Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Draft report for public consultation

Health technology assessment of a PrEP programme for populations at substantial risk of sexual acquisition of HIV

23 April 2019

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Office of the Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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Particular thanks are due to the Expert Advisory Group (EAG) and the individuals within the organisations listed below who provided advice.

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Conflicts of interest

None

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1 Introduction

1.1 Background to the request

In August 2018, the Health Information and Quality Authority (HIQA) commenced work on a health technology assessment (HTA) on a pre-exposure prophylaxis (PrEP) programme for populations at substantial risk of sexual acquisition of the human immunodeficiency virus (HIV). The HTA was requested by the Clinical Lead in Sexual Health at the Health Service Executive (HSE), with the endorsement of the Department of Health.

PrEP is a form of HIV prevention whereby oral anti-retrovirals (most commonly a combination of tenofovir and emtricitabine) are taken by individuals at substantial risk of HIV acquisition to prevent infection. There were 492 new HIV diagnoses notified in Ireland in 2017, giving rise to a notification rate of 10.3 per 100,000 population (based on Irish census data).[(1)] The National Sexual Health Strategy 2015–2020 has called for a comprehensive restructuring of its HIV prevention initiatives, with Priority Action 3 calling for "the appropriate use of antiretroviral therapy in HIV prevention".[(2)] It is envisaged that PrEP is made available as part of an overall HIV prevention package, with an overarching aim of reaching zero HIV transmissions.

There is increasing evidence that PrEP is safe and effective at preventing HIV in those at risk of infection. A number of countries (including France and Scotland) have introduced national PrEP programmes to combat the spread of HIV. Individuals taking PrEP must be monitored closely for side effects and require frequent testing for HIV (in addition to other sexually transmitted infections [STIs]). Individuals taking PrEP are also offered advice and support regarding safer sex practices and adherence to treatment is reinforced. PrEP refers to the antiretroviral medication itself, whereas a PrEP programme includes holistic assessment, preventive PrEP treatment, education and advice for individuals at substantial risk of infection.

The aim of this assessment is to examine the clinical and cost-effectiveness of introducing a PrEP programme in Ireland. Based on the available evidence, the HTA will inform decision making by the Department of Health and the HSE.

1.2 Terms of reference

Informed by this HTA, the Minister for Health and the HSE will make decisions regarding the potential introduction of a PrEP programme in Ireland.

The Terms of Reference, agreed with the Department of Health and the HSE, are to:

- describe the epidemiology of HIV infection in Ireland
- examine the clinical effectiveness and safety of oral pre-exposure prophylaxis (PrEP) to reduce sexual acquisition of HIV in individuals at substantial risk of infection
- review the evidence of the cost-effectiveness of PrEP
- evaluate the cost-effectiveness and budget impact of introducing a PrEP programme in Ireland
- estimate the organisational and resource implications of a PrEP programme in Ireland
- consider the wider ethical or societal implications that the introduction of PrEP may have for patients, the general public or the health care system.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA, the Department of Health and the HSE.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders, including the Department of Health, the HSE, the Health Protection Surveillance Centre, clinicians with specialist expertise in HIV and sexual health, the National Centre for Pharmacoeconomics and relevant advocacy groups. The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group are to:

- contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive
- contribute fully to the work, debate and decision making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis
- support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprising staff from the Health Technology Assessment Directorate to carry out the assessment.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. Draft findings on the epidemiology of HIV in Ireland and the clinical effectiveness and safety of PrEP were also discussed at that meeting. Considerations regarding the cost-effectiveness, budget impact, organisational, social and ethical implications of providing a PrEP programme in Ireland were discussed at the second meeting of the group. Draft versions of this report were circulated for review by the Expert Advisory Group before a final draft report was prepared for public consultation. After the public consultation is complete, a final version of this report will be circulated for review by the Expert Advisory Group before it is submitted to the Board of HIQA for approval. The completed assessment will be submitted to the Minister for Health and the Health Service Executive as advice and published on the HIQA website.

2 Description of technology

Key points

- Pre-exposure prophylaxis (PrEP) is a HIV prevention strategy that uses antiretroviral medications to protect HIV-negative people from acquiring HIV.
- The World Health Organisation (WHO) recommends oral pre-exposure prophylaxis (PrEP) containing tenofovir as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches. The WHO defines 'substantial risk' as a risk of HIV acquisition that is greater than 3 per 100 person-years in the absence of PrEP.
- Once daily oral tenofovir/emtricitabine as a fixed dose combination tablet has been licensed and available for use as PrEP in Ireland since 2016. While licensed, it is not reimbursed through the Primary Care Reimbursement Service. Therefore, individuals with a valid prescription for PrEP must pay for it themselves.
- Policy provision for PrEP is contained in the National Sexual Health Strategy 2015–2020. The strategy recommends a comprehensive restructuring of HIV prevention initiatives, with Priority Action 3 calling for "the appropriate use of antiretroviral therapy in HIV prevention".
- The HSE Sexual Health and Crisis Pregnancy Programme (SHCPP) has developed clinical guidance documents (including eligibility criteria) and national standards for PrEP use in Ireland. These recommend that PrEP medications should be provided as part of a holistic programme that includes frequent monitoring for adherence and side effects, testing for HIV and other sexually transmitted infections (STIs), and counselling and advice on safer sex practices.
- Twelve countries have introduced national PrEP programmes. France became the first country in Europe to provide PrEP through its public health system in 2015. Elsewhere in Europe, Belgium, Norway, Portugal and Scotland also provide PrEP through national programmes. PrEP has also been made available in a large number of other countries through demonstration projects, implementation projects or clinical trials.

2.1 Background

Pre-exposure prophylaxis (PrEP) is a HIV prevention strategy that uses antiretroviral medications to protect HIV-negative people from acquiring HIV. In addition to PrEP, these antiretroviral medications are prescribed to prevent the onward transmission of HIVin the following cases:

- as post-exposure prophylaxis (PEP) following occupational or sexual exposure (PEPSE) to HIV by a person who is HIV-negative
- by HIV positive people, as early and effective antiretroviral treatment suppresses the viral load decreasing the risk of virus transmission (treatment-as-prevention [TasP]).

It is intended that antiretroviral medicines are used in addition to other effective prevention strategies, including HIV/STI testing and treatment, provision of condoms, health promotion and risk reduction education around sexual behaviour, and support and education around alcohol and substance misuse.

In 2012, the World Health Organization (WHO) first made conditional recommendations on PrEP use in serodifferent couples (where one partner is HIV negative and the other HIV positive) and men/transgender women who have sex with men. They recommended PrEP delivery through demonstration projects to ascertain its optimal delivery approaches. Subsequently, in 2014, the WHO developed consolidated HIV guidelines for key populations, including gay, bisexual and other men who have sex with men (MSM), people who inject drugs (PWID), sex workers, transgender people, and people in prisons and other closed settings. In this assessment, the term MSM will include gay, bisexual and other men who have sex with men. The primary populations that the planned PrEP programme intends to engage include both MSM and trans women who have sex with men.

In 2016, WHO issued updated consolidated guidelines.[(3)] The following recommendation was made:

> Oral pre-exposure prophylaxis (PrEP) containing TDF [tenofovir disoproxil fumarate] should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high quality evidence).

Substantial risk was defined by WHO as a risk of HIV acquisition that was greater than three per 100 person-years in the absence of PrEP.

2.2 Regulatory status of PrEP

In the US, the Food and Drug Administration (FDA) approved in 2012 a once daily oral fixed-dose combination pill containing tenofovir disoproxil fumarate and emtricitabine (Truvada®) for use as PrEP to prevent sexual acquisition of HIV-1.[4] The US Centers for Disease Control and Prevention (CDC) subsequently released clinical guidelines on the use of PrEP in 2014.[5] These guidelines recommended PrEP use in individuals at substantial risk of sexually acquired HIV.

In August 2016, Truvada® was officially granted marketing authorisation in Europe for use as PrEP.[6] Treatment is indicated in combination with safer sex practice to reduce the risk of sexually-acquired HIV-1 infection in adults at high risk. The marketing authorisation allows for the marketing of Truvada® for PrEP in all 28 countries of the EU, subject to national regulatory authority approval of required pharmacovigilance materials in each country. In 2017, the EMA extended the use of Truvada® for PrEP to include adolescents over the age of 13 at substantial risk. In July 2017, Truvada® came off patent, and a number of generic formulations have since become available in Ireland.

2.3 Product information

Much of the product information in this section is listed in the Summary of Product Characteristics (SmPC) of marketed PrEP medications in Ireland.[7-9] The formulations of the tenofovir /emtricitabine fixed dose combinations licensed and marketed for use as PrEP in Ireland differ. Each tablet of the Truvada® formulation contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of its active metabolite, tenofovir disoproxil. Sources may express this as Truvada 200 mg/245 mg (disoproxil dose) or Truvada 200 mg/300 mg (disoproxil fumarate dose). Generic formulations contain emtricitabine and alternative tenofovir disoproxil salts, such as tenofovir disoproxil maleate or phosphate. For the remainder of this HTA, tenofovir disoproxil refers to the active component of the salt of tenofovir (tenofovir disoproxil fumarate, maleate or phosphate) and tenofovir/emtricitabine refers to oral tenofovir disoproxil and emtricitabine fixed dose combination medication for use as PrEP to prevent HIV acquisition.

2.3.1 Mechanism of action

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil, which is converted in vivo to tenofovir, is a nucleotide analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity against HIV-1, HIV-2 and hepatitis B virus. Following phosphorylation by cell enzymes, emtricitabine and

tenofovir both competitively inhibit HIV-1 reverse transcriptase. This results in DNA chain termination. By inhibiting HIV-1 from replicating as it enters the body, it is thought that tenofovir/emtricitabine prevents the virus from establishing permanent infection.

The time to onset of protection after starting tenofovir/emtricitabine is unknown and the treatment is not always effective in preventing the acquisition of HIV. The effectiveness in reducing the risk of acquiring HIV is strongly correlated with adherence, as demonstrated by measurable drug levels in blood. It should, therefore, only be used for PrEP as part of an overall HIV prevention strategy, including consistent and correct condom use, knowledge of HIV status and regular testing for other sexually transmitted infections. The effectiveness and safety of emtricitabine/tenofovir disoproxil when taken as PrEP in preventing acquisition of HIV is reviewed in detail in Chapter 4.

2.3.2 Dosing schedule

The recommended dose of tenofovir/emtricitabine for treating or preventing HIV is one tablet, taken orally, once daily. To optimise the absorption of tenofovir, it is recommended that the treatment is taken with food.

While only licensed as a daily regimen, event-based dosing has been suggested in certain jurisdictions due to the success of one trial that confirmed the safety and effectiveness of event based (also known as 'on demand') PrEP[(10)] (see Chapter 4 for further details). The recommendation is as follows: take two pills before sex as a double dose (two pills) and a single pill 24 and 48 hours after. If sex continues as multiple episodes, individuals should continue taking one pill every 24 hours for the days condomless anal sex is occurring, and, after the last episode of condomless anal sex, continue taking PrEP for two more days. Event-based dosing is only recommended for those at risk of HIV through anal sex and not vaginal sex due to the fact that evidence for event-based dosing is specific to the MSM group.[(10)]

2.3.3 Adverse events

The safety data contained in the SmPC for tenofovir/emtricitabine are largely derived from its use as treatment in people who are HIV positive. The risk of adverse effects when tenofovir/emtricitabine is used for PrEP is less well described. The most frequently reported adverse reactions considered possibly or probably related to treatment with emtricitabine or tenofovir are nausea (12%) and diarrhoea (7%).

The SmPC for tenofovir/emtricitabine states that emtricitabine and tenofovir are primarily excreted by the kidneys. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy have been reported with

the use of tenofovir for treating HIV infection. Creatinine clearance should be calculated in all individuals before starting tenofovir/emtricitabine for either treatment or prevention, and renal function should also be monitored during use. Tenofovir/emtricitabine for use as PrEP is not recommended in people with creatinine clearance less than 60 ml/min. There are also cautions around use in people with impaired renal function and use of nephrotoxic medicines.

Small decreases in bone mineral density of the hip and spine were seen in a study of treatment with tenofovir in people who were antiretroviral-naive, but there was no increased risk of fractures or evidence for clinically relevant bone abnormalities.

People with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Emtricitabine and tenofovir individually and in combination have shown activity against hepatitis B virus in pharmacodynamic studies, and discontinuation of tenofovir/emtricitabine in people infected with hepatitis B virus may be associated with severe acute exacerbations of hepatitis.

Tenofovir/emtricitabine alone does not constitute a complete regimen for treating HIV, and resistant mutations have emerged in people with undetected HIV infection who are only taking this treatment as dual therapy. It should, therefore, only be used for PrEP in people who have been confirmed to be HIV negative, and this should be reconfirmed at frequent intervals (for example, at least every three months) using a combined antigen/antibody test. PrEP is contraindicated in people with unknown or positive HIV-1 status.

2.4 PrEP use in Ireland

Two PrEP monitoring clinics are operational in Ireland: one at the Gay Men's Health Service and another at the Mater Misericordiae University Hospital. These clinics do not dispense PrEP. A number of other STI clinics also prescribe PrEP, as well as GPs and primary care centres. While daily oral tenofovir disoproxil/emtricitabine as PrEP is licensed for the prevention of sexually acquired HIV in Ireland, PrEP is not reimbursed through the Primary Care Reimbursement Service (PCRS). Therefore, while individuals can redeem their prescriptions for PrEP though community pharmacies, they must pay for it themselves. There is also evidence that some individuals are ordering PrEP online.

Policy provision for PrEP is contained in the National Sexual Health Strategy 2015–2020.[(2)] The strategy recommends a comprehensive restructuring of HIV prevention initiatives, with Priority Action 3 calling for "the appropriate use of antiretroviral therapy in HIV prevention". The HSE Sexual Health and Crisis Pregnancy Programme

(SHCPP) has responsibility for implementing this strategy. To inform its work, SHCPP convened a multisectoral working group to develop recommendations in relation to the use of HIV PrEP in Ireland (the PrEP Working Group).

This group, with community representation, developed clinical guidance documents and national standards in relation to the use of PrEP in Ireland. These standards were reviewed by SHCPP's Sexual Health Strategy Implementation Group and SHCPP's Clinical Advisory Group and they will inform future work on the preparedness of STI clinics to implement PrEP programmes in line with these standards. In time, if PrEP is available through the HSE, it is intended that the finalised standards will be used in all centres providing PrEP.

2.4.1 Eligibility criteria

The PrEP Working Group has developed evidence-based eligibility criteria for PrEP in Ireland and provides guidance on its provision as well as the assessment and monitoring of those at risk of HIV. Guidelines from the British Association for Sexual Health and HIV (BASHH) and the British HIV Association (BHIVA) were used as a reference, particularly in relation to evidence around PrEP dosing schedules and clinical monitoring of those on PrEP.[11]

Indications for PrEP per the PrEP Working Group

Three populations were identified by the PrEP Working Group as being eligible for PrEP to prevent the sexual transmission of HIV:

1. MSM or transgender women having sex with men at substantial risk.

   Individuals must be HIV negative, sexually active with likelihood of remaining sexually active in the next three months, and report at least one of the following:

   - condomless anal sex with at least two casual partners over the last six months
   - an episode of documented or reported acute STI over the last 12 months (excluding anogenital warts and non-primary herpes simplex virus)
   - documented or reported use of HIV post-exposure prophylaxis following sexual exposure (PEPSE) over the last 12 months
   - engagement in chemsex over the last six months.

2. HIV negative individuals having condomless sex with a HIV positive person who is not stably suppressed on antiretroviral therapy, specifically when the

person living with HIV:

- is not on antiretroviral therapy
- has initiated antiretroviral therapy but is not yet on treatment for six months with virological suppression (an individual is considered virologically suppressed when the viral load is less than 200 copies/mL)
- has loss of virological control on antiretroviral therapy and the risk of HIV transmission has been deemed by a consultant physician specialising in HIV medicine to be substantial and warrant PrEP for the HIV negative partner.

3. Other HIV negative heterosexual men, heterosexual women and transgender men considered by a senior clinician specialising in HIV medicine to be at substantial risk for sexual acquisition of HIV.

The following individuals are not eligible for PrEP:

- individuals in a monogamous relationship with a HIV positive partner who is confirmed to be stably suppressed on antiretroviral therapy for at least six months
- individuals in a monogamous relationship with a partner who is known to be HIV negative
- individuals unwilling to attend for follow up.

The PrEP Working Group does not recommend PrEP for the prevention of HIV through injection drug use. People who inject drugs may nonetheless be at risk of sexual acquisition of HIV and, therefore, may otherwise meet the eligibility criteria for PrEP.

PrEP in pregnancy

The PrEP Working Group recommends that pregnant females at substantial risk of sexual acquisition of HIV should be informed of the protective effect of PrEP in averting HIV infection and informed of the available information in relation to the safety of use of tenofovir disoproxil and emtricitabine in pregnancy. Females at substantial risk of HIV who meet eligibility criteria should be offered PrEP as part of combination HIV prevention regardless of pregnancy status or risk of conception. However, pregnancy status should be established in females being considered for PrEP and in women taking PrEP.

PrEP contraindications (at baseline or during follow up)

PrEP comprises dual antiretroviral therapy and is, therefore, not indicated in individuals who are HIV positive. It is also contraindicated in circumstances of poor adherence with continued high risk exposure, as individuals who seroconvert are at increased risk of developing antiretroviral resistance. Therefore, PrEP is contraindicated in individuals who:

- are HIV positive
- have an undocumented HIV status
- are poorly adherent to PrEP (that is, less than four days per week of a daily dosing schedule) with continued high risk exposure
- are allergic to tenofovir or emtricitabine.

Impact of suppressive antiretroviral therapy on risk of HIV acquisition

As indicated above, PrEP is indicated in HIV negative individuals who engage in condomless anal sex with a HIV positive person only when the HIV positive person is not stably suppressed on antiretroviral therapy. When the HIV-infected partner is suppressed on antiretroviral therapy, PrEP is not indicated. The HPTN 052 clinical trial[12] and the HIV Partner cohort study[13] underpin the efficacy of suppressive antiretroviral therapy in preventing onward transmission of HIV in serodifferent sexual couples over a range of different sexual exposure types. The results of the HIV Partner cohort study, where the health outcomes of partners of HIV positive individuals on suppressive antiretroviral therapy were measured, are given in Table 2.1 below. Note that while the incidence of HIV was zero in all comparisons, the upper 95% Confidence Interval was high (and above 3 per 100 couple-years) for some. This reflects low number of couples in the analysis of these comparisons (for example, the upper limit of 12.71 per 100 couple-years in the ‘anal sex with ejaculation in heterosexual women’ was based on 29 couple-years of data, compared with 1,238 couple-years for the overall group).

Table 2.1. Efficacy of suppressive antiretroviral therapy in preventing onward transmission of HIV in serodifferent couples, by sexual exposure type

	Number of infections	HIV incidence per 100 couple years	Upper limit 95% CI
Overall	0	0	0.3
Heterosexual women			
Any sex	0	0	0.97
Vaginal sex ejaculation	0	0	1.50
Vaginal sex no ejaculation	0	0	1.55
Anal sex ejaculation	0	0	12.71
Anal sex no ejaculation	0	0	8.14
Heterosexual men			
Any sex	0	0	0.88
Insertive anal sex	0	0	7.85
MSM			
Any sex	0	0	0.84
Insertive anal sex	0	0	1.00
Receptive anal sex ejaculation	0	0	2.70
Receptive anal sex no ejaculation	0	0	1.68

Source: HIV PARTNER observational study

2.4.2 Components of a PrEP programme

PrEP medications should be provided as part of a holistic programme that includes frequent monitoring for adherence and side effects, testing for HIV and other STIs, and counselling and advice on safer sex practices. Clinical management guidance, national standards for a PrEP programme and a monitoring framework have been developed by the PrEP Working Group.

2.4.2.1 Clinical management guidance

The PrEP Working Group outlines four key stages in the assessment and monitoring of individuals on PrEP:

Stage 1: Identification of people at high risk of HIV, determination of eligibility for PrEP and baseline assessment
Stage 2: The starting PrEP visit
Stage 3: Subsequent visits
Stage 4: Continuing PrEP visits (after one year).

The following sections outline the key elements that have been identified for each of these stages.

Stage 1: Identification of people at high risk of HIV, determination of eligibility for PrEP and baseline assessment

The guidelines noted that some people may recognise their risk of HIV and self-refer for PrEP assessment and some may have been referred for PrEP assessment.

Consultations should be able to identify people at substantial risk of HIV (and eligible for PrEP) from their sexual history, history of STIs, history of PEPSE (post-exposure prophylaxis after sexual exposure) use and history of chemsex (use of drugs such as methamphetamine, mephedrone or gamma hydroxybutyrate [GHB] during sex). Table 2.2 lists these key elements in a patient's history

Table 2.2. Key elements in patients' sexual history

Elements of consultation	Notes
Last sex	▪ Type of sex (anal, vaginal, oral and active, passive or both) ▪ Use of condoms
Number of sexual partners in the last 3 months	▪ Type of sex (anal, vaginal, oral and active, passive or both) ▪ Use of condoms
For MSM or trans women having sex with men	Number of condomless anal sex partners in the last 6 months
HIV status of sexual partners	If partner is HIV positive, document treatment status and virological suppression status
STIs in the last 12 months	
PEPSE in the last 12 months	
Use of chemsex in the last 6 months	

PEPSE=post-exposure prophylaxis after sexual exposure
'Slamming'=injection drug use during sexual episodes, typically methamphetamine, mephedrone or GHB

For individuals at high risk of HIV, the guidelines recommend that consultation should include the additional elements listed in Table 2.3.

