NHS England

Evidence Review:

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

[October 2015]

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1 Acronyms & Definitions

ART – antiretroviral therapy

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

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

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

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

PWID – people who inject drugs

Serodiscordant / serodifferent Used to describe sexual partners with different HIV status.

STI – sexually transmitted infection

TDF – tenofovir disoproxil fumarate - a nucleoside reverse transcriptase inhibitor antiretroviral

Transgender: Refers to 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 born as a male but identifies themselves as a woman.

Trans man – a person who is born as a woman but identifies themselves as a man.

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

Viral load – refers to the activity of HIV in a bodily fluid (e.g. blood, semen).

2 Introduction

2.1 HIV epidemiology

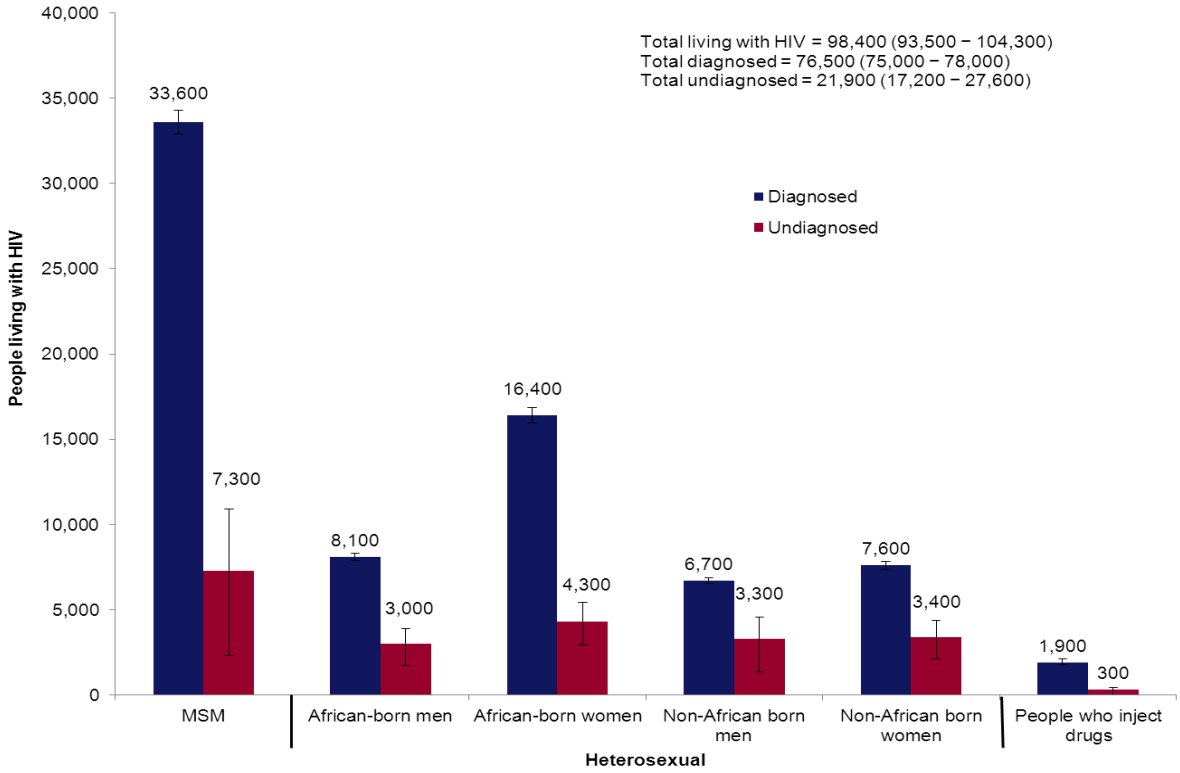
HIV is a disease of major importance in the UK. The life expectancy for those who are diagnosed in time and who have access to high quality care is equivalent to that of people who are HIV free. However, treatment is life long and the quality of life for people with HIV is frequently compromised making it a difficult and complex condition to live with. 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, transgender women (transwomen) and other men who have sex with men (MSM) are at the highest risk of acquiring HIV in the UK (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 a move towards earlier initiation of antiretroviral therapy (ART), which renders most patients non-infectious within six months (Brown et al., 2014, Wilson, 2012) Increasing evidence shows the positive impact of ART used by people living with HIV, in terms of prevention of onward transmission, to both the individual and to the wider population. Effective therapy lowers the amount and activity of the virus, making the person with HIV less infectious. Data from the START (strategic timing of antiretroviral treatment) (Insight Start Study Group et al., 2015) and TEMPRANO (Temprano ANRS Study Group et al., 2015) studies have confirmed the wider health benefits of early ART for reducing the risk of serious illnesses and other infections in people with HIV.

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), to prevent transmission to HIV negative partners as well as to treat HIV infection, has recently been approved in a separate clinical commissioning policy by NHS England (NHS England, 2015). An innovative and effective approach is the use of antiretroviral drugs before exposure, given to people who do not have HIV to prevent an established infection, referred to as pre-

exposure prophylaxis (PrEP). This review examines the available evidence for the clinical efficacy, clinical effectiveness, clinical safety and cost-effectiveness for the use of PrEP in HIV negative individuals.

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%).

Figure 1. Estimated number of people living with HIV (both diagnosed and undiagnosed): UK, 2012*



Source: PHE
*2012 figures used as these are relevant to the latest available from GUMCAD (see Tables 2 & 3). There are more recent (2013) figures available for numbers estimated to be living with HIV in the UK (Public Health England, 2014).

Among attendees at specialist sexual health clinics, which is likely to be the primary clinical service providing PrEP in any proposed national PrEP programme, the incidence of HIV among all MSM is nearly eightfold higher than the incidence in Black African heterosexuals (Table 1). This has significant implications for the likely cost-effectiveness of any programme (see below). Analyses of national surveillance data suggest that it is possible to identify sub-populations of MSM attending sexual health clinics with particularly high incidence, for example those who attended two or more times in the previous year, and those presenting for post-exposure HIV prophylaxis (Table 2). An important group of heterosexual individuals, who are likely to be in contact with sexual health services and in whom HIV incidence might be high, are the regular partners of people with newly diagnosed HIV.

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.

2.2 Pre-exposure prophylaxis (PrEP)

In the UK, Truvada (fixed dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)) has been licensed for the treatment of HIV-1 infection in adults (18 years and above) for more than a decade. It is not currently licensed for PrEP in the UK, although Gilead is planning to submit to the European Medicines Agency for a license for this indication. The components of Truvada are licensed for single agent use i.e. tenofovir 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 tenofovir or emtricitabine. The UK summary of product characteristics supports the use of Truvada as an option to treat HIV-1 infection in pregnant women.

The patent for Truvada expires in 2018 in the UK. The patent for emtricitabine (single agent) is set to expire in 2016 followed by the patent for tenofovir (single agent) in 2017. There is no guarantee that there will be generic versions of either of these drugs available on the UK market. It is highly likely, however, that there will be multiple generic suppliers for tenofovir and probably also for emtricitabine if there is sufficient demand.

Daily oral tenofovir or Truvada are used extensively in the UK as part of triple therapy in HIV infected populations and are generally very well tolerated although nausea, gastro-intestinal symptoms and headache are common in the first few weeks. Deterioration in renal function is a more serious, but rare, side effect of tenofovir 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 Truvada 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

provider concerns by the World Health Organisation in July 2014 when it recommended PrEP for use in MSM (World Health Organisation, 2014):

"Among men who have sex with men, ***pre-exposure prophylaxis (PrEP)*** *is recommended as an additional HIV prevention choice within a comprehensive HIV prevention package for PrEP"*

Two European studies, one in England (PROUD) and one in France and Canada (IPERGAY), were started in 2012 and reported in 2015. The studies recruited MSM and in both studies the comparator arm, without PrEP, had a much higher rate of HIV infection than expected (McCormack et al., 2015, Fonsart et al., 2014, Molina and et al, 2015). PROUD set out to assess the net benefit of efficacy and risk compensation in an open-label design in which MSM who knew they were taking PrEP were compared to MSM who did not have access to PrEP (McCormack et al., 2015). IPERGAY set out to assess an "on-demand" regimen that MSM took before and after sex, based on the rationale that lower drug exposure would have the advantage of less risk of toxicity as well as reduced cost. This was compared to placebo as there was uncertainty about the biological efficacy of an "on-demand" regimen (Fonsart et al., 2014).

Following on from reports of these two trials, the ECDC updated their statement in April 2015 as follows (European Centre for Disease Prevention and Control, 2015): *"on the basis of the new evidence, EU Member States should give consideration to integrating PrEP into their existing HIV prevention package for those most at-risk of HIV infection, starting with MSM. Issues related to larger-scale PrEP implementation, such as cost-effectiveness, appropriate models of care and access points, provider training, routine monitoring of patients, including adherence to treatment and regular testing for HIV and other sexually transmitted infections, will need to be assessed and carefully addressed in the context of each Member State's health system."*

2.3 Cost-effectiveness

Cost-effectiveness evaluations, mainly based on data from the USA, suggest that the use of PrEP among high-risk MSM can be cost-effective with significant budgetary impact. In the English setting, cost-effectiveness will need to consider local factors such as HIV incidence in the target group offered PrEP, patient adherence to taking PrEP, levels of condomless sex and numbers of sexual partners. In addition, considerations in published economic evaluations, such as the perspective taken (e.g. provider) and level of discount rates may differ from those used in England and will affect whether the incremental cost-effectiveness ratio (ICER) for PrEP falls within a defined threshold.

3 Research Questions

This systematic literature review has been undertaken to inform NHS England decision-making about integrating PrEP into the existing HIV prevention package for those most at risk of HIV infection in England.

The research question was: is oral PrEP clinically efficacious, clinically effective and what factors affect cost-effectiveness? The populations considered were:

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

4 Methodology

4.1 Clinical efficacy, effectiveness and safety for each risk population

A literature search was conducted using broad terms in order to capture as many papers as possible relating to clinical efficacy, effectiveness and safety. Those selected were then divided by risk group. The cost-effectiveness search was done separately and is also reported here.

Papers reporting intent-to treat analyses that were modified by exclusion of individuals who were found to be HIV positive at enrolment were included. This was not considered to have introduced bias, as this is standard practice in HIV prevention RCTs

Studies that changed following an interim analysis were considered to have some degree of bias, as were efficacy studies in which the majority of participants did not take the study drug.

4.2 Search strategy

Two electronic databases: PubMed and Embase were searched limiting the search to a ten year period from 15th October 2004 to 15th October 2014. References of all studies included in the review were searched for further relevant studies.

The intervention (I), comparator (C) and outcome (O) questions were the same for each population i.e. for each population of MSM/trans women, heterosexual men and women, serodiscordant/serodifferent couples and PWID they were:

I: Oral PrEP

C: Placebo or no-PrEP

O: HIV infection, adverse event, risk behaviours or risk compensation (condom use, number of sexual partners, STIs), adherence

The broad search terms used were:

HIV AND (pre-exposure prophylaxis OR preexposure prophylaxis OR PREP)

Full title screen was performed to remove obviously irrelevant articles. Shortlisted titles underwent full abstract review. Abstracts were grouped into population and subject groups: MSM, PWID, heterosexual, serodiscordant/serodifferent partnership, attitudes, uptake, cost-effectiveness and modelling. Transgender women were considered within the MSM population as they were eligible to take part in the same trials. Full papers were shortlisted using the eligibility criteria above.

4.3 Inclusion & exclusion criteria

To be included in the review, articles had to meet the following criteria:

1. Randomised control trial, non-randomised control trial, cohort study evaluating the use of oral PrEP to prevent HIV infection.
2. Measured one of the key outcomes: HIV infection, any adverse event, any stage 3 or 4 adverse event, condom use, number of sexual partners, STIs and adherence
3. Published in a peer-reviewed journal or presented as an abstract at a scientific conference between 15th October 2004 and 15th October 2014.

Only human and English language studies were included in the review.

Studies among people who "*use" rather than "inject"* drugs were not included as HIV risk and transmission differ in these groups.

4.4 Data extraction and management

Data were extracted using a standardized extraction form. The following information was gathered from each included study:

1. Study design and intervention details: design, summary of patient pathway, number of patients, inclusion/exclusion criteria, patient characteristics, intervention, comparator
2. Outcomes measures

3. Results: HIV incidence, adherence, factors associated with benefit, STI rate, reported risk behaviour

A separate extraction table was generated for clinical safety, which included details of grade 3 and 4 adverse events, resistance mutations, renal function, bone safety and any other safety events of note.

The literature search was updated for all risk populations as follows:

- MSM/trans women – the literature search was re-run from 1 January 2014 to 28 August 2015 using the search terms: HIV AND (pre-exposure prophylaxis OR preexposure prophylaxis OR PREP) and (men who have sex with men OR MSM OR transgender women OR trans women)
- Heterosexual & serodiscordant/serodifferent couples - The search was re-run using the same search strategy to include all papers up to 31 July 2015;
- PWID – the search was re-run using the same search strategy up to 31 July 2015.

Data presented at conferences (abstracts published) where these have not, at the time of this review, been published in the peer reviewed literature and where they provide useful information have been included.

The main evidence is tabulated in the Results section below and scored and graded using the Scottish Intercollegiate Guideline Network (SIGN) levels and grades of evidence (Tables A & B).

4.5 Cost-effectiveness

4.5.1 PrEP modelling and cost-effectiveness evidence review (updated July 2015)

A literature review of the evidence on cost-effectiveness of PrEP in high income countries with concentrated HIV epidemic was conducted. We attempt to answer the following questions:

1. Is PrEP cost-effective?

2. In what setting?

3. Under what assumptions?

4.5.2 Search strategy

PubMed, Embase, Ovid, Web of ScienceTM Core Collection, Current Contents Connect®, Derwent Innovations IndexSM, MEDLINE®, BIOSIS Citation IndexSM were searched limiting the search to between 15th October 2004 and 10th July 2015. We added a presentation made by Cambiano *et al.* at the BASHH conference in June 2015, and an abstract reporting the Public Health England cost-effectiveness model presented at Public Health England Annual Conference (September 2015) as the abstracts were not picked up by the searches.

The PICO questions were modified, where necessary, to be specific to cost-effectiveness considerations and are given below:

P: All HIV negative populations, regardless of risk group, living in a high income country with concentrated HIV epidemic

I: Oral PrEP

C: Placebo, no-PrEP, treatment as prevention (TasP), post-exposure prophylaxis (PEP), condoms, behavioural interventions

O: HIV incidence/prevalence over time, total and incremental costs, quality-adjusted-life-years (QALYs) gained or disability-adjusted life-years (DALYs) averted, incremental cost-effectiveness ratio (ICER)

The search terms used were:

HIV AND (pre-exposure prophylaxis OR preexposure prophylaxis OR PREP) AND (cost or cost-effectiveness or economic or economics or economic evaluations).

Full titles were screened to eliminate clearly irrelevant articles. Full abstract review was performed on shortlisted titles. Full-text papers were shortlisted using the eligibility criteria above. Data presented at conferences (abstracts available, but not published in peer reviewed journals at the time of this review) have been included.

