



Clinical Commissioning Policy Proposition:

**Pre-exposure prophylaxis (PrEP) to prevent the
acquisition of HIV in adults**

Reference: NHS England F03X06

First published: TBC

Prepared by NHS England Specialised Services Clinical Reference Group for HIV

Published by NHS England, in electronic format only.

Draft for public consultation

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1 Executive Summary

Policy Statement

NHS England proposes to routinely commission Pre Exposure Prophylaxis for the treatment of adults at high risk of HIV acquisition in accordance with the criteria outlined in this document.

In creating this policy proposition NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Antiretrovirals (ARVs) are drugs used to treat HIV. These drugs can also be given to people who do not have HIV as a way of preventing infection. ARVs have been used for many years as post-exposure prophylaxis (PEP) – this is when an HIV-negative person who may have been exposed to HIV (e.g. via condomless sex) takes ARVs. Pre-exposure Prophylaxis (PrEP) is when the drugs are given **before and after** possible exposure. Several studies have shown PrEP to be effective at preventing

HIV in people at high risk of getting HIV such as gay men and people with HIV-positive partners. Most studies have used Truvada®; this is a tablet that contains two ARVs, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Side effects are not common and in all the PrEP studies the drug has been shown to be safe. When taken as advised it is more than 80% effective (this means that for every 10 people who get HIV more than 8 could be prevented with PrEP). The drug can be taken every day or can be taken just before and after sex (2 tablets between 2 and 24 hours before sex and then 1 tablet a day for 2 days after sex) – this is called ‘event-driven PrEP’. Event-driven PrEP has only been studied in gay men so is not recommended for other groups of people.

The groups of people considered to be at high risk and covered by this policy are:

- High risk Men who have sex with Men (MSM), trans women and trans men who have had anal sex without a condom in the last 3 months and likely to again in the next 3 month
- Partners of people living with HIV where they are not known to be on successful HIV treatment. When people with HIV are on effective treatment they have an ‘undetectable’ level of HIV in their body which means they are very unlikely to transmit HIV to others and PrEP adds no benefit. If they do not have an undetectable viral load (i.e. they are not on treatment or have stopped treatment) then PrEP is beneficial.
- Heterosexuals assessed to be at similar high risk to MSM

Deciding if someone needs PrEP is based on an assessment by sexual health staff. If PrEP is considered suitable then a HIV test will be done to confirm that person is still HIV-negative. Prescriptions will be for no more than 3 months and people using PrEP will be asked to attend for regular sexual health check-ups (every 3 months) and kidney checks (urine test and occasional blood tests). PrEP does not prevent transmission of other infections and clinics will provide advice about risk reduction including the use of condoms.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission pre exposure prophylaxis.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether Pre Exposure Prophylaxis for adults at high risk of HIV acquisition will be routinely commissioned is planned to be made by NHS England in 2016 following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

HIV is a disease of major importance in the UK. The average cost of one person treated over their lifetime, in the UK, has been estimated at around £360,000 (based on median life expectancy of 71.5 years), which is largely down to the cost of antiretrovirals. (Nakagawa et al., 2015).

Gay, bisexual, and other men who have sex with men (MSM) continue to be the group most affected by HIV infection (Public Health England, 2014). Among MSM, annual numbers of new diagnoses reported for the past decade have not declined, and modelling estimates suggest that HIV incidence has actually increased (Phillips et al., 2013). These trends have occurred despite increased HIV testing (Public Health England, 2014, Sonnenberg et al., 2013), and high levels of people with diagnosed HIV being on treatment and having undetectable viral load, which results in most people living with HIV being non-infectious within six months (Brown et al., 2014, Wilson, 2012).

Although HIV testing and promotion of condoms are core strategies for reducing risk, additional approaches have been proposed for HIV negative people at high risk

of infection. Treatment as prevention (TasP), providing earlier treatment to a person diagnosed with HIV to prevent transmission to HIV negative partners as well as to treat HIV infection, has been approved in a separate clinical commissioning policy by NHS England (NHS England, 2015). An estimated 25% of those with HIV infection are unaware of their HIV status and so are unable to inform partners of the potential HIV risks.

The use of antiretroviral drugs before exposure, given to people who do not have HIV to prevent an established infection is referred to as pre-exposure prophylaxis (PrEP) and has been the subject of three randomised studies demonstrating effectiveness, two of which were in Europe

4 Definitions

ART / ARV – antiretroviral therapy or treatment (HIV medication)

CD4 count – is a measure of the strength of a person's immune system. A low CD4 count, which occurs in HIV infection, indicates that the patient is at risk of opportunistic infections and illness.