Table 2.3. Consultation requirements — individuals at high risk

Elements of consultation	Notes, additional actions
Provision of information on HIV/STI risk reduction	Safer sex practices, provision of condoms, brief intervention regarding alcohol, drugs (including information around safer injecting and needle exchange for individuals 'slamming' drugs) and further support/referral if required
Documentation of medical conditions	Renal conditions and other medical conditions that may impair renal function, for example, diabetes mellitus and hypertension Bone conditions or risk factors for low bone mineral density
Documentation of current medication(s)	If PrEP is being considered, medications that may be nephrotoxic
Documentation of drug allergy status	
Clinical examination as required	
Appropriate investigations including	▪ 4th generation venous blood HIV test ▪ HBV testing, directed by history unless documented as HBV immune ▪ HAV IgG testing if previous vaccination not reported or not documented as HAV immune ▪ syphilis serology ▪ HCV testing ▪ chlamydia and gonorrhea NAAT testing from all relevant anatomical sites (can be self-taken or provider taken) ▪ where indicated gonorrhea culture from urethra, pharynx and rectum
Provide treatment as required, including PEPSE	
Provide vaccination as indicated	Hepatitis A and B, HPV (if aged under 26 years)

PEPSE=post-exposure prophylaxis after sexual exposure; HBV=hepatitis B virus; HAV=hepatitis A virus; HCV=hepatitis C virus; IgG=immunoglobulin G; NAAT=nucleic acid amplification test; HPV=human papilloma virus

If found to be eligible for PrEP, the guidelines recommend that consultation should include the elements listed in Table 2.4.

Table 2.4. Consultation requirements — individuals eligible for PrEP

Elements of consultation	Notes, additional actions
Assess and document PrEP eligibility	
Discuss PrEP and provide written information and offer/arrange starting PrEP visit and document patient's decision.	The starting PrEP visit must be within four weeks of the baseline HIV test and, if not, a repeat HIV test must be performed. For patients requiring PEPSE, arrangements should be made for the starting PrEP visit at the end of the PEPSE course.
Check serum creatinine and eGFR	

PEPSE=post-exposure prophylaxis after sexual exposure; eGFR=estimated glomerular filtration rate

Stage 2: Starting PrEP visit

Table 2.5 lists the guideline recommendations for the key elements of the first PrEP visit (when PrEP is initiated).

Table 2.5. Key elements of starting PrEP visit

Elements of consultation	Notes, additional actions
Confirm previously documented eligibility criteria	
Reiterate HIV/STI risk reduction strategies	Safer sex practices, provision of condoms, brief intervention regarding alcohol, drugs and further support/referral if required
Confirm HIV negative 4th generation venous blood HIV test within last four weeks	Determine if need for repeat HIV test at four weeks (for example, if there is concern individual is in HIV window period at time of test or if individual has just completed PEPSE)
Check results from previous visit	Treat STIs, offer vaccination where required
Check serum creatinine and eGFR results	Review medical history and determine when next creatinine check indicated
Discuss PrEP and document patients decision regarding starting	Discuss lead in times, adherence and dosing schedule
Address any queries in relation to PrEP and follow up	
Prescribe one to three months tenofovir disoproxil /emtricitabine one tablet once daily or event-based dosing, if appropriate	
Confirm contact details and preferred mechanism for contacting where need arises	

PEPSE=post-exposure prophylaxis after sexual exposure

Stage 3: Subsequent visits

Patients must return every three months following PrEP initiation. Table 2.6 lists the key elements outlined in the guidelines of these subsequent visits.

Table 2.6. Key elements of subsequent PrEP visit

Elements of consultation	Notes, additional actions
Determine if still taking PrEP	If no longer taking, determine and document reason(s) for stopping
Reassess eligibility criteria	Document if still eligible or no longer eligible
Reiterate HIV/STI risk reduction	Safer sex practices, provision of condoms, brief intervention regarding alcohol, drugs and further support/referral if required
Take sexual history	Document sexual exposure history in last three months. Determine if symptoms of STI.
Examination as required	
Investigations	▪ 4th generation venous blood HIV test syphilis serology ▪ HCV testing (annually unless otherwise indicated) ▪ chlamydia and gonorrhea NAAT testing from all relevant anatomical sites (can be self-taken or provider taken) ▪ where indicated, gonorrhea culture from urethra, pharynx and rectum
Vaccination follow up as required	

HCV=hepatitis C virus; NAAT=nucleic acid amplification test

Stage 4: Continuing PrEP

In addition to the requirements of 'subsequent' visits, the guidelines recommend a 'continuing visit' beyond one year which will require the elements listed in Table 2.7. The additional laboratory investigation is measurement of creatinine and estimated glomerular filtration rate (yearly).

Table 2.7. Key elements of continuing PrEP visits

Elements of consultation	Notes, additional actions
Measure serum creatinine, eGFR if indicated	Clinical assessment checklist available for frequency of renal monitoring and recommendations in the setting of impaired renal function
Assess and document dosing schedule and adherence	Reinforce adherence where required
Prescribe three months tenofovir disoproxil/emtricitabine one tablet once daily or for event-based dosing if appropriate	
Confirm contact details and preferred mechanism for contacting where need arises	

eGFR=estimated glomerular filtration rate

2.4.2.2 National standards for PrEP

The PrEP Working Group has developed a set of national standards for the provision of PrEP as part of combination HIV prevention strategies in Ireland. The standards represent best practice and outline the responsibilities of services, service managers, service providers and healthcare professionals, as well as establishing the expectations of service users. The standards are in line with the goals of the National Sexual Health Strategy regarding sexual health services, specifically "Equitable, accessible and high quality sexual health services, which are targeted and tailored to need".

Six standards were developed. They relate to:

1. Access
2. Service Configuration and Structure
    - 2.1. Availability of appropriate combination HIV prevention and STI management tools
    - 2.2. Links to other services
    - 2.3. Surveillance, monitoring and evaluation
3. Clinical Assessment and Management
4. Management of Results
5. Information Governance
6. Patient and Public Engagement.

2.4.2.3 PrEP monitoring framework

The PrEP Working Group has also developed a PrEP monitoring framework

document that fulfills PrEP Standard 2.3: Surveillance, monitoring and evaluation. The following quality standards are included:

1. **Disease Surveillance**: It is a core requirement that all PrEP services meet statutory disease notification and surveillance requirements within a reasonable timeframe.

2. **PrEP monitoring and evaluation**: It is a core requirement that all PrEP services participate in national monitoring and evaluation requirements for PrEP within a reasonable timeframe.

2.5 International PrEP programmes

As mentioned previously, daily oral PrEP using a fixed dose combination of emtricitabine/tenofovir is licensed in all EU/EEA member states by the European Commission (2016) and in the US by the FDA (2012).

Many countries offer PrEP through dedicated programmes, such as national programmes, demonstration projects, implementation projects and clinical trials. Overall, PrEP is available in 49 countries worldwide through one or more of these programmes. Appendix 1 lists all countries where PrEP is available through a dedicated programme.

Twelve countries provide PrEP through national programmes, and four countries are planning to introduce national programmes (see Table 2.8 and Figure 2.1). France became the first country in Europe to offer PrEP through its public health system in 2015.[14] It did this through an 'emergency recommendation for temporary use', which became permanent in April 2017. Other European countries that have national programmes in place include Belgium, Norway, Portugal and Scotland. Northern Ireland introduced a pilot PrEP clinic based in the Belfast Trust in August 2018.[15]

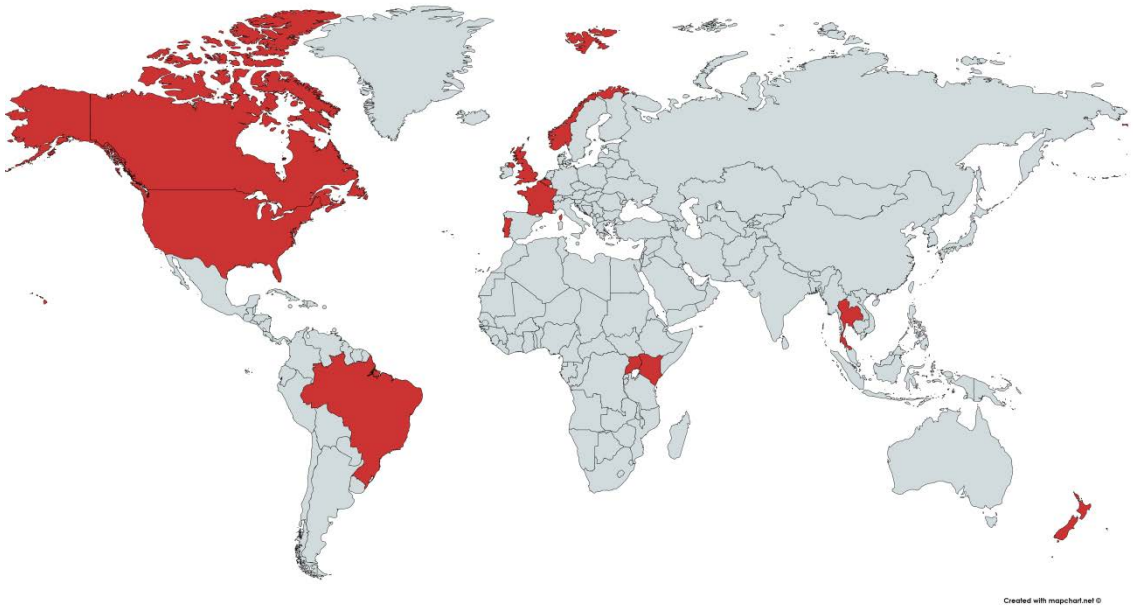
Table 2.8. Countries with ongoing or planned national programmes

Ongoing National PrEP Programmes	
Country	**Relevant guideline/policy document**
Belgium	HIV plan 2014–2019 Belgium[16]
Brazil	Clinical Protocol and Therapeutic Guidelines for Management of HIV Infection in Adults (2018)[17]
Canada	1. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis[18] 2. Guidance for the use of PrEP in British Columbia (2016)[19]
France	ANSM Pre-exposure Prophylaxis Guidelines (2017)[20]
Kenya	Framework for the Implementation of Pre-Exposure Prophylaxis of HIV In Kenya (2017)[21]

New Zealand	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines[22]
Norway	Not identified
Portugal	Not identified
Scotland	Scottish Medicines Consortium Truvada Assessment (2017)[23]
Thailand	Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017[24]
Uganda	1. National HIV AND AIDS Strategic Plan 2015/2016 - 2019/2020[25] 2. Consolidated Guidelines for Prevention and Treatment of HIV in Uganda (2016)[26]
USA	National HIV/AIDS Strategy for the United States: Updated to 2020[27]
Wales	Preparing for PrEP full report 2017[28]
Planned National PrEP Programmes	
Country	**Guideline**
Botswana	Not identified
Israel	Not identified
Namibia	National Guidelines For Antiretroviral Therapy (2016)
Taiwan	Taiwan National Pre-Exposure Prophylaxis Guidelines (2016)

Source: Global Advocacy for HIV prevention (AVAC) 2018

Figure 2.1. Countries with ongoing or planned national programmes



Countries are: Belgium, Brazil, Canada, France, Kenya, Norway, New Zealand, Thailand, Portugal, Uganda, Scotland & NI (UK), and USA

2.6 Discussion

Pre-exposure prophylaxis (PrEP) is the most recent development in the field of HIV prevention. It involves the pre-emptive use of oral antiretroviral therapy in HIV negative people to reduce the risk of HIV infection. In their latest guidelines, WHO recommends that oral PrEP containing tenofovir disoproxil is offered as part of a comprehensive HIV prevention programme to people at 'substantial risk of HIV infection'.[3] PrEP is available in 49 countries worldwide and over ten countries have implemented national programmes for PrEP delivery.

Policy provision for PrEP in Ireland is contained in the National Sexual Health Strategy 2015–2020.[2] The strategy recommends a comprehensive restructuring of HIV prevention initiatives, with Priority Action 3 calling for "the appropriate use of antiretroviral therapy in HIV prevention".

Once daily oral tenofovir/emtricitabine as a fixed dose combination tablet has been licensed and available for use as PrEP in Ireland since 2016. While evidence exists for other dosing schedules (such as event-based[29]), only daily dosing is licensed. PrEP differs from a PrEP programme in that a programme provides PrEP as part of a holistic service that includes frequent monitoring for adherence and side effects, testing for HIV and other STIs, and counselling and advice on safer sex practices.

While licensed, PrEP is not reimbursed through the Primary Care Reimbursement Service. Therefore, individuals with a valid prescription for PrEP must pay out-of-pocket at community pharmacies. Additionally, some users are obtaining PrEP online. This raises concerns regarding potential inequity in that access to PrEP is limited to those who can afford to pay. Additionally, those acquiring PrEP online may not be enrolled in a programme and are, therefore, not undergoing testing for HIV and other STIs, monitoring for side effects and obtaining advice on safer sex practices.

3 Epidemiology of HIV in Ireland

Key points

- HIV is a notifiable disease in Ireland. All new diagnoses notified in Ireland are reported nationally by the Health Protection Surveillance Centre (HPSC).
- There were 492 diagnoses of HIV notified in Ireland in 2017, representing a rate of 10.3 per 100,000 population. An increasing proportion (39%) of diagnoses in Ireland in 2017 was in people known to be previously diagnosed HIV positive abroad and the majority of these (88%) had transferred their care to Ireland.
- Of the 492 new diagnoses, just over half (53%) were among gay, bisexual and other men who have sex with men (MSM). The proportion of MSM previously diagnosed HIV positive before arrival in Ireland has increased from 16% of cases in 2012 to 42% in 2017. Of those previously diagnosed HIV positive abroad in 2017, 91% were transferring their care to Ireland. Among MSM without a previous HIV positive diagnosis, there was a 3% decline in diagnoses between 2016 and 2017 and a 14% decline between 2015 and 2016.
- Heterosexuals accounted for 33% (163) of diagnoses in 2017, an increase of 13% compared with 2016. Of these, 41% were previously diagnosed positive in another country, of whom 85% had transferred their HIV care to Ireland. Overall, 61% of heterosexual cases were born in sub-Saharan Africa.
- There were 17 (4%) diagnoses among people who inject drugs (PWID) in 2017, a decrease from the numbers in 2016 (21) and from 2014-2015 when there was an outbreak of HIV in Dublin among homeless drug users.
- The prevalence of HIV in Ireland is not known, but was estimated in 2018 to be 7,205 people (95% Confidence Interval: 6,456 to 8,056).
- While comparing favourably with the WHO European region, Ireland has yet to meet the UNAIDS has set '90-90-90' targets for HIV diagnosis and treatment (90% of people with HIV know their status, 90% of those who know their status on ART, 90% of those on ART virally suppressed [<200copies/µl]). In Ireland it is estimated that 87% know their status, of which 83% (95% CI: 74.5% to 93.0%) are on antiretroviral therapy (ART) and 95% are virally supressed.

- The Men who have sex with men Internet Survey Ireland 2015 (MISI 2015) was a large-scale community based survey among adult MSM living in Ireland. This survey estimated that the HIV prevalence in MSM who have been tested is 7.8%, with an overall prevalence (tested and untested) of 5%. This is very similar to UK MSM prevalence (7.7%).
- Only 67% of MSM were sure of their HIV status in the MISI 2015 survey. Of HIV positive men, 79% were currently on ART, and of those on ART, 91% were virally suppressed.
- Very little data were identified on other populations at substantial risk, such as PWID, sex workers or prisoners.

3.1 Introduction

HIV infection is a notifiable disease in Ireland and is of major public health importance. The objective of this chapter is to describe the epidemiology of HIV infection in Ireland. First the notification rate of HIV infection is described (Section 3.2) and then the number of people living with HIV in Ireland (i.e., the prevalence of HIV infection) is described (Section 3.3). Finally, the proportion of gay, bisexual and other men who have sex with men (MSM) who may be eligible for PrEP is described (Section 3.4).

Most of the data on the epidemiology of HIV in Ireland come from published reports by the Health Protection Surveillance Centre (HPSC) including collaborations between the HPSC and the HSE's Sexual Health and Crisis Pregnancy Programme (SHCPP) and the Joint United Nations Programme on HIV and AIDS (UNAIDS). Important published survey data include the Men who have sex with men Internet Survey Ireland 2015 (MISI 2015)[30] and the Healthy Ireland Survey 2017.[31]

3.2 HIV notifications in Ireland

3.2.1 HIV testing and case definition

HIV infection became a notifiable disease in Ireland in September 2011. As a consequence, all clinicians and clinical directors of laboratories have a statutory obligation to notify all new diagnoses of HIV to the Health Protection Surveillance Centre (HPSC).[32] Acquired immunodeficiency syndrome (AIDS) is *not* a notifiable disease; however, the stage of infection should be reported on HIV surveillance forms for all new HIV diagnoses. From January 2012 onwards, only AIDS-defining illnesses that occur at the time of HIV diagnosis have been recorded and included in reports by the HPSC.

Fourth generation assays that simultaneously test for anti-HIV antibodies and the p24 antigen are recommended for HIV screening. Assays available in Europe have excellent sensitivities (99.78–100%) and specificities (99.5–99.93%).[33] Following a reactive screening test for HIV, confirmatory testing should always be undertaken in a laboratory with experience in HIV confirmation. In Ireland, the National Virus Reference Laboratory (NVRL) undertakes all HIV confirmatory testing. Since January 2015 (for HSE East) and January 2016 (for all other HSE areas), the NVRL notify new diagnoses of HIV based on confirmatory testing on a single sample (previously two separate samples were required) and then notify the relevant Department of Public Health).[1]

Once the NVRL confirms a new diagnosis, they enter relevant information into the Computerised Infectious Disease Reporting (CIDR) system.[34] The CIDR is a

confidential name-based surveillance system for managing infectious disease notifications in Ireland. CIDR has received ISO 27001 accreditation which is a European certification for best practice in information security and system availability.

All HIV-exposed infants are referred to the Rainbow Clinic at Our Lady's Children's Hospital in Crumlin. Once a new paediatric HIV diagnosis has been confirmed by the clinic, it is notified directly by the Rainbow Clinic to the relevant Department of Public Health. Paediatric infections are not notified to the CIDR by the NVRL.

3.2.2 Notification rate in 2017

Due to the fact that data on HIV diagnoses in 2018 are provisional at present (see Section 3.2.2), the most recent year with complete data is 2017. Data presented in this section are taken from the *HIV in Ireland 2017 Annual Epidemiological Report*, published by the HPSC.[35]

There were 492 new HIV diagnoses notified in Ireland in 2017, giving rise to a notification rate of 10.3 per 100,000 population (based on Irish census data). The notification rate for the period 2015 to 2017 ranged from 10.1 to 10.5 per 100,000.

Prior to this, there was a large increase (30%) in notifications between 2014 and 2015. A change in the case definition for surveillance which was introduced in 2015 in HSE East (and all other HSE areas in 2016) may partly explain this increase. Previously, confirmatory testing by the NVRL was required on two separate samples prior to notification. From January 2015 onwards, confirmatory testing by NVRL on one sample was sufficient prior to notification.

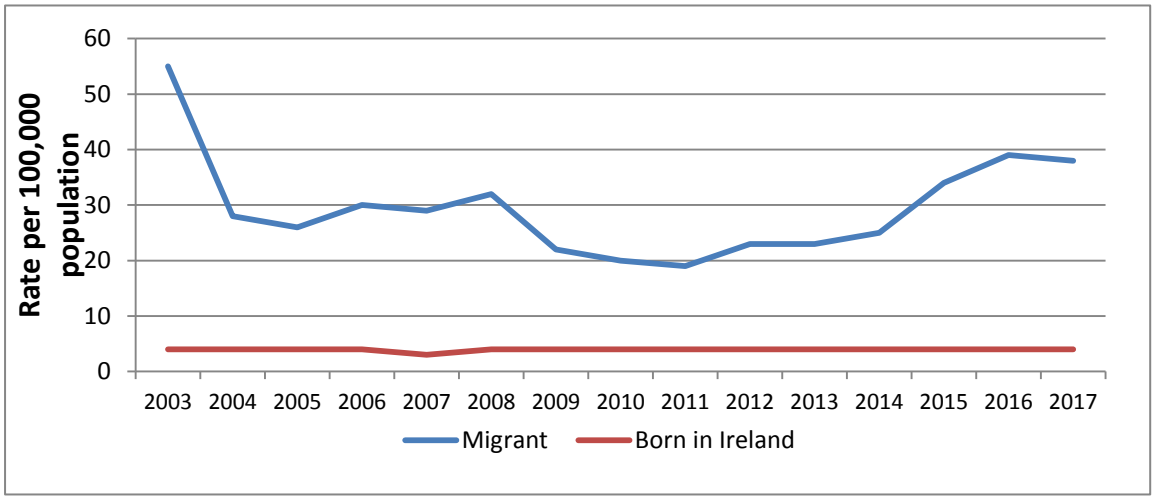
In 2017, 76% (n=376) of HIV diagnoses were in men and 24% (n=116) were in women, with a male to female ratio of 3.2. Men had higher age-specific rates than women in all age groups. The median age of adult cases at HIV diagnosis was 35 years (range: 18 to 75 years). Eight percent of HIV diagnoses were in young people (15-24 years) and 14% were in those aged 50 years and older. Additional demographic data related to diagnoses in 2017 is provided in Appendix 2.

Information on probable route of transmission was available for 90% (n=442) of diagnoses. Among all notifications, sex between men was the predominant mode of HIV transmission (53%). Notifications among MSM decreased by 4% between 2016 and 2017. Heterosexuals accounted for 33% of diagnoses, an increase of 13% compared with 2016. Four per cent of notifications were among people who inject drugs (PWID). There were no cases where the route of transmission was reported as mother to child transmission (MTCT).

In terms of region of birth, 26% (n=130) of people diagnosed with HIV were born in Ireland, 63% (n=308) born outside of Ireland and 11% (n=54) did not have information on country of birth. Geographic origin varied by route of transmission. The majority (66%) of MSM were born in Ireland or Latin America. The majority of heterosexual females (74%) were born in sub-Saharan Africa with roughly equal proportions of heterosexual males born in Ireland (43%) and sub-Saharan Africa (40%). The majority of PWID (76%) were born in Ireland or Central and Eastern Europe.