4.5.3 Inclusion & exclusion criteria

To be included in the review, articles had to meet the following criteria:

1. PrEP cost-effectiveness/costing study
2. Evaluating the provision of PrEP in a high-income country with concentrated HIV epidemic
3. Published in a peer-reviewed journal or presented as an abstract at a scientific conference between 15th October 2004 and 10 July 2015.
4. Relating to humans and written in English.

4.5.4 Data extraction and management

The following information was selected from each included study:

1. Cost-effectiveness model design and intervention details: Study population & setting, study perspective; intervention used; comparator; modelling and statistical extrapolation; willingness-to-pay threshold; time horizon; discount rate; currency and year; cost estimates used (direct/productivity costs), short and long term costs considered, consideration of non-cash resource use; scenarios considered; sensitivity and uncertainty analysis
2. Outcome measure, analysis of effectiveness and measure of benefits
3. Results: Costs; estimated benefits; ICER; sensitivity and uncertainty analysis results
4. Comments: Conclusion from the paper, and comments from critical appraisal of the evidence

The evidence is tabulated in the Results section below and scored and graded using the Scottish Intercollegiate Guideline Network (SIGN) methodology checklist for economic evaluations (Appendix 2). Note that this is a different SIGN checklist compared with that used in the clinical: efficacy, effectiveness and safety section.

4.5.4.1 Table A: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–*	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance
2+	Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance
2–*	Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance
3	Non-analytical studies (eg case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence (–) should not be used as basis for making recommendations. *Source*: adapted from SIGN (2001).	

4.5.4.2 Table B: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence

Grades of recommendations
Grade 'A'   At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or***   A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
Grade 'B'   A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or***   Extrapolated evidence from studies rated as 1++ or 1+
Grade 'C'   A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or***   Extrapolated evidence from studies rated as 2++
Grade 'D'   Evidence level 3 or 4 ***or***   Extrapolated evidence from studies rated as 2+

Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001

5 Results

A total of 339 papers were identified in the original literature search (covering the time period 15 October 2004 to 15 October 2014) for all risk groups. The numbers of papers identified are given below, by risk group, and include those found in the updated literature searches.

5.1 MSM / trans women

The literature search was updated on 28 August 2015 and two conference abstracts reporting efficacy/effectiveness were identified one of which has subsequently been published online on 09 September 2015 (McCormack et al., 2015).

Across both searches, 9 full papers were reviewed for clinical efficacy, clinical effectiveness and safety of PrEP for MSM of which 6 were RCT, 5 with placebo-control, and 2 with no-PrEP controls.

Of these, the following are included in this review: one Phase 3, and two Phase 3 that reported in the pilot phase report efficacy and/or effectiveness (Grant et al., 2010, McCormack et al., 2015, Molina and et al, 2015) and two Phase 2 that reported safety (Grohskopf et al., 2013, Mutua et al., 2012). Three further papers related to the Phase 3 iPrEX study provided further details on adherence, risk behaviours, and association with drug levels and HSV acquisition (Liu et al., 2014, Marcus et al., 2013, Marcus et al., 2014); two further papers related to the US Safety trial cohort (Grohskopf et al., 2013) were included in the safety tables (Liu et al., 2011, Liu et al., 2013).

One cohort study, which was an open label extension of the Phase 3 RCT that reported efficacy was also included in the review (Grant et al., 2014).

5.2 Heterosexual / serodiscordant / serodifferent

Four full papers were reviewed for clinical efficacy and safety of PrEP for heterosexuals. Of these, two RCTs were included in the final review(Thigpen et al.,

2012, Van Damme et al., 2012); and two papers related to this trial providing further details on baseline characteristics, risk behaviours and adverse events (Headley et al., 2014, Kasonde et al., 2014a).

Of 339 abstracts reviewed, 10 full papers were reviewed for clinical efficacy, effectiveness and safety of PrEP for serodiscordant couples. Of these, there was one Phase 3 randomized control trial (Baeten et al., 2012). All other publications were subset- or pilot analyses of the same study(Celum et al., 2013, Celum et al., 2014, Curran et al., 2012, Curran et al., 2013, Kahle et al., 2012, Mugwanya et al., 2013, Mujugira et al., 2011, Murnane et al., 2013, Baeten et al., 2014a).

The search was re-run using the same search strategy to include all papers up to 31 July 2015. It identified 572 papers published since 15 October 2014, which after de-duplication and hand searching through titles was reduced to 56 unique and relevant papers. 12 papers and one conference abstract were added to the evidence review. One paper was a Phase 3 RCT previously reported as a conference abstract (Marrazzo et al., 2015), and all other publications were sub-analyses of studies already included (Baeten et al., 2014b, Baeten et al., 2014c, Chirwa et al., 2014, Grant et al., 2015, Kasonde et al., 2014a, Lehman et al., 2015, Mandala et al., 2014, Mugo et al., 2014a, Mugo et al., 2014b, Mugwanya et al., 2015, Murnane et al., 2014, Ndase et al., 2015).

5.3 PWID

Nine full papers were reviewed for clinical efficacy and safety of PrEP for PWID. Of these, one randomized placebo-controlled trial was included in final review (Choopanya et al., 2013); and four papers related to this trial providing further details on baseline characteristics, risk behaviours and adverse events (Choopanya et al., 2013, Martin et al., 2011, Martin et al., 2014a, Martin et al., 2014b).

The literature search was re-run using the same criteria on 30 July 2015 and identified two additional papers both of which related to the initial Choopanya *et al* RCT (Vanichseni et al., 2015, Martin et al., 2015).

5.4 Cost-effectiveness

Of the 1,402 titles reviewed, seven full-text papers (Chen and Dowdy, 2014, Desai et al., 2008, Juusola et al., 2012, Ouellet et al., 2015, Paltiel et al., 2009, Schneider et al., 2014, Kessler et al., 2014), five conference abstracts (Anderson and Cooper, 2009, Vaidya and Campbell, 2015, Drabo et al., 2015, Cambiano et al., 2015, Ong et al., 2015) and one correspondence (Koppenhaver et al., 2011) were included in the final review of cost-effectiveness and modelling of PrEP.

5.5 Tables summarising studies identified

5.5.1 Table 3: Clinical efficacy / effectiveness by risk group

Drugs have been reported using alternative names (brand or generic) in different papers. For ease of comprehension, they are as follows: Truvada (tenofovir / emtricitabine or TDF/FTC); tenofovir (TDF); emtricitabine (FTC).

Clinical efficacy / effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	MSM / trans women				
1+	PROUD Study design and pathway Randomised, open label, wait-listed design to immediate or deferred PrEP. No screening visit. 3 monthly visits from enrolment, with additional 1 month safety and adherence visit. HIV test at each quarterly visit, STI screen 3-6 monthly Design changed on13 October 2014 following recommendation of Steering Committee to offer all participants PrEP(163 of 269 still deferred at the time). Number of patients and their characteristics 544 (465 person years for effectiveness analysis) HIV negative MSM or transgender women reporting condomless anal intercourse in past 3 months and likely to do so again in the next 3 months, previously attended and had a HIV/STI screen. Exclude if Truvada contra-indicated, symptoms suspicious of seroconversion, or treatment for hepatitis B indicated. Countries: England (40% born outside UK); median age35 (IQR 29-43)81% white ethnicity Bacterial STI in previous 12 months 64%; rectal gonorrhoea or chlamydia previous 12 months 33%; PEP use in previous 12 months 34% Intervention Truvada - One tablet once a day Comparator No PrEP[1]	HIV incidence Adherence Safety Risk compensation	HIV incidence (90%CI): in the deferred group was 9.0/100pyrs (6.1-12.8) and in immediate group 1.2/100pyrs (0.4-2.9), which is an 86% reduction (64-96). The rate difference was 7.8 (4.3-11.3) suggesting13 (9-23) individuals from a similar population would need to be treated to avert one infection. The number of participants with incident HIV infections were: 20 in the placebo group and three in the immediate group (one acquired before PrEP started, one did not take the PrEP and one probably got infected after running out of PrEP) Adherence: 14 (5%) had no further prescriptions after the enrolment visit. Adherence was high according to prescription records with 88% of study days potentially covered by drug. Samples were collected from 52 participants who reported taking PrEP in the preceding 7 days and who attended one of 5 clinics able to process samples for pharmacokinetics. Drug was detected in all samples. Safety: 28 adverse events led to interruption of PrEP in 21 (8%) of participants. All bar one restarted PrEP. Risk compensation: there was wide variability in the total number of anal sex partners in the last 3 months reported at baseline and at month 12 (or when starting PrEP) and no significant difference between the groups in the latter. There was evidence of risk compensation in that a larger proportion of participants on PrEP than those not on PrEP reported 10 or more condomless anal sex partners at month 12 (21% compared to 12%; p=0.03 test for trend). 57% immediate and 50% deferred had a bacterial STI during follow-up, most commonly gonorrhoea and chlamydia; 36% immediate and 32% deferred had rectal gonorrhoea or chlamydia. After adjusting for the larger number of screens performed in immediate participants (4.2 versus 3.6), there was no difference in the proportion of participants with an individual STI or overall. There were 6 incidence hepatitis C infections (3 immediate, 3 deferred)	McCormack Lancet, 2015	Randomised open-label design in order to assess the net effect of biological efficacy and any change in behavior, by comparing PrEP to no-PrEP. Design changed after interim analysis because of the high rate of HIV in non-PrEP group and high level of effectiveness. HIV incidence 7-fold higher in those in the no-PrEP group compared to estimates from MSM attending sexual health clinics. Higher protection than reported in previous placebo-controlled trials, refuting concerns that effectiveness would be less in the real-world. No evidence of an increase in STIs in the PrEP group compared to the no-PrEP group, despite a suggestion of risk compensation amongst some PrEP recipients.

[1] Waitlist control group receives treatment at some later point. Advantage: for PrEP this design measures net effect of efficacy and risk compensation.

1+	IPERGAY Study design and pathway Randomised placebo-controlled design. Participants screened, and seen at months 0, 1, 2 then 2 monthly with HIV testing every visit, STI testing every 6 months or when indicated. Design changed on 23 October 2014 following recommendation of Data and Safety Monitoring Board recommendation Number of patients and their characteristics 414 HIV negative adult MSM and transgender women reporting condomless anal intercourse with 2 or more partners in past 6 months. Exclude if Truvada contra-indicated. Countries: France; median age 35, white ethnicity 90%. Baseline: bacterial STI 25%; PEP use 31%; median sex acts previous 4 weeks 10; median partners 2 months 8 Intervention Truvada On demand according to anticipated risk (2 pills 2-24 hours before sex, 1 pill 24 hours after the first dose and a second pill 48 hours after the first dose) Comparator Placebo	HIV incidence Adherence Safety Risk behaviours	HIV incidence in the placebo group was 6.6/100pyrs and in immediate group 0.94/100pyrs, which is an 86% reduction (95%CI 40-99; p=0.002). The rate difference was 5.66 suggesting 18 individuals from a similar population would need to be treated to avert one infection. The number of participants who acquired HIV while in the study was: 14 in the placebo group and two in the immediate group. Both of those in the immediate group were deemed to be a result of non-adherence to PrEP. Adherence: 14 (7%) had no further prescriptions after the enrolment visit. Median pills per month was 16 (IQR 10-23). Adherence in terms of correct use of PrEP per sex act was modest with only 43% of reported sex acts covered by a dose of Truvada before and after sex based on data collected in 319 participants on 1212 sex acts. No PrEP was used in 28% of sex acts In an earlier report (Fonsart 2014) based on 113 participants in whom: plasma samples were collected: TFV and FTC were detected in 86% (82-100% according to study visits) and 82% (75-100%) of pts in the TDF/FTC arm, and 4% (0-6%) and 3% (0-6%) in the placebo arm respectively. Safety: gastro-intestinal adverse events more common in Truvada group (13% vs 6%; p=0.013), as was mild elevation in serum creatinine (14% vs 7%; p=0.042) Risk: the number of partners, frequency of sex and condom use remained similar throughout follow-up in both groups. 276 STIs diagnosed in 141 (34%) participants during follow-up, most commonly gonorrhoea and chlamydia; there were no differences between the groups. There were 6 incidence hepatitis C infections (3 Truvada, 3 placebo)	Molina, CROI 2015 (Molina and et al) Fonsart IAS 2014	Placebo control needed in this randomised design as clinical pharmacologists not confident that the on-demand regimen would have biological efficacy, therefore risk behavior had to be the same in both groups (achieved by participants not knowing whether or not they are on active drug). Design changed after interim analysis because of the high rate of HIV in the placebo group, and the high level of effectiveness in the Truvada group. HIV incidence more than twice what the research team expected in the placebo group. Higher protection than reported in previous placebo-controlled trials, and this was in spite of modest adherence per sex act, suggesting that MSM tailored the on-demand regimen to periods of risk extremely well. Overall, drug used approximated to half that required to support a daily regimen.

1++	iPrEx Study design Phase 3 RCT HIV negative MSM or transgender women randomised to Truvada or placebo. Monthly HIV testing, adherence counselling, risk reduction counselling, condoms and STI testing (at baseline and 6 monthly, including HSV serologic testing). Number of patients and their characteristics 2499 (3324 person years of follow up) Countries: USA, Peru, Brazil, Ecuador, S Africa, Thailand Inclusion: born male, age >18, HIV negative, evidence for high risk of HIV infection. Mean age 27.5 (on PrEP vs 26.8 on placebo; p=0.04) Male MSM/trans 18% white ethnicity on PrEP Intervention Truvada One tablet once a day Daily dosing Comparator Placebo	HIV incidence Adherence- self reported and drug concentrations	HIV incidence: MITT reduction in HIV incidence in Truvada group 44% (95% CI 15-63%; p=0.005) MITT after adj for age reduction in HIV incidence in Truvada group 43% (95% CI 14-62) Adherence: Self-reported pill use: similar after week 8 (prior to this lower in Truvada group), mean 95%. Receptive UAI (efficacy 58%, 95% CI 32-74%) Detectable drug (efficacy 92%; 95% CI 40-99%, adj for RUAI efficacy 95%; 95% CI 70-99%) Decreases in condomless RAI associated with never had HIV test previously. Decrease in condomless RAI less likely among transgender, younger age, depression. No differences in STS/Gc rates No difference in HSV-2 seroincidence among Truvada vs placebo group (HR 1.1, 95% CI 0.8-1.5; p=0.64) or among those with high TDF concentrations vs placebo (HR 1.0, 95% CI 0.3-3.5; p=0.95)(Marcu 2014) Similar in both groups at all time points. Overall number of partners decreased (p<0.001), percentage using condom increased (p<0.001).	Grant NEJM 2010 Marcus PLoS One 2013 (risk compensation) Marcus PLoS One 2014 (HSV)	It scored highly on randomization method, concealment, blinding, outcome measurement and analysis. Of note, there was a relatively high loss to follow up (15%) and although triangulation of adherence measures included self-report, pill count and drug levels, MEMS cap monitoring could have been used. However, this was overall a high quality study conducted in a multi-centre multi-country setting with findings that are likely to be generalizable to an English population.