DOT- directly observed therapy – a treatment method in which patients are under direct observation when they take their medication

FTC – Emtricitabine – a nucleoside reverse transcriptase inhibitor antiretroviral

IDU – Injecting drug users, a term now largely replaced by people who inject drugs

Incidence – Measurement of new individuals who contract a disease during a particular period of time

MSM - Men who have sex with men which refers to all men, including bisexual men, who engage in sexual and/or romantic relations with other men.

PEP - Post-exposure prophylaxis: ARV given to someone who has or may have been exposed to HIV, to prevent them from becoming infected.

PLWH – People living with HIV

PrEP Pre-exposure prophylaxis: ARV given to someone who is at risk of exposure to HIV, prior to the exposure, to prevent them from becoming infected.

Prevalence – Measurement of all individuals affected by a disease or condition at a particular time.

PWID – People who inject drugs

Serodiscordant / serodifferent - sexual partners with different HIV status.

STI – sexually transmitted infection

TDF – tenofovir disoproxil fumarate - a nucleoside reverse transcriptase inhibitor

Transgender:-People who have a different sex, gender identity, and/or gender expression than the one assigned to them at birth.

Trans woman – A person who is assigned male at birth but identifies themselves as a woman (male to female transgender person).

Trans man – A person who is assigned female at birth but identifies themselves as a man (female to male transgender person).

Treatment as prevention (TasP) - Use of ART, in HIV positive individuals, with the aim of preventing HIV transmission to others rather than primarily for their own clinical benefit.

Truvada® - a co-formulated combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), hereafter referred to as TDF/FTC.

Viral load – Levels / activity of HIV in a bodily fluid (e.g. blood, semen) and usually measured in the blood

5 Aims and Objectives

This policy proposition considered the following questions with regard to preventing HIV acquisition:

Is oral PrEP clinically efficacious, clinically effective and what factors affect cost-

effectiveness?

Is PrEP cost-effective? In what setting? Under what assumptions and conditions?

The populations considered were:

- men who have sex with men
- transgender women / trans women
- heterosexual men and women
- Couples who have different HIV status (serodiscordant / serodifferent)
- people who inject drugs / injecting drug users

The evidence review focused on the use of oral PrEP compared to placebo or no-PrEP. The outcomes assessed were HIV infection, adverse events, sexual risk behaviours or risk compensation (changes in condom use, number of sexual partners, STIs) and adherence.

The objectives were to:

- Assess whether it is clinically and cost effective for NHS England to fund the use of antiretroviral drugs for pre-exposure prophylaxis.

6 Epidemiology and Needs Assessment

In the UK, 107,000 (95% credible interval 101,600 – 115,800) people were estimated to be living with HIV in 2013 (PHE annual report 2014), giving an overall prevalence of 2.8 per 1,000 population aged 15 – 59 years old (1.9 per 1000 women; 3.7 per 1000 men) (Public Health England, 2014). It is estimated that around one quarter of people with HIV were unaware of their infection (26,100 individuals) (Public Health England, 2014). This presents a major public health challenge since undiagnosed individuals, who may have condomless sex without appreciating the risk posed to partners, contribute disproportionately to ongoing transmission in the population.

Retention in care once diagnosed is high in the UK, such that 68% (72,800/107,000) of all patients with HIV were receiving antiretroviral therapy in 2013, and 64% (68,7000/107,000) of people living with HIV were virally suppressed, with little risk of onward transmission (Public Health England, 2014).

MSM remain the group most at risk of acquiring HIV in the UK, with an estimated 43,500 (95% credible interval 40,200 – 48,200) men infected (Figure 1), giving an overall prevalence of 59 per 1,000 MSM aged 15 to 59 years old (Public Health England, 2014). HIV also disproportionately affects people of black-African ethnicity (Figure 1) although, like other groups at risk, most do not have HIV.

Around two-thirds (38,700/59,500) of heterosexual people living with HIV in England in 2013 were of black-African ethnicity, and the prevalence of HIV in this group was 56 per 1,000 population aged 15-59 years old (Public Health England, 2014).

