increasing with or without PrEP) will be critical. However, an additional increase in STIs is still likely (as was the case historically with similar major developments such as the introduction of oral contraceptives) and the health services need to plan for this eventuality.

- PrEP should be provided as part of a comprehensive package which will also allow for earlier diagnosis and linkage to care of STIs and for other interventions that may reduce the incidence of STIs.

- Surveillance systems should be adapted in order to monitor the use of PrEP, including use outside public health systems, and PrEP failures to ensure suitable measures are carried out to maximise the effectiveness of this prevention strategy.

Conclusions

PrEP should not be considered in isolation but as an additional option for people at substantial risk of HIV infection as one element of a combination prevention approach. There may be several models of service provision that may deliver PrEP effectively to those population groups at highest risk of HIV and the final choice will be determined by the specificities and organisation of countries' health services. The current cost of PrEP remains the main obstacle for implementation in the European setting. The second main obstacle is the potential impact of PrEP on risk behaviour by an already high risk population. However, a well-planned PrEP service will make good use of the need for PrEP users to attend regular check-ups ensuring prompt diagnosis, treatment and the offer of partner notification, while providing specific support to MSM who want to reduce their risk behaviour. Meeting participants identified a number of priority activities that that could be considered to support policy and implementation of PrEP in the EU/EEA, including: updating the current ECDC evidence-based guidance on HIV and STI prevention among MSM to include the new evidence on PrEP implementation; developing a model/tool to support comparable national cost-effectiveness studies; working with Member States to identify minimum standards and principles for service delivery; exploring the possibility of using national surveillance data to estimate the number of people in need of PrEP; identify standard indicators to monitor PrEP and explore the potential to use European HIV cohorts to monitor PrEP use and impact.

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Conflict of interest

None.

Authors' contributions

TN wrote the first draft of the manuscript. AP critically reviewed the paper and gave input to the content, which was incorporated in the report. Both authors read and approved the final manuscript.

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