2+	iPReX OLE (Open Label Extension) Study design and pathways Cohort formed by offering PrEP to participants in iPrEX, US PrEP safety study and Project PrEPare. Drug levels were measured in quarterly samples collected from seroconvertors and a random selection of seronegative controls to estimate relative efficacy. Participants were screened then seen at weeks 0, 4, 8, 12 and every 12 weeks until week 72, tested for HIV at every visit when samples for drug detection were also collected; STIs were checked every 24 weeks or at interim visits if symptomatic. Number of patients and their characteristics 1603 HIV negative adult MSM and transgender women. Participated in one of three previous PrEP studies (described elsewhere in these tables). Countries: USA, Brazil, Peru, Ecuador, South Africa and Thailand; mean age 28 ; white ethnicity 17% Intervention Truvada One tablet once a day Comparator No PrEP historical placebo group)	Uptake Adherence HIV incidence Safety Risk compensation (numbers of partners, STIs)	Uptake: 76% took up the offer of PrEP; 39% of those with HIV risk at baseline had clinically significant PrEP use through to week 12. Adherence: drug detected in 71% (83% in USA). Higher adherence assoc with: - older age, higher education, receptive condomless AI, more sexual partners, history of syphilis or herpes HIV incidence: 1.8 per 100 py in PrEP group 2.6 per 100 py in no-PrEP group (HR 0.51, 95% CI 0.26-1.01, adj for sexual behaviours) 3.9 per 100 py in historical placebo group (HR 0.49, 95% CI 0.31-0.77) By drug detection: 4.7 per 100 py if no drug detected 2.3 per 100 py if drug concentration suggested <2 tab per week 0.6 per 100 py for 2-3 tab per week 0.0 per 100 py if >4 tab per week (p<0.0001) Safety: interruptions: due to participant preference (6.6%), side effects (3.7%), unrelated comorbidity (1.1%), relocation (2.4%), other (1.8%) Risk compensation: syphilis incidence similar between PrEP and no-PrEP groups (7.2 infections per 100 py vs 5.4 infections per 100 py, HR 1.35, 95% CI 0.83-2.19) Decrease among PrEP and no-PrEP recipients over course of study for self-reported total number sexual partners, receptive UAI, insertive UAI . No difference in decline between the 2 groups	Grant Lancet ID 2014	Open label cohort inviting iPrEx and other PrEP study participants to join. Drug levels measured every quarter and used the results in a case-control analysis of seroconvertors compared to seronegative controls by dividing follow-up time into estimated number of pills taken each week. Not randomized control so it is possible that those who were good at taking their pills were also at lower risk. However, there were no seroconversions seen when drug level was compatible with 4 or more pills a week. Uptake of PrEP was high including in those who were more often engaged in high risk sexual practices, who also had good adherence Very low proportion interrupted due to side-effects. Overall, retention was lower in younger men. Reported risk went down with time among PrEP and no-PrEP recipients. Syphilis rates similar between groups.

Level of Evidence	Study design & Intervention	Outcome measure(s)	Results	Reference	Comments
	HETEROSEXUALS				
1+	TDF-2 Study design Phase III double blinded placebo controlled RCT Number of patients and their characteristics Men and women at high risk of HIV; Median age 21-29 Male (54%) Female (46%) Heterosexual Botswanan N=1219 Inclusion: HIV negative, sexually active, age 18-29, normal biochem and haematological tests, negative for HbsAg, no chronic illness or long term medication use. Women willing to use contraception Exclusion: pregnant, breastfeeding Countries: Botswana Intervention Randomised to Truvada or placebo 1:1 ratio; Truvada 300mg Once a day. Confirmed HIV negative at screening using Determine and either Uni-Gold Recombigen or Oraquick tests. Monthly visits with HIV test (rapid test), pregnancy test, adherence check and counselling and condom distribution. At 3 monthly tests, biochemical and risk reduction counselling. At 6 monthly checks, examination, STI screen. Comparator: Placebo	HIV incidence Adherence Safety Risk behaviours (STIs, number of partners, condom use)	HIV incidence: 10 infections in Truvada group, 26 infections in placebo group. Incidence was 1.2 and 3.1 infections per 100py in TDF-FTC and placebo control group respectively. Efficacy 61.7% (95% CI 15.9 to 82.6; p=0.03) ITT analysis mITT (excluding baseline infections) efficacy 62.2% (95% CI 21.5 to 83.4; p=0.03). Equates to 1.2 and 3.1 infections per 100py PPA: efficacy 77.9% (95% CI 41.2 to 93.6; p=0.01) Protective in sub-group analyses by sex, but not significant due to very small numbers Adherence: Similar adherence in both groups by pill count (84.1% Truvada arm vs 83.7% placebo arm; p=0.79) and self report for preceeding 3 days (94.4% vs 94.1%; p=0.32). Significant difference in detected drug levels in seroconverters compared to matched controls (50% seroconverters vs 80% non-seroconverters) STIs: Ct and Gc rates similar in both groups (Ct 12.4% Truvada vs 12.3%Placebo; p=0.80) (Gc4.6% Truvada vs 3.0 Placebo; p=0.10) Reported risk behavior: Condom used with main or most recent casual sexual partner similar between the two groups (81.4% in Truvada arm vs 79.2% in placebo arm; p=0.66) and remained stable over time. Reported number of sexual partners declined similarly in both groups. None of the participants reporting anal sex (2.6% in Truvada group vs 2.5% in placebo group) seroconverted.	Thigpen NEJM 2012 Kasonde PLoS One 2014 (Bone)	Summary: Primary limitation was that a high proportion of participants did not complete the study per protocol, introducing an acceptable risk of bias. The study provides good evidence for the efficacy (62.2%) and safety of daily Truvada in heterosexuals. 8-10% loss to FU Study judged to have relatively high internal validity. Randomisation was well conducted, adequate concealment was used, subjects and investigators were blinded, relevant outcomes were measured and an intention to treat analysis was performed. However, study was concluded early because 33% did not complete the study per protocol and nearly 10% were permanently lost to follow up. For this reason, the study was downgraded to having an acceptable risk of bias. The study was underpowered to detect efficacy by gender subsets.

			There was no difference in grade 3 or 4 events between the 2 arms of the study (3.1% Truvada arm vs 4.8% placebo arm) 2 participants developed resistance (1 placebo and 1 Truvada arm). In 1 of the Truvada group with unrecognised wild-type infection at baseline developed K65R, M184V, A62V at high levels. 1 of the placebo group had K65R mutation at low levels after seroconversion. There was no difference in elevated creatinine levels between the 2 arms. There was no difference in bone fractures between 2 groups (7 in Truvada group, 6 in placebo group; p=0.74) In a sub-study of 220 participants (108 Truvada, 112 Placebo) who had DXA BMD measurements: 6.8% had low baseline BMD, associated with being underweight (p=0.02), high blood urea (p=0.02), high ALP (p=0.03), low CrCl (p=0.04). BMD loss at any anatomical site was higher in Truvada group (34/68: 50%) vs 26/79: 32.9% placebo; p=0.04. There was a small but significant difference in mean percentage change in BMD from baseline for Truvada group vs placebo at month 30 p=0.01 forearm p=0.0002 spine, p=0.003 hip (Kasonde et al., 2014b) The commonest adverse events were nausea, vomiting and diarrhoea which were more frequently reported in the Truvada group (nausea p<0.001, vomiting p=0.008, dizziness p=0.03). All lessened after a month		

Level of Evidence	Study design & Intervention	Outcome measure(s)	Results	Reference	Comments
1+	FEM-PrEP Study design Phase III double blinded placebo controlled RCT Number of patients and their characteristics N=2120 Mean age 24.2 Female Heterosexual African Countries: S Africa, Kenya, Tanzania Inclusion: Women aged 18-35, who had vaginal sex at least once in the past 2 weeks or more than one sexual partner in the past month. Exclusion: pregnant, breastfeeding, HbsAg pos, abnormal hepatic or renal function Intervention Women at high risk of HIV randomised to Truvada or placebo 1:1 ratio. Truvada, 300mg once a day Confirmed HIV negative at baseline. Monthly visits for up to 60 weeks (52 weeks on study drugs and 8 weeks after) received study drug, rapid HIV testing, pregnancy test, AE assessment, adherence and risk reduction counselling, free condoms. Less frequent hepatic and renal function. Comparator Placebo	HIV incidence Adherence Safety Sexual risk behavior (condom use, numbers of partners)	HIV incidence: 33 infections in Truvada arm (incidence 4.7 per 100 py) and 35 in placebo arm (incidence 5.0 per 100py). Efficacy HR 0.94 (95% CI 0.59 to 1.52; p=0.81) Adherence: Low adherence: less than 40% of HIV negative women in Truvada group had evidence of recent pill use in case control study matched to seroconverters STI rate: Baseline: 5.7% Gc, 14.0% Ct, 41.8% BV No between group difference at final visit for TV (3.5% in Truvada vs 5.8 in placebo, p=0.20), Gc (4.9% vs 3.2%, p=0.25), Ct (13.3% vs 12%; p=0.65). Note less than half underwent pelvic examination Reported risk behaviours: Baseline: 43% ≥1 sexual partner (Bondo) 12.5% (Pretoria), median number partners in past 7 days =1 (Bondo). 82% vaginal sex without condom with primary partner in past 4 weeks (Bondo) (64.5% Pretoria)- associated with being older, married, living with primary partner. 57% having sex with another partner in past 4 weeks did not always use a condom (Bondo), (27.9% Pretoria). 51% did not know primary partners HIV status (Bondo) 31% (Pretoria) (Headley PLoS One 2014) Baseline: 3.7 vaginal sex acts, 1.9 sex acts without condom, 1.0 sex partners in last 7 days. 12.6% exchanged sex for money/gifts with non-primary partner in past 4 weeks. 66% injectable contraceptive, higher oral contraceptive use in Truvada group vs placebo (32% vs 28.2%) No increased risk behaviour during trial. Small but significant reduction in number of partners (median decrease 0.14, p<0.001) and condomless sex (mean decrease 0.46, p<0.001) at last visit compared to baseline.	van Damme NEJM 2012 Headley PLoS One 2014 (baseline sexual risk) Mandala et al, BMC Pharmacol toxicol, 2014. (Mandala et al., 2014)	**Summary** For interpretation purposes, this study is limited by very low adherence to the study drug in the intervention arm. It provides no evidence for the clinical efficacy (HR = 0.94 (0.59-1.52) of daily Truvada as PrEP when given to heterosexual women in sub-Saharan Africa. Randomisation was well conducted, adequate concealment was used, subjects and investigators were blinded, relevant outcomes were measured and an intention to treat analysis was performed. Loss to follow up was 11-14% and the the study was downgraded to having an acceptable risk of bias. The study was stopped early due to high HIV incidence in the treatment arm. However, there was a large loss to follow up (11-14%) that meant that the study was downgraded to having an acceptable risk of bias. Furthermore, the study was stopped early due to high HIV incidence in the treatment arm so did not reach completion. Adherence was low

			There was no difference in grade 2 events between the study arms. Grade 4 events were not reported 5 participants had FTC-resistant HIV infections. 1 was in the placebo arm, 3 in the Truvada arm and 1 in the Truvada arm who had not been on study medication for a long period of time. All may have been infected at enrollment Rate of discontinuation because of renal or hepatic insufficiency was higher in the Truvada arm (p=0.051), but there was no difference in grade 1 or 2 creatinine between 2 arms Cumulative probability of creatininaemia1+ phosphateamia2+ were higher for truvada arm but not significantly (p=0.128 and p=0.621). Cumulative prob of AST and/or ALT toxicity 1+ at 4wk versus baseline higher for truvada arm (p=0.025 for both). 8 participants in truvada arm vs 8 in control arm developed grade3+ AST and/or ALT toxicity Elevated AST/ALT was observed more frequently among participants with previous exposure to HBV. Overall, study limited in assessing toxicity due to poor adherence, but did not find evidence of renal toxicity and did find some evidence of ALT/AST toxicity in treatment arm. The commonest adverse events were nausea, vomiting and raised ALT among the Truvada arm (p=0.04, p<0.001, p=0.03) More pregnancies among PrEP arm compared to placebo (11.2% versus 7.5%)		

1+	VOICE Randomised, phase IIb, double-blinded, placebo controlled trial with oral TDF, oral TDF/FTC, and vaginal TFV gel 5029 women enrolled in South Africa, Uganda, and Zimbabwe, with retention of 91% (median age 24y) <u>Inclusion</u> <u>HIV negative women aged 18-45y, not pregnant nor breast-feeding, but reporting recent vaginal sex, using effective contraception, and with normal renal, hepatic.</u> <u>Exclusion</u> HIV positive (33% of excluded), failure to complete screening and enrollment within 56d (21%), abnormal lab results, including HBV and abnormal smear (16%), pregnant, (5.9%). Intervention Daily oral TDF (300mg), oral TDF-FTC (300mg/200mg), vaginal 1% TFV gel Comparator: Placebo <u>Monthly HIV test, with study drug withheld if rapid HIV test positive, pregnant, breastfeeding, or clinical or lab adverse event.</u>	HIV incidence Adherence Safety	HIV incidence: Overall = 312 infections, incidence 5.7/100py Oral TDF = 52, incidence 6.3/100py (4.7-8.3), HR=1.49 (0.97-2.29) Oral TDF/FTC = 61, incidence 4.7 (3.6-6.1), HR=1.04(0.73-1.49) Vag TFV = 61, incidence 6.0 (4.6-7.6), HR=0.85(0.61-1.21) mITT effectiveness: Oral TDF = -49% (not sig) Oral TDF/FTC = -4.4% (not sig) Vag TFV = 14.5% (not sig) Adherence: Good self-reported adherence, but drug detection in plasma from a random subcohort (647) found drug in a mean of 25-30% of plasma samples. STI rate not provided after baseline Reported risk behaviours: Not provided after baseline Elevated serum creatinine in participants receiving TDF-FTC (1.3% vs 0.2%, p=0.0004), but no other differences were seen in adverse events One case of resistance (M184V) mutation was observed where participant was negative for HIV at baseline. Two cases of resistance (M184V) were observed in participants determined after enrollment to have been HIV infected at baseline.	Marrazzo et al, (Marrazzo et al., 2015)	**Summary** For interpretation purposes, this large study was limited by very low adherence to drug in the study arm. It provides no evidence of clinical efficacy for daily Truvada (HR 1.04 (0.73-1.49) or Tenofovir (HR 1.49 (0.97-2.29) when used as PrEP in heterosexual women in sub-Saharan Africa. Randomisation was well conducted, with adequate concealment and blinding. Study was very large, and retention was 91%. Analysis was a modified intention to treat analysis. The study was graded as having an acceptable risk of bias. The major problem with the study was in adherence (albeit that the participants self-reported high adherence). There were significant differences found between those using and not using the products (measured by serum drug level), and the likelihood of HIV exposure may also have differed. The groups receiving oral TDF and vaginal TFV were stopped early due to futility.
	<u>SERODISCORDANT / SERODIFFERENT</u>				