While prevalence in MSM is similar to that in people of black-African ethnicity in the UK, the incidence of new infections is different: 76% (2,470) of reported infections in MSM were probably acquired in the UK in 2013, compared to 57% (1,500) of infections in heterosexual men and women (Public Health England, 2014). The proportion of new diagnoses that were recent was also higher among MSM than heterosexual men and women (30% versus 13%).

Among attendees at specialist sexual health clinics, the incidence of HIV among all MSM is nearly eightfold higher than the incidence in Black African heterosexuals (Table 1).

Table 1. Estimated HIV incidence among sexual health clinic attendees in 2012

Group of attendees (N=3930)	Estimated incidence	95% CI
All	0.15%	0.13%-0.17%
MSM	1.34%	1.15%-1.53%
Heterosexuals	0.03%	0.02% -0.04%
Black African heterosexuals	0.17%	0.08%-0.27%

71% (150/212) of clinics submitted specimens for recent infection testing; 50% of which related to MSM.
Available at: http://sti.bmj.com/content/91/Suppl_1/A2.1.abstract

Table 2. HIV incidence in HIV negative MSM who re-attended at STI clinics in 2012

Category	HIV incidence (per 100 py)	95% CI
HIV test 42-365 days prior to current attendance	2.4	2.0-2.8
Diagnosed with bacterial STI in previous year and/or at current attendance	3.3	2.8-4.0
Diagnosed with rectal bacterial STI in previous year and/or at current attendance	5.2	3.7-6.7
Received post-exposure prophylaxis (PEP) in previous year	3.3	1.7-6.3

Source: GUMCAD, HIV& STI Department, Health Protection, PHE, HIV incidence analyses:2012

Compared to many countries, the prevalence of HIV among people who inject drugs (PWID) is low in the UK, largely due to highly successful needle exchange programmes (Public Health England et al., 2014, Public Health England and National Infection Service, 2015). In 2013, there were just 130 new HIV diagnoses thought to have been acquired through injecting drug use, and the number of diagnoses in this group has fallen or remained stable over the past eight years.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of Pre Exposure Prophylaxis for specific sub groups of adults at high risk of HIV acquisition as set out in the commissioning criteria.

PrEP: The drug treatment

The majority of the studies examining the impact of PrEP have involved the use of a co-formulated combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) and hereafter TDF/FTC. In the UK, this drug has been licensed for the treatment of HIV-1 infection in adults (18 years and above) for more than a decade. It was announced in February 2016 that the application to vary the licence for once-daily Truvada® (emtricitabine 200mg/tenofovir disoproxil fumarate 300mg) for use in combination with safer sex practices to reduce the risk of sexually acquired HIV-1

infection among uninfected adults at high risk has been fully validated and is under evaluation by the European Medicines Agency (EMA). In July 2016, the EMA recommended granting market authorisation for this indication which is anticipated by the end of 2016. Both TDF and FDC are licensed for single agent use i.e. TDF and/or emtricitabine in children (less than 18 years of age) for the treatment of HIV-1 infection. Data, from a moderate number of pregnant women, have not indicated any malformations or foetal / neonatal toxicity associated with either TDF or emtricitabine. The UK summary of product characteristics supports the use of the TDF/FTC combination as an option to treat HIV-1 infection in pregnant women.

In the UK, patent protection for emtricitabine, tenofovir disoproxil, tenofovir disoproxil fumarate and Truvada ® ranges from 2016 to 2021/22. Availability and use of generic formulations will depend on the patent position of the components and Truvada ®, demand and whether generic suppliers make these medicines available to the UK market.

Daily oral TDF or TDF/FTC are used extensively in the UK as part of triple therapy in people with HIV and are generally very well tolerated. Nausea, gastro-intestinal symptoms and headache are common in the first few weeks but these are mild, resolve after a few weeks and rarely result in discontinuation. Deterioration in renal function is a more serious, but rare, side effect of TDF seen in HIV positive populations. Although there is measurable loss of bone mineral density, it is not clear if this will be clinically relevant in the long-term.

The US Food and Drug Administration licensed the TDF/FTC combination for use as PrEP in July 2012 for individuals at risk of acquiring HIV through sexual exposure. The European Medicines Agency and the European Centre for Disease Control and Prevention issued statements in 2012, as did the British Association for Sexual Health and the British HIV Association, calling for more research to address several areas of concern. These included: whether PrEP would lead to a reduction in the use of condoms and a subsequent increase in other sexually transmitted infections (STIs) and how cost-effective it would be. Risk compensation and cost were noted as wider concerns by the World Health Organisation in July 2014 when it

recommended PrEP for use in MSM (World Health Organisation, 2014).