Figure 3.1, below, demonstrates the trends in the rate of notification for Irish born and migrants over the last fifteen years (2003-2017). The rate of diagnosis among those born in Ireland has remained stable since 2003, ranging from 3.4 to 4.2 per 100,000. There has been much greater fluctuation in the rate among migrants, increasing from 18.4 in 2011 to 38.4 per 100,000 in 2016, reversing a previous downward trend.

Figure 3.1. Trend in rate of HIV diagnosis by migrant status, 2003 to 2017

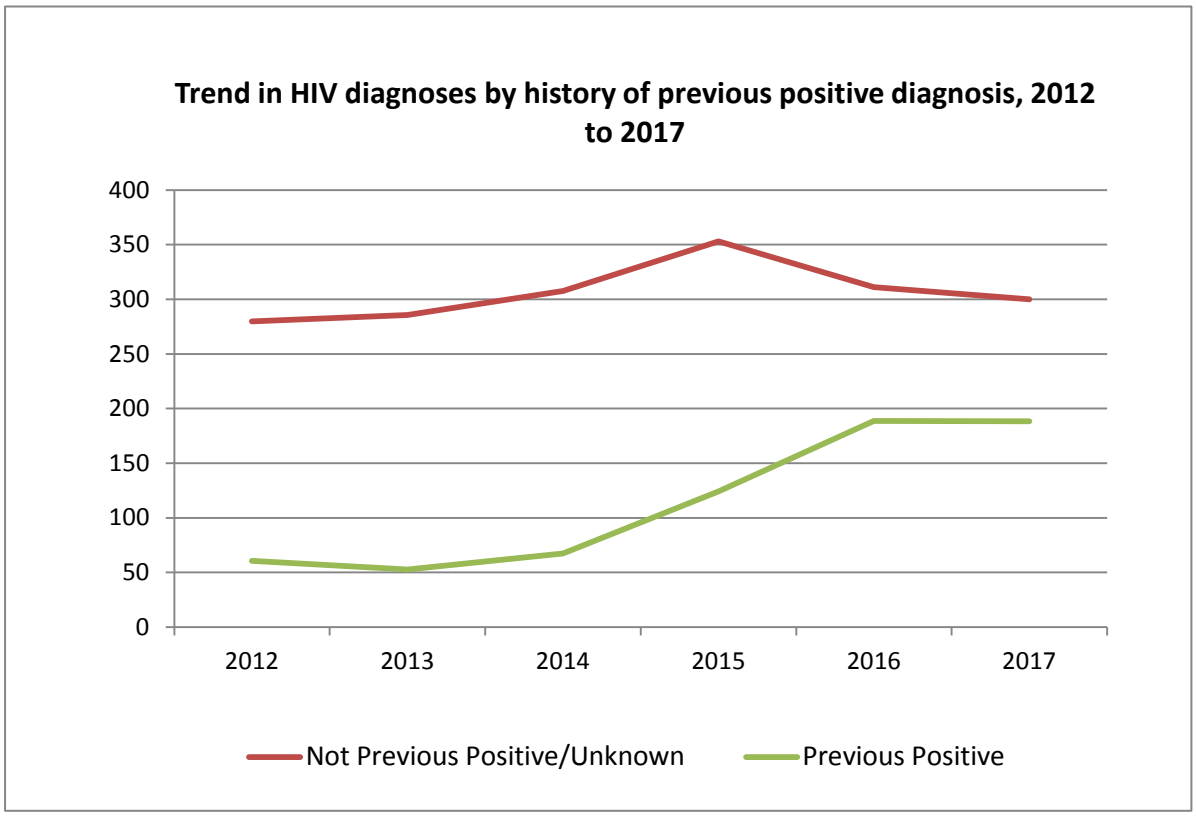


HSE East (counties Dublin, Wicklow and Kildare) consistently reports higher diagnosis rates than other regions. In 2017, 346 new HIV cases (70%) were diagnosed in people living in HSE East giving a rate of 20.2 per 100,000 population. This was almost twice the national rate (10.3 per 100,000).

Notifications of HIV to the HPSC include all people who are diagnosed HIV positive for the first time in Ireland and include a number of people who have been previously diagnosed HIV positive abroad. The number previously positive has continued to increase in recent years, from 15% (n=51) in 2012[36] to 39% (n=192) in 2017.[35]

Figure 3.2 demonstrates the trend of “previous positive” and “new diagnosis” (not previously positive or unknown) for the last six years (2012-2017). In 2017, the number of cases with no previous history of HIV diagnosis abroad (new diagnoses) decreased by 4% compared with 2016 (from 313 to 302 cases). Since 2015, data have been collected on whether a person has transferred their HIV care from another country to a service within Ireland. Thirty four percent of people diagnosed in 2017 were “transfer of care”. This represents 88% of those who were previously diagnosed HIV positive abroad.

Figure 3.2. Trend in HIV notifications by history of previous positive diagnosis, 2012 to 2017



3.2.2.1 HIV infection by risk group

This section reports characteristics of HIV diagnoses by risk group. Further demographic characteristics of these groups are provided in Appendix 2.

Men who have sex with men (MSM)

MSM remain the population most affected by HIV in Ireland. In 2017, the HPSC were notified of 262 HIV cases among MSM, representing 53% of all notifications they received that year. The majority of these men were born abroad (68%), with the highest number of these from Latin America (55%).

Forty two percent of the notifications received by the HPSC in 2017 in MSM had a previous HIV diagnosis abroad and 91% of these had transferred their HIV care from abroad to Ireland. Therefore, 58% of notifications in the MSM group were new diagnoses (n=151). Among MSM without a previous HIV positive diagnosis, there was a small reduction in diagnoses in recent years (14% reduction in notifications between 2015 and 2017).

Heterosexuals

Heterosexual transmission accounted for 33% (n=163) of HIV notifications to the HPSC in 2017, with 100 (61%) among females and 63 (39%) among males. Similar to the MSM group, 41% of heterosexual cases notified to the HPSC were previously diagnosed HIV positive abroad and 85% of these people transferred their care to Ireland. The majority of heterosexual cases were born in sub-Saharan Africa (61%), an area of the world which has a generalised HIV epidemic.

People who inject drugs (PWID)

There were 17 notifications (4% of all diagnoses) among PWID in 2017, 14 (71%) among males and three (29%) among females. This is a decrease compared with the number of diagnoses among PWID in 2016 (n=21). This continues the decrease in new cases compared with 2014 (n=27) and 2015 (n=49) when there was an outbreak of HIV among homeless PWID living in Dublin. The outbreak was declared over in February 2017. Of note, parenteral transmission of HIV is out of scope of this HTA and only HIV infection in PWID where the risk factor is sexual is considered.

3.2.2.2 Morbidity and mortality

Co-infections

Co-infections with other sexually transmitted infections (STIs) are common at time of diagnosis. Among MSM, 23% were co-infected with an acute bacterial STI (chlamydia, gonorrhoea and/or early infectious syphilis) in 2017. Over 70% of PWID were co-infected with hepatitis C and 7% of heterosexuals were co-infected with tuberculosis.

Clinical stage of infection at diagnosis

Of all HIV notifications in 2017, 52% (n=255) were asymptomatic, 12% (n=61) were symptomatic (non-AIDS), 6% (n=29) had an AIDS-defining illness, 2% (n=11) had an acute seroconversion illness and the clinical stage was not reported for the remaining 27% (n=135). Of the 29 people with an AIDS-defining illness at the time of HIV notification, 13 were MSM, 12 were heterosexual, one was a PWID and the

risk group for three was unknown.

Late presentation and advanced infection

Late diagnosis refers to a CD4 count of less than 350 cells per microlitre at diagnosis or an AIDS-defining illness at diagnosis (excluding those with acute HIV infection). Advanced infection refers to a CD4 count of less than 200 cells per microlitre at diagnosis or an AIDS-defining illness at diagnosis (excluding those with acute infection).

Where information on CD4 count or AIDS defining illness at diagnosis was available, 41% of all notifications in Ireland in 2017 were classified as late presenters and 22% as having advanced HIV infection. The proportion presenting late and the proportion presenting with advanced infection was higher than 2016 (late presenter: 38%; advanced stage: 19%). Among the people who did not have a previous positive diagnosis, the proportion who presented late was 55% including 32% who presented with advanced HIV infection.

Deaths

Data on deaths are obtained from either clinician's reports via enhanced surveillance forms or from data reported to the Central Statistics Office (CSO). Of note, it is not possible to link these two sources of information. Data from enhanced surveillance forms in 2017 documented that three people (all male) died at the time of HIV notification.

Data from CSO Vital Statistics reported that there were 11 deaths reported to the CSO in 2017 where the cause of death was AIDS or HIV, seven males and four females.

3.2.3 Historical notifications

Between 1982 to the end of 2017, a total of 8,826 HIV notifications were received in Ireland.[35] However, this number does not represent the number of people living with HIV in Ireland, as it does not take factors such as death and migration into account (see Section 3.3 for prevalence estimates).

UNAIDS estimated that 7,205 people (95% confidence intervals: 6,456-8,056) were living with HIV in Ireland at the end of 2017 with 13% of these people unaware of their infection.[37]

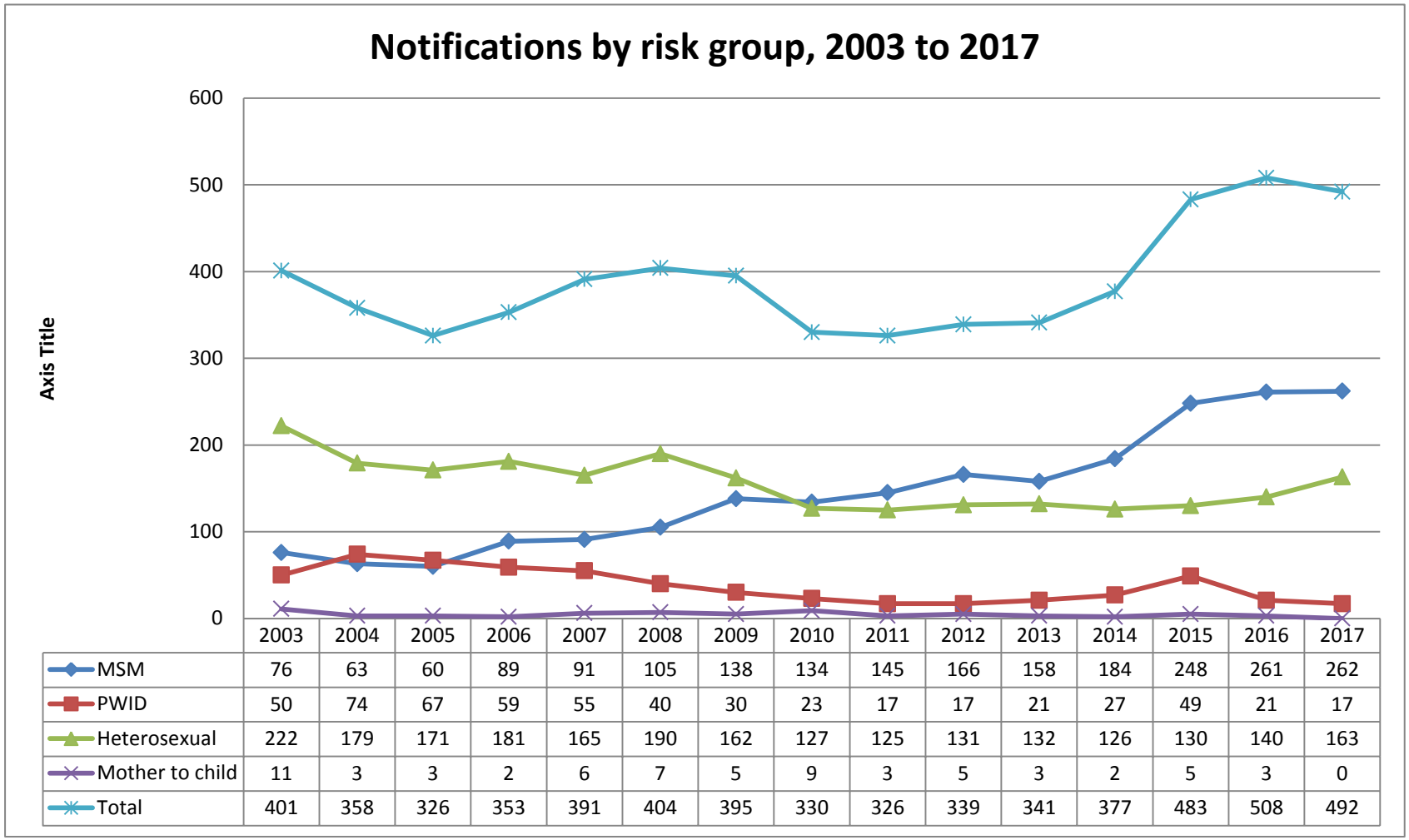
Table 3.1 and Figure 3.3 give the historical number of notifications by risk group (that is, probable route of transmission).

Table 3.1. Number and proportion of HIV notifications by risk group, 2003 to 2017

Risk group	MSM		PWID		Heterosexual		Mother to child		Unknown /other		Total
Year	N	%	N	%	N	%	N	%	N	%	
2003	76	19	50	12.5	222	55.4	11	2.7	42	10.5	401
2004	63	17.6	74	20.7	179	50	3	0.8	39	10.9	358
2005	60	18.4	67	20.6	171	52.5	3	0.9	25	7.7	326
2006	89	25.2	59	16.7	181	51.3	2	0.6	22	6.2	353
2007	91	23.3	55	14.1	165	42.2	6	1.5	74	18.9	391
2008	105	26	40	9.9	190	47	7	1.7	62	15.3	404
2009	138	34.9	30	7.6	162	41	5	1.3	60	15.2	395
2010	134	40.6	23	7	127	38.5	9	2.7	37	11.2	330
2011	145	44.5	17	5.2	125	38.3	3	0.9	36	11	326
2012	166	49	17	5	131	38.6	5	1.5	20	5.9	339
2013	158	46.3	21	6.2	132	38.7	3	0.9	27	7.9	341
2014	184	48.8	27	7.2	126	33.4	2	0.5	38	10.1	377
2015	248	51.3	49	10.1	130	26.9	5	1	51	10.6	483
2016	261	51.4	21	4.1	140	27.6	3	0.6	83	16.3	508
2017	262	53.3	17	3.5	163	33.1	0	0.0	50	10.2	492

Source: *HIV in Ireland 2017 Annual Epidemiological Report*, published by the HPSC

Figure 3.3. Historical HIV notifications in Ireland, 2003-2017, by possible route of transmission



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
MSM	76	63	60	89	91	105	138	134	145	166	158	184	248	261	262
PWID	50	74	67	59	55	40	30	23	17	17	21	27	49	21	17
Heterosexual	222	179	171	181	165	190	162	127	125	131	132	126	130	140	163
Mother to child	11	3	3	2	6	7	5	9	3	5	3	2	5	3	0
Total	401	358	326	353	391	404	395	330	326	339	341	377	483	508	492

Source: *HIV in Ireland 2017 Annual Epidemiological Report*, published by the HPSC

3.2.4 Recent infection

In order to monitor the ongoing transmission of HIV, it is important to determine the proportion of new diagnoses which are recent HIV infections. Recent Infection Testing Algorithms (RITA) attempt to differentiate recent from longer standing infections. They combine results of recent infection assays and supplementary laboratory and clinical information that together are used to classify a HIV infection as likely to be recent or not recent. In addition, the HIV p24 antigen test which is designed to detect a protein (the p24 protein) associated with HIV can be used to indicate acute infection with HIV.

The HPSC reports recent infections in Ireland using the Recent Infection Testing Algorithm (RITA) or a p24 antigen positive status.[38] In 2017, it was estimated that 13% of HIV diagnoses (of those tested) were likely to be recent infections (within four months), using the RITA or a p24 antigen positive status. By probable routes of transmission, MSM had the highest proportion of likely recent cases (16%) followed by PWID (14%). Higher proportions of likely recent infections were also seen in young people (15-24 years) (29%); people born in Ireland (23%); and people who acquired their infection in Ireland (28%).

3.3 Prevalence of HIV in Ireland

Limited data were retrieved on the prevalence of HIV in Ireland. In the absence of national prevalence data, estimates are based on three sources: a study by Tuite et al. (2015)[39], a national treatment audit (2018)[40] and modelling estimates carried out by UNAIDS (2018).[37]

3.3.1 Study by Tuite et al. 2015

The earliest study to estimate the national prevalence of HIV in Ireland was published in 2015.[39] The primary objective of the study was to retrospectively identify the number of patients accessing specialist ambulatory care for HIV infection in Ireland over a 12-month period between July 2009 and June 2010.

The six sites for specialist adult (age 17 or over) HIV care in Ireland were audited: St James's Hospital, Mater Misericordiae University Hospital and Beaumont Hospital (all in Dublin) and Cork University Hospital, Galway University Hospital and Limerick Regional Hospital (outside of Dublin). In Ireland, all newly diagnosed adult patients are referred to one of these six centres for care. In total, 3,254 patients were identified as accessing specialist ambulatory over this period; 81.1% accessed care in Dublin (53.6% at St James's Hospital, 16.5% at Mater Misericordiae University Hospital, 11.0% at Beaumont Hospital), whilst 18.8% accessed care outside of Dublin (11.2% at Cork University Hospital, 5.2% at University College Hospital Galway and 2.4% at Limerick Regional Hospital).

For known HIV cases, the crude prevalence rate amongst 15 to 59-year olds was estimated at 1.09 per 1,000 nationally and 2.25 per 1,000 in the Dublin area.

A limitation of this study, however, was that patients who did not receive outpatient care, either because they are not engaged in care or they only accessed inpatient care, were not captured by the audit. There is a large discrepancy between the number of patients identified and the number of new diagnoses ever reported to the HPSC at the time of the study (n=6,979). Even taking into consideration natural attrition due to reported deaths (505 recorded deaths at the time of the study) and emigration, there remained a large proportion of patients unaccounted for.

3.3.2 Treatment audit – 2018

In 2018, a national audit of all patients who attended HIV treatment services in the previous year was undertaken, using standardised definitions recommended by the European Centre for Disease Prevention and Control (ECDC).[40] This study included the six specialist treatment centres previously audited, in addition to St Vincent's

University Hospital, Dublin, and the joint paediatric HIV service of Our Lady's Children's Hospital, Crumlin and Temple St. Children's University Hospital, Dublin. This large-scale audit measured the total number of patients attending HIV services in 2017. Additionally, treatment outcomes were documented: the proportion of patients who were receiving antiretroviral therapy (ART) and the proportion of patients who were virally suppressed were recorded.

A total of 5,317 patients attended HIV services in 2017, significantly higher than previously recorded. Of these, 98.3% (n=5,227) were on ART and 95.4% (n=4,986) of these were virally suppressed (defined as fewer than 200 copies of HIV RNA per millilitre of blood). Additionally, 90.6% (n=4,735) of those on ART had an undetectable viral load (defined as fewer than 50/mL HIV RNA copies). Viral suppression greatly reduces the risk of onward HIV transmission.[41]

3.3.3 UNAIDS 2018

In 2018, the Joint United Nations Programme on HIV and AIDS (UNAIDS) modeled HIV incidence curves to provide the most comprehensive estimate of the prevalence of HIV (both diagnosed and undiagnosed) in Ireland to date.[37] This was accomplished by close collaboration between UNAIDS and the HPSC and the CSO. To develop the estimates for Ireland, the HPSC provided HIV case-reporting data and other data including the number of adults and children on ART and the number of women accessing services for the prevention of mother-to-child transmission (PMTCT). UNAIDS also used vital registration data (deaths) from the CSO. UNAIDS modeled this data using their 'Spectrum' software, an epidemiological modeling tool that was designed to assist countries in mapping their HIV epidemic.

UNAIDS Spectrum estimated that the total population in Ireland living with HIV was 7,205 (95% CI: 6,456 to 8,056) in 2017. By gender, approximately 2,400 women (95% CI: 2,200 to 2,700) and 4,800 men (95% CI: 4,100 to 5,400) were living with HIV (aged 15+). This represented 0.2% of all adults, between 0.1 and 0.2% of all women and between 0.2 and 0.3% of all men.

The proportion living with diagnosed HIV was estimated at 87.1% (n=6,276 people, 95% CI: 5,623 to 7,017) and the proportion with undiagnosed HIV was 12.9% (n=929 people; 95% CI: 833 to 1,039). Of the estimated 6,276 (95% CI: 5,623 to 7,017) people diagnosed with HIV, an estimated 83.3% (95% CI: 74.5% to 93.0%) were on antiretroviral therapy (ART).

Of the 5,227 people on ART, 95.4% were virally suppressed (data obtained from the 2018 Treatment Audit). Therefore, it was estimated that 73% (95% CI: 65 to 81%; approximately 5,200 people) of all people living with HIV were receiving ART and

69% (n=5,000) were virally suppressed.

The inputs were modified in an iterative process between HPSC and UNAIDS so that the best fit to the data could be obtained. A limitation of this type of epidemiological modeling is that it is particularly sensitive to inward and outward migration. This is of particular relevance in Ireland where a large proportion of people newly diagnosed with HIV in Ireland are not born in Ireland and there is considerable inward and outward migration of HIV positive people. The SPECTRUM modeling tool is being improved on an ongoing basis and UNAIDS are currently working to determine how the model can better account for migration.

3.3.4 Additional estimates by risk group

3.3.4.1 MSM

The 2017 Healthy Ireland survey, which is a nationally representative probability based survey, found that 4% of men had reported that their last sex was with a man.[31] In 2018, there were 1,802,395 men aged between 16 and 80 in Ireland.[42] Applying Healthy Ireland figures results in approximately 72,096 MSM in Ireland. The 2015 Healthy Ireland survey reported a higher estimate (6%).[43] Another survey of young people (My World Survey National Study of Youth Mental Health, 2012) reported that 4% of respondents were gay and a further 4% were bisexual.[44] These data, however, relate to both males and females aged 12 to 19 years.