1+ (RCT Baeten, J *et al 2012, NEJM*)	Partners PrEP Double-blinded placebo controlled Phase 3 RCT, comparing single and dual agent ARV with placebo 4758 couples enrolled, 4747 couples followed All other studies referenced were pilots or sub-studies of the original RCT. <u>Inclusion</u> <u>HIV negative</u>: age 18-65 years, HIV negative on parallel rapid tests and screening and enrollment, sexually active (≥6 episodes vaginal intercourse with HIV pos partner in past 3 months), CrCl≥60ml/min, normal hepatic function (transaminases <2x ULN, bili≤1.5 x ULN), normal haematology (Hb> 11, Plt>125, neutrophils >1.3), no evidence of chronic active HBV infection (neg sAg test) <u>HIV pos</u>: age >18 years, sexually active, CD4≥250, no history of AIDS <u>Exclusion</u> <u>HIV neg:</u> pregnant or planning to be pregnant, breastfeeding, repeated ≥1+ urine dip for glycosuria or proteinuria, ongoing therapy with certain drugs, history of pathological bone fractures not related to trauma <u>HIV pos</u>: current use of ARV Median age 33 years; HIV positive partner male in 62% of couples; Median CD4 count among HIV positive partner495 (IQR 375-662) Heterosexual couples Ugandan or Kenyan Intervention: Oral daily tenofovir 300mg or Oral daily Truvada (300/200) Comparator: Placebo	HIV incidence HSV2 incidence Adherence Safety Risk behaviours (STIs, condom use)	HIV incidence: <u>Tenofovir vs Truvada vs placebo</u> HIV-1 prevention efficacy 67% TDF vs placebo (95% CI 44-81; p<0.001). 17 infections, incidence 0.65 per 100py in tenofovir group. HIV-1 prevention efficacy 75% for Truvada vs placebo (95% CI 55-87; p<0.001). 13 HIV infections, HIV incidence 0.5 per 100py in Truvada group. 52 infections in placebo group (HIV incidence 1.99 per 100 py) No significant difference between Truvada and tenofovir (p=0.23) at point where placebo stopped. No significant difference in protection by sex <u>Tenofovir vs Truvada</u> TDF HIV incidence 0.7 per 100 py Truvada HIV incidence 0.5 per 100 py No difference between HIV incidence in Truvada and tenofovir arms (HR 0.67, 95% CI 0.39-1.17; p=0.16) <u>Case control (seroconverters vs non-seroconverters)</u> Detectable drug level associated with 85% reduction in HIV incidence for tenofovir and 93% for Truvada (both p<0.001) Further study (Donnell et al) showed detectable drug associated with 88% protective effect for tenofovir and 91% for Truvada, higher drug concentration associated with older age, shorter time on study, and lower drug concentration more likely when participant reported no sex with HIV+ partner Adherence: Study medication in use 92.1% of total FU time (reported adherence and pill counts/dispensing records) Time off study medication due to pregnancy and breastfeeding accounted for 5.3% of follow-up time in women (2.0% among all participants) <u>Substudy using mobile phone adherence logs:</u> among 96 participants, 96.9% reported taking PrEP on ≥80% days, 69.8% missed at least one dose. No sex associated with missing PrEP dose (adj OR 1.87). (Curran AIDS Behav 2013)	Baeten 2014 Topics in Antiviral Med (CROI 2014 conference)- post IDMC update (Baeten et al., 2014a) Celum Ann Int Med 2014 (HSV) **Baeten NEJM 2012** Curran, K Int Assoc Physic AIDS Care 2012 (pilot SMS adherence) Kahle, E JAIS 2012 (substudy high risk groups) (Mugwanya et al., 2015) (risk behaviour pre and post unmasking) Mujugira PLoS One 2011 (baseline data) (Murnane et al., 2014) (Heffron et al., 2014) (Mugo et al., 2014b)	Summary This was a large multi-country RCT without serious methodological limitations. It provides evidence of clinical efficacy for daily Truvada (75% (55%-87%) or Tenofovir (67% (44%-81%) when used as PrEP in heterosexual men and women in sero-different couples in sub-Saharan Africa. It scored highly on randomization method, concealment, blinding, outcome measurement and analysis. However, the study was stopped by the IDMC in July 2011. Therefore, the placebo group was suspended earlier than anticipated, resulting in shorter comparison of the active arms compared to placebo arm than planned and may therefore overestimate treatment effects. Of note, adherence measure included pill count; MEMS cap monitoring could have been used. However, overall, the study was a multi-country RCT without serious methodological limitations Early closure of placebo arm due to evidence of protection from PrEP SMS pilot recruited participants who were highly educated and younger than the other Partners PrEP participants and majority received an income.

	Partners PrEP ctd.		STI rate: 5.8% any STI rate in tenofovir group, 4.3% in Truvada group, 4.8% in placebo group; no significant difference <u>Herpes Simplex Virus</u> (Celum 2014) HSV incidence 5.6/100py in Truvada/tenofovir groups and 7.7/100py in placebo group. HR for HSV-2 acquisition for PrEP overall 0.7 (95% CI 0.49 to 0.99; p=0.047), 0.76 for tenofovir and 0.64 for Truvada. Among HIV negative partners of HIV positive HSV-2 positive partners (i.e. known exposure to HSV-2), HR for PrEP was 0.67 (95% CI 0.46-0.98; p=0.038) Case-cohort analysis: detection of tenofovir was not associated with HSV-2 protection (HR 1.72 (95% CI 0.86 to 3.44; p=0.123) Reported risk behavior: <u>Condomless sex:</u> Baseline 27% partners reported condomless sex. Declined to 13% at 12 months and 9% at 24 months. Similar across study groups Post-unmasking: no change in reported frequency of unprotected sex comparing before unmasking (av freq unprotected sex with HIV pos study partner (59 per 100person months) compared to after unmasking (53 per 100person months); p=0.25. Significant increase in unprotected sex with outside partner after unblinding, but small effect size. No increase in incidence STIs comparing pre- and post-unmasking periods. <u>Outside partnerships</u>: 29.7% in tenofovir group, 29.9% in Truvada group, 29.1% in placebo group. No difference between study groups (Mugywana Lancet ID) Other: <u>Substudy of higher risk serodiscordant couples</u> (age of HIV-neg partner, number children, circumcision of male HIV neg partner, maried/cohabiting, self-reported unprotected sex, viral load in HIV pos partner): 22.9% of Partners PrEP cohort with highest risk. In highest risk subgroup, HIV incidence 5.0 per 100py in placebo group, 1.3/100 py (95% CI 0.5 to 2.8) among tenofovir group, 1.1/100py (95% CI 0.4 to 2.4) in Truvada group. In highest risk sub-group, estimated PrEP efficacy 72% tenofovir (95% CI 33 to 88%); p=0.02, and 78% for Truvada (95% CI 46 to 91%; p=0.006) (Murnane AIDS 2013)	(Mugwanya et al., 2015) (Ndase et al., 2015) (Lehman et al., 2015) (Baeten and Heffron, 2014) Baeten et al, CROI, 2015 (Baeten, 2015)	

	Partners PrEP ctd.		Murnane et al, AIDS, 2014: <u>Contraception</u> Women using no contraception had incidence of 15.4% per year. Women reporting oral contraceptive use had comparable pregnancy incidence to those using no contraception, and this was similar for truvada and placebo arms (17.5% versus 10.0% incidence per year; p=0.24) Women reporting injectable contraception had lower pregnancy incidence which was not different by arm (5.1% versus 5.3% per year; p=0.47) Noteworthy that PrEP adherence was high, while oral contraception adherence was apparently not Heffron et al, AIDS, 2014: <u>Contraception</u> Secondary analysis of using depot MPA for contraception at some point during follow up. PrEP efficacy estimates were similar among women using DMPA and those not using contraception, and did not differ for men whose HIV+ve partners used DMPA compared to those whose partners did not use contraception. Mugo et al, JAMA, 2014: <u>Pregnancy outcome</u> A total of 431 pregnancies occurred during the study. Pregnancy incidence did not differ between control arm (10.0 per 100py), TDF (11.9/100py) and TDF+FTC (8.8/100py). There were not statistically significant differences between intervention and control arm for pregnancy loss, preterm birth, congenital anomalies, or growth. However, tenofovir/Truvada were discontinued when birth was detected, and CIs were wide – meaning that definitive statements about the safety of these drugs in the perinatal period in HIV negative women cannot be made. Mugwanya et a, JAMA Int Med, 2015: <u>Renal function</u> Small relative decline was observed in eGFR for truvada arm versus control (-1.59mL/min/1.73m^2), and the decline appeared at 1m, was stable and then waned. The proportion of participants with confirmed 25% decline in eGFR from baseline to 12m and 24m was not different to control arm (1.3% and 1.8% versus 0.9% and 1.3%). Overall, a small nonprogressive change was seen in eGFR, which was not accompanied by increase in clinically relevant changes.		

	PWID / INJECTING DRUG USERS				
1+	The Bangkok Tenofovir Study Study design and pathway Double blind placebo controlled RCT 1:1 randomisation of PWID to tenofovir or placebo. Screening visit and the majority opted for daily DOT (able to switch in and out). Otherwiser monthly visits withpoint of care HIV test, risk reduction , counselling, condoms and methadone if part of reduction package. Safety bloods months 1,2,3 and quarterly, and HIV ELISA in addition quarterly Women asked to use contraception and all participants who required it offered HBV vaccination. Number of participants and characteristis N=2413 (9665 py follow-up) HIV negative men or non-pregnant, non-breast feeding women aged 20-60 who had injected drugs in the previous year and who had no significant laboratory or clinical abnormalities, contraindications to tenofovir or were hepatitis B surface antigen positive. Country: Thailand; mean age 32 (SD 8.4), male 80%, MSM 5% (tenofovir group 4%, placebo 6%) Injected drugs in the last 12 weeks 63%; shared needles 18%; sex with casual partner in last 12 weeks 38% (tenofovir group 36%, placebo 40%) Intervention: Tenofovir 300mg One tablet once a day Comparator: Placebo	HIV incidence Adherence Safety Risk behaviours	HIV incidence: 17/1204 in tenofovir group (incidence 0.35 per 100 py) vs 33/1209 in placebo group (0.68 per 100 py, indicating 48.9% reduction in HIV incidence (95% CI 9.6-72.2; p=0.01)by mITT (modified intention to treat) analysis and 51.8% reduction by ITT analysis Greater efficacy seen in females (78.6 per 100 py (95% CI 16.8 to 96.7); p=0.03, and in older age groups (88.9 per 100py in those aged >40 compared, 33.6 in those aged 20-29 Younger age (20-29 years) (HR 2.0, 95% CI 1.1-3.5; p=0.02), sharing needles (HR 9.6, 95% CI 1.0-3.5; p<0.001), incarceration in prison (HR 3.1, 95% CI 1.6-5.7; p=0.002) were associated with incident HIV infection. UAI with live in partner associated with lower HIV risk (HR 0.4, 95% CI 0.2-0.9; p=0.02). Adherence: reported adherence: drug taken mean 83.3% of days (SD 23.0, IQR 79.2-98.7) with no difference by treatment group (p=0.16) or time on study (p=0.22). DOT on 86.9% of days (SD 24.7) and adherence on DOT was 94.8% (IQR 80.3-98.8) and non-DOT 100% (91.6-100) Adherence better in older age (>40 years), women. Safety: nausea and vomiting more common in the tenofovir grouo (8% vs 5%) but this resolved by the second month of follow-up. Mild to moderate elevations in liver transaminases also more common in the tenofovir group (53% vs 49%). No tenofovir associated mutations observed. Risk Compensation: no differences between the groups, but a large reduction by 12 months follow-up in injecting drug use (63% to 23%) and sharing needles (18% to 2%); sex with >1 partner (22% enrollment to 6% month 72; 4.8% men reported sex with male partner in past 3 months at baseline, declined to 1% at month 72.	Choopanya Lancet 2013 Martin PLoS One 2011 Martin PLoS One 2014	First and only placebo controlled trial in PWID, using single agent tenofovir. Randomisation was well conducted, adequate concealment was used, subjects and investigators were blinded, relevant outcomes were measured and an intention to treat analysis was performed. However there was a relatively large loss to FU in both groups, introducing some bias. No difference between the groups for the first 3 years of follow-up. One possible explanation is that tenofovir had little impact on risk from injecting drug use, and the benefit from sexual risk only emerged after the injecting drug use risks had reduced considerably in the study population. Generalisability to a UK population is difficult as the injecting risk behaviours differ and we have needle-exchange programmes which have successfully contained the epidemic in PWID.

	PEOPLE WHO INJECT DRUGS contd		Martin AIDS 2015: Analysis of effectiveness according to reported adherence in RCT cohort. 9665 pyrs of follow-up in 2413 individuals followed for an average of 4 yrs (maximum 6.9 yrs). 628 (26.0%) were in daily directly observed therapy follow-up throughout, 1711 (70.9%) switched between daily and monthly visits, and 74 (3.1%) were in monthly follow-up throughout. Overall, 86.9% of days were DOT with 1534 (63.9%) of participants spending 95% or more time in DOT. Participants and staff signed the study diaries which were used to assess adherence (84.4% days in DOT and 88.9% in non-DOT). Adherence was better in older participants ($p<0.001$) and after controlling for age, in women ($p=0.04$). Factors associated with lower adherence included incarceration ($p=0.02$), injecting methamphetamine ($p=0.04$) and having a casual partner in the 3 months before enrolment ($p<0.001$). Effectiveness increased as adherence improved, from 48.9% overall to 83.5% reduction in HIV incidence in those with >97.5% adherence.	Martin AIDS 2015	The participants were allowed to switch from DOT to monthly throughout, although the majority of time was spent in DOT. DOT attendance was reimbursed and this would not be the case in practice, so adherence may be overestimated. There were relatively few HIV infections so confidence intervals were wide.

5.5.2 Table 4: Clinical safety results by risk group

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	MSM / TRANS WOMEN				
	US MSM Safety Trial Study design Phase 2 RCT. HIV negative MSM randomised to 1:1:1:1 immediate or delayed TDF or placebo. 3 monthly study visits with 1 month safety visit to month 24. Bloods, urine, STI testing, risk reduction and adherence counselling at each visit. MEMS cap and pill count, self report for adherence. Cohort sub-study (Lui 2011): DEXA scan of 200 participants at baseline, 9 months (deferred), 12 months (immediate) and 24 months Countries: USA Inclusion: HIV negative, UAI in past 12 months with man, CrCl≥70, Hep B sAg neg, normal haem/biochem/urinanalysis Exclusion: active untreated STS, uncontrolled HTN, mutual monogamy ≥1 year with HIV neg, CRF, osteoporosis, osteomalacia, osteopaenia, BMD Z score<-2.5, current treatment for low BMD, currnet ARV use, need for immunomodulatory therapy, GI malabsorption Number of patients and their characteristics N=373. Median age 36 years, Male, MSM; 79.6% white ethnicity Intervention Truvada 300mg, One tablet once a day, Daily dosing Comparator Placebo	Safety HIV incidence STIs Adherence Sexual behavior risk reduction	No difference in grade 3 or 4 AEs between the 2 groups (adj IRR 1.08 (95%CI 0.57 to 2.03); p=0.820) Commonest depression (4 on TDF, 2 on placebo) No K65R mutations among seroconverting participants No grade>3 elevation in creatinine and grade 1/2 not associated with use of TDF. Hypophosphataemia- no difference between the groups: grade 3 in 1 participant on TDF vs 4 on placebo (p=0.20), grade 4 in 1 placebo participant No association of bone fractures with TDF (Adj IRR 1.90 (95% CI 0.50 to 7.17); p=0.327 Longitudinal cohort sub-study (Liu 2011): TDF use resulted in a small significant decline in BMD at total hip (0.8% mean decline; p=0.003) and femoral neck (mean decline 1.1%; p=0.004) Small decrease in cholesterol in Truvada group at week 24 (total -9.2, HDL -3.6, non-HDL -5.4; p=0.03), but rebounded by week 72 (Mulligan 2014) HIV incidence: 7 seroconversions (4 placebo, 3 delayed, 0 TDF) Adherence: 92% pill use by pill count, 77% by MEMS Reported risk behavior: Number of partners Overall decrease in mean number of sex partners (7.25 at baseline to 6.02 at months 3-9, 5.71 at months 12-24; p<0.001) and no difference between immediate and delayed arms (p=0.67) or between pre- and post-drug in deferred arm (p=0.22). Decrease in number of HIV positive partners during follow up overall. Association with higher number of partners: poppers, sexual enhancing drugs e.g. sildenafil. Amphetamine use may be associated with greater number of partners (p=0.07)	Grohskopf JAIDS 2013 Liu et al PLoS One 2011 Liu JAIDS 2013 (behaviour)	Phase II safety study, not powered for efficacy, small numbers. SS was calculated to detect a difference in AEs of 5-6%, but no difference was seen. Very strict eligibility criteria, making generalisation of findings difficult.