Biological efficacy would be expected to be generalizable independently but adherence and, therefore, effectiveness are likely to be influenced by healthcare infrastructure, socio-cultural and socio-economic factors.

The evidence review supports the use of either intermittent or daily dosing in high risk MSM based on the IPERGAY and PROUD study findings. As intermittent dosing is as clinically effective as daily dosing but at lower cost, a policy for intermittent dosing for high risk MSM in line with IPERGAY is proposed. It is recognised that clinical assessment may indicate that daily dosing is required to meet individual clinical need so the evidence would support the policy permitting this as indicated. No trial evidence is available to support intermittent dosing in high risk heterosexuals and it is known that there are lower levels of drug in the cervico-vaginal tissues compared to the rectum. Therefore based on the evidence, the policy recommendation for dosing in high risk heterosexuals is limited to daily dosing.

MSM and transgender women

The iPrEx study (Grant et al., 2010), a high quality phase 3 RCT involving 2499 MSM and trans women across six countries (USA, Peru, Brazil, Ecuador, South Africa and Thailand) showed an age adjusted reduction in new HIV infections of 43% (95% CI: 14% - 62%) in those taking TDF/FTC compared with those on placebo. There was no difference in syphilis or gonorrhoea rates between the two groups, but the placebo was included to control for risk behaviours. Both groups reported a reduction in the number of sexual partners and an increased use of condoms, which could be explained by the additional health education and safe sex promotion provided by the trial over and above the local standard of prevention care. Self-reported adherence was high at an average of 95% in both groups after 8 weeks, but adherence as measured by detectable drug was low; only a quarter of participants in the active arm had drug levels compatible with daily dosing, which almost certainly accounted for the lower reduction in new infections than expected and the wide 95% confidence interval. Pre-specified subgroup analyses, using drug detection in the blood, suggested biological efficacy was very high (>90%). After

completing and reporting this trial, 1603 participants from iPrEx and other PrEP studies were invited back to participate in an open-label extension, iPrEx OLE (Grant et al., 2014) to determine uptake, and HIV infection rates according to the level of drug detected in red blood cells. 76% took up the offer. No infections were seen during periods when the drug level suggested the participant had taken 4 or more tablets a week.

The PROUD study (McCormack et al., 2015) looked at the pre-exposure option for reducing HIV in the UK and was an open-label randomisation to immediate or deferred daily TDF/FTC for HIV negative gay men at high risk. The pilot phase of the RCT enrolled 543 HIV-negative MSM and 1 trans woman (total 544) through 13 sexual health clinics between November 2012 and April 2014. The median age of the study group was 35 years and 81% were in the white ethnic group. One arm (n=275) was offered once daily TDF/FTC from enrolment, and the offer was deferred in the remaining 269 until they had completed 12 months of follow-up. However, the deferred period was terminated early following a recommendation from the Data and Monitoring Board, as PrEP was highly effective at reducing the risk of acquiring HIV (86% (90% CI 64% - 96%; p=0.0001)), and the risk of HIV in the deferred group was much higher than expected (9.0 per 100 person years). Participants incorporated PrEP into their existing risk reduction strategies that continued to include condom use, with no difference in STIs between those on PrEP and those not on PrEP. Reported adherence to TDF/FTC was high and it appeared to be safe and well tolerated, with only 1 of 13 participants who stopped taking it, as a result of an adverse event, not re-starting it. Three out of 6 individuals, who had primary infection when they started TDF/FTC, acquired resistance to emtricitabine. No resistance to TDF was seen. There are no plans to do any further studies in the UK as the pilot study demonstrated such a high level of effectiveness.

Another well-conducted efficacy study, considered to have an acceptable form of bias, is IPERGAY. This study was undertaken in France and Canada (Molina and et al, 2015, Fonsart et al., 2014). The IPERGAY study was a double-blind placebo controlled RCT looking at an event-driven use of PrEP (TDF/FTC) versus placebo in MSM in France and Canada. The intermittent dosing involved taking two tablets 2-24 hours before sex and two further tablets after sex (24 and 48 hours after the first

dose). 414 participants were recruited to the pilot phase; the median age was 35 years and 90% were of white ethnicity. Adherence was assessed by self-report, hair and plasma drug levels. Self-reported adherence by 319 participants across 1212 sex acts was 43% (range 35% -51%) and the median number of pills used by the study population each month was 16 (IQR 10-23). The placebo arm of this study was halted, on recommendation from the Independent Drug Monitoring Committee after an interim review, due to high HIV incidence in the placebo arm (6.6 per 100 person years) and a high level of effectiveness observed in the group taking PrEP (86%; 95% CI 40-99%, $p=0.002$).