HIV prevalence data in the MSM group in Ireland were obtained from the MISI 2015 survey.[30] MISI 2015 was a large-scale community based survey among adult MSM living in Ireland. It focused on HIV and STI testing, sexual behaviour, substance use, access to and use of HIV prevention interventions (condoms and PEP), knowledge about HIV and STIs, and awareness and impact of Irish health promotion materials. The survey was open for online self-completion by men 18 years and older for 13 weeks between 1 March and 31 May 2015. The analysis included 3,090 responses.

More than a third of respondents (36.7%) had never tested for HIV and 61.6% had not tested for HIV in the last year. A total of 4.9% of respondents had been diagnosed with HIV. Of those who ever tested for HIV, 7.8% were HIV positive and among those who tested in the last 12 months, 1.5% were HIV positive. Two thirds of men (67%) were definite about their HIV status, either positive or negative. However, the remaining third were unsure of their HIV status; 29% thought it was probably negative, 0.2% thought probably positive and 4% didn't know. The proportion of men who were unsure was significantly higher among those who never tested (38%) compared with those who had previously tested negative (32%).

HIV prevalence was highest in the 40 to 49 age category (13.6%). In terms of area of residence, prevalence was highest in Dublin (8.1%). Of HIV positive men, 79% surveyed were currently on ART, and of those on ART, 91% were virally suppressed. Of the HIV positive men, 41% had been diagnosed late (CD4 count < 350 cells per microlitre) including 22% diagnosed with advanced HIV infection (CD4 count < 200 cells per microlitre).

Table 3.2 outlines the key characteristics of the MSM group in Ireland. Almost five per cent of respondents had been diagnosed with HIV. Of those who ever tested for HIV, 7.8% were HIV positive and among those who tested in the last 12 months, 1.5% were HIV positive.

Table 3.2. Prevalence estimates in MSM group

Epidemiological parameter	Value	Source
Male MSM prevalence	4%	Healthy Ireland survey 2017[2]
Population size estimate	72,096	Source: CSO male population estimates 2018 (males aged 16 to 80) and 4% MSM estimate from Healthy Ireland Survey 2017
HIV prevalence	7.8%*	Source: MISI MSM Internet Survey 2015 (proportion who ever had a HIV test who tested positive)
Knowledge of HIV status**	67%	Source: MISI MSM Internet Survey 2015
ART coverage	79%	Source: MISI MSM Internet Survey 2015
ART who are virally suppressed	91%	Source: MISI MSM Internet Survey 2015

ART – antiretroviral therapy; HIV – human immunodeficiency virus, MSM – men who have sex with men.
*Of those tested
**Two thirds of men (67%) were definite about their HIV status, either positive or negative.

3.3.4.2 People who inject drugs

The estimated population of PWID in Ireland was 19,000 in 2014. [45] Of note, only sexual transmission of HIV is considered in this assessment. However, due to the higher prevalence of HIV in this group, PWID may also be at increased risk of sexual acquisition of HIV.

Over a 20 year period from 1997 to 2017, depending on the population and setting chosen, the HIV prevalence rate in PWID in Ireland ranges from 1% to 19% across studies.[46] It is evident that certain areas within Dublin's inner city have very high rates (19%) of HIV among PWID.[47] The most recent peer-reviewed study indicated a prevalence rate of 8%.[48] It is clear that although HIV prevalence among PWID has been measured by a number of studies, there is a lack of recent and nationally representative data.

An estimated 60.5% of all PWID have access to prescribed opioid substitution therapy and the average number of needles and syringes distributed per person who injects drugs is 168 per year.

3.3.4.3 Sex workers

Little is known on the scale of sex work in Ireland. Keller et al. studied sex workers over a 12-month period between December 2007 and December 2008.[49] The authors reported that there is a minimum of 1,000 women in indoor prostitution in Ireland at any one time. Global AIDS Monitoring 2018 (part of UNAIDS) estimated that 80% of sex workers were knowledgeable about their HIV status and 80% used condoms.[50] No up-to-date data on the number of sex workers living with HIV were

identified.

3.3.4.4 Prisoners

There were 3,738 prisoners in Ireland in November 2017.[51] HIV prevalence in this group is estimated to be 1.9%.[52] Therefore, approximately 71 prisoners may have HIV in Ireland. The rate of Hepatitis C and HIV co-infection is 1.3%, indicating sharing needles was the likely route of HIV transmission for the majority of this group.

3.3.5 International comparison

UNAIDS provides global epidemiological data on HIV. Ireland is in the Western/Central Europe and North America region for the purposes of analyses. Table 3.3 compares Ireland with the overall region in terms of HIV incidence and prevalence.[53] Overall prevalence is somewhat lower in Ireland relative to the rest of this region.

Table 3.3. Ireland and regional comparison

Epidemiological parameter	Ireland	Regional (West/Central Europe and N America)
HIV incidence (all ages)	0.1 per 1,000**	0.07 per 1,000*
HIV incidence (age 15 to 49)	0.2 per 1,000**[Ŧ]	0.15 per 1,000*
HIV prevalence (age 15 to 49)	0.2%*	0.3%*

Source: UNAIDS 2018 and HPSC.
*Relates to 2017 data.
**Relates to 2016 data
[Ŧ]Actual data are for 15 to 44 year olds

The most up-to-date data on regional comparisons for HIV treatment identified was an ECDC presentation on the HIV continuum of care in Europe and Central Asia, July 2018.[54] Table 3.4 compares Ireland to the WHO European region and WHO Western Europe for HIV diagnosis and treatment parameters.

Table 3.4. Ireland and Europe comparison

Epidemiological parameter	Ireland	WHO European region	WHO Western Europe
Proportion of people with HIV who know their status	87.1%	80%	86% (range: 74 to 93%)
Proportion of people who know their status on ART	83.3%	64%	90% (range: 58 to 100%)
Proportion of people on ART who are virally suppressed	95.4%	85%	92% (range: 32 to 98%)

Source: ECDC 2018
Key: ART – antiretroviral treatment; HIV – human immunodeficiency virus.

UNAIDS has set '90-90-90' targets for each of the three variables in Table 3.4 (90% of people with HIV know their status, 90% of those who know their status on ART, 90% of those on ART virally suppressed). Ireland has not reached the 90% target for the first two. However, Ireland compares favourably to the WHO European region as a whole, achieving higher figures for all targets. Ireland has achieved comparable success compared with the WHO Western Europe region, although significant variation between countries was noted.

Table 3.5 compares the MSM group in Ireland to select countries in the WHO Western Europe region and the USA, per UNAIDS 2018. Note that in Table 3.5, the proportion of MSM who know their HIV status is presented, which is not the same as the proportion with HIV who know their status (this estimate is presented in Table 3.4 for the general population). The proportion of MSM who know their status was obtained from MISI data, which noted 36.7% had never tested for HIV (and 61.6% had not tested for HIV in the last year).

Table 3.5. International comparison, MSM group

Epidemiological parameter	Ireland	UK	France	Spain	Germany	USA
HIV prevalence	7.8%*	7.7%	14%	11.3%	7.5%	14.5%
Proportion of MSM who know their HIV status	63.3%	88%	48.8%	NR	NR	NR
Proportion of people who know their status on ART	78.9%	84.1 %	77.8%	NR	87.6%	NR
Condom use	56.9%	60%	44.5%	76.5%	65.8%	42%

Source: UNAIDS 2018.
Key: ART – antiretroviral treatment; HIV – human immunodeficiency virus.

*Of those tested

These data indicate that Ireland most closely resembles the UK (MSM prevalence of 7.8% in Ireland compared with 7.7% in the UK).

3.4 MSM sexual behaviour data

A substantial volume of sexual behavior data among MSM was collected in MISI 2015.[30] Overall, 96% of those responding to the MISI survey reported ever having sex with a man with 90% reporting sex with a man in the last 12 months. Among respondents who reported ever having sex with a man, 71% had condomless anal intercourse (CAI), 55% had CAI within the last 12 months and 47% had CAI within the last six months. Fifty-five percent of respondents had sex with one or more steady male partners in the last 12 months. Of the respondents who had CAI with a steady male partner in the last 12 months, 15% had non-concordant CAI (that is, where HIV status is different or unknown). For men who had CAI with a non-steady partner, 54% had non-concordant CAI.

In April 2017, the HSE SHCPP and the HPSC estimated the population likely to avail of a PrEP programme in the first year of its availability in Ireland in its report *HIV Pre-Exposure Prophylaxis (PrEP) in Ireland: PrEP estimates for populations at risk of sexual acquisition of HIV,* or the 'PrEP Cascade', using the MISI 2015 dataset.[55] In this report, French PrEP eligibility criteria were applied to the MISI dataset, with some adaptations. An estimated 23% (95% CI: 22.7 to 23.3%) of respondents were found to be eligible, or 706 out of 3,045 respondents (further details are presented in Table 3.6).

Table 3.6. French PrEP eligibility criteria applied to MISI dataset

Survey questions	MISI data N (%)
Aged 18-64 years	3,045 (100)
Man/transman	3,045 (100)
Never received an HIV test result/last test was negative*	2,870 (94)
CAI with 2 or more non-steady partners in last 12 months**	370 (12)
Diagnosed with an STI in last 12 months	243 (8)
Ever treated with PEP***	119 (4)
Use of crystal meth, GHB/GBL, mephedrone, ketamine in last 12 months****	181 (6)
Eligible for PrEP‡	**706 (23)**

*Number of men who reported to be HIV negative or did not know their HIV status
French implementation guidance is CAI with two or more partners in the **past six months
***Using MISI variable "ever used PEP" as a proxy for multiple PEP as in French PrEP eligibility criteria
**** French PrEP eligibility criteria broader in terms of drugs, and narrower in terms of their use during sex “use of drugs during sexual intercourse”
‡Number eligible for PrEP based on overlapping survey responses

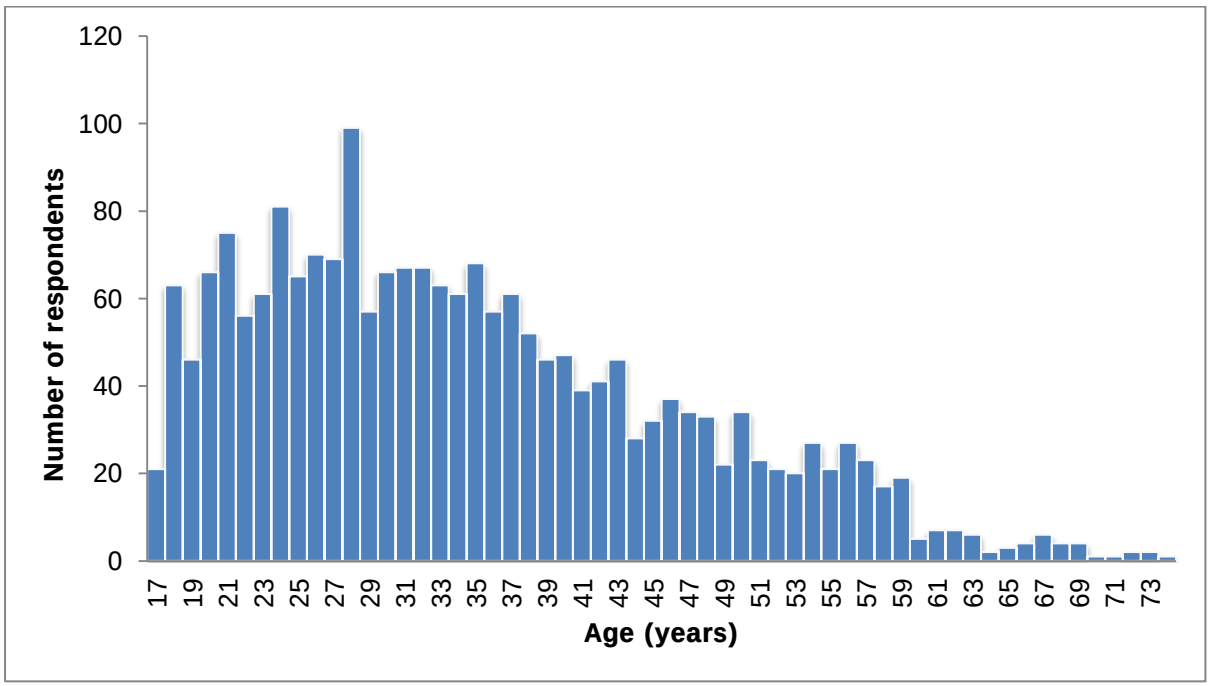
While the design of the MISI 2015 was robust and comparable to similar international studies enrolling MSM, there are a number of limitations to the methodological approach and the sampling strategy that should be considered when interpreting the findings. The convenience sampling strategy used will have introduced selection bias, as participants who took part in the survey are more likely to have access to gay social media, social networks and gay social settings. Additionally, the survey was only provided in English.

Since then, in 2017, Ireland participated in a pan-European MSM survey, the European Men who have sex with men Internet Survey (EMIS 2017), the results of which are expected later this year. EMIS 2017 was an online cross-sectional behavioural surveillance survey of MSM, conducted across Europe and elsewhere including Ireland, and available in 33 languages. The overall aim of EMIS 2017 was to generate data useful for the planning of HIV and STI prevention and care programmes and for the monitoring of national progress in this area by describing the level and distribution of HIV transmission risk and precautionary behaviours.

In Chapter 6, Section 6.2.1, the target population for PrEP in Ireland is estimated. One necessary parameter is the proportion of MSM who would be considered eligible for PrEP (as in, at substantial risk of sexual acquisition of HIV). Following discussion at the EMIS Ireland 2017 Steering committee meeting on 25 March 2019, there was agreement that the EMIS Ireland 2017 dataset should be used to provide the most up to date percentage of MSM at substantial risk of sexually acquired HIV and therefore eligible for PrEP. The following results were provided to HIQA by the EMIS Ireland 2017 Steering committee (please see the acknowledgements section of the report for additional details relating to the EMIS Ireland 2017 study).

The EMIS Ireland 2017 report included 2,083 qualifying cases of men/trans-men aged between 17 and 74 with respondents from each county in Ireland. Fewer than 1% identified as trans-men. Figure 3.4 shows the distribution of ages across the entire sample.

Figure 3.4. Age distribution of respondents (N=2,083)



The median age of respondents was 33 years (range 17 to 74 years) and the mean was 34.7 years. Table 3.7 outlines the distribution of respondents by age group.

Table 3.7. Distribution of respondents by age group (N=2,083)

Age group	Number	Percentage
<25	469	22.5
25-39	968	46.5
40-54	484	23.2
≥55	162	7.8

Seventy five percent of respondents were born in Ireland and 25% were born abroad. Of those born abroad, 38% were born in European countries (excluding Ireland and the UK) and 26% were born in the UK (see Table 3.8). Eighteen percent of men born abroad were from Latin America and the Caribbean. Respondents not born in Ireland were born in 65 different countries. The most common countries of birth were England (n=80), Brazil (n=62), Northern Ireland (n= 34), Poland (n=29) and Germany (n=25).

Table 3.8. Distribution of respondents born outside of Ireland by region of birth as per WHO classification (N=514, missing n=3)

Region of birth	Number	Percentage
Europe (excluding Ireland and UK)	193	37.5
United Kingdom	134	26.1
Latin America & Caribbean	95	18.5
Canada, USA	30	5.8
Western Pacific Region (excluding Australia and New Zealand)	29	5.6
African region	16	3.1
South East Asia	8	1.6
Eastern Mediterranean	7	1.4
Western Pacific Region: Australia and New Zealand	2	0.4

For use in this HTA, the EMIS study authors applied Irish PrEP eligibility criteria (as above) to the Irish portion of responses for the purposes of economic modelling. Table 3.9 shows the number and percentage of MSM at substantial risk for sexually acquired HIV and eligible for PrEP using the Irish criteria. The number eligible for PrEP based on overlapping survey responses was 647 (31%). Note that a number of adjustments to the Irish PrEP eligibility criteria had to be made based on the EMIS Ireland 2017 dataset.

Table 3.9. Eligibility for PrEP using the EMIS Ireland 2017 dataset

Criteria used	EMIS 2017 N (%)
Aged ≥ 17 years	2,083 (100)
Man/ transman	2,083 (100)
Sexually active	2,083 (100)
Never tested for HIV/last HIV test negative	1,929 (93)
ONE of the following	
CAI with ≥ 2 non-steady partners last 12 months*	457 (24)
STI diagnosis in last 12 months	252 (13)
Ever had ≥2 treatments of PEP **	42 (2)
Use of stimulant drugs during sex last 6 months**	181 (9)
Eligible for PrEP†	**647/2083 (31)**

* Irish eligibility criteria is CAI with two or more casual partners in the past six months.
** Irish eligibility criteria is reported use of PEP over last 12 months
***The stimulant drugs included in this definition were: ecstasy/MDMA, cocaine, amphetamine (speed), crystal methamphetamine (Tina, Pervitin), mephedrone and ketamine. Irish eligibility criteria define drugs used during sex as "crystal meth, GHB/GBL, mephedrone and ketamine"
† Number eligible for PrEP based on overlapping survey responses

Note that the results of EMIS and MISI are not directly comparable, as different eligibility criteria for PrEP were used to identify the eligible population. Other reasons why the two surveys are not directly comparable include differences in study design (for example, MISI was only available in English and EMIS was available in 33 languages), differences in the age profile of the respondents, and other demographic factors such as differences in the proportion who were born in Ireland. It is, nonetheless, of concern that high risk behaviour has increased in the MSM group in Ireland over a relatively short time period. The number who reported 'CAI with two or more non-steady partners in past 12 months' doubled, from 12% in MISI 2015 to 24% in EMIS 2017. A smaller increase was noted for acute STI diagnoses and there may have been an increase in chemsex use.

3.5 Discussion

In general, good-quality data were retrieved on overall population-based estimates of HIV notifications and HIV prevalence in Ireland, including epidemiological data specific to the men who have sex with men (MSM) group. Estimates were also retrieved on the proportion of MSM likely to avail of PrEP in Ireland, if a programme were introduced. Unfortunately, very limited data were identified on other groups at substantial risk of HIV acquisition.

HIV infection remains a significant public health threat in Ireland. The HIV notification rate in Ireland has remained relatively stable between 2015 and 2017, following a large increase between 2014 and 2015. A change in the case definition used by the HPSC (whereby confirmatory HIV testing required only one sample as opposed to two) and a rise in HIV testing may partly explain the increase compared with the previous year. The rate of HIV in Ireland is high compared with other countries in Western Europe, many of which have seen declines in their HIV rates in recent years.[47] This highlights the need to consider combination prevention approaches in order to halt transmission of HIV.

Migration plays an important role in the changing epidemiology of HIV in Ireland. Overall, 63% of the notifications to the HPSC in 2017 were for individuals born outside Ireland (compared with 26% born in Ireland and 11% unknown country of birth). In the MSM group, 61% of the notifications received in 2017 were for individuals born outside Ireland, with the highest number from Latin America. Additionally, there has been an increase in the proportion of notifications who were

previously diagnosed HIV positive abroad: in 2017, these comprised 39% of all notifications. A majority of these had transferred their care to Ireland (88%). The proportion of MSM previously diagnosed HIV positive before arrival in Ireland has increased from 16% of cases in 2012 to 42% in 2017. Of those previously diagnosed HIV positive abroad in 2017, 91% were transferring their care to Ireland.

Between 2015 and 2017 there was a slight increase in HIV notifications among MSM (from 248 to 262). However, among MSM without a previous HIV positive diagnosis, there was a 14% reduction in notifications. This highlights that while notifications overall have risen in recent years, this does not reflect a true increase in HIV transmission due to the fact that many notifications in Ireland were already known to be HIV positive prior to arrival in the country. Nonetheless, given over 150 new diagnoses of HIV in MSM this would suggest that current HIV prevention strategies are insufficient to halt the spread of HIV, emphasising the need to consider combined prevention approaches that includes PrEP.

Given the increasing number of cases new to Ireland already known to be HIV positive, it is essential to focus on early engagement in care and immediate initiation of ART (or optimisation of therapy in those transferring care). The HSE recommends immediate ART initiation regardless of HIV count.[56] In addition to the clinical benefits of early ART initiation, viral suppression reduces onward HIV transmission. Maintaining an undetectable viral load is highly effective at preventing onward HIV transmission.[41]

It was noted that significant regional variation exists in Ireland, with HSE East consistently reporting higher rates than other regions. Regional variation in transmission rates has implications for the organisation of care.

HIV notifications reported by the HPSC accurately reflect all new cases of HIV infection that are detected by the health system in Ireland. However, the variable and often long time lag between infection and diagnosis means that HIV case surveillance does not directly reflect current patterns of virus transmission or incidence. Trends in HIV notifications reported by the HPSC may reflect true trends in incident infections, trends in uptake of HIV testing or both. Most individuals self-present for HIV testing, with the exception of certain groups, such as voluntary routine opt-out antenatal HIV testing (introduced nationally in April 1999[57]), opt-out emergency department testing for HIV, Hepatitis B and Hepatitis C (introduced at St James's Hospital in July 2015)[58] and routine testing of health care workers and blood donors. HIV incidence data is therefore incomplete and it is notable that more than a third of MSM in Ireland have never had a HIV test.

Significant work was undertaken in 2018 to estimate the prevalence of HIV in Ireland, which included modelling undertaken by UNAIDS (in collaboration with the HPSC and the SHCPP)[37] and a comprehensive national treatment audit.[40] In summary, 7,205 (95% CI: 6,456 to 8,056) people are estimated to be living with HIV in Ireland; 87.1% which are aware of their HIV status and 83.3% have initiated ART (UNAIDS 2018 data). Of these, 95.4% are virally suppressed (2018 treatment audit). UNAIDS has set a target of 90% for each of these three measures. While not achieving this target for the first two goals, Ireland compares favourably to the WHO Europe region as a whole.