			UAI No difference between immediate and deferred arms reporting UAI (p=0.41) and overall decrease seen from baseline to months 3-9 (p=0.001) and months 12-24 (p=0.03). UAI report with HIV + partner declined during study overall and no difference immediate vs deferred. Association with greater UAI: younger age, poppers, amphetamines, sexual enhancing drugs.		

1+	Kenya MSM/FSW (female sex worker) study <u>Study design</u> Phase 2 RCT. Blinded for placebo versus active treatment Exploratory study to assess safety, adherence and acceptability of intermittent PrEP MSM and FSW randomised to daily oral Truvada or placebo or intermittent (twice weekly plus post coital/2 hours after sex, not more than 1 pill per day) oral Truvada or placebo in 2:1:2:1 ratio. Monthly follow up for 4 months. Sexual activity data via daily SMS Country: Kenya two sites with very high HIV 1 prevalence: Nairobi and Kilifi Recruitment: October 19 and December 10 2009; follow up to May 2010 Inclusion: HIV negative MSM or FSW aged 18-49 yrs reporting at least one of current or previous STI, multiple episodes of UAI or UVI, engaging in transactional sex. Enrollment of women was limited in order to maintain a primarily MSM study Exclusion: Chronic HBV infection (sAg pos), CrCl<80 mL/min, pregnant or lactating mothers Women childbearing age needed to use non-barrier contraception (IUD or hormonal contraception) <u>Number of patients and their characteristics</u> 67 men and 5 women (women were only enrolled from Kilifi) Mean age 26-27 yrs Men and women MSM and FSW <u>Intervention</u> Truvada Daily: one tablet once a day. Comparator: placebo	Adherence to intermittent PrEP Safety Change in HIV associated risk behavior HIV-specific immune responses (IFN gamma ELISpot)	HIV incidence: 1 HIV infection in placebo group at week 16 Adherence: No difference in adherence between treatment and placebo groups. Median MEMS adherence 83% (IQR 63-92) for daily dosing, 55% (IQR 28-78) for fixed intermittent dosing; p=0.003. Adherence to any post-coital dose 26% (IQR 14-50). Reported risk behavior: Median number sex partners in past month increased from 3 (IQR 2-4) at baseline to 4 (IQR 2-8) at month 4 (? In all arms). Thought to be skewed by data from one site. 83% (60/72) willing to use pill regimen most or all of the time if shown to be safe and effective and inexpensive or free. No difference in acceptability between daily or intermittent groups (80% vs 86%) or between active and placebo arms (86% vs 80%). Proportion with moderate or above AE did not differ by regimen (daily 53%, intermittent 56%; p=1.00) or treatment group (active 60%, placebo 42%; p=0.14) No drug related SAE 1 seroconversion Mild creatinine elevations (1.1-1.3 x ULN) in 3 participants on Truvada, resolved spontaneously on stopping drug	Mutua PLoS One 2012	Small sample size, phase II safety, adherence, acceptability study. Therefore unable to evaluate efficacy. Short follow up time (4 months) Difficulties with SMS responses (problems with providers, outages) led to low rates of response using this method and requirement to use timeline followback self report data. This may have led to an overestimation of pill taking and sexual activity as median percentages for both went up to 100%. High alcohol use before sex (almost 50%), relatively high frequency of transactional sex and travel for it may have meant volunteers missed post coital doses. These factors together with the low proportion of women and African ethnicity limits its generalizability to the UK population.

	HETEROSEXUALS				
Use table 1 to establish level of evidence	FEM-PrEP TDF-2		See results in Table 3 (Clinical Effectiveness)	Thigpen NEJM 2012 Kasonde PLoS One 2014 (Bone) van Damme NEJM 2012 Headley PLoS One 2014 (baseline sexual risk)	
	SERODISCORDANT / SERODIFFERENT COUPLES				
1+	PARTNERS-PrEP Study design Double-blinded placebo controlled RCT, Phase 3 Number of patients and their characteristics 4758 couples enrolled, 4747 couples followed Median age range 25-34; HIV positive partner male in 62% of couples; Median CD4 count among HIV positive partner 495 (IQR 375-662) Heterosexual couples Ugandan or Kenyan Intervention: Oral daily tenofovir or Oral daily Truvada Comparator: Placebo	Adverse events among HIV negative partner	Adverse events: No difference in any grade 3 event of tenofovir vs placebo (p=0.35) or Truvada vs placebo (p=0.24) No difference in any grade 4 event of tenofovir vs placebo (p=0.64) or Truvada vs placebo (p=0.58) 8 of active arm infected with HIV at baseline; 2 developed ARV resistance: 1 in tenofovir group had K65R and 1 in Truvada group had M184V No M184V or K65R resistance among those infected after randomisation	Baeten NEJM 2012	As for PARTNERS PrEP in Table 3 (clinical effectiveness)

			Grade 2 or 3 elevated creatinine seen in <1% tenofovir group and <1% Truvada group. No difference compared to placebo (p=0.62 for both) Neutropaenia seen more commonly in Truvada group compared to Tenofovir and placbeo groups. Modestly increased reports of GI and fatigue in active arms compared to placebo.		
	INJECTING DRUG USERS / PWID				
1+ (Vanichseni Am J PH 2015)	**PEOPLE WHO INJECT DRUGS contd**	Safety	SAFETY Post-hoc analysis of CrCl showed small but significant decline in CrCl by Cockroft Gault calculation in tenofovir arm compared to placebo arm (p<0.0001), but resolved when drug stopped and remeasured median of 20 months later (Martin CID 2014). Analysis of causes of hospitalization and death in RCT cohort. 9786 pyrs of follow-up in 2413 individuals followed for an average of 4 yrs (maximum 6.9 yrs). All-cause mortality rate was 10.9 per 100 pyrs (95% CI 9-13.2) and standardised mortality rate was 2.9 (2.4-3.6), with commonest causes being drug overdose and traffic accidents. Increasing risk of death if aged 40-59 compared to 20-29 (HR 2.5; 95% CI 1.4, 4.3), injecting drugs (HR 2.4; 1.1, 5.4) and after controlling for injecting those using midazolam were more likely to die than those who did not (HR 3.6; 1.8, 7.1). Participants reporting sex with a live in partner were less likely to die (HR 0.6, 0.4, 1.0). No difference between those on tenofovoir compared to placebo as previously reported.	Martin CID 2014 (Renal function) Vanichseni et al Am J Pub Health 2015	The cohort was mainly HIV negative and untested for HCV, and a substantial morbidity and mortality comes from these two infections, so the mortality amongst PWID in Thailand is likely to be higher overall. Patterns of drug use in Bangkok and the prevalence of HIV and HCV amongst PWID differ considerably between Thailand and the UK.

5.5.3 Table 5: Cost-effectiveness

Cost-effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Conference abstract; not possible to ascertain how well the model/study was conducted	Study population & setting: Australian MSM; baseline HIV prevalence 9%, model allowed for changes in prevalence over time Study perspective: health sector, government as third party payer Intervention used: [1] continuous PrEP of tenofovir and emtricitabine; [2] intermittent PrEP Comparator: no PrEP Modelling and statistical extrapolation: dynamic, compartmental, Markov model Willingness-to-pay threshold: $50k/QALY Time horizon: 40 years Discount rate: 3% Currency and year: US$ (year not stated)	Cost per QALY gained	Costs: National PrEP program would cost $330m per year. Estimated benefits: If continuous PrEP was 90% effective and the program covered only HIV negative MSM having high risk sex, after 40 years prevalence of HIV would be 4.36% compared to 13.6% with no program; with intermittent PrEP, taken 50% of time, HIV prevalence would remain 9% ICER: Continuous PrEP would cost $47,745/QALY; Intermittent PrEP, taken 50% of time, would cost $6,816/QALY if 90% effective and remain cost-effective if > 46% effective sensitivity and uncertainty analysis results: Use of PrEP by MSM with low risk sexual behaviours and small increases in risk behaviour (2% per year) would render the intervention no longer cost-effective; threshold values for ICER<$50k/QALY: PrEP effectiveness >87%; baseline HIV prevalence >8%; cost of PrEP program $7536/year; cost of HIV management $13920/year; prevalence of resistance to PrEP <3%; serious adverse events <4%	Anderson & Cooper (2009)	Conclusion: PrEP could reduce HIV prevalence and be cost-effective in a country with a HIV epidemic in MSM, if it is more than 87% effective and coverage is targeted. Intermittent PrEP taken 50% of the time remained cost-effective as long as effectiveness was >46%. Adverse events, resistance and changes in risk behaviours would affect this finding. Budget impacts would be high and exploration of effectiveness of intermittent PrEP is warranted. Comment: Prevalence among MSM in the UK was estimated at 5.9% in 2013 and the effectiveness within the PROUD study, conducted among MSM in the UK, was estimate to be 86%.

Conference abstract; not possible to ascertain how well the model/study was conducted	Study population & setting: MSM in the UK Study perspective: health sector Intervention used: PrEP in five subgroups: [1] MSM who had had condomless anal sex in the last three months; [1a] assuming HIV testing rates in MSM remain at the current level and no change in condom use, [1b] assuming that the increased awareness and interest in PrEP leads to a substantial increase in HIV testing, in order to get PrEP, and that 25% of MSM starts using PrEP instead of condom. [2] MSM who had had condomless sex with at least one casual partner in the last three months; [3] MSM diagnosed with a bacterial sexually transmitted infection in the previous three months; [4] MSM who had had condomless sex with at least five casual partners in any three-month period during the last year. Comparator: no PrEP Modelling and statistical extrapolation: individual-based, stochastic, dynamic model Willingness-to-pay threshold: £20,000k/QALY Time horizon: 80 years Discount rate: 3% Currency and year: £ (2015) Costs estimates: For people on PrEP: HIV testing prior to initiation and every 3 months, visit for PrEP initiation, antiretroviral drugs used for PrEP, monitoring. For all MSM: HIV testing and post-exposure prophylaxis if used For HIV positive people: use of healthcare services in HIV+, antiretrovirals, CD4, VL and resistance test Outcome measures: cost per QALY gained (compared to a scenario of no PrEP)	Cost per QALY gained (compared to a scenario of no PrEP)	Costs: The cost of one year continuously on PrEP is assumed to be around £5,000 and one year on ART (if CD4>200 cells/mm^3) Estimated benefits: Over 80 years the introduction of PrEP would avert between 72% [option 1a] and 86% [1b and 2] of HIV infection and between 10% [option 1a] and 13% [option 1b, 2 and 3] of deaths compared to a scenario where PrEP is not introduced. ICER: assuming the cost of antiretroviral drugs [used for PrEP and ART] do not decreases, the cost per QALY gained [compared to the scenario in which PrEP is not introduced] is respectively: £9,500 [1a], £57,100[1b], £39,300 [2], £9,300 [3], cost-saving [4]. Sensitivity and uncertainty analysis results: If the drugs cost is reduced by 50%, after patent expiry date, then PrEP would become cost-saving as well in scenarios 1a and 3 and borderline cost-effective in 1b.	Cambiano et al. (2015)	Conclusion: The preliminary conclusion from this study is that the use of PREP among MSM will have a dramatic impact on the HIV epidemic. It suggests it is cost-effective when targeted to men reporting five condomless partner or more in the last year [3] or presenting with a bacterial STI [4], when offered to men having condomless sex but no increase in condomless sex or HIV testing occurs [1] or when the cost of antiretrovirals is reduced by 50%. Comment: This model has been previously published and used to evaluate the impact of increasing testing rates and expanding the treatment eligibility criteria for HIV positive patients.

High quality	Study population & setting: HIV negative, high risk MSM Study perspective: societal perspective Intervention used: PrEP for 1 year; PrEP efficacy considered: 44% or 92% but PrEP efficacy assumed to be highly dependent on adherence, thus, authors modelled PrEP at differing levels of adherence as per iPrEx subgroup analyses Comparator: no PrEP Modelling and statistical extrapolation: decision analysis model; assumed all sex acts present an independent risk of HIV acquisition; secondary transmission ignored; base case epidemiological parameters reflect generic US-wide estimates Willingness-to-pay threshold: not indicated Time horizon: 1-year duration of PrEP intervention costs and effectiveness but lifetime economic analysis time horizon Discount rate: 3% discount rate applied for costs occurring beyond 1 year in the future Currency and year: 2012 US$, adjusted using the Medical Care component of the consumer price index Scenarios considered: [1] base case (general MSM): 44% PrEP efficacy, 19% background HIV prevalence, 40% condom use, no behavioural disinhibition; [2] behavioural disinhibition (hypothetical scenario where PrEP use leads to riskier sexual behaviour: 15% decrease in condom use,15% increase in sexual encounters, and resulting 15% increase in STI prevalence among those taking PrEP); [3] High-adherence: 92% PrEP efficacy, reflective of iPrEx participants with detectable serum emtricitabine-tenofovirdisoproxil fumarate drug levels; [4] High-risk: 35% background HIV prevalence; [5] High-risk and high-adherence: 35% background HIV prevalence and 92% PrEP efficacy; [6] Monogamous, serodiscordant relationship with	Cost per QALY gained	ICER: [1] base case $160k/QALY (95% uncertainty range: cost saving to $740k); [2] behavioural disinhibition $320k/QALY ($45k to $1million); [3] higher adherence $3k/QALY (cost saving to $200k); [4] high baseline HIV prevalence $27k (cost saving to $160k); [5] high HIV prevalence and high adherence: cost saving (range cost saving to $10k/QALY); [6] monogamous serodiscordant relationships with partner ART use $280k ($14k to $670k); [7] 100% condom use $840k (range $230k to $2.5 million) sensitivity and uncertainty analysis results: • at low adherence and high behavioural disinhibition, PrEP was harmful, leading to an increased risk of HIV acquisition; • in populations where PrEP adherence was low, ICER exceeded $100k/QALY for all scenarios except those with high HIV prevalence of at least 35% and low behavioural disinhibition (less than 10% change in sexual risk); • cost per QALY was more than $100k at 44% PrEP efficacy and HIV prevalence below 25%; • at expected adherence (44% PrEP efficacy), ICER was highly dependent on degree of behavioural disinhibition; behavioural disinhibition had little impact on cost-effectiveness when PrEP was taken at high adherence; • at high adherence, PrEP becomes cost saving at HIV prevalence above 21%; • other parameters with high impact on ICER were baseline risk of HIV acquisition per sex act, QALYs gained per case of HIV averted and annual PrEP cost (reducing PrEP cost by 50% in base case to below $4772, PrEP becomes cost-saving)	Chen & Dowdy (2014)	Conclusion: cost-effectiveness of PrEP highly dependent on condom use, HIV prevalence, PrEP adherence and degree of behavioural disinhibition. Comment: This study focuses on a group with a 19% HIV prevalence, substantially higher than among the all MSM in the UK. HIV incidence was not reported. In addition, the cascade of care for people living with HIV in the US is different from the UK. Given the PROUD results, the closest scenario, in terms of efficacy, is the one with 92% efficacy.