The US MSM Safety trial (Grohskopf et al., 2013), a phase 2 RCT involving 400 MSM with a median age of 36 years and 79.6% white ethnicity, randomised participants into immediate or delayed once daily TDF/FTC compared to placebo arms. None of those randomised to immediate TDF/FTC acquired HIV during the study period. Adherence was high (92% by pill count). Overall, there was a slight decrease in average number of sexual partners (from 7.25 to 5.71 after up to 24 months, $p<0.001$) and a reduction in the number of HIV positive partners and UAI during follow up. The most commonly reported adverse event (AE) was depression (4 on PrEP and 2 on placebo); there was no difference in grade 3 or 4 AEs between the two groups (adjusted RR 1.08 (95% CI: 0.57-2.03; $p=0.820$) and no K65R viral mutations in participants who seroconverted.

The recommendation is taken from the PROUD study findings (1+) undertaken on a UK population and the IPERGAY study findings (1+), both of which are considered to be directly applicable to the target population. Although both studies reported a small number of people in the active group who acquired HIV, the narratives suggest these five individuals were most likely exposed when not on PrEP.

Heterosexuals / serodiscordant/serodifferent populations:

Two RCTs (Baeten et al., 2012, Thigpen et al., 2012) achieved high medication adherence and provided good evidence of the clinical efficacy of daily oral PrEP in preventing HIV acquisition when given to heterosexual men and women at high risk of HIV (TDF2 in heterosexual men and women with mITT efficacy of 62.2% (15.9-82.6), and Partners PrEP in men and women in serodiscordant / serodifferent

partnerships, where TDF/FTC efficacy was 75% (55-87) and TDF efficacy was 67% (44-81)). The studies were large, well-conducted, and did not have excessive losses to follow-up. The findings are therefore likely to be valid.

Two RCTs (FEM-PrEP (Van Damme et al., 2012) and VOICE (Marrazzo et al., 2015)), both in heterosexual women, did not provide evidence leading to reliable conclusions about the efficacy of daily oral PrEP. Both studies were well-conducted and the null results (and inconsistency when compared to TDF-2 and Partners PrEP) are thought primarily attributable to low adherence to the study drug.

Overall, there was minimal evidence of safety concerns across all four trials (although less than 30% of participants took active drug in Fem-PrEP and VOICE); TDF and TDF/FTC appear safe to take orally on a daily dosing schedule with regular monitoring. Although small changes were observed in estimated glomerular filtration rate, bone and liver profiles, these were also seen in placebo recipients and there were no significant differences between the PrEP and placebo groups in adverse events other than early gastrointestinal symptoms in the studies. Abnormal laboratory results tended to revert to baseline after discontinuing the drug.

To date, there is no evidence that TDF alone or TDF/FTC compromise oral or injectable contraceptive efficacy and there is no evidence that these drugs are associated with abnormal pregnancy outcomes. Although these findings should be interpreted with caution due to small sample sizes in the HIV negative populations, the pregnancy outcome data gathered in HIV positive women taking these drugs as part of the antiretroviral therapy are reassuring.

In all studies, small numbers of people were found to be infected with HIV carrying resistance mutations, the acquisition of which may have been attributable to the selection pressure exerted by PrEP. Patients recently infected and testing negative at enrolment were identified as being at particular risk of acquiring virus with such mutations. These findings suggest national monitoring of HIV resistance must be sustained to support any intended PrEP programme in England.

TDF-2, Partners PrEP, Fem-PrEP and Voice were all conducted in Sub-Saharan Africa, which limits the extent to which findings can be generalised to England. This is not because of any differences in biological efficacy, but rather because the healthcare systems and access to them as well as HIV incidence are substantially different. The incidence of HIV in the control arms of these studies was 2.0 to 5.0 per 100py, which compares to an incidence of 0.17 per 100py in Black Africans attending specialist sexual health services in England.