UNAIDS used Spectrum, an epidemiological modeling tool, to calculate these estimates and has been calculating global HIV estimates since 2002. While there have been improvements in estimates over time, resulting from enhanced availability, quality and completeness of country data and modifications in modeling software, the quality of the results still depends on the quality of input data. There are concerns that the model does not capture sudden changes and that it does not adequately capture issues of migration, a significant contributor to the HIV epidemic in Ireland. Estimates also vary significantly according to the assumptions used in the model. It is notable that in Greece, a separate modeling tool created by the ECDC generated different estimates for people living with HIV, with the Spectrum estimates being lower and not capturing a recent HIV outbreak that occurred among people who inject drugs.

Regarding populations at significantly elevated risk of HIV acquisition, very little data were identified in any group other than MSM. Healthy Ireland, a nationally representative survey, found that 4% of men had reported that their last sex was with a man in 2017.[31] The true MSM proportion may be higher however, as the question posed by Healthy Ireland may not capture all bisexual men. The Men who have sex with men Internet Survey Ireland 2015 (MISI 2015) was a large-scale community based survey among adult MSM and provided a wealth of data on HIV and sexual behaviour in MSM in Ireland. Overall, 63.3% of respondents had ever had a test for HIV and 7.8% of those were HIV positive. Of HIV positive men, 79% surveyed were currently on ART, and of those on ART, 91% were virally suppressed. HIV prevalence and sexual behaviour in Irish MSM was found to be broadly comparable between Ireland and other Western European countries, in particular MSM in the UK.[59]

Two internet surveys were identified that gathered sexual behaviour data on MSM in Ireland (MISI 2015 and EMIS 2017 [unpublished data]). Provisional data from EMIS suggest an increase in high risk sexual behaviour in the MSM group compared with MISI (for example, CAI with two or more non-steady partners in the previous 12

months doubled, from 12% to 24%). A smaller increase was noted for acute STI diagnoses and there may have been an increase in chemsex use. Note that the results of EMIS and MISI are not directly comparable, as different eligibility criteria for PrEP were used to identify the eligible population. Other reasons why the two surveys are not directly comparable include differences in study design (for example, MISI was only available in English and EMIS was available in 33 languages), differences in the age profile of the respondents, and other demographic factors such as differences in the proportion who were born in Ireland.

These results of surveys like MISI and EMIS must be interpreted with caution due to the fact that they are not nationally representative samples and the sampling strategy should be considered carefully when interpreting the findings. The convenience sampling strategy used will have introduced selection bias, as participants who took part in the survey are more likely to have access to gay social media, social networks and gay social settings. In addition, as behaviour is self-reported, recall bias, social desirability bias and interpretation bias may be introduced. It is also possible that internet surveys under-represent populations such as migrants and older MSM. On the other hand, internet surveys may be better at exploring small subgroups and hidden behaviour (behaviours that are difficult to report, such as deliberately risky or violent behaviour). In any case, trends can be obtained when comparing with previous similar surveys and allows comparison with international surveys with similar design.

4 Systematic review of clinical effectiveness and safety of PrEP

Key points

- A systematic review undertaken to assess the clinical effectiveness and safety of oral PrEP retrieved 15 randomised control trials (RCTs) that compared PrEP with placebo, delayed PrEP or with another PrEP medication or dosing schedule. Four distinct patient populations were assessed. Six RCTs enrolled MSM, five enrolled heterosexual participants, three enrolled serodifferent couples and one enrolled people who inject drugs.
- Included studies involved 25,051 participants encompassing 38,289 person-years of follow-up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 8,239 (55%) received tenofovir/emtricitabine fixed dose combination and 6,823 (45%) received single agent tenofovir.
- Studies were conducted in high-, middle- and low-income countries. Prevalence of HIV varied widely across studies, with the highest rates noted in sub-Saharan Africa (23.1% in Botswana). Follow-up periods ranged from 17 weeks to 6.9 years.
- Overall, RCTs were judged to have a low risk of bias.
- Adherence varied greatly across studies. Plasma drug monitoring was considered the most objective measurement for adherence assessment: adherence by this measurement ranged from 25% to 88%. Trial-level adherence greater than 80% was selected a priori as 'high' adherence for the purpose of analyses.
- PrEP was found to be highly effective in preventing HIV acquisition in MSM with a risk reduction of 75% across all trials (relative risk (RR) 0.25, 95% confidence interval (CI): 0.1 to 0.61; data from six RCTs, high-quality evidence). In trials with adherence above 80%, risk was reduced by 86% (RR 0.14, 95% CI: 0.06 to 0.35; data from three RCTs, high-quality evidence).
- PrEP was found to be effective in preventing HIV acquisition in HIV-uninfected partners of serodifferent couples, with a risk reduction of 75% (RR 0.25, 95% CI: 0.14 to 0.46; data from two RCTs, high-quality evidence).
- PrEP was found to be effective in preventing heterosexual HIV transmission in one trial where adherence was high (RR 0.39, 95% CI 0.18 to 0.83; high-quality evidence). PrEP was not found to be effective in trials enrolling heterosexual participants where adherence was low.

- PrEP was found to be effective in preventing HIV transmission in people who inject drugs in the only trial retrieved that enrolled drug users, which was conducted in Bangkok. Risk was reduced by 49% (RR 0.51, 95% CI: 0.29 to 0.92; high-quality evidence). This trial may not be directly applicable to the Irish context due demographic differences and the high prevalence of HIV in people who inject drugs in Thailand.
- A meta-regression found that efficacy was strongly associated with trial-level adherence ($p<0.001$). On average, an increase in adherence of 10% increased efficacy by 13%.
- PrEP was found to be safe. PrEP did not increase the risk of 'any' adverse event (RR 1.01, 95% CI: 0.99 to 1.03), serious adverse events (RR 0.91, 95% CI 0.74 to 1.13) or death (RR 0.83, 95% CI: 0.6 to 1.15) compared with placebo.
- Adverse events were common in trials (78% of patients reported 'any' adverse event), while serious adverse events and deaths were rare. A reduction in creatinine clearance was noted in some trials; however, this returned to baseline upon discontinuation of study drug. No deaths occurred that were attributable to PrEP.
- Eleven trials measured changes in sexual behaviour. Studies showed either no change in condom use throughout the duration of the study (n=4 studies) or increases in condom use (n=4 studies). There was no difference in condom use between intervention and control arms.
- Six studies showed no change in the number of sexual partners throughout the duration of the study, four studies showed a slight reduction in number of sexual partners and one showed an increase. There was no difference between intervention and control arms.
- Five studies recorded changes in the incidence of STIs; no studies reported an increase in STIs or a between-group difference in STI diagnoses.
- In the only study to enrol intravenous drug users, a reduction in intravenous drug use, needle sharing and number of sexual partners was observed over the course of the study.
- Patients randomised to receive PrEP who had acute HIV infection at enrolment were at increased risk of developing resistance mutations to the study drug (RR 3.3, 95% CI: 1.17 to 8.27; high-quality evidence). Most conferred resistance to emtricitabine.

Summary of findings table: Efficacy of PrEP

Patient or population: HIV prevention in participants at substantial risk **Intervention**: PrEP **Comparison**: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				
HIV infection: MSM (all clinical trials)	40 per 1,000	**10 per 1,000** (4 to 24)	**RR 0.25** (0.10 to 0.61)	5,103 (6 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in MSM with a risk reduction of 75%
HIV infection: MSM, trials with high (>80%) adherence	66 per 1,000	**9 per 1,000** (4 to 23)	**RR 0.14** (0.06 to 0.35)	960 (3 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is highly effective in preventing HIV acquisition in MSM in trials with high adherence (over 80%) with a risk reduction of 86%
HIV infection: Serodifferent couples	20 per 1,000	**5 per 1,000** (3 to 9)	**RR 0.25** (0.14 to 0.46)	5,237 (2 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV acquisition in serodifferent couples with a risk reduction of 75%
Heterosexual transmission (all clinical trials)	41 per 1,000	**32 per 1,000** (19 to 53)	**RR 0.77** (0.46 to 1.29)	6,821 (4 RCTs)	⊕⊕⊕⊕ HIGH	PrEP is not effective in preventing heterosexual HIV transmission (all trials)
Heterosexual transmission: trials with high (>80%) adherence	31 per 1,000	**12 per 1,000** (6 to 26)	**RR 0.39** (0.18 to 0.83)	1,524 (1 RCT)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing heterosexual HIV transmission in trials with high adherence (over 80%) with a risk reduction of 61%
People who inject drugs	7 per 1,000	**3 per 1,000** (2 to 6)	**RR 0.51** (0.29 to 0.92)	9,666 (1 RCT)	⊕⊕⊕⊕ HIGH	PrEP is effective in preventing HIV transmission in people who inject drugs with a risk reduction of 49%

Summary of findings table: Efficacy of PrEP

Patient or population: HIV prevention in participants at substantial risk **Intervention**: PrEP **Comparison**: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings table: Safety of PrEP

Patient or population: HIV prevention in participants at substantial risk Intervention: PrEP Comparison: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				
Safety outcome: Any adverse event	776 per 1,000	784 per 1,000 (768 to 799)	RR 1.01 (0.99 to 1.03)	17,358 (10 RCTs)	⊕⊕⊕⊕ HIGH	Adverse events do not occur more commonly in patients taking PrEP compared with placebo. Adverse events were common in trials (78% of patients reporting 'any' event).
Safety outcome: Serious adverse events	81 per 1,000	73 per 1,000 (60 to 91)	RR 0.91 (0.74 to 1.13)	17,778 (12 RCTs)	⊕⊕⊕⊕ HIGH	Serious adverse events do not occur more commonly in patients taking PrEP compared with placebo. Serious adverse events occurred in 7% of patients in trials but most were not drug related.

Summary of findings table: Safety of PrEP

Patient or population: HIV prevention in participants at substantial risk **Intervention**: PrEP **Comparison**: no PrEP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Person-years of follow up (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PrEP	Risk with PrEP				
Safety outcome: Deaths	13 per 1,000	10 per 1,000 (8 to 15)	RR 0.83 (0.60 to 1.15)	12,720 (11 RCTs)	⨁⨁⨁◯ MODERATE [a]	Deaths did not occur more commonly in people taking PrEP compared with placebo in trials. No deaths were related to PrEP.
Safety outcome: Drug resistance mutations in patients with acute HIV at enrolment	53 per 1,000	174 per 1,000 (62 to 435)	RR 3.30 (1.17 to 8.27)	44 (5 RCTs)	⨁⨁⨁◯ MODERATE [b]	Patients randomised to receive PrEP who had acute HIV at enrolment were at increased risk of developing resistance mutations to the study drug. Most conferred resistance to emtricitabine.

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Imprecision was detected due to few observations. b. Imprecision was detected due to few observations. Additionally, only a minority of studies tested for resistance mutations.

4.1 Objective

The objective of this chapter is to assess the clinical effectiveness and safety of oral antiretroviral pre-exposure prophylaxis (PrEP) therapy to prevent HIV acquisition. A systematic review of randomised trials that assessed the efficacy and or safety of PrEP was undertaken to achieve this goal.

4.2. Methods

A systematic review of randomised controlled trials (RCTs) was performed.

4.2.1 Criteria for considering studies for this review

Table 1 outlines the population, intervention, comparison, outcomes, study design (PICOS) criteria for inclusion of studies. It was decided a priori that subgroups would be defined by population at risk of acquiring HIV (men who have sex with men [MSM], serodifferent couples, people who inject drugs [PWIDs] and heterosexuals).

Table 4.1. PICOS criteria

PICOS criteria: study selection	
Population	Anyone at elevated risk of HIV acquisition. Populations include: 1. men who have sex with men 2. serodifferent couples 3. people who inject drugs (PWIDs) 4. heterosexuals.
Intervention	Pre-exposure prophylaxis (any oral antiretroviral formulation): • tenofovir only versus placebo or no treatment • tenofovir + emtricitabine versus placebo or no treatment • tenofovir only versus tenofovir + emtricitabine.
Comparator	Placebo, no treatment or alternative oral PrEP medication (including alternative dosing schedule)
Outcomes	Primary outcome: HIV incidence Secondary outcomes: 1. adherence to PrEP (as measured by the primary studies, plasma drug concentration favoured over self-report) 2. adverse events associated with PrEP (frequency and type of adverse effects or complications, including 'any' adverse event, serious adverse events and deaths, as reported in primary studies) 3. incidence of other sexually transmitted infections (STIs) and behaviour change associated with PrEP administration (such as episodes of condomless anal intercourse, number

	of new sexual partners and recreational drug use). 4. viral drug mutations that confer resistance to tenofovir and or emtricitabine
Studies	Randomised clinical trials

Note: for the remainder of this assessment 'tenofovir/emtricitabine' refers to tenofovir and emtricitabine fixed dose combination.

4.2.2 Search methods for identification of studies

Electronic searches were conducted in Medline (PubMed), Embase, the Cochrane Register of Controlled Trials, CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), and Eurosurveillance reports. Furthermore, hand-searching of journals was also performed. Databases were searched on 31 July 2018.

The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for ongoing or prospective trials.

No restrictions were placed based on location of the intervention. No language restrictions were used. Articles in languages other than English were translated where necessary.

The detailed search strategies for each of the databases MEDLINE via PubMed, EMBASE and the Cochrane Central Register of Controlled Trials are provided in Appendix 3.1.

4.2.3 Data collection

Two reviewers independently read the titles, abstracts and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles were obtained for all citations identified as potentially relevant for inclusion. Both reviewers independently inspected these to establish the relevance of the articles according to the pre-specified criteria. Studies were reviewed for relevance based on study design, types of participants, interventions and outcome measures (see Table 4.1).

4.2.4 Data extraction and management

Data were independently extracted using an agreed data extraction proforma. Both reviewers verified the extracted data. Extracted information included the following:

- Study details: citation, study design and setting, time period and source of funding.

- Participant details: study population demographics, eligibility criteria for trial enrolment, risk characteristics, population size and attrition rate.
- Intervention details: type of drug, comparator, dosing schedule, duration and route of administration.
- Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP, adverse events ('any' events, serious adverse events and deaths), behavioural change (condom use, number of sexual partners and other STI infections) and study drug mutations that confer resistance to tenofovir and or emtricitabine.

Review Manager 5.3 software was used to record extracted data.[60] Data were independently extracted and entered into RevMan by both reviewers; all disagreements were resolved by discussion. Where appropriate, results were pooled using a random effects model to estimate Mantel–Haenszel risk ratios.

Appendix 3.2 provides additional details on the data collection, management and analysis plan as presented in the study protocol.

4.2.5 Assessment of risk of bias in included studies

Two reviewers independently examined the components of each included trial for risk of bias using a standard form. The Cochrane Risk of Bias tool was employed.[40] This included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies were assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arise, they were resolved by discussions with a third reviewer.

An overall assessment of the quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[37]

4.2.6 Measures of treatment effect

Outcome measures for dichotomous data were calculated as risk ratios (RRs) with 95% confidence intervals (CIs). The risk of HIV infection represents the number of HIV infections that occurred per person-years of follow up data. The RR represents the risk of HIV infection in the intervention (PrEP) group compared with the control

group. The modified intention-to-treat was used in all analyses — the denominator in this case represents the total post-randomisation number less the number of participants found to be HIV positive at enrolment.

A meta-analysis was performed to provide a pooled risk if there was sufficient homogeneity across studies (all statistical analysis was performed in Review Manager 5.3 or STATA SE).

4.2.7 Dealing with missing data

As per the study protocol, authors would be contacted to provide further information on study results if data were missing (this was not necessary).

4.2.8 Assessment of heterogeneity

Clinical heterogeneity was assessed by the reviewers based on the description of the interventions and comparators in the RCTs. Statistical heterogeneity was examined using the I^2 statistic. An I^2 statistic above 50–70% implied significant heterogeneity.

4.2.9 Subgroup analysis

It was decided a priori that all analyses would be stratified by the population group investigated. The four populations were MSM, serodifferent couples, heterosexuals and people who inject drugs (PWIDs). Typically, trials reported that the presence of any of the following in the prior 12 month period resulted in an elevated risk of infection: condomless intercourse with a HIV positive or a partner of unknown status from a population with high HIV prevalence, the use of illicit drugs during sex (chemsex), anal STI diagnoses or prior treatment with post-exposure prophylaxis. In the case of serodifferent couples, the higher the viral load in the HIV-infected partner, the higher the risk to the HIV-uninfected partner. PrEP is not indicated in serodifferent partnerships where the HIV positive individual is on antiretroviral treatment and virally suppressed (less than 200 copies/mL). In the case of people who inject drugs, risk relates to the mode of potential HIV transmission (through sharing of needles or sexual transmission) and background prevalence of HIV in this group.

Subgroup analysis was subsequently performed across the different population groups. First, studies were assessed by dosing schedule and by comparator. While the only licensed indication for PrEP is daily oral administration, alternative schedules have been examined in RCTs, such as 'on-demand' PrEP during high-risk periods.[29] Studies that compared PrEP with placebo, PrEP with no treatment and PrEP with another PrEP medication or dosing schedule were all analysed separately.

Studies were then stratified by high (>80%) and low (<80%) trial-level adherence. Adherence was typically measured by self-report, pill count or plasma drug concentration monitoring. Plasma drug monitoring was favoured over self-report/pill count for the purpose of assessing adherence as it is the most objective method and minimises recall bias.

In the assessment of the safety of PrEP, adverse events were analysed separately in three subgroups. These subgroups consisted of 'any' adverse events, serious adverse events and deaths. The definitions for adverse events and serious adverse events followed the definitions used in the primary studies.

In the assessment of behaviour change, the effect of PrEP on condom use, number of sexual partners and change in STI diagnoses were assessed. If there was a lack of data or agreed definitions for these outcomes, a narrative review was performed.

Finally, drug resistance to study medications was assessed among seroconverters. Subgroups included mutations in patients who were enrolled with acute HIV infection at the time of enrolment (unknown to investigators) and those who seroconverted during the course of the trial. Resistance mutations to tenofovir and or emtricitabine were documented among seroconverters who were prescribed study drug and compared with mutations documented among seroconverters who were prescribed placebo or not on treatment.

4.2.10 Reporting guidelines

Reporting adhered to the PRISMA reporting guidelines for systematic reviews.[61]

4.3 Results

4.3.1 Description of included studies

In total, 15 RCTs were retrieved (see Figure 4.1 for flow diagram of study selection). Seven RCTs were placebo-controlled trials that evaluated daily oral PrEP.[62-68] Two studies randomised participants to receive either immediate or delayed PrEP.[69, 70] Three placebo-controlled trials investigated non-daily PrEP, including intermittent and 'on-demand' (also known as event-based) PrEP.[10, 71, 72] Two RCTs did not contain a control arm: one compared two different PrEP formulations (tenofovir and tenofovir/emtricitabine)[73] and one compared three different PrEP dosing schedules.[74] One study contained three arms: PrEP, placebo and 'no pill'.[75]

Four distinct patient populations were assessed. Six RCTs enrolled MSM,[10, 66, 69-71, 75] five enrolled heterosexual participants,[63-65, 68, 74] three enrolled serodifferent couples[67, 72, 73] and one enrolled PWIDs.[62] Of the MSM trials, one also enrolled

female sex workers and one also enrolled transgender women. Of the heterosexual trials, three enrolled women only, one enrolled women and men, and one enrolled women and transgender males.

Included studies involved 25,051 participants encompassing 38,289 person-years of follow-up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 8,239 (55%) received combination tenofovir/emtricitabine and 6,823 (45%) received single agent tenofovir. Follow-up periods ranged from 17 weeks to 6.9 years. Four trials were conducted in high-income countries (USA, England, France and Canada), eleven were conducted in low- or middle-income countries (including nine trials in sub-Saharan Africa) and one was a multicenter trial conducted across four continents. The characteristics of included studies are provided in Tables 4.4 to 4.7.