	partner ART use: 100% background HIV prevalence, 100% prevalence of partner ART use; [7] High condom use: 100% background condom use Sensitivity and uncertainty analysis: one-way sensitivity analysis and PSA performed, with three-way sensitivitiy analysis on 3 key model parameters (HIV p revalence, behavioural disinhibition and PrEP adherence/efficacy) Economic parameters: • annual cost of PrEP $10,331 (range 4,772-15,000); • lifetime cost per HIV patient, discounted $305,521 (range 150,000-500,000); • average cost per case of STI treated (men) $197 (range 99-295); • average cost per STI test $58 (range 27-80); • QALY gained per case of HIV averted, discounted 2.24 (1.07-3.2); • QALY lost per additional STI 0.02 (0.01-0.03) Epidemiological parameters: • Probability of HIV acquisition per sex act with HIV+ partner 0.0082 (0.004-0.14); • HIV prevalence in MSM aged 13-64 0.19 (0.05-0.4)				

High quality	Study population & setting: high-risk HIV- MSM (defined as those who in the past 6 months reported unprotected sex with an HIV-infected person, unprotected sex in exchange for money or drugs, anonymous sex, >=5 sexual or needle-sharing partners or were diagnosed with a STI; thought to be 30% of the general MSM population) in a large US metropolitan area (using published epidemiological and survey data from New York City (NYC)); HIV prevalence 14.6% (90% CI: 8.1-18.4%) Study perspective: US healthcare system and includes costs of PrEP programme and savings in HIV/AIDS care Intervention used: once-daily, self-administered oral PrEP Comparator: no PrEP Modelling and statistical extrapolation: epidemiological projections derived from dynamic mathematical modelling (compartmental model simulating HIV infection acquisition and progression and effects of HIV/AIDS care on survival and HIV transmission); all simulations modelled participation of either 1500 or 15000 individuals, corresponding to 2.5% and 25% coverage of high-risk MSM of NYC (15,000 high-risk MSM covering 5% of entire susceptible MSM in NYC); assumed an annual dropout rate of 40% equal to the recruitment rate, keeping the total enrollment of high-risk MSM constant; Willingness-to-pay threshold: $50k/QALY and $100k/QALY Time horizon: all simulated interventions began in 2008 and continued until 2013 (6 years) Discount rate: costs and QALYs were discounted at 3% Currency and year: US $ year 2007 Base case: 50% PrEP efficacy, 15,000 coverage, 50% adherence Scenarios considered: 36 hypothetical scenarios	Cost per QALY gained	Costs: if PrEP cost US$11,315/year, present value of a 5-year program for 15,000 MSM is $900 million, present value of HIV/AIDS costs avoided is $546 million, i.e. incremental costs of PrEP are $354 million Estimated benefits: the epidemiological model predicted 3,880 new HIV infections in 2008 = 1.35% annual HIV incidence (90% CI: 0.92-1.87%); PrEP prevented 0.3 to 23.1% of HIV cases over a broad range of programmatic assumptions; in the base case, indirectly prevented HIV cases represent 59% of all HIV cases prevented ICER: • base case (50% adherence, 50% efficacy) ICER $31,972/QALY, daily threshold price above which program ICER>$50k/QALY is $39; • cost-saving at 70% efficacy, 95% adherence, and the threshold price was $92; • if efficacy was 50%, adherence 33%, ICER was $81,699, threshold PrEP price was $23; • ICER is higher if the cost of HIV care is lower and lower if HIV care cost is higher; • lower adherence increases ICER; • across all assumptions and 90% CI for cases prevented (as predicted by the epidemiological model), PrEP was cost-effective 75% of the time at a threshold of $50k/QALY and 87.5% of the time at threshold of $100k/QALY sensitivity and uncertainty analysis results: • uncertainty in no. of sexual partners and epidemiological parameters imply that the expected no. of cases of HIV infections prevented will vary by +/- 1300 cases, and when coverage is 2.5%, the expected no. of HIV+ prevented in <1300, so there is a possibility of no population-wide benefit from PrEP;	Desai (2008)	Conclusion: authors found PrEP coverage important to the results, that when 2.5% of high-risk MSM were enrolled, PrEP did not prevent enough HIV cases to justify the intervention but when coverage increase to 25% of high-risk MSM, this led to 4-23% reductions in HIV infections (dependent on assumptions about efficacy, mechanism of protection and coverage); assumptions about lifetime HIV treatment costs generally did not affect whether the ICERs were within threshold; if there was a 4.1% increase in sexual partners among those on PrEP and not on PrEP in the base case scenario, it is sufficient to fully offset the no. of infections prevented Comment: substantial herd protection projected by the model. Maximum effectiveness assumed was 70%.

	considered, including different combinations of mechanisms of protection, efficacy, adherence (65, 50 or 33%) and population coverage; 3 mechanisms of PrEP protection: [1] efficacy 50 or 70%, partial individual adherence confers 0% efficacy; [2] efficacy 50 or 70%, partial individual adherence confers reduced efficacy of 30 or 50%; [3] complete individual adherence confers 50 or 70% efficacy at moderate levels of HIV exposure and 30 or 50% at high and sustained level of exposure e.g. multiple unprotected sexual or needle-sharing encounters with HIV+ partner in primary phase of infection, commercial sex workers in high prevalence areas or persons engaging in high-risk behaviour with multiple, high-risk partners Sensitivity and uncertainty analysis: lifetime treatment costs adjusted by 30%; for economic analysis, ICERs and daily PrEP threshold prices were estimated for all combinations of program parameters and 3 estimates of lifetime treatment costs, as well as for the low and high limits of the 90% CI around expected no. of cases prevented; supplementary analysis looked at 10-90% variations in PrEP efficacy and population-wide increase of 0-20% in annual no. of sexual partners as a consequence of introducing PrEP. Costs estimates: tenofovir/emtricitabine 2007 US average wholesale price from producer US$11,315/year; average 5-year per-participant program cost US$ 5,370 (discounted at 3%); assumed that all participants incurred these costs, regardless of actual adherence; average 5-year combined cost for drug and support services was US$ 58,700 per participant; base case HIV-related lifetime treatment cost US$343,130 Outcome measures: base case HIV-related lifetime QALYs loss 6.95		population-wide increase in annual no. of new sexual partners following PrEP will counterbalance any expected benefit of PrEP (e.g. if PrEP efficacy is 50%, 4.1% increase in annual no. of new sexual partners will offset the 1710 new cases of HIV+, which would otherwise be expected)		

Conference abstract; not possible to ascertain how well the model/study was conducted	Study population & setting: MSM aged 15-65 in Los Angeles County Study perspective: societal perspective Intervention used: expanded HIV testing and initiation of treatment at CD4≤500, expanded HIV testing and initiation of treatment at diagnosis (test-and-treat); PrEP; Comparator: status quo policy ((current HIV testing with antiretroviral therapy [ART] initiation at CD4 ≤ 500) Modelling and statistical extrapolation: "mathematical epidemiological model" that simulates HIV incidence among 15-65 year old MSMs Willingness-to-pay threshold: $27,500 Time horizon: not stated cost and effectiveness time horizon: not stated Discount rate: not stated Currency and year: not stated Scenarios considered: 624 variants of the testing, test-and-treat and PrEP strategies considered (no further details provided) Sensitivity and uncertainty analysis: Uncertainty analysis were conducted on the HIV epidemic, cost and effectiveness. They did not list all the sensitivity analyses performed, but they included: PrEP adherence, ART adherence and initiation rates.	Cost per QALY gained	ICERs relative to status quo: test-and-treat: $21,000 / QALY gained; PrEP: $26,000 / QALY gained; Testing: $27,500 / QALY gained Sensitivity and uncertainty analysis results: Findings generally robust to uncertainty in the epidemic, cost, and effectiveness parameters. The relative effectiveness of PrEP was sensitive to PrEP and ART adherence and initiation rates.	Drabo (2015)	Conclusion: PrEP and interventions involving an increase in HIV test and earlier initiation of treatment are cost-effective alternatives to the status-quo for HIV prevention in Los Angeles County MSM. When affordable, aggressive combinations of these strategies should be implemented. The effectiveness of these strategies could be enhanced with greater adherence to ART and PrEP Comment: Conference abstract. Not clear the type of model that has been used, the time horizon and the discount rate, population size and incidence.

High quality	Study population & setting: MSM aged 13-64 in the US; 20% assumed high risk, defined as average 5 annual partners, initial HIV prevalence 20%, initial annual incidence 2.3%; initial HIV prevalence: 12.3%, annual incidence 0.8% (average in US); average duration of asymptomatic HIV 7 years (range 6-10 years); annual no. of male partners 3; condom usage with male partners 40%; reduction in sexual infectivity due to ART 90% (range 50-99%) Study perspective: societal Intervention used: PrEP for [1] general MSM population; [2] high-risk MSM; 44% PrEP efficacy Comparator: no PrEP (status quo) Modelling and statistical extrapolation: deterministic dynamic compartmental model of HIV transmission and progression combined with economic analysis Willingness-to-pay threshold: not stated Time horizon: PrEP strategies over 20-year time horizon/until aging out of model (20 years on PrEP) Discount rate: costs and QALYs discounted at 3% per annum Currency and year: US $ 2010 Scenarios considered: [1] PrEP for general MSM [2] PrEP for high-risk MSM; coverage 20%, 50% and 100% Sensitivity and uncertainty analysis: considered earlier start of cART (CD4+>350); varied PrEP efficacy to account for different adherence; examined impact of changes in no. of sexual partners and condom use as a result of PrEP; decreased quality of life while on PrEP to account for minor side-effects e.g. nausea Costs estimates: • Cost of PrEP (tenofovir/emtricitabine) $776 oer 30 tablets plus STI tests $54 plus blood urea nitrogen and serum creatinine testing	Cost per QALY gained	Costs: 20% all MSM over 20 years $95 billion ($98 billion PrEP, average $4.9 billion per year, minus $3 billion savings in HIV care): $2 million per HIV infection prevented; if 100% MSM on PrEP for 20 years, total cost $480 billion; high risk MSM only: PrEP for all high-risk MSM for 20 years cost $75.5 billion in total (PrEP drug and monitoring cost $85.2 billion, average $4.3 billion per year, HIV+ averted savings $10 billion) and $600k/HIV infection prevented; if only 20% of high-risk MSM start PrEP, cost over 20 years $16.6 billion, average $828 million per year, $460k/infection averted Estimated benefits: if 20% MSM on PrEP, 10% reduction in HIV+ in first year but by 20 years, 17% reduced HIV incidence, if 50% MSM, incidence reduction by 24% (year 1), 37% (year 20), if 100% MSM, incidence reduction by 45% (year 1), 60% (year 20) ICER: [1] PrEP to 20% MSM, ICER $172k/QALY compared to no PrEP; [2] giving PrEP to 50% of MSM, ICER: $188k/QALY compared to no PrEP; $216.5k/QALY for 100% MSM coverage compared to no PrEP and $254k/QALY compared to 50% coverage; [3] PrEP in high-risk MSM only: $52.4k/QALY compared to no PrEP; if only 20% high-risk MSM then ICER $40k/QALY, if 50% high-risk MSM then $44.6k/QALY, both compared to no PrEP sensitivity and uncertainty analysis results: • PrEP cost and efficacy considerably affected ICER: PrEP use in 20% all MSM has an ICER <$100k/QALY if daily PrEP cost <$15 or if PrEP efficacy>75%, PrEP in high-risk MSM only, daily cost <$30 will still give ICER<$100k/QALY; • effectiveness and ICER not substantially impacted by moderate changes in no. of sexual partners or condom use (accounting for the effect of behavioural disinhibition); starting ART at CD4+ 500 did not qualitatively change effectiveness and ICER	Juusola (2012)	Conclusion: PrEP is costly but if targeted use in high-risk MSM, will be more economically efficient (ICER 20% all MSM $172k/QALY compared to all high-risk MSM (estimated 20% of all MSM) ICER $50k/QALY) (diminishing returns); although PrEP provides good value, it has large budgetary impact, thus affordability is questionable.. Authors highlight importance of identifying high-risk MSM, and suggested questions such as number of sexual partners and consistency of condom use, as these are two key drivers of risk of HIV acquisition.