People who inject drugs (PWID)

The one study among PWID that met all the inclusion criteria was the Bangkok Tenofovir Study (Choopanya et al., 2013). This double blinded placebo controlled RCT recruited 2,413 PWID who were HIV negative. This RCT study was graded as 1+ in which there are some concerns of bias. The mITT analysis found a 48.9% reduction in HIV incidence (95% CO 9.6-72.2; $p=0.01$) in the PrEP group. The study involved regular contact with participants, and a subset of the population received medication through Directly Observed Therapy (DOT), which may not be feasible to deliver in the real world and may have increased adherence (drug was taken a mean of 83.3% of days (SD 23.0, IQR 79.2-98.7)) with no difference by treatment group.

Although the study was well designed, the findings are not generalizable to the UK situation. The HIV prevalence among PWID in Thailand is much higher than in the UK, at around 20-30% (Dutta et al., 2013) compared to around 1% in England (Public Health England and National Infection Service, 2015). The incidence of HIV among PWID is also likely to be very much higher in Thailand. In Thailand, amphetamine type stimulants (ATS) are the predominant type of drug injected; in the UK it is brown heroin (Public Health England et al., 2014). The drug preparation and injecting practices associated with these two drugs are different. In particular, ATS are generally injected much more frequently than heroin, and the use of ATS has been associated with increased injecting and sexual risk behaviours (Fischer et al., 2013).

There is insufficient evidence to support routine commissioning for this sub

population.

Cost-effectiveness

The literature identified seven full-text publications, assessing the cost-effectiveness of PrEP in high income countries. Most of the papers looked at PrEP delivered to a target group of high-risk MSM, with Juusola *et al.* (Juusola et al., 2012) and Schneider *et al.* (Schneider et al., 2014) also evaluating the cost-effectiveness of PrEP given to MSM (without targeting specific higher risk subgroups); Kessler *et al.* (Kessler et al., 2014) included MSM, PWID and high-risk heterosexuals in their target population; and Ouellet *et al.* (Ouellet et al., 2015) looked at non-PWID MSM. The identified papers considered the MSM population in the US (Chen and Dowdy, 2014, Desai et al., 2008, Juusola et al., 2012, Kessler et al., 2014, Paltiel et al., 2009), Canada (Ouellet et al., 2015), and Australia (Schneider et al., 2014).

The level of PrEP efficacy used in base case estimates ranged from around 44% to 50%, although in sensitivity analyses additional levels of efficacy were considered (e.g. 92% (Chen and Dowdy, 2014); 10-90% (Paltiel et al., 2009)). Four of the publications were based on dynamic models (Desai et al., 2008, Juusola et al., 2012, Kessler et al., 2014, Schneider et al., 2014), two used a static model (Chen and Dowdy, 2014, Paltiel et al., 2009) and one used number needed to treat based on the iPrEx trial to estimate cost-effectiveness (Ouellet et al., 2015). These base-case efficacy estimates (44%-50%) were lower than the 86% reported in both the PROUD and IPERGAY trials.

In terms of PrEP regimen, all studies assumed a daily regimen although Ouellet *et al.* investigated the use of daily dosing for 'event-driven' risk, the most expensive scenario. All of the papers were thought to be of high/acceptable quality using the SIGN checklist (Appendix 2).

In the papers that evaluated PrEP targeted at MSM only, the incremental cost-effectiveness ratios (ICER) depended on assumptions about the target population: their age, HIV incidence, HIV prevalence, PrEP drug cost, level of condom use, adherence to PrEP or efficacy, rate of HIV diagnosis in the population and PrEP toxicity. Four of the papers (Chen and Dowdy, 2014, Juusola et al., 2012, Paltiel et

al., 2009, Schneider et al., 2014) found that the cost of PrEP had a large impact on the ICER. Desai *et al.* (Desai et al., 2008) noted that the ICER was inversely proportional to the cost of treating an HIV positive patient i.e. the ICER was higher if the cost of treatment was lower. They also found that PrEP coverage had important implications for the ICER, as low coverage (2.5% of the very high risk MSM population of New York city, N=1,500) had limited impact on the number of infections prevented, which would not provide sufficient justification for investing in a PrEP programme.

Juusola *et al.* (Juusola et al., 2012) highlighted the potential challenge of whether it would be realistic to offer PrEP by risk level, the potential challenge of identifying the target population, and questioned how policy could be implemented selectively to prioritise access to PrEP given the substantial budgetary implications.