Figure 4.1. Flow diagram of study selection

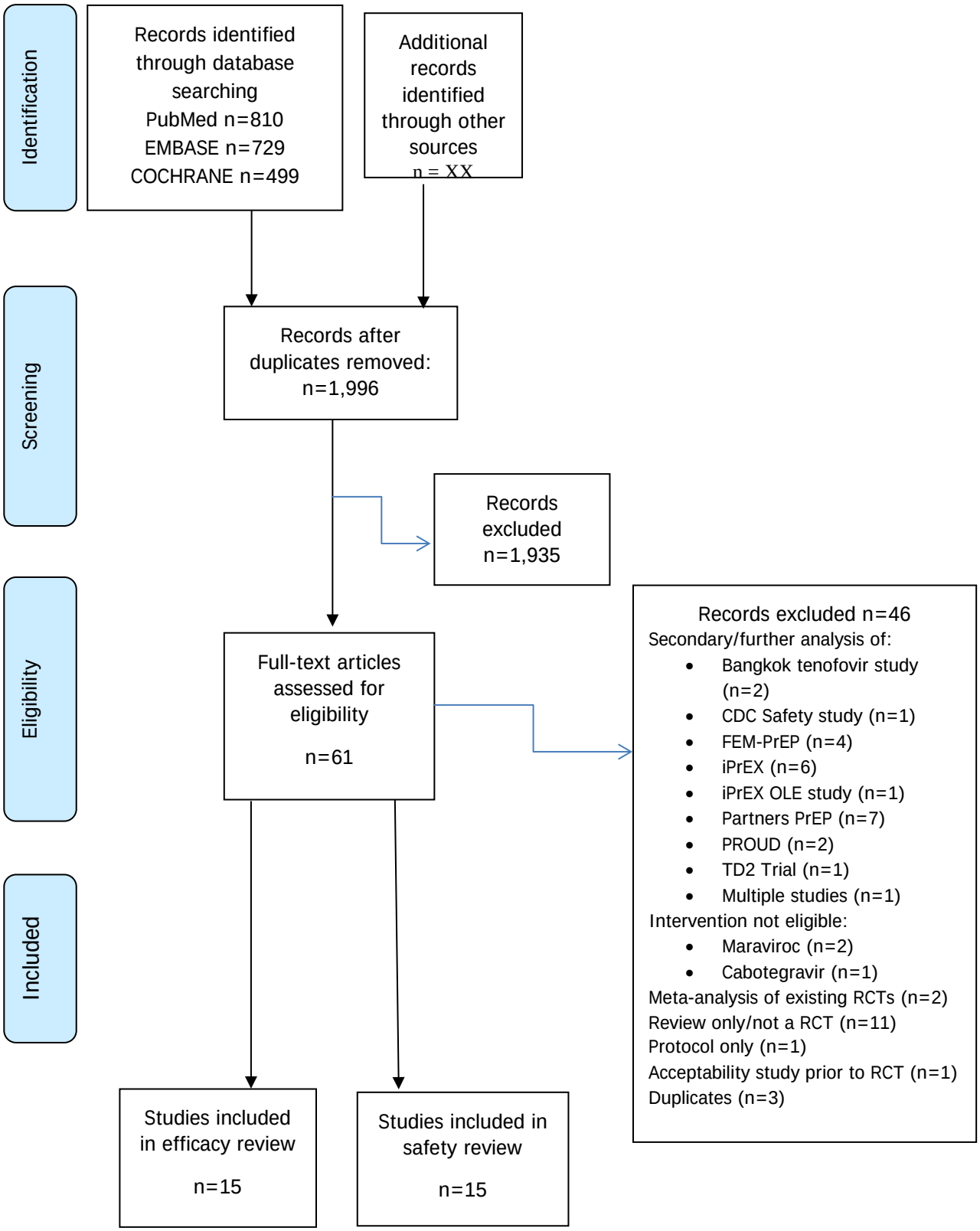


Table 4.4. Study characteristics: MSM population

Study	Location	Population	Intervention[ɣ]	Comparison	Background country HIV prevalence	Number of participants	Follow-up period
Hosek 2013 (Project PrEPare)	United States	Young MSM. Median age: 19.97 years (range: 18–22) Sex: 100% men	Tenofovir/ emtricitabine	Daily PrEP with placebo and to 'no pill'	MSM HIV prevalence = 14.5% in 2014*	58	24 weeks; 27 person-years
Grohskopf 2013 (CDC Safety Study)	United States	MSM. Age range: 18–60 years	Tenofovir	Immediate/delayed PrEP with immediate/delayed placebo. 1:1:1:1 trial design: tenofovir, placebo, delayed tenofovir and delayed placebo groups	MSM HIV prevalence = 14.5% in 2014*	400	2 years; 800 person-years
iPrEx (Grant 2010)	Peru, Ecuador, South Africa, Brazil, Thailand, and United States	MSM and transgender women. Age range: 18–67 years. Sex: 100% male at birth; 1% female gender identity	Tenofovir/ emtricitabine	Daily PrEP with placebo	Varies by country	2499	3324 person-years (median, 1.2 years; maximum, 2.8 years)
McCormack 2015 (PROUD)	England	MSM. Median age: 35 years Sex: 100% men	Tenofovir/ emtricitabine	Immediate PrEP with delayed PrEP	MSM HIV prevalence = 7.7% in 2016*	545	504 person-years. Maximum: 48 weeks

Molina 2015 (IPERGAY)	France and Canada	MSM. Median age 35 PrEP group, 34 placebo group; Sex: 100% men	Tenofovir/ emtricitabine	Intermittent ('on demand') PrEP with placebo. Participants were instructed to take a loading dose of two pills of tenofovir-emtricitabine or placebo 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later.**	France MSM HIV prevalence = 17.7% in 2011; Canada MSM HIV prevalence = 14.9% in 2011*	400	431.3 person-years. Maximum: 24 months. Median 9.3 months
Mutua 2012 (IAVI Kenya Study)	Kenya	Female sex workers and MSM. Mean age: 26 years (range: 18–49); Sex: 67 men; 5 women	Tenofovir/ emtricitabine	Daily/intermittent PrEP to daily /intermittent placebo	MSM HIV prevalence = 18.2% in 2010*	72	4 months; 24 person-years

Tenofovir = Tenofovir Disoproxil Fumarate
ɣ In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg
*UNAIDS 2018 (www.epidem.org)
**In case of multiple consecutive episodes of sexual intercourse, participants were instructed to take one pill per day until the last sexual intercourse and then to take the two postexposure pills.

Table 4.5. Study characteristics: Serodifferent couples

Study	Location	Population	Intervention[ɣ]	Comparison	Background country HIV prevalence	Number of participants	Follow-up
Kibengo 2013 (IAVI Uganda Study)	Uganda	Sero-discordant couples. Mean age: 33 years (range: 20–48); Sex: 50% women; 50% men	Tenofovir/ emtricitabine	Daily/intermittent PrEP with daily/intermittent placebo	6.6% in 2013, adults 15 to 49 years*	72 couples	4 months; 24 person-years
Baeten 2012 (Partners PrEP Study)	Kenya and Uganda	Sero-discordant couples. Age range: 18–45 years; Sex: seronegative partner was male in 61–64% of couples (depending on group assignment)	Tenofovir/ emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	Daily PrEP with placebo	5.5 to 6.7% in 2012, adults 15 to 49 years*	4,747 couples	7,830 total person-years. Median: 23 months, IQR 16–28, range 1–36 months
Baeten 2014 (Partners PrEP Study Continuation)	Kenya and Uganda	Sero-discordant couples. Age range: 28–40 years; Sex: 62–64% men (depending on group assignment)	Tenofovir/ emtricitabine and tenofovir (Two Active Arms)	Tenofovir/emtricitabine combination versus tenofovir	5.5 to 6.7% in 2012, adults 15 to 49 years*	4,410 couples	8,791 person-years. For those assigned active PrEP at the initial randomisation: median 35.9 months; IQR 30–36 months. For those re-randomised from placebo: median 12 months; IQR 12–12 months

Tenofovir = Tenofovir Disoproxil Fumarate, SD = standard deviation, IQR = interquartile range.
ɣ In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg
**Source=UNAIDS 2018 (www.epidem.org)

Table 4.6. Study characteristics: Heterosexual population

Study	Location	Population	Intervention[ɣ]	Comparison	Background country HIV prevalence	Number of participants	Follow-up
Bekker 2018 (ADAPT Cape Town)	South Africa	Women and transgender males. Median age of women was 26 years (IQR 21–37; range 18–52)	Tenofovir /emtricitabine	Daily, time and event-driven PrEP[≠]	18.8% among adults 15–49 in 2017*	191	29 weeks, 99 person-years follow-up
Marrazzo 2015 (VOICE)	South Africa, Uganda, and Zimbabwe	Women. Median age: 24 years (range: 18–40); Sex: 100% women	5 arms: tenofovir/ emtricitabine, tenofovir and 1% tenofovir vaginal gel (compared with placebo oral PrEP and placebo vaginal gel)	Daily PrEP with placebo	6.3 to 18.8% in 2015, adults 15-49 years*	4,969	5,509 person-years of follow-up. Maximum: 36 months
Peterson 2007 (West African Safety Study)	Nigeria, Cameroon, and Ghana	Women. Age range: 18–34 years; Sex: 100% women (mostly sex workers)	Tenofovir	Daily PrEP with placebo	Prevalence among sex workers unknown	936	428 person-years. Maximum: 12 months
Thigpen 2012 (TENOFOVIR2)	Botswana	Heterosexual men and women. Age range: 18–39 years; Sex: 54.2% men; 45.8% women	Tenofovir/ emtricitabine	Daily PrEP with placebo	23.1% in 2012*	1219	1,563 person-years (median: 1.1 years; maximum: 3.7 years)

VanDamme 2012 (FEM-PrEP)	Tanzania, South Africa, and Kenya	Women. Median age: 24.2 years (range: 18–35); Sex: 100% women	Tenofovir/ emtricitabine	Daily PrEP with placebo	Range: 3.4 to 18.4% in adults 15–49, 2012*	2,120	1407.4 person-years. Maximum: 52 weeks

Tenofovir = Tenofovir Disoproxil Fumarate. SD = standard deviation.
ɣ In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg
*Source: UNAIDS 2018. Available at www.epidem.org
≠; time-driven = twice a week plus a post-sex dose; event-driven = one tablet both before and after sex

Table 4.7 Study characteristics: People who inject drugs

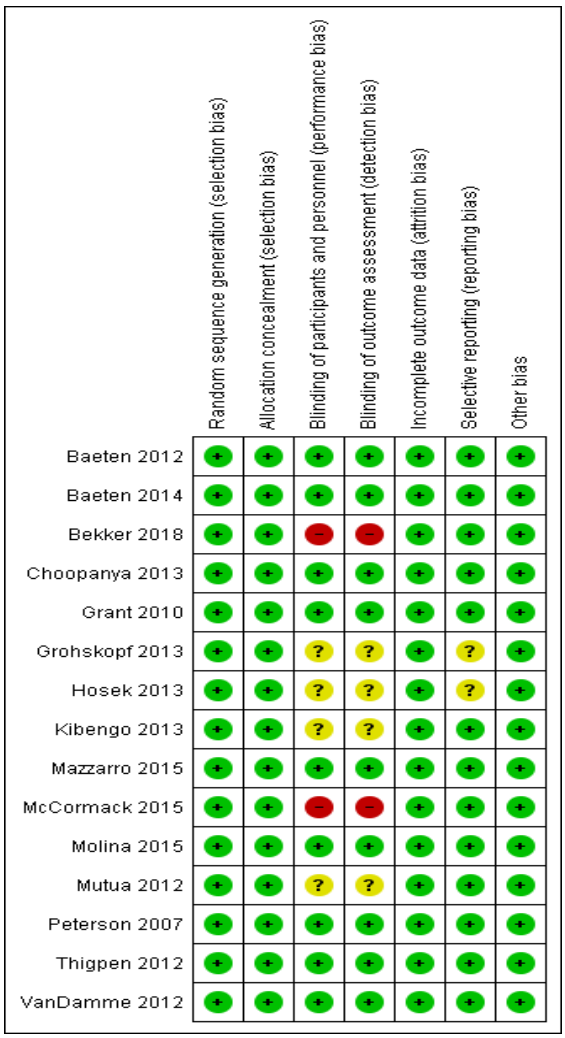
Study	Location	Population	Intervention[ɣ]	Comparison	Background country HIV prevalence	Number of participants	Follow-up
Choopanya 2013 (Bangkok Tenofovir Study)	Thailand (Bangkok)	People who inject drugs. Median age: 31 years (range: 20–59) 80% male	Tenofovir	Daily PrEP with placebo	Prevalence of HIV in PWID in Thailand: 19% in 2014*	2,413	9,665 person-years (mean 4.0 years, SD 2.1; maximum 6.9 years)

Tenofovir = Tenofovir Disoproxil Fumarate. SD = standard deviation. PrEP – pre-exposure prophylaxis
ɣ In all cases, tenofovir dose was 300mg and emtricitabine dose was 200mg
*Source: UNAIDS 2018. Available at www.epidem.org

4.3.2 Risk of bias

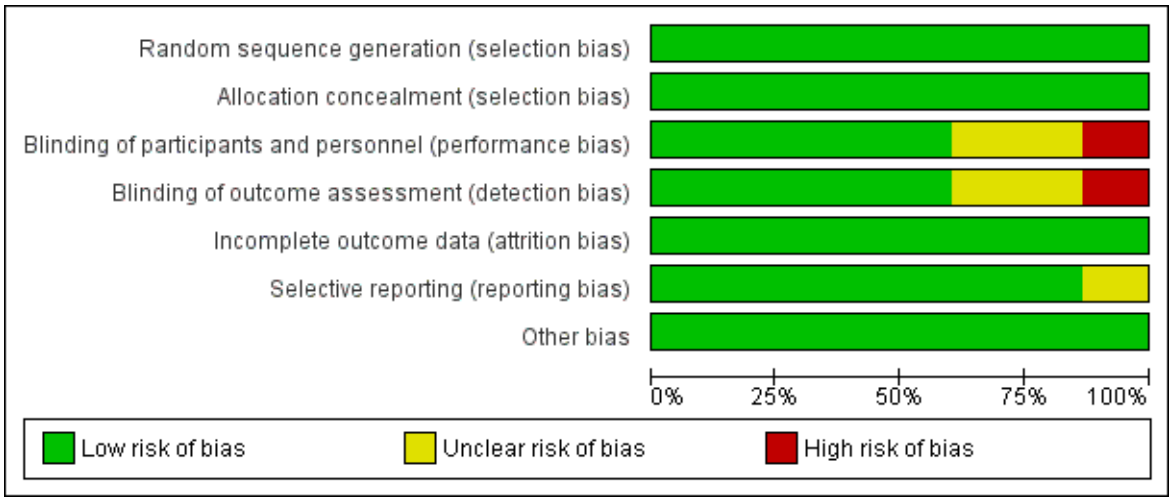
All included RCTs were judged to have low risk of bias (Figures 4.2 and 4.3). Two studies were open-label trials and, as such, blinding of participants or investigators was not possible; these were, therefore, deemed at high risk of bias. A further three studies were placebo-controlled trials that additionally investigated alternate dosing schedules; while participants and investigators were blinded to drug assignment, they could not be blinded to regimen assignment. One study contained a 'no pill' arm that could not be blinded in addition to a placebo arm. Two studies had unclear risk for reporting bias due to the fact that study protocols were not available.

Figure 4.2. Risk of bias summary



This graph represents the review authors' judgements about each risk of bias item for each included study

Figure 4.3. Risk of bias graph



This graph represents the review authors' judgements about each risk of bias item presented as percentages across all included studies

4.3.3 Adherence

Adherence was measured in a number of ways across trials. Commonly used measures included self-report, pill counts, a medication event monitoring system (MEMS), structured interviews and plasma drug detection methods. Adherence varied greatly across studies. Plasma drug monitoring is considered the gold standard for adherence assessment. The highest rates of adherence by drug monitoring were obtained in the MSM-only studies by Molina et al. (86% had tenofovir detectable)[29] and McCormack et al. (88% were prescribed sufficient study drug, and drug plasma concentration was 100% in a sample of participants who reported that they took the drug).[70] In contrast, adherence by plasma drug detection was exceptionally low in two studies (<30%).[63, 68]

In general, estimates of adherence using self-report and pill counts were far higher than those estimated using plasma drug monitoring. In the study by Marrazzo et al., stark differences existed between self-report and plasma drug measurements.[68] Participants' adherence reached 90% by self-report, 86% by returned products, and 88% as assessed with audio computer-assisted self-interviewing (ACASI). However, in a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine fixed dose regimen, and tenofovir gel, respectively.

In the study by Van Damme et al., 95% of participants reported that they had usually or always taken the assigned drug.[63] Drug-level testing, however, revealed much lower levels of adherence. Among women with seroconversion in the tenofovir/emtricitabine group, the target plasma level of tenofovir was identified in 7

of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

For the purpose of analysis in the following sections, adherence greater than 80% was deemed high and anything lower suboptimal. Table 4.8 provides a summary of adherence across studies.

Table 4.8. Adherence, as measured in primary studies

Study	Intervention	Adherence
Bekker 2018 (ADAPT Cape Town)	Tenofovir/emtricitabine (daily, time and event-driven PrEP)	• 75% (7,283 of 9,652 doses taken) for daily regimen; 65% (2,367 of 3,616 doses taken) for time-driven regimen and 53% (1,161 of 2,203 doses taken) for those event-driven regimen by electronic drug monitoring.
Baeten 2012 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (three arms: two active arms and one placebo arm)	• Factoring in missed visits, other reasons for non-dispensation of study medication and non-adherence to dispensed study pills, 92.1% of follow-up time was covered by study medication. • Among 29 subjects on the tenofovir and emtricitabine/tenofovir arms who acquired HIV-1, 31% had tenofovir detected in a plasma sample at the seroconversion visit compared with 82% of 902 samples from a randomly-selected subset of 198 subjects who did not acquire HIV-1.
Baeten 2014 (Partners PrEP)	Tenofovir/emtricitabine and tenofovir (two active arms)	• Study medication was taken by participants on 90.0% of days during follow-up time (factoring in protocol-defined study medication interruptions, missed visits, and non-adherence to dispensed study pills, as measured by monthly pill counts of returned study tablets). • Among subjects who acquired HIV-1, the minority (14/51, 27.5%) had tenofovir detected in a plasma sample at the visit at which HIV-1 seroconversion was detected, compared with the majority (1,047/1,334, 78.5%) of samples from a randomly selected subset of subjects who did not acquire HIV-1.
Choopanya 2013 (Bangkok Tenofovir Study)	Tenofovir (daily)	• Adherence was assessed daily at directly observed therapy (DOT) visits and monthly at non-DOT visits using a study drug diary. On the basis of participants' study drug diaries, participants took the study drug an average (mean) of 83.8% of days. • Plasma samples were obtained from 46 participants with incident HIV infections the day infection was detected, and from 282 HIV-negative participants to test for the presence of tenofovir. Tenofovir was detected in one (1%) of 177 participants in the

		placebo group and 100 (66%) of 151 participants in the tenofovir group. • In the case-control analysis in participants assigned to tenofovir, tenofovir was detected in the plasma of 5 (39%) of 13 HIV-positive participants and 93 (67%) of 138 HIV-negative participants.
Grant 2010 (iPrEx)	Tenofovir/emtricitabine (daily)	• The rate of self-reported pill use was lower in the emtricitabine–tenofovir group than in the placebo group at week 4 (mean, 89% vs. 92%) and at week 8 (mean, 93% vs. 94%) but was similar thereafter (mean, 95% in the two groups). • The percentage of pill bottles returned was 66% by 30 days and 86% by 60 days. • Among subjects in the emtricitabine–tenofovir group, at least one of the study-drug components was detected in 3 of 34 subjects with HIV infection (9%) and in 22 of 43 seronegative control subjects (51%).
Grohskopf 2013 (CDC Safety Study)	Tenofovir (daily)	• Adherence was measured by pill count, medication event monitoring system (MEMS) and self-report; adherence ranged from 77% (pill count) to 92% (MEMS).
Kibengo 2013 (IAVI Uganda Study)	Tenofovir/emtricitabine (daily or intermittent)	• Median MEMS adherence rates were 98% (IQR: 93–100) for daily PrEP regimen, 91% (IQR: 73–97) for fixed intermittent dosing and 45% (IQR: 20–63) for post-coital dosing. • There was no difference in adherence rates between active and placebo groups, thus these two groups were combined for the adherence analyses.
Hosek 2013 (Project PrEPare)	Tenofovir/emtricitabine (daily)	• Self-reported medication adherence averaged 62% (range 43–83%) while rates of detectable tenofovir in plasma of participants in the emtricitabine/tenofovir arm ranged from 63.2% (week 4) to 20% (week 24).
Mazzarro 2015 (VOICE)	Tenofovir (oral), tenofovir/emtricitabine (oral) and vaginal tenofovir gel (all daily)	• 90% by self-report, 86% by returned products and 88% as assessed with audio computer-assisted self-interviewing (ACASI). • In a random sample, tenofovir was detected in 30%, 29% and 25% of available plasma samples from participants randomly assigned to receive tenofovir, tenofovir/emtricitabine and tenofovir gel, respectively.
McCormack 2015 (PROUD)	Tenofovir/emtricitabine (daily)	• Overall, sufficient study drug was prescribed for 88% of the total follow-up time. • Tenofovir was detected in plasma of all 52 sampled participants (range 38–549 ng/mL) who reported that they were taking PrEP.
Molina 2015 (Ipergay)*	Tenofovir/emtricitabine (intermittent)	• Median pills per month: 15 pills. • In the tenofovir–emtricitabine group, the rates of detection were 86% for tenofovir and 82% for emtricitabine, respectively, a finding that was consistent with receipt of each drug within the previous week. Tenofovir and emtricitabine were also detected in eight participants in the placebo group, three of whom were receiving postexposure prophylaxis. • Computer-assisted structured interviews also performed to assess most recent sexual episode.

		Overall, 28% of participants did not take tenofovir-emtricitabine or placebo, 29% took the assigned drug at a suboptimal dose and 43% took the assigned drug correctly.
Mutua 2012 (IAVI Kenya Study)	Tenofovir/emtricitabine (daily or intermittent)	• There was no difference in adherence rates between treatment and placebo groups, thus these groups were combined for the adherence analyses. Median MEMS adherence rates were 83% (IQR: 63–92) for daily dosing and 55% (IQR:28–78) for fixed intermittent dosing (p=0.003).
Peterson 2007 (West Africa Study)	Tenofovir (daily)	• The amount of product used was estimated by subtracting the number of pills returned from the number dispensed, and dividing this number by the total number of days in the effectiveness analysis. • Drug was used no more than 69% of study days. Excluding time off product due to pregnancy, drug was used for no more than 74% of study days.
Thigpen 2012 (TENOFOVIR2)	Tenofovir/emtricitabine (daily)	• The two groups had similar rates of adherence to the study medication as estimated by means of pill counts (84.1% in the tenofovir–emtricitabine group and 83.7% in the placebo group, P = 0.79) and self-reported adherence for the preceding 3 days (94.4% and 94.1%, respectively; P = 0.32). • Among the four participants in the tenofovir–emtricitabine group who became infected with HIV during the study, two (50%) had detectable levels of tenofovir and emtricitabine in plasma obtained at the visit before and closest to their estimated seroconversion dates. among the 69 participants, matched by sample date, who did not undergo seroconversion, 55 (80%) and 56 (81%) had detectable levels of tenofovir and emtricitabine, respectively.
VanDamme 2012 (FEM-PrEP)	Tenofovir/emtricitabine (daily)	• At the time of study-drug discontinuation, 95% of participants reported that they had usually or always taken the assigned drug. Pill-count data were consistent with ingestion of the study drug on 88% of the days on which it was available to the participants. • In contrast, drug-level testing revealed much lower levels of adherence. Among women with seroconversion in the tenofovir–emtricitabine group, the target plasma level of tenofovir was identified in 7 of 27 women (26%) at the beginning of the infection window (excluding six women for whom the window started at enrolment), in 7 of 33 (21%) at the end of the window, and in 4 of 27 (15%) at both visits. Among the uninfected control participants, the numbers of women with target-level tenofovir were somewhat higher: 27 of 78 women (35%) at the beginning of the infection window, 35 of 95 (37%) at the end of the window, and 19 of 78 (24%) at both visits.