	\$23 plus physician visit \$100); cost of HIV testing with antibody test: [1] uninfected \$13 [2] infected \$66; pre-test counselling \$13; post-test counselling HIV- \$7; post-test linkage/counselling HIV+ \$14; cost of HIV diagnosis \$491 • HIV-related care costs per year: [1] acute HIV \$30 [2] untreated asymptomatic HIV \$4130 [3] untreated symptomatic HIV \$6934 [4] symptomatic HIV treated with ART \$6181 [5] untreated AIDS \$21863 [6] AIDS treated with ART \$9950; annual non-HIV-related healthcare costs for uninfected and infected individuals? \$4061; annual cost of ART \$15589 Quality of life values: [1] HIV-, no PrEP 1 [2] HIV-, PrEP 1 [3] acute HIV, undiagnosed 0.92 [4] diagnosed acute HIV 0.86 [5] symptomatic diagnosed HIV 0.72 [6] symptomatic diagnosed HIV and on ART 0.83 [7] age-specific multiplier 0.96		Limitations: sexual mixing between low- and high-risk MSM not modelled		
High quality	Study population & setting: MSM, people who inject drugs and high risk heterosexuals in New York City (NYC) Study perspective: health care payer perspective Intervention used: Several independent pre-exposure prophylaxis prioritization strategies (PPS) were considered and compared with no Prep and a scenario where PrEP was available for all HIV negative persons for whom PrEP might be considered a prevention option: 1) High risk heterosexuals 2) any susceptible MSM 3) High risk MSM 4)people who inject drugs 5)all at risk (any susceptible person from all the above categories). Simulations conducted of every mutually exclusive combination of the PPS (n=12). Identification of combination of PPS delivering the greatest health	Incremental cost-per-infection averted	Costs: Cost per infection averted under best case scenario is \$11 million. Total estimated budgetary cost is \$7500 million annually. Hypothetical condition of PrEP available for all susceptible (i.e. entire HIV negative population of NYC), Cost per infection averted >\$54 million. Total estimated budgetary cost for implementation of PrEP throughout entire population is \$52 000 million annually. Sensitivity and uncertainty analysis results: • Operating characteristics of PreP implementation, including uptake, effectiveness and cost, had profound impact on the value of PrEP, as measured by cost-per-infection averted (>75% difference in cost-per-infection averted) across all PPS;	Kessler (2014)	Conclusion: PrEP implementation among high-risk MSM could have a significant impact on the HIV epidemic. Prioritisation to high risk MSM could achieve cost savings under set(s) assumptions regarding effectiveness and cost that are potentially achievable. Further expansion would provide greater impact, but attendant costs may be prohibitive. Comment: Outcomes not presented as QALYs averted. Assumed PrEP efficacy of 44%.

	benefit with a budget scenario by calculating ICER of all possible combinations of strategies. PrEP efficacy: 44%. Comparator: no PrEP Modelling and statistical extrapolation: Mathematical model integrating equilibrium results from a Monte Carlo simulation of HIV progression with a deterministic compartmental model of HIV transmission. Uptake was assumed to be 50% under initial assumptions. PrEP was assumed to be immediate and continued for the entirety of the simulation time horizon (20 years) Willingness-to-pay threshold: Threshold of $360 000 per infection averted was selected as cost-saving. A cost-per-infection averted ratio between $0.36 million and $1 million was considered as likely cost-saving Time horizon: 20 years Discount rate: costs and benefits not discounted Currency and year: 2012 US dollars Scenarios considered: Base case scenario (no PrEP available from 2010) vs best case (all at risk susceptible individuals able to use PrEP). Other scenarios where PrEP implemented among different groups (high risk heterosexual, MSM, high risk MSM, people who inject drugs) Sensitivity and uncertainty analysis: One-way sensitivity analyses on key model parameter inputs Cost: annual PreP costs $9,672 estimation (midpoint between two published estimates)		• If cost of PrEP is reduced by 50% ($4,836 annually) and uptake of PrEP is at least 50%, prioritization to all MSM could reach cost savings; • If uptake 90%, cost $4,836 annually, effectiveness 75%, prioritisation to all MSM could prevent nearly 50% of new infection; • If uptake is 70-100% and cost is 50% of initial estimates, prioritization to high-risk MSM would achieve cost savings. • Under no scenario investigated was prioritization to high-risk heterosexuals alone cost saving. • If PrEP effectiveness was 25%, PrEP would not be cost saving under any scenario. • If prioritised to high risk MSM at lower cost, utilised by majority of community (50-100%) and equally effective as initial estimates, it may still be cost-effective. • Even if effectiveness of PrEP was 75%, PrEP would only be cost saving with high-risk MSM. Limitations: 1) study may have overestimated the actual health benefits of PrEP assuming that PrEP use itself does not further modify assumption of sexual identities and behavioural pattern. 2) No stratification of effect of PrEP on HIV transmission by type of sexual partnership or positioning. 3) Did not account for potential improvements over time in PrEP uptake and/or costs resulting from increased awareness and easier, cheaper regimens becoming available.		

Correspondence; not possible to ascertain how well the study was conducted	Study population & setting: MSM in New York City (epidemic data used), national-level behavioural data; n=193851 MSM, HIV prevalance 17.5%; 1st year: 160,043 susceptible MSM received PrEP; 25% of susceptible and undiagnosed MSM tested for HIV per year (based on model projections corresponding to current epidemic trends) Study perspective: Intervention used: PrEP in all susceptible MSM; PrEP efficacy 44% but 73% among those who are highly adherent i.e. taking >90% of doses Comparator: Modelling and statistical extrapolation: dynamic compartmental model that shows changes over time in the number of susceptible and infected individuals and various disease stages of infected individuals; model assumed all susceptible MSM received PrEP Willingness-to-pay threshold: $50k-$100k/QALY saved (authors provided a more recent estimate $109-$297k/QALY saved) Time horizon: 20-year Discount rate: future costs, infections averted and QALYs discounted at 3% per year Currency and year: not reported Scenarios considered: [1] normal adherence (PrEP efficacy 44%) [2] all patients highly adherent (PrEP efficacy 73%) Costs estimates: tenofovir/emtricitabine $22/day; assumed all susceptible MSM received PrEP and quarterly HIV testing and monitoring for adverse events; assumed PrEP costs fully incurred regardless of adherence	Cost per QALY gained	Costs: of the 160,043 susceptible MSM receiving PrEP in the 1st year, the implementation cost was $1.4 billion Estimated benefits: [1] PrEP was associated with 35,887 fewer infections over 20 years (61% reduction); [2] if all patients were highly adherent, PrEP was associated with 50,502 fewer infections over 20 years (86% reduction) ICER: [1] $871k/infection averted; $570k/QALY saved; incremental PrEP cost compared to no PrEP averaged $1.34 billion each year, benefits increased over time: year 1 prevented 1275 infections, saved 3 QALYs, year 20 prevented 1930 (undiscounted) infections, saved 3767 (discounted) QALYs; [2] high adherence: $631,791/infection averted, $354k/QALY, year 1 prevented 2,092 infections and saved 5 QALYs compared to no PrEP, year 20 prevented 2,552 (undiscounted) infections and 5,328 (discounted) QALYs	Koppenhaver (2011)	Conclusion: PrEP may have significant impact on HIV epidemic but at a high cost; authors suggested the following factors contributed to high ICER: [1] effectiveness of PrEP reduces HIV prevalence over time, savings in HIV treatment prevented offset by increases in PrEP costs; [2] incremental QALYs saved from PrEP are far greater in the future due to delayed QALYs saved from preventing HIV infections, survival and quality of life in both PrEP and no PrEP arms were similar initially but over time, greater proportion of HIV+ in no PrEP arm led to worse quality of life and more deaths; authors suggested further studies/analyses on differential coverage, dosing regimens/delivery strategies to highest risk MSM, which could potentially accrue similar benefits to a program in which all MSM receive PrEP but at a much lower cost Comment: Article published in letters to the editor in 2-pages, detailed modelling not presented.

Correspondence; not possible to ascertain how well the model/study was conducted	Study population & setting: HIV negative MSM attending genitourinary medicine (GUM) clinics in England, Year 1 HIV incidence 3.3% Study perspective: NHS England, Clinical Commissioning Groups, and Local Authorities Intervention used: daily oral tenofovir-emtricitabine PrEP for one year Comparator: no PrEP Modelling and statistical extrapolation: decision analytical model incorporating GUM clinic activity data to estimate HIV incidence in year one and subsequently. Willingness-to-pay threshold: not stated Time horizon: lifetime Discount rate: 3.5% Currency and year: GBP 2013/14 Scenarios considered: [1] PrEP effectiveness 86% [2] PrEP effectiveness 64% plus an HIV risk compensation incidence increase of 20%	Cost per QALY gained	[1] PrEP effectiveness 86%, ICER +£3,390/QALY gained; [2] PrEP effectiveness 64% plus an HIV risk compensation incidence increase of 20%, ICER +£34,100 Sensitivity analysis: The ICER was highly sensitive to year one HIV incidence, PrEP effectiveness, and PrEP-related drug costs. Breakeven for the year one investment (£26.8 million) occurs in year 29 [1], or year 48 [2].	Ong et al. (2015)	Conclusion: Authors concluded that to be cost-effective, the PrEP programme needs sustained targeting to high-risk MSM and high adherence (effectiveness). Although such a programme will prevent HIV acquisition, the budgetary impact will be great unless substantial reductions in drug costs are negotiated. Comment: work based on the GUMCAD data in England.
Acceptable quality	Study population & setting: Non-injection drug-using MSM in Canada Study perspective: Societal cost of HIV, Canada Intervention used: 'on demand' PrEP, model used most expensive scenario of daily drug use, for one year. The number needed to treat (NNT) used in the model was 51.78. Comparator: No PrEP Modelling and statistical extrapolation: NNT of 51.78 to calculate the annual average cost of 'on demand' PrEP interventions required to prevent one infection, based on the event rate of 5% in the control group	Cost per QALY gained	Costs: One year of daily 'on demand' PrEP cost $12,001 per year and $621,390 per infection prevented. At 0%, 3%, and 5% discount rates, lifetime HIV infection treatment and societal costs were $1.5 million, $690k, and $486k, respectively (in the most expensive scenario). Estimated benefits: PrEP strategy resulted in 14.88 (0% discount), 4.24 (3% discount), and 1.88 (5% discount) life-years gained; and 16.99 (0% discount), 5.53 (3%	Ouellet (2015)	Conclusion: Authors concluded that "on demand' PrEP for non-IDU MSM has favourable ICERs. Comment: Authors did not consider impact on ICER if NNT changes, sensitivity analysis were only conducted on a limited number of scenarios. It was not clear what the threshold for cost-effectiveness was. It is important to bear in mind that the number needed to treat depends on HIV incidence within the trial.

	and 3% in the PrEP group Willingness-to-pay threshold: not indicated Time horizon: Lifetime cost of an HIV infection considered, assuming infection at age 30, remaining 35.2 years Discount rate: 0%, 3%, 5% Currency and year: 2012 Canadian dollars Sensitivity and uncertainty analysis: Sensitivity and uncertainty analysis: second-line introduction at year 4 after diagnosis rather than 1; HIV treatment; age of infection at 20, or 40 Costs estimates used (direct/productivity costs): PrEP cost follows IPERGAY clinical trial protocol (six outpatient visits per year, condoms supplied at each visit, and cost of Truvada). Indirect costs included hours of work missed for each outpatient appointment. Direct HIV costs comprised outpatient, inpatient and emergency department costs, psychosocial costs and antiretroviral costs. Indirect costs included employment/work-related costs. Outcome measure: Life-years and QALYs; Asymptomatic HIV patient = 0.94 of one year of life for a healthy individual.		discount), and 2.86 (5% discount) QALYs gained. ICER: PrEP strategy was cost-saving if discount rate was 0% or 3%. At 5% discount rate, the ICER was $47,338 (most expensive scenario)- $60,223 (least expensive) per QALY gained.		

High quality	Study population & setting: high risk MSM (1.6% mean annual HIV incidence) in the US; mean HIV incidence 1.6% (range 0.1-3.1%) Study perspective: societal perspective Intervention used: PrEP (tenofovir/emtricitabine), base case efficacy 50% (range 10-90%) Comparator: no PrEP (current practices of HIV prevention and care) Modelling and statistical extrapolation: population model output estimates of lifetime infection risk under alternative PrEP scenarios and conveys information to the Cost-Effectiveness of Preventing AIDS Complications Model (disease model) on HIV infection status (whether/when HIV detected, followed-up and linked to care, patient previously on PrEP?), disease model then combine this information with its output of timing of AIDS-defining complications to establish treatment of each care of HIV+; assumed resistance in all HIV+ patients with history of PrEP, assumed elimination of efavirenz-based regimens for patients who took PrEP because of the low resistance threshold, assumed 5% reduction in rates of virologic suppression for all lines of ART in patients infected after PrEP. Willingness-to-pay threshold: not stated Time horizon: not stated Discount rate: 3% annual discount rate Currency and year: 2006 US dollars Sensitivity and uncertainty analysis: considered mean age as low as 20+/-2 years and annual population-wide HIV incidence of 0.1-3.1%; HIV screening frequency monthly - 3 years - never; PrEP efficacy range 10%-90%; varied reduction in suppression on all lines of therapy (from resistance) 0%-15%; considered toxicity with reductions in quality of life and survival; modelled potential effects of behavioural disinhibition as % reduction in PrEP efficacy	Cost per QALY gained	Costs: no PrEP, mean discounted lifetime cost $81k per person; with PrEP, discounted lifetime cost increased to $232.7k per person Estimated benefits: no PrEP, estimated lifetime HIV infection risk 44%, mean survival 39.9 years, discounted survival for entire population totalled 21.7 QALYs per person; PrEP at 50% efficacy reduced lifetime infection risk to 25%, increased survival to 40.7 years, discounted QALYs increased to 22.2 QALYs per person; if PrEP efficacy was higher, lifetime HIV infection risk decreased ICER: • PrEP (50% efficacy) compared to no PrEP $298k/QALY gained; • PrEP (90% efficacy), ICER $107k/QALY gained; • if baseline HIV incidence was 3.1%, ICER $150k/QALY; • if PrEP cost was reduced by 50%, ICER $114k/QALY Sensitivity and uncertainty analysis: • ICER was more favourable if assumed younger target population or target population at higher risk of infection, reduced PrEP costs and reduced rates of HIV case identification for persons no on PrEP; • parameters for which uncertainty over plausible ranges produced sizeable changes in ICER were PrEP efficacy, HIV incidence in target population, PrEP cost, rate of HIV detection among no PrEP MSM, age of target population, and PrEP toxicity; • lost of ART efficacy and the risk of developing tenofovir resistance in breakthrough infections had little impact on ICER	Paltiel (2009)	Conclusion: PrEP ICER threshold of $100k-$200k/QALY can only be achieved through either increased efficacy to 70%, annual incidence 2.4% or PrEP price reduction to $4700 per year or target mean age 20 years; combination of these optimal parameters will produce lower ICERs e.g. 60% effectiveness, cost $4700 per year, targeted at 20-year-olds and annual incidence 1.5%, ICER will be $50k/QALY; reducing PrEP price to $2500 per year will be cost-saving; questions remain as to who should receive PrEP, paid for by who, over what duration PrEP should be offered and what is the frequency of administration; ICER can be improved through better PrEP efficacy, targeting or pricing approaches Limitations: model ignored secondary transmissions averted when a primary case of HIV infection is prevented; did not consider the possibility of optimising duration of PrEP as a function of patient age and risk behaviour e.g. older patients may have lower HIV incidence Comment: assumed lifetime PrEP once started, unless becomes HIV+; PrEP price reductions greatly improves ICERs, reductions possible through lower ART price when used for PrEP or through lower dosages/frequency (intermittent PrEP?)