Kessler *et al.* (Kessler et al., 2014) estimated the cost per infection averted of five different PrEP strategies: 1. high-risk HIV negative heterosexuals; 2. any susceptible MSM; 3. high-risk MSM only; 4. susceptible PWID only; 5. all at risk (any susceptible person from all the above categories). They did not find any scenario in which prioritising high-risk heterosexuals alone was cost-saving. However, they found that prioritising high-risk MSM could be cost-saving under certain assumptions. Further expansion of PrEP to high risk groups other than MSM would provide greater impact on the HIV epidemic but the associated costs might be prohibitive.

Two analyses (Cambiano et al., 2015, Ong et al., 2015) specific to the UK MSM context have been developed to estimate PrEP cost effectiveness and to explore the sensitivity of cost-effectiveness to changes in critical conditions. Both models assumed use of the daily dosing regimen used in PROUD. The abstract by Cambiano et al. (Cambiano et al., 2015) was based on a UK-based dynamic model. The authors concluded that daily PrEP use among MSM was cost-effective when targeted at MSM reporting five or more condomless sex partners in the last year, when presenting with a bacterial STI, or in men having condomless sex if the cost of antiretrovirals (for treatment and for use as PrEP) was reduced by 50% of the

current (2015) British National Formulary list price. The abstract by Ong et al. (Ong et al., 2015) used a static model to evaluate cost-effectiveness of daily PrEP offered to selected GUM clinic attendees in England for a one-year period compared to their life-time risk. The model suggested that PrEP is cost saving when delivered to MSM with HIV incidence of 5 per 100 person years, if PrEP effectiveness is at least 64%. In both analyses the period over which PrEP is cost effective and cost saving is most sensitive to the estimated HIV incidence in those eligible and to the price of ARVs.

The estimates of cost-effectiveness, budgetary impact, and public health impact of PrEP provision have included various sensitivity analyses, including the impact of use of the intermittent IPERGAY regimen, which has the potential to reduce the cost impact.

8 Proposed Criteria for Commissioning

Prescribing of ARVs for HIV pre-exposure prophylaxis

TDF/emtricitabine will be prescribed as an intermittent regimen for MSM, trans women and trans men clinically assessed as being at high risk of HIV acquisition. Based on clinical assessment of individual clinical need, a daily regimen may be indicated and this will need to be fully documented. Daily TDF/emtricitabine will be prescribed for heterosexuals clinically assessed as being at high risk of HIV acquisition.

Indications

PrEP (TDF/emtricitabine) prescribed as an intermittent regimen based on IPERGAY protocol dosing or daily regimen based on PROUD protocol dosing will be routinely commissioned following a documented and full sexual and clinical risk assessment by a suitably qualified healthcare professional in a level 3 GU service.

The following criteria should be applied to establish there is a high risk of HIV acquisition and eligibility for PrEP:

PrEP will be made available for persons who are:

1. MSM, trans women or trans men who are currently HIV negative and who are clinically assessed to be at high risk of HIV acquisition through fulfilling the following criteria:
 - a) Have a documented confirmed HIV negative test during an earlier episode of care in the preceding year (i.e. 42-365 days ago); and
 - b) Report condomless intercourse in the previous 3 months and this is documented in the clinical notes; and
 - c) Affirm their likelihood of repeated condomless intercourse in the next 3 months and this is documented in the clinical notes.

OR

2. The HIV negative partner (confirmed by a current documented negative HIV test) of a diagnosed person with HIV who is not known to be virally suppressed and with whom condomless intercourse is anticipated and so is clinically assessed and considered to be at high risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors treatment as part of an active risk reduction intervention including health education, safer sex promotion, and exploration of treatment as prevention for the HIV positive partner;

OR

3. HIV negative heterosexual men and women clinically assessed and known to have had condomless sex with a person with HIV (who is not known to be virally suppressed) within the past 3 months and for whom it is anticipated that this will occur again, either with the same person or another person with similar status, and so is clinically assessed and considered to be at high risk of HIV acquisition. PrEP should be recommended where the treating clinician recommends and monitors as part of an active risk reduction intervention including health education and safer sex promotion.

AND

- a) Where the treating clinician recommends and monitors PrEP as part of an active risk reduction intervention including health education and safer sex

promotion; AND

- b) Where the patient is and remains actively involved in the risk reduction intervention and is able to affirm their appropriate adherence to PrEP); AND
- c) The use and outcomes of the intervention is recorded via the agreed prior approval and monitoring systems.