Tenofovir = Tenofovir Disoproxil Fumarate
* non-daily regimen

4.3.4 HIV acquisition

HIV infection was measured in 11 trials comparing PrEP with placebo and three RCTs comparing PrEP with no PrEP. Three trials enrolled very few participants (≤ 72 participants) and followed patients for a very short duration (≤24 weeks); these trials, therefore, detected very few seroconversions, with two trials detecting no HIV infections in either treatment or placebo arms.

The following sections present the HIV acquisition rate by each distinct population group investigated. Additionally, analyses are stratified by comparator (placebo or no treatment) and by trial-level adherence (high >80% or low <80% adherence). In all analyses, the risk of HIV infection is by modified intention-to-treat — participants found to be HIV positive at enrollment (but after randomisation) were excluded. The RR represents the ratio of risk (number of events per person-year) in the intervention group compared with control.

4.3.4.1 MSM population

Six studies investigated the effects of PrEP in the MSM population. A meta-analysis of all studies demonstrated a risk ratio of 0.25 (95% CI: 0.1 to 0.61; 5,103 person-years of data), indicating a 75% reduction in the risk of HIV acquisition. Point estimates all favoured treatment, although not all were statistically significant. Five studies compared PrEP with placebo (Figure 4.5) and one compared PrEP with no treatment (Figure 4.6).

Figure 4.4. Forest plot: PrEP in MSM (all studies)

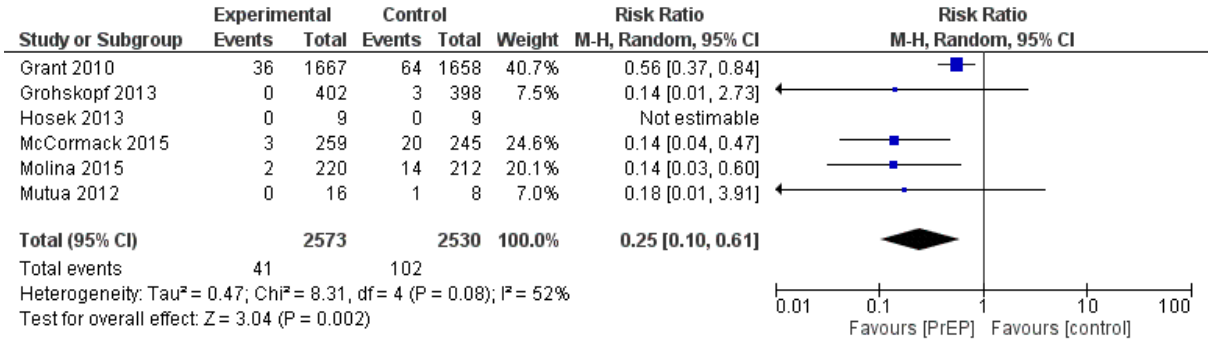


Figure 4.5. Forest plot: PrEP versus placebo

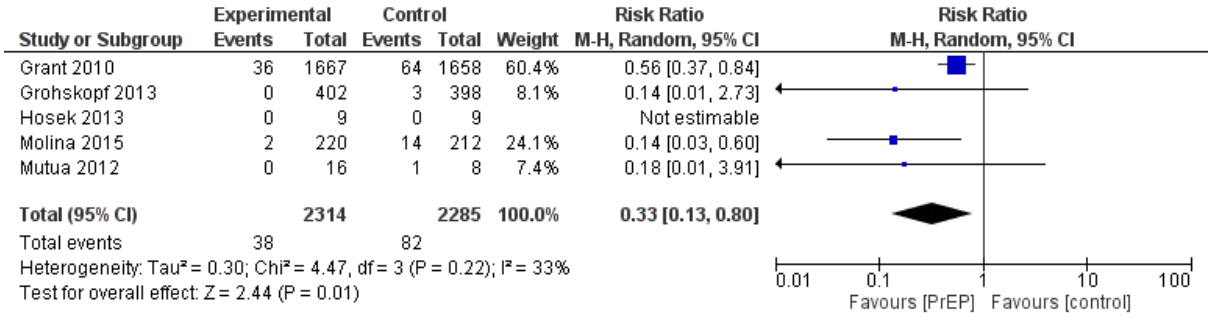
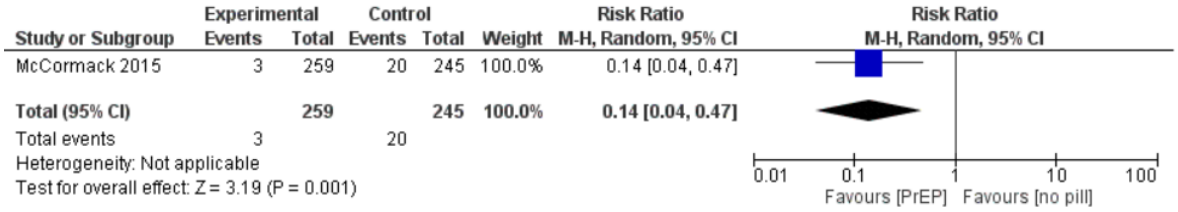


Figure 4.6. Forest plot: PrEP versus no treatment



When stratified by adherence, heterogeneity was greatly reduced (I^2 reduced from 52% to 0%). PrEP was most effective in studies with high adherence, as expected, where risk of HIV acquisition was reduced by 86% (RR 0.14; 95% CI 0.06 to 0.35; n=3 studies, 960 person-years of data). When adherence was under 80%, PrEP risk of acquisition was reduced by 45% (RR 0.55, 95% CI 0.37 to 0.81; n=3 studies, 4,143 person-years of data). Figures 4.7 and 4.8 provide forest plots of these meta-analyses.

Figure 4.7. Forest plot: High adherence (>80%)

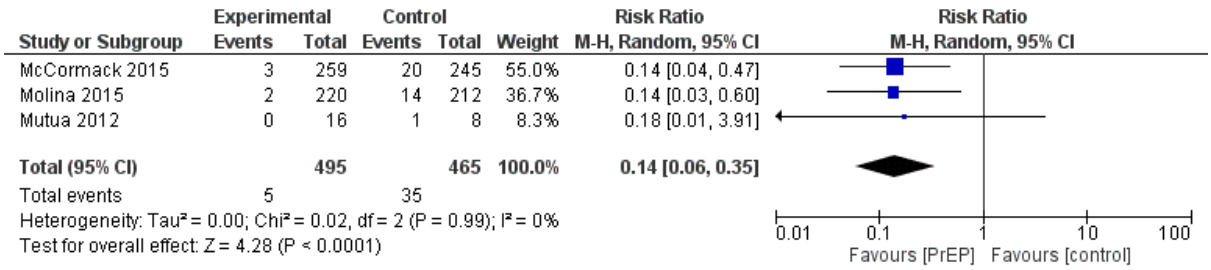
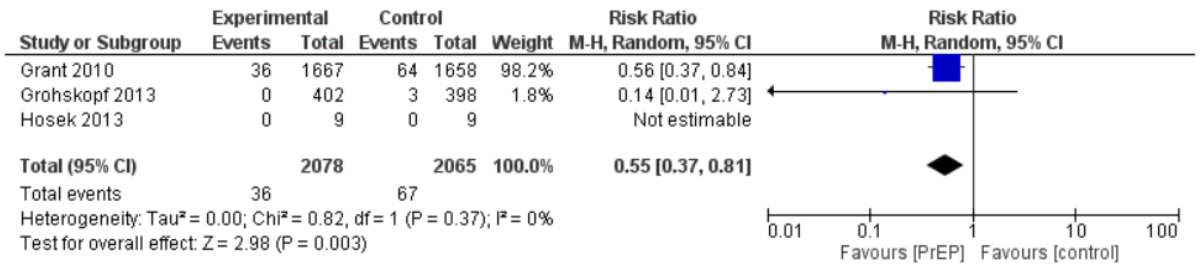


Figure 4.8. Forest plot: Low adherence (<80%)



Two open-label extensions were conducted following the conclusion of these trials. First, the iPrEx Open-label Extension[36] enrolled 1,603 HIV-negative men who were previously part of three PrEP trials.[66, 69, 75] Participants were offered daily tenofovir/emtricitabine and were followed up for 72 weeks after enrolment. HIV incidence was 1.8 infections per 100 person-years compared with 2.6 infections per 100 person-years in those who concurrently did not choose PrEP (hazard ratio [HR]: 0.51, 95% CI: 0.26 to 1.01, adjusted for sexual behaviours). Drug levels were also examined by dried blood spot testing, and these levels were extrapolated to pill taking and compared to HIV incidence. No seroconversions were seen when drug levels were compatible with taking four or more pills per week.

Second, the IPERGAY Open-label Extension enrolled 362 individuals to take on-demand tenofovir–emtricitabine and followed them for a median of 11.7 months, of whom 299 (83%) completed follow-up.[33] One HIV infection occurred (0.19 per 100 person-years, 95%: CI 0.01 to 1.08).

4.3.4.2 Serodifferent couples

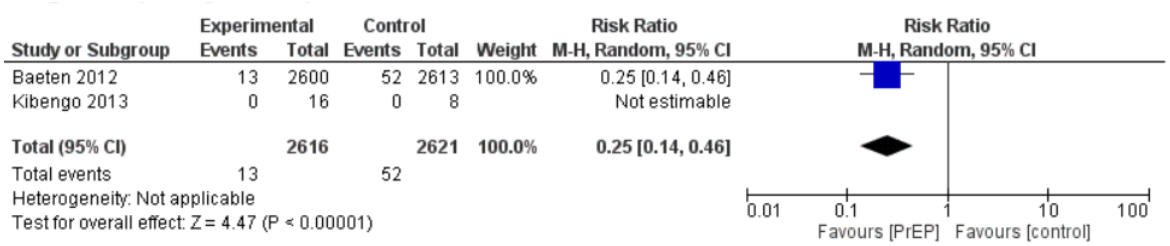
Three studies investigated the impact of PrEP on HIV transmission in serodifferent couples. In all three studies, the HIV-infected partner was not on antiretroviral therapy (studies were conducted in Kenya and Uganda; HIV-infected participants did not meet criteria for ART initiation at the time of enrolment). Details on the CD4 count (a type of cell that HIV infects) or viral load of the HIV-infected partners was not reported.

Two studies investigated the effect of PrEP compared to placebo. A total of 4,849 couples were enrolled, and the seronegative individual was male in the majority (>60%) of cases. One trial enrolled few participants (n=24), and the duration of the trial was very short (4 months). Therefore, the results did not contribute to the effect estimates as no seroconversions were reported.

The trial by Baeten et al., 2012, consisted of three arms: tenofovir/emtricitabine

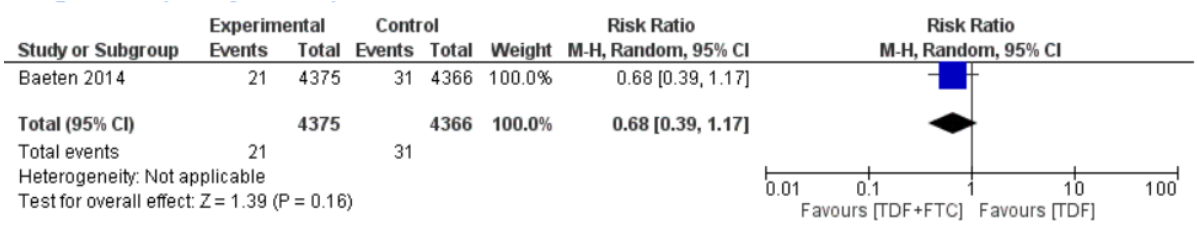
(n=1,568 participants), tenofovir alone (n=1,572 participants) and placebo (n=1,568 participants). Tenofovir/emtricitabine resulted in a 75% risk reduction (RR 0.25, 95% CI: 0.14 to 0.46) and tenofovir alone resulted in a 67% risk reduction (RR 0.33, 95% CI: 0.19 to 0.56). Adherence was high in this trial: sufficient drug was redeemed to cover 92.1% of follow-up and 82% of 902 samples from a randomly-selected subset of 198 subjects (who did not acquire HIV) tested positive for study drug.

Figure 4.9. Forest plot: PrEP in serodifferent couples, tenofovir/emtricitabine versus placebo



One study investigated the effect of tenofovir/emtricitabine combination therapy compared with single-agent tenofovir in the prevention of HIV in serodifferent couples. This study was a continuation of the 2012 study by Baeten et al.; once efficacy was confirmed in PrEP versus placebo analysis, serodifferent couples in the placebo group were re-randomised to receive PrEP containing tenofovir/emtricitabine or tenofovir. Of the original sample, 4,410 couples were re-randomised and contributed 8,741 person-years of data to the study. There was no statistically significant difference between the groups; however, the point estimate favoured tenofovir/emtricitabine (RR 0.68, 95% CI: 0.39 to 1.18). HIV transmission was rare, at a rate of 6 cases per 1,000 person-years.

Figure 4.10. Forest plot: tenofovir+emtricitabine versus tenofovir



4.3.4.3 Heterosexual transmission

Five studies enrolled heterosexual participants, four were placebo-controlled and one compared different drug schedules. Four enrolled only women, and one enrolled

both men (54.2%) and women (45.8%).

Placebo-controlled trials encompassed 7,252 participants in total. A meta-analysis of studies did not demonstrate a statistically significant reduction in HIV acquisition (Figure 4.11); however, three of the four studies reported low adherence (Figure 4.13). Thigpen et al., 2012, achieved adherence >80% and reported a risk reduction of 61% (RR 0.39, 95% CI 0.18 to 0.83; 1,524 person-years of data) (Figure 4.12).

Figure 4.11. Forest plot: PrEP in heterosexual participants (all studies)

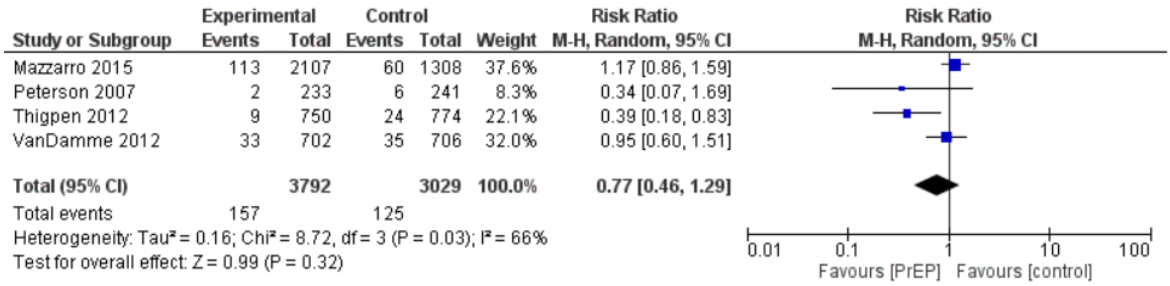


Figure 4.12. Forest plot: high adherence (>80%)

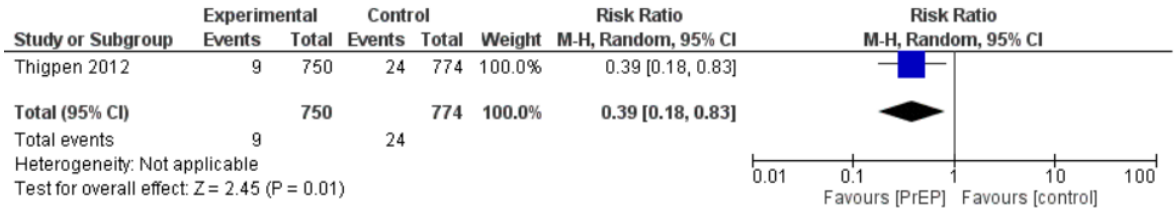
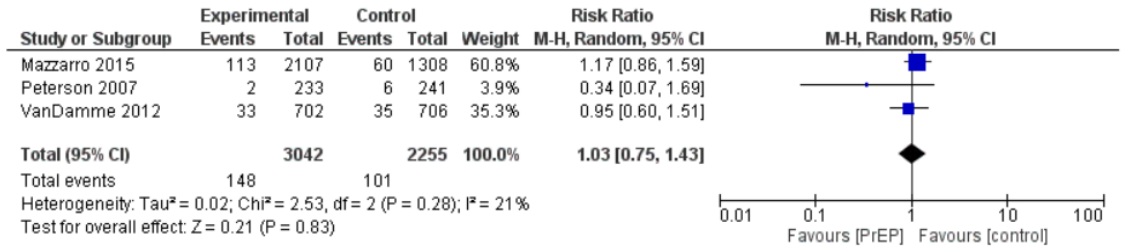


Figure 4.13. Forest plot: low adherence (<80%)



In a separate analysis, the efficacy results from Thigpen et al. were assessed by participant sex. Efficacy was only achieved in males, with a risk reduction of 80% (RR 0.2, 95% CI 0.04 to 0.91). Females achieved a reduction of 51%; however,this failed to reach statistical significance. Appendix 3.5 provides details of these separate analyses.

The study by Marrazzo et al. included four arms in total: tenofovir,

tenofovir+emtricitabine, 1% tenofovir vaginal gel and placebo. In the above meta-analyses, both active arms were combined. Comparing each arm compared with placebo showed that none of the interventions reduced the risk of HIV acquisition. Adherence was extremely low (<30%) in all arms.

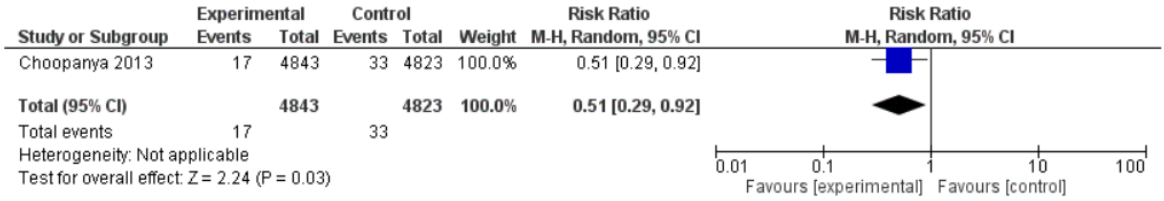
Finally, Bekker et al., 2018, compared different PrEP regimens in 191 women in South Africa. Intervention arms included daily PrEP, time-driven PrEP and event-driven PrEP. Time-driven indicated PrEP taken twice a week plus a post-sex dose and event-driven PrEP indicated one tablet taken both before and after sex. Fewer infections occurred in the daily PrEP arm; however, there were no statistically significant differences in HIV acquisition comparing either event or time-driven PrEP with daily PrEP.

4.3.4.4 People who inject drugs

Only one study was identified that investigated PrEP use among people who inject drugs. Daily oral tenofovir (300mg) was compared to placebo in this trial. PrEP was found to be effective, with a 49% reduction in HIV acquisition (RR 0.51, 95% CI: 0.29 to 0.92; 9,666 person-years of data). Adherence was 67% in a sample of HIV-uninfected individuals in this trial.

In this study, HIV transmission may have occurred sexually or parenterally. Methamphetamine was the most common drug injected by participants.

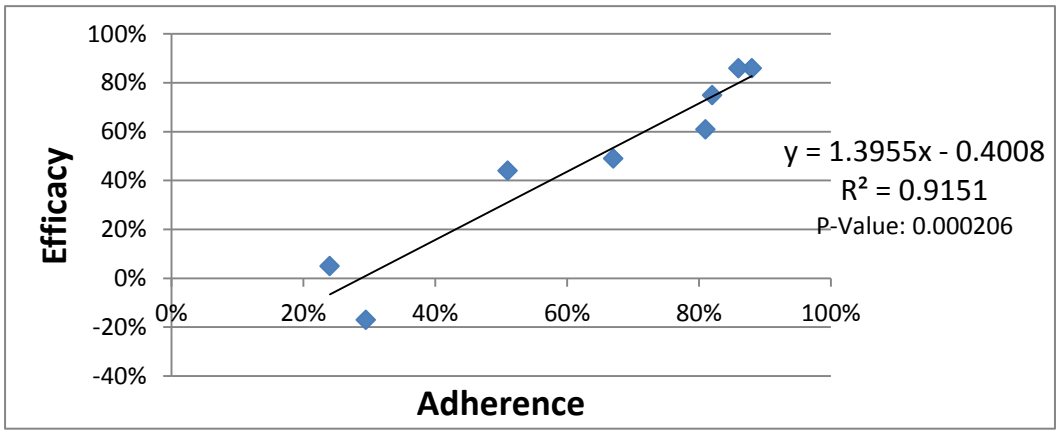
Figure 4.14. Forest plot: PrEP in people who inject drugs



4.3.4.5 Relationship between efficacy and adherence

Efficacy was closely related to participants' adherence to PrEP across trials. Figure 4.15 shows a scatterplot comparing efficacy and adherence (measured by plasma drug concentration; n=7 trials). A regression model yielded a R^2 of 0.92; adherence therefore, explains 92% of the variation in efficacy across trials (Figure 4.15). This result was significant (p<0.001).