	Costs estimates: monthly costs: • PrEP (tenofovir/emtricitabine) $753 (range $101-753): includes drug cost $724 plus quarterly laboratory monitoring (complete blood cell counts, comprehensive metabolic panels and chemistry panels), semiannual physical examinations and annual full lipid panels, totalled at $28/month • ART therapy [1] tenofovir/emtricitabine plus efavirenz $1,139 [2] ritonavir-boosted atazanavir plus 2 nucleoside reverse-transcriptase inhibitor $1741 [3] ritonavir-boosted lopinavir plus 2 nucleoside reverse-transcriptase inhibitor $1748 [4] raltegravir plus optimised background regimen $2209 [5] 50% enfuvirtide plus optimised background regimen; 50% maraviroc plus optimised background regimens with or without enfuvirtide $3338 [6] optimised background regimen $1549				

High quality	Study population & setting: MSM in New South Wales (NSW), Australia Study perspective: health provider perspective Intervention used: PrEP; Assumed a maximum coverage of 30% based on studies of willingness to use PrEP and informal PrEP use among MSM; PrEP efficacy of 95% against wild-type virus and 40% against PrEP-drug resistant virus (based on the iPrEX trial) assumed PrEP provided no protection for those with poor adherence and therefore undetectable drug. The base case analysis assumes that 75% of MSM taking PrEP have detectable drug in each scenario, representing a 75% probability of adherence among MSM taking PrEP Comparator: no PrEP Modelling and statistical extrapolation: stochastic agent-based model of HIV transmission and progression that tracks HIV transmission within 60 000 men. It simulates the formation of, sexual activity within, and breakup of regular, casual, and group partnerships in the population. The model updates variables describing infection and disease status of HIV, disease progression, treatment status, sexual activity level, partnership availability, and current sexual partners of each individual in daily time-steps. Within the model, the characteristics associated with the type of sexual encounter determine the probability of HIV transmission. It incorporate PrEP interventions, the development of drug-resistant HIV due to PrEP, and the use of antiretroviral therapy (ART) regimens incorporating PrEP drugs Willingness-to-pay threshold: not stated Time horizon: 10-year Discount rate: costs/health outcomes at 3.0% annually Currency and year: 2013 Australian dollars Scenarios considered: [1] prioritizing PrEP for 10%–30% of the general MSM population;	Cost per QALY gained	Costs: using PrEP in 10-30% of entire NSW MSM population was projected to cost an additional $316-952 million over 10 years; targeted PrEP offered to MSM with >10->50 partners within 6 months cost $31-331 million Estimated benefits: PrEP in 30% MSM reduced HIV incidence by 30% and resulted in 2,142 additional QALYs (no PrEP 2,388 new HIV+; PrEP at 30% coverage 1,670 new HIV+) ICER: [1] 30% all MSM in NSW $445k/QALY; [2] 15% MSM with >50 partners per 6 months $134k/QALY; [3] 30% MSM with >50 partners per 6 months $114k/QALY; [4] 15% MSM in discordant regular partnerships $8k/QALY; [5] 30% MSM in discordant regular partnerships $11.6k/QALY Sensitivity and uncertainty analysis: • PrEP cost had large impact on ICER; if PrEP cost reduced from $9.6k per annum of the base case to $3k per annum, budget impact reduced to $112-338 million over 10 years and ICER of $158k/QALY at 30% coverage and made targeting 15% MSM in discordant regular partnerships cost-saving; • 1-way sensitivity analysis showed that 75% reduction in condom use where 1 partner is taking PrEP increased ICER of the 15% coverage in discordant regular partnerships from $8k to $18k/QALY; • reducing adherence from 75% to 40% reduced ICER from $8k to $7k/QALY	Schneider (2014)	Conclusion: PrEP is most cost-effective when targeted for HIV-negative MSM in a discordant regular partnership, with ICER ranging between $8,399 to $11,575 for coverage ranging between 15%-30%, respectively; however, this highly targeted strategy would not have large population-level impact Comment: Reduction in ICER by reducing adherence may be due to reduction in PrEP dispensed, which may be different if PrEP are still collected, only not used.

	[2] 15%–30% of MSM with >10–50 sexual partners per 6 months; [3] 15%– 30% of HIV-negative MSM in discordant regular partnerships; assumed no change in increased partners or unsafe sex in our base case analyses Sensitivity and uncertainty analysis: • Probability of adherence varied between 40% and 90%; • simulated scenarios with 25%–75% reductions in condom use in partnerships where 1 partner is taking PrEP; • no or 5% discounting for both costs and outcomes, discounting costs only at 5% Costs estimates: • PrEP drug cost $9597 per annum, PrEP monitoring (HIV antibody testing and screening for STIs every 2–3 months and monitoring serum creatinine levels every 3 months) cost $765; costs associated with receiving PrEP adjusted according to an individual's adherence level in the model • First, second, third, and subsequent lines of ART was estimated to cost $10,685, $19,364, $31 411, and $28,162, per patient per year, respectively; medical costs at CD4+>=500 $3,097, CD4+350-499 $4,402, CD4+200-349 $4,762, CD4+<200 $7,883, respectively Utility: HIV- 1, CD4+>500 0.935, CD4+ 350-499 0.935, CD4+ 200-349 0.818, CD4+<200 0.702				

Conference abstract; not possible to ascertain how well the model/study was conducted	Study population & setting: HIV negative MSM at substantial high risk of contracting HIV in the US Study perspective: US payer provider Intervention used: PrEP in all HIV negative MSM for their lifetime; Comparator: no PrEP and usual care alone (i.e. consistent condom, HIV testing and counselling, sexually transmitted diseases testing, 100% adherence to antiretroviral therapy for all HIV positive MSM from entry into care; assumed that HIV negative MSM are on prophylaxis throughout their lifetime) Modelling and statistical extrapolation: static decision analytical model using Excel Willingness-to-pay threshold: $45,000-$50,000 per life year gained Time horizon: 3-years for HIV cases averted and lifetime for life years gained and lifetime HIV costs Discount rate: not indicated Currency and year: US dollars Scenarios considered: not stated Sensitivity and uncertainty analysis: PrEP effectiveness; Condom effectiveness; HIV+lifetime cost; Truvada cost	Cost per HIV cases averted; Cost per life year gained	Costs: Over 3 years the expected costs are respectively $60,046 with PrEP + usual care vs $3,871 with usual care alone. Over lifetime the expected costs are respectively $88,726 with PrEP+usual care vs $67,212 with usual care alone. Estimated benefits: Over 3 years 0.95 HIV cases are expected to be averted with usual care vs 0.99 if PrEP is introduced. Over lifetime 48.7 lifeyears are expected to be gained with usual care, 49.3 if in addition PrEP is introduced. ICER: • $1,369,784 per HIV infection averted over 3 years; • $34,973 per LYG over lifetime horizon. Sensitivity and uncertainty analysis: As condom effectiveness decreases below 92% or as cost of PrEP decreases to below $30 per pill, PrEP becomes cost saving.	Vaidya 2015	Conclusion: In the short term (i.e. 3 years), the introduction of PrEP may not be cost-effective. Conference abstract with poster. Target population risk of HIV and PrEP efficacy not stated.

6 Summary of the Evidence

The summary below is taken from the evidence tables in the preceding Results section. These tables give an indication of how robust the study findings are considered to be, and whether they can be considered to be directly generalizable to the UK setting. 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.

6.1 MSM / trans women

The iPrEx study (Grant et al., 2010), a high quality phase 3 RCT involving 2499 MSM/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 Truvada 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%).

The PROUD study (McCormack et al., 2015) looked at the pre-exposure option for reducing HIV in the UK and was an open-label randomization to immediate or deferred daily Truvada for HIV negative gay men. The pilot phase of the RCT enrolled 544 HIV-negative MSM (1 was a trans woman) 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 Truvada 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 Independent Data Monitoring Committee, 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 Truvada 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 even, not re-starting it. Three out of 6 individuals, who had primary infection when they started Truvada, acquired resistance to emtricitabine. No resistance to tenofovir was seen. There are no plans to do any further RCTs in this group 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 and is reported here as it has been accepted for publication (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 (Truvada) 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 International 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, randomized participants into immediate or delayed once daily Truvada compared to placebo arms. None of those randomized to immediate Truvada 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, these five individuals were most likely exposed when not on PrEP.

6.1.1 Recommendation: MSM / trans women (Grade A)

PrEP (tenofovir/emtricitabine daily or on demand) is recommended for HIV negative MSM / trans women, in the context of a clinical risk assessment, who fulfil all of the following criteria:

- Have had a documented negative HIV test in the preceding year;
- have had condomless anal intercourse in the previous 3 months;
- are anticipated to have condomless anal intercourse in the next 3 months.

6.2 Heterosexual/Serodiscordant/Serodifferent

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 in the intervention arm.

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 eGFR, 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 tenofovir alone or Truvada 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 patients 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 enrollment 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.

The recommendation is based on two studies rated as 1+ that provided evidence of the clinical efficacy of PrEP in preventing infection when given to heterosexual men and women at high risk of HIV, and good evidence that daily oral dosing was safe.

6.2.1 Recommendation: Heterosexual & serodifferent (Grade B)

PrEP (daily tenofovir/emtricitabine or tenofovir as a single agent) is recommended for the HIV negative partner (confirmed by a documented negative HIV test in the preceding year) of a diagnosed person with HIV who is not known to be virally suppressed and where condomless sex is anticipated. It is also recommended for HIV negative heterosexual men and women at similar high risk of HIV acquisition, in the context of a clinical risk assessment, where condomless sex is anticipated.

6.3 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 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).

6.3.1 Recommendation: People who inject drugs (Grade B)

PrEP is not recommended for reducing the risk of HIV acquisition due to injecting drug use because of a lack of evidence that it would be effective for this indication in the UK over and above the existing harm reduction interventions available to people who inject drugs (e.g. needle exchange programmes).

6.4 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 on-demand PrEP, the most expensive on-demand 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 prioritizing 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. The abstract by Cambiano et al. (Cambiano et al., 2015) was based on a UK-based dynamic model. The authors concluded that 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 a one-year programme offered to selected GUM clinic attendees in England. The authors concurred with Cambiano et al in concluding that a substantial price reduction of anti-retroviral drugs used for

PrEP would provide the necessary assurance of cost-effectiveness for an affordable public health programme of sufficient size.

The cost-effectiveness and budgetary impact of PrEP provision are being calculated for inclusion in the integrated impact assessment.

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8 Appendices

8.1 Appendix 1

Document K: Population, Intervention, Comparator and Outcomes (PICO) template

1. Topic details

Intervention: Pre exposure prophylaxis

Indication: prevention of HIV

Programme of Care: Blood and infection

Clinical Reference Group: HIV

Accountable Commissioner: Claire Foreman

Unique Reference Number (URN): F03X06

2. Background

Pre Exposure Prophylaxis (PrEP) involves use of antiretroviral (ARV) drugs in HIV negative individuals who are at ongoing high risk of acquiring the disease. The aim is to prevent primary infection.

NHS England is the commissioner of all ARVs irrespective of use and for the treatment and care of all HIV positive individuals. Local Authorities are currently responsible for commissioning HIV prevention

International studies have found that PrEP is an effective intervention for those populations at highest risk of infection, such as men who have sex with men (MSM).and heterosexual / serodifferent couples (who have different HIV status). The mechanism of ARV prevention of HIV is through inhibition of replication of the HIV virus as it enters the body, which helps stop the virus from establishing permanent infection.

There remain several outstanding questions about exactly how a service would be organised - the exact commissioning criteria for access and the cost-effectiveness of PrEP.

Search strategy

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be	*HIV negative adult populations, particularly those that have a higher risk of exposure to the virus and/or in whom incidence and prevalence is higher than that in the general population. These groups include MSM, injecting drug users and sex workers and their clients.*

considered?	
I – Intervention Which intervention, treatment or approach should be used?	All available ARVs used for PrEP and all available regimens (e.g. continuous or intermittent).
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Placebo, no-PrEP, PEP, condoms, behavioural interventions
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* Numbers who acquire HIV while on PrEP and exposed to HIV Numbers in whom HIV is prevented while on PrEP and exposed to HIV Impact on risk compensation /STIs *Important to decision making:* Safety measures e.g. adverse events, abnormal biomarkers Measures of cost-effectiveness Measures of adherence to treatment regime Quality of life measures (including physical and social functioning) Treatment failure Drug resistance Measures of unplanned health care e.g. emergency admissions Equality of access (to treatment)

Assumptions / limits applied to search

Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.

Study types:

- Systematic review and meta-analysis
- RCT
- Other controlled trials
- Non-controlled trials
- Guidelines

Limits:

- *Humans;* English language

Published in a peer-reviewed journal or presented as an abstract at a scientific conference between October 2004 and October 2014 (when this review was undertaken)

Published in a peer-reviewed journal or presented as an abstract at a scientific conference

between 2004 and the present

3. Research Questions

- Which patient groups are shown to benefit?
- What criteria for access were used in the studies?
- How much was the benefit compared to available alternatives?
- Which is the most effective combination of antiretrovirals for PrEP?
- What does PrEP depend on to be effective?
- What are the factors which impact on cost-effectiveness?
- What are the factors which impact on clinical effectiveness?
- Is it transferable into a real world setting on an ongoing basis?
- What are the pathway components of the intervention?
- What is the impact on other health concerns / risk compensation?

4. Quality assurance criteria of PICOs

The following criteria should be used to quality assure the PICO template prior to commissioning the evidence review:

1. Are the aims and objectives for the evidence review clearly stated?
2. Is/are the research question(s) clearly stated?
3. Do the research question(s) fully address the aims and objectives?
4. Does the PICO framework address all the issues raised in the questions?

8.2 Appendix 2

SIGN	**Methodology Checklist 6: Economic Evaluations** *This checklist is based on the BMJ requirements for authors submitting economic studies for publication in that journal. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996:313;275*

Study identification (*Include author, title, year of publication, journal title, pages*)		
Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper an economic study (ie assessing the cost-effectiveness of something), or is it just a study of costs? REJECT IF THE LATTER IS TRUE.
2. Is the paper relevant to the key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Not an economic study □ 2. Paper not relevant to key question □

3. Other reason □ (please specify):

8.2.1.1.1 Section 1: Internal validity

In a well conducted economic study…		**8.2.1.2 Does this study do it?**	
1.1	The study addresses an appropriate and clearly focused question	Yes ☐ Can't say ☐	No ☐
1.2	The economic importance of the question is clear	Yes ☐ Can't say ☐	No ☐
1.3	The choice of study design is justified	Yes ☐ Can't say ☐	No ☐
1.4	All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	Yes ☐	No ☐
1.5	The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	Yes ☐ Can't say ☐	No ☐ Not applicable ☐
1.6	If discounting of future costs and outcomes is necessary, it been performed correctly	Yes ☐ Can't say ☐	No ☐ Not applicable ☐
1.7	Assumptions are made explicit and a sensitivity analysis performed	Yes ☐ Can't say ☐	No ☐
1.8	The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	Yes ☐	No ☐
1.9	The results provide information of relevance to policy makers	Yes ☐	No ☐

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study conducted?	High quality (++)☐ Acceptable (+)☐ Unacceptable – reject 0
2.2	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes ☐ No ☐
2.3	**Notes.** Summarise the author's conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

8.3 Appendix 3

Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1		Introduction written Search strategy, including updated one, inserted Evidence identified, summarised and inserted into tables, additional evidence from updated searches summarised and inserted into the tables Evidence review summaries, by risk population, written and inserted; cost-effectiveness evidence summary inserted	20 August 2015 21 August 2015	LP MD, LP, VH, NF, SM, KJO, VC LP, MD, NF, SM, KJO, VC LP, VH, NF, SM, KJO, VC
2		Introduction finalised Results updated Evidence tables ordered, titles of tables changed (clinical efficacy/effectiveness), text reduced and key findings emphasised to make the takeaway message easier to identify Response to comments/suggestions of other members of PrEP subgroup incorporated Produced some recommendations by risk group for	17 Sept 2015	LP, SM, NF, KJO, VC

		discussion among the PrEP subgroup members		
3		General formatting Tables modified (one still to do) References inserted Recommendations finalised after discussion at subgroup meeting on 21 September 2015 and email discussion among evidence review authors	V0.5 27 Sept 2015	LP SM NF KJO VC AP
4		Final modifications, referencing and other corrections made	V1.0 30 Sept	LP SM NF KJO VC
5		Some modification to text of introduction and cost-effectiveness sections Recommendations for policy proposition agreed with HIV CRG	V1.4 29 October 2015	LP/All
6		Some modification to text following stakeholder testing	V2 February 2016	All
7				
8				
9				
10				