Exclusions

- a) Individuals in monogamous relationships with a partner who is known to be diagnosed with HIV and whose viral load is undetectable.
- b) Individuals without a current confirmed negative HIV test result (to minimise the risk of patients with undiagnosed HIV starting PrEP and developing drug resistant virus)
- c) Individuals who do not or no longer meet the criteria for high risk of HIV acquisition
- d) Individuals whose only risk of HIV acquisition is due to injecting drug use (as the current HIV incidence in this group in the UK is too low for PrEP to be cost effective)
- e) People known to be diagnosed with HIV
- f) Individuals under 16 years of age
- g) Treatment outside of Level 3 GUM services

Starting and stopping criteria

PrEP will be started based on the following criteria

- a) Confirmation of eligibility
- b) Confirmed HIV negative using a rapid point of care test or based on negative serology (antigen and antibody) within the preceding 4 weeks (for MSM this is in addition to the HIV test 42-365 days ago – see Point 1a above)

PrEP will be stopped based on the following criteria

- a) Eligibility for PrEP is no longer met (individuals may re-start should criteria be met at a later stage)
- b) Person taking PrEP has confirmed HIV infection. In this scenario, the individual requires immediate referral to HIV care and treatment service.

Evidence of hypersensitivity or contraindications to the component drugs TDF or FTC (e.g. eGF R<50mLs/min and hepatitis B infection) should be taken into account in starting / stopping treatment.

Monitoring

Based on clinical assessment of individual clinical need, an intermittent (based on the IPERGAY study protocol) or a daily regimen (based on the PROUD study protocol) may be indicated and this will need to be fully documented. Daily TDF/emtricitabine will be prescribed for heterosexuals clinically assessed as being at high risk of HIV acquisition.

Recording in the clinical notes should demonstrate the role of PrEP as part of a risk reduction intervention and be available for audit.

9 Proposed Patient Pathway

Currently the pathway for sexual health services and HIV prevention services is open access and involves a wide range of NHS trust, GPs and other providers offering testing, treatment, health promotion and support.

The pathway for HIV prevention using antiretrovirals for those assessed as being at high recent risk of HIV acquisition is via A&E and / or GUM services. This is post exposure prophylaxis and is provided as an urgent intervention.

The proposed pathway for PrEP requires agreed Level 3 GUM clinics providing the intervention and to embed this as part of the risk reduction support package to those at high risk of sexual poor health and infection.

10 Proposed Governance Arrangements

Local Authority commissioners are responsible for commissioning sexual health services. NHS England has worked with local authorities to confirm the service model required. Approved Level 3 GUM service providers would undertake the following as part of sexual health services to high risk individuals:

- Identification of risk and assessment of need for PrEP in the risk

management strategy

- Prescribing and advising on the use of PrEP in accordance with policy and prior approval criteria
- Regular review of risk and the need for PrEP in the risk management strategy, HIV status, STI testing and treatment, and review of any drug toxicities
- Reporting for central monitoring and outcomes of PrEP

With regard to the quality, safety and appropriate use of antiretrovirals (the responsibility of NHS England), the following specification and governance would apply:

- Access to PrEP will be via approved named providers who will have access to a prior approval system which will be used to validate that patients meet the criteria for routine commissioning and to record outcome data on the intervention.
- All selected providers will need an agreed pathway for referral into HIV care and treatment for all patients who are tested as HIV positive before PrEP is initiated and in the event that PrEP fails to prevent HIV acquisition.
- All selected providers will need to ensure they are able to separately record and invoice for use of drug for PrEP.

11 Proposed Mechanism for Funding

NHS England commissions antiretroviral drugs for the treatment of HIV infection. NHS England will reimburse the cost of antiretroviral drugs used for PrEP at specified providers where the patient has been validated via a prior approval process and where data on outcomes is provided.

Local authorities are the commissioners of sexual health services and will fund the service costs associated with PrEP.

12 Proposed Audit Requirements

All selected providers delivering PrEP must submit

- Individual requests for prior approval (this does not need to delay treatment)

initiation or require additional attendances)

- Monitoring data via Public Health England surveillance systems
- STI data via GUMCAD and monitoring of impact of PrEP on STI rates

This policy should remain under regular review to take account of evidence

- To support the inclusion of other sub populations where there is sufficient clinical and cost effectiveness
- To amend the policy if the clinical and cost effectiveness is not realised.

13 Documents That Have Informed This Policy Proposition

BHIVA / BASHH PrEP position statement:

http://www.bhiva.org/documents/Publications/PreP_BHIVA_BASHH_Update_14_September15_Final.pdf

World Health Organisation guidelines

<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/>

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by December 2016).

END