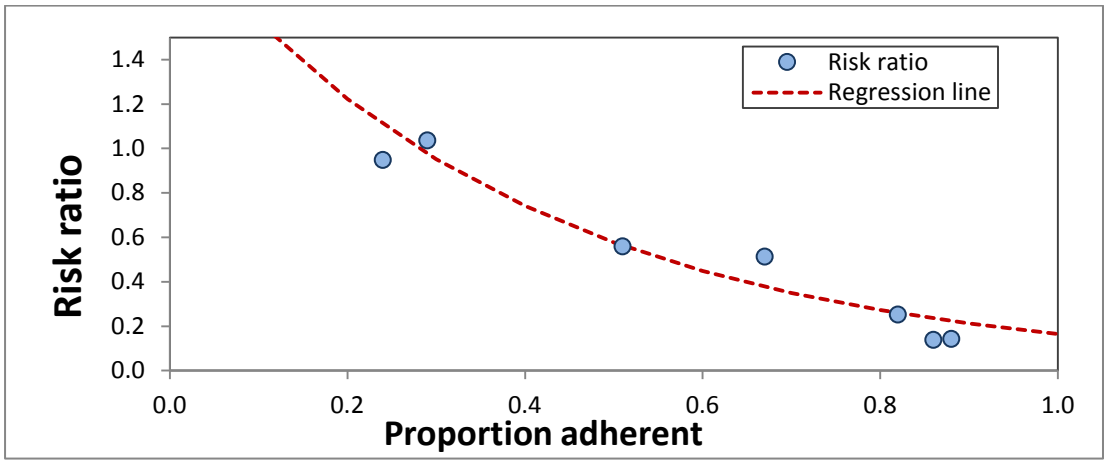
Figure 4.15. Efficacy as a function of adherence



Only trials that reported plasma drug concentrations contributed to anlaysis: (Baeten 2012 (Partners PrEP), Choopanya 2013 (Bangkok Tenofovir Study), Grant 2010 (iPrEx), Mazzarro 2015 (VOICE), McCormack 2015 (PROUD), Molina 2015 (Ipergay), Thigpen 2012 (TDF2 study), VanDamme 2012 (FEM-PrEP)

A meta-regression was performed to account for trial size. Figure 4.16 gives the meta-regression line. Efficacy (as RRs) and adherence (by proportion with plasma drug detectable) were strongly associated (p<0.001). As the proportion adherent increases from 0.5 to 0.6, the RR decreases by 0.13. Therefore, on average, a 10% increase in adherence increases efficacy by 13%.

Figure 4.16. Fitted meta-regression line of the relationship between trial-level PrEP adherence and efficacy



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4.3.5 Safety

It was decided a priori to stratify adverse events into three groups: 'any' adverse event, serious adverse events and deaths. The definition of what constituted a serious adverse event was not described in most primary studies. Whether serious adverse events or deaths were considered drug-related was also recorded. Expected adverse events were recorded, including reversible renal insufficiency and changes in bone mineral density.

4.3.5.1 Any adverse event

Overall, 12 studies reported data on 'any' adverse events; ten compared PrEP with placebo and two compared tenofovir alone to tenofovir/emtricitabine. A meta-analysis of participants reporting 'any' adverse events comparing PrEP with placebo demonstrated no significant difference between groups (RR 1.01; 95% CI 0.99 to 1.03; 17,358 participants). Comparing tenofovir with tenofovir/emtricitabine, one study noted a small increase in adverse events in the tenofovir/emtricitabine group (RR 1.23; 95% CI 1.03 to 1.33) and another failed to show any difference. Figures 4.15 and 4.16 provide forest plots of these findings.

Figure 4.15. Forest plot: PrEP versus placebo

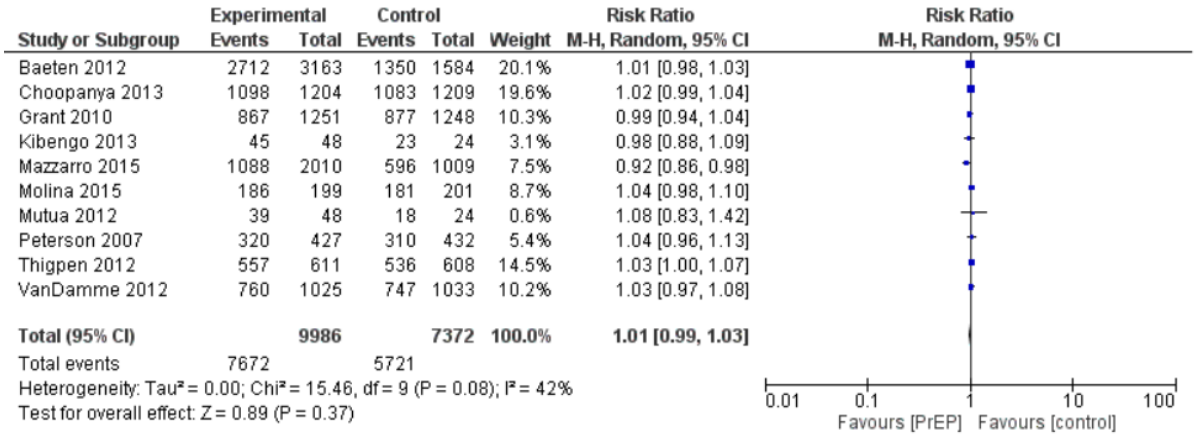
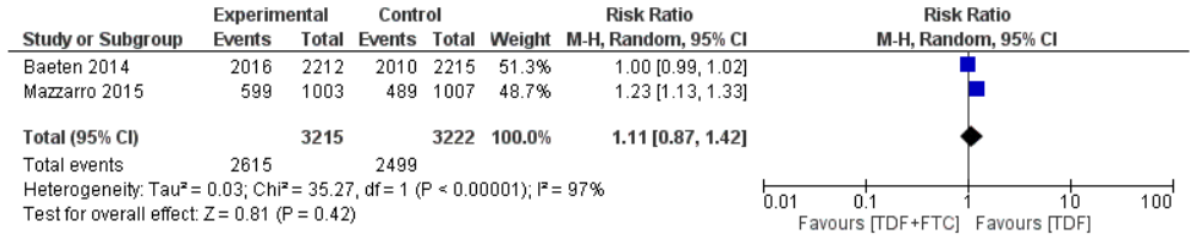


Figure 4.16. Forest plot: tenofovir/emtricitabine versus tenofovir



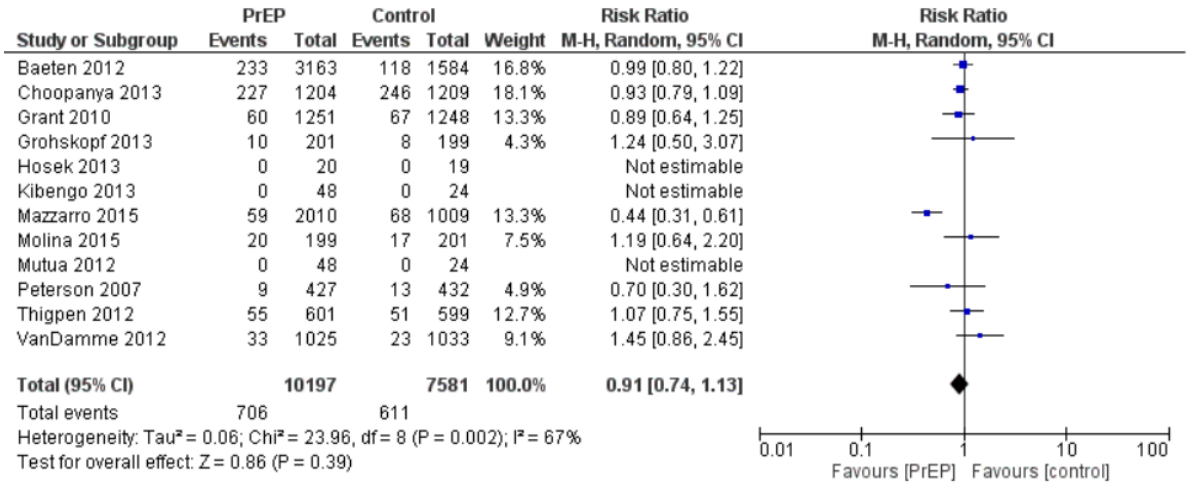
Several studies reported mild decreases in renal function among PrEP users that returned to normal following discontinuation of PrEP use,[29, 63] while a reduction in creatinine clearance (a measure of renal function) was not observed in others.[62, 67]

4.3.5.2 Serious adverse events

All 15 studies reported data in relation to the risk of serious adverse events: 12 were placebo-controlled, one compared PrEP with no PrEP and two compared tenofovir/emtricitabine with tenofovir.

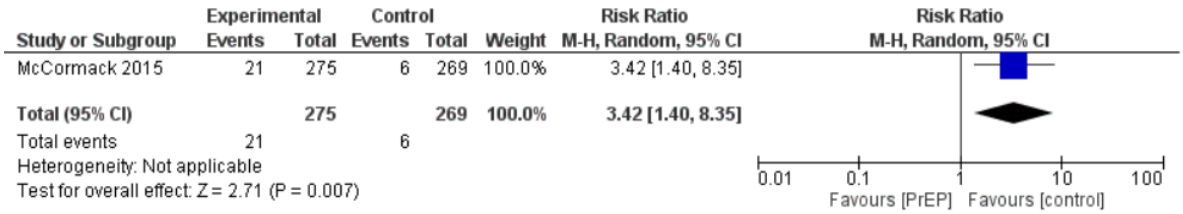
In the placebo-controlled trials, none showed an increased risk of serious adverse events associated with PrEP use and one study actually demonstrated a statistically significant reduced risk (RR 0.44; 95% CI 0.31 to 0.61). In three studies, the risk was not estimable as there were no serious adverse events recorded. The meta-analysis demonstrated a pooled RR of 0.91 (95% CI: 0.74 to 1.13; 17,778 participants). The overall rate of serious adverse events was 6.9% across treatment arms.

Figure 4.17. Forest plot: PrEP versus placebo — serious adverse events



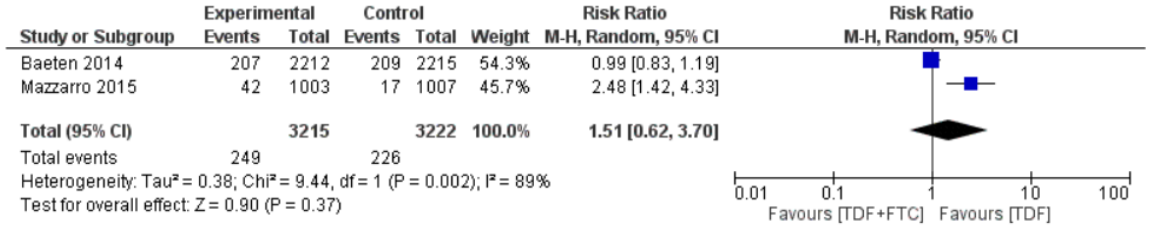
Only one trial compared PrEP with no treatment. An increased rate of serious adverse events was noted in the treatment arm (RR 3.42; 95% CI 1.4 to 8.35; see Figure 4.18). It is noteworthy, however, that study authors did not consider any of the 27 serious adverse events to be study drug-related.

Figure 4.18. Forest plot: PrEP versus no treatment — serious adverse events



Two studies compared tenofovir and tenofovir/emtricitabine. One study found no significant difference between groups and another found a statistically significant increased rate of serious adverse events in the tenofovir/emtricitabine group (RR 2.48; 95% CI: 1.42 to 4.33). Overall, 7 per 1,000 additional serious adverse events occurred in the tenofovir/emtricitabine group.

Figure 4.19. Forest plot: Tenofovir/emtricitabine versus tenofovir



4.3.5.3 Deaths

Fourteen studies provided data on deaths. There were no deaths recorded in any arm of five trials. Across subgroups (PrEP versus placebo, prep versus no treatment and tenofovir/emtricitabine versus tenofovir), there was no statistically significant increase in the number of deaths in the PrEP group. Of the deaths that occurred, none were considered to be drug-related in any trial. Figures 4.20 to 4.22 present forest plots of these meta-analyses.

Figure 4.20. Forest plot: PrEP versus placebo

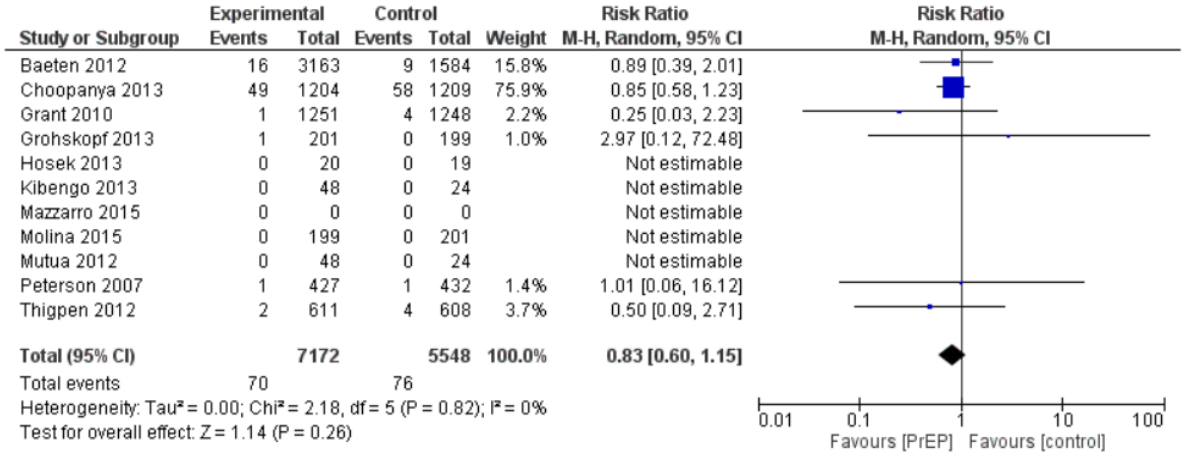


Figure 4.21. Forest plot: PrEP versus no treatment

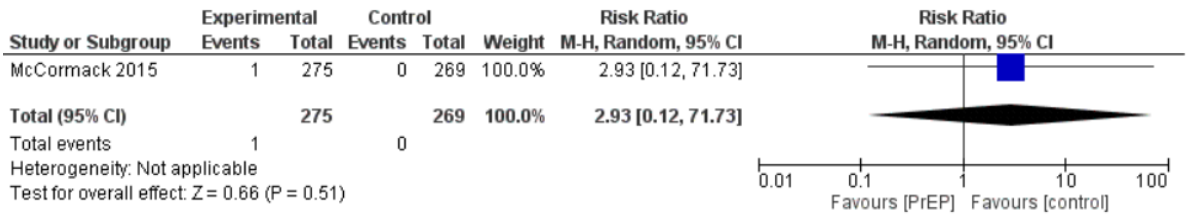
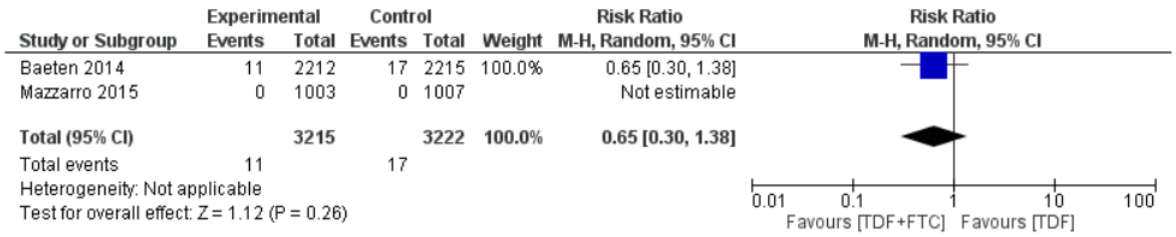


Figure 4.22. Forest plot: Tenofovir/emtricitabine versus tenofovir



4.3.6 Change in behaviour and STI rates

Eleven trials measured changes in behaviour while taking PrEP. The most common methods for assessing sexual behaviour were condom use (measured in eight studies) and number of sexual partners (measured in 10 studies). One trial assessed changes in recreational drug use. Five trials assessed the change in STI rates. Table 4.9 provides details in the changes in behaviour and STI diagnoses across studies.

Due to the differences in how sexual behaviour was reported, including differing definitions and at different time points, a meta-analysis of behavioural change was not possible. Studies consistently showed no difference in condom use between intervention and control arms. Studies showed either no change in condom use throughout the duration of the study (n=4 studies) or increases in condom (n=4 studies). This observation was similarly found in studies comparing PrEP with no treatment, which possibly better reflects real-world situations.

Similarly, no studies that assessed the number of sexual partners showed differences between the intervention and control arms. Most studies showed no change in the number of sexual partners throughout the duration of the study (n=6 studies); four studies showed a slight reduction in number of sexual partners and one showed an increase. In the study that showed an increase, investigators noted the possibility of partner underreporting at baseline.[71] For this reason, authors also compared the median number of sexual partners at month two and month four, which was the same at both time points.

Five studies recorded changes in the incidence of STIs. No study reported an increase in STIs or a between-group difference in STI diagnoses. The study by McCormack et al.,[70] an open-label study comparing PrEP with no treatment in MSM, measured the incidence of rectal chlamydia/gonorrhea as a proxy for condomless anal intercourse. This study benefitted from the fact that it better represents 'real-world' situations by virtue of its open-label design. No difference in the occurrence of rectal gonorrhoea or chlamydia was observed between groups, despite a suggestion of risk compensation among some PrEP recipients (an increase in risky sexual

behaviour when on PrEP). Van Damme et al.[63] also assessed STI incidence in women by pelvic examination and similarly did not note a difference between treatment and control groups.

Choopanya et al., 2013, the only study to enroll intravenous drug users, noted a reduction in intravenous drug use and needle sharing over the course of the study.[62] Study authors also noted a reduction in the number of sexual partners.

Table 4.9. Change in sexual behaviour/STI rates

Study	Measure	Outcome
Baeten 2012 (Partners PrEP)	• Having sex without a condom with HIV-positive partners in prior month • STI diagnoses from sex acts outside partnership	• At enrolment, 27% of HIV-1 seronegative partners reported sex without condoms with their HIV-1 seropositive partner during the prior month. This percentage decreased during follow-up (to 13% and 9% at 12 and 24 months) and was similar across the study arms. • The proportion reporting outside partnerships and who acquired sexually transmitted infections during follow up did not differ across the study arms.
Baeten 2014 (Partners PrEP)	Unreported	
Bekker 2018 (ADAPT Cape Town)	Unreported	
Choopanya 2013 (Bangkok Tenofovir Study)	• Drug use behaviour • Number of sexual partners	• Tenofovir and placebo recipients reported similar rates of injecting and sharing needles and similar numbers of sexual partners during follow up with no interactions between time and treatment group. • Overall, number of participants reporting injecting drugs or sharing needles reduced over time. • Sex with more than one partner decreased from 522 (22%) at enrolment to 43 (6%) at month 72.
Grant 2010 (iPrEx)	• Number of anal sex acts • Proportion of anal sex acts with a condom • STI diagnoses	• Sexual practices were similar in the two groups at all time points. • The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after subjects enrolled in the study. • There were no significant between-group differences in the numbers of subjects with syphilis, gonorrhea, chlamydia, genital warts

		or genital ulcers during follow-up.
Grohskopf 2013 (CDC Safety Study)	Unreported	
Hosek 2013 (Project PrEPare)	Male-to-male unprotected anal sex acts	• No significant differences among the three treatment groups across visits. • Insignificant trend from baseline to week 24 of decreasing unprotected anal sex acts across all treatment arms.
Kibengo 2013 (IAVI Uganda Study)	HIV behaviour change	• The median number of sexual partners in the past month remained at 1 (IQR: 1–1) during the trial. • No other HIV risk behaviours reported at baseline changed during the trial
Mazzarro 2015 (VOICE)	Unreported	
McCormack 2015 (PROUD)	• Number of sexual partners • Incident STIs	• Total number of different anal sex partners varied widely between baseline and year 1. No significant difference between groups at one year was detected. • Proportion with confirmed rectal chlamydia/gonorrhea was similar in immediate and delayed arms (proxy for condomless anal intercourse). • Adjusted odds ratio for rectal chlamydia or gonorrhea: 1.00 (0.72–1.38) (adjusted for number of sexual health screens)
Molina 2015 (Ipergay)	• Total number of sexual intercourse events • Proportion of events without a condom • Number of sexual partners • Incident STIs	• Sexual practices did not change overall among the participants during the study period as compared with baseline: there were no significant between group differences in the total number of episodes of sexual intercourse in the four weeks before, in the proportion of episodes of receptive anal intercourse without condoms, or in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. • There was a slight but significant decrease in the number of sexual partners within the past two months in the placebo group as compared with the tenofovir—emtricitabine group (7.5 and 8, respectively; p = 0.001). • The proportions of participants with a new sexually transmitted infection (of the throat, anus, and urinary tract combined) during follow-up were similar, with 41% in the tenofovir—emtricitabine group and 33% in the placebo group (P = 0.10).
Mutua 2012	HIV behaviour	• The median number of sexual partners in the

(IAVI Kenya Study)	change	past month increased from three (IQR 2–4) at baseline to four (IQR 2–8) at month 4 during the trial. • Because there may have been underreporting of sex partners at baseline, authors also compared the median number of sexual partners month 2 (4) and at month 4 (4).
Peterson 2007 (West Africa Study)	• Condom use at last sex • Number of sex acts • Number of partners	• During screening, participants reported an average of 12 coital acts per week with an average of 21 sexual partners in the previous 30 days (including 11 new partners). During follow-up, participants reported an average of 15 coital acts per week, with an average of 14 sexual partners in the previous 30 days (six new partners). Of note, most participants in this study were sex workers. • Self-reported condom use increased from 52% at screening (average across all sites during the last coital act prior to screening) to approximately 92% at the enrolment, month 3, month 6, and month 9 visits, to 95% at the month 12 visit (for acts occurring during the last seven days). The average condom use during the follow-up period was 92%.
Thigpen 2012 (TENOFOVIR2)	• Protected sex episodes with main/ most recent casual partner • Number of sexual partners	• The percentage of sexual episodes in which condoms were used with the main or most recent casual sexual partner was similar in the two study groups at enrolment (81.4% [range, 76.6 to 86.4] in the tenofovir–emtricitabine group and 79.2% [range, 71.6 to 87.6] in the placebo group, P = 0.66) and remained stable over time. • The reported number of sexual partners declined in both groups during the course of the study.
VanDamme 2012 (FEM-PrEP)	• Number of partners • Sex acts without a condom • Pelvic STIs	• There was no evidence of increased HIV risk behaviour during the trial, with modest but significant reductions in the numbers of partners (mean reduction, 0.14; P<0.001 by paired-data t-test), vaginal sex acts (mean reduction, 0.58; P<0.001), and sex acts without a condom (mean reduction, 0.46; P<0.001) reported by women at the last follow-up visit, as compared with seven days before enrolment. • Fewer than half the study participants agreed to undergo a pelvic examination. There were no significant between-group differences in the prevalence of pelvic STIs.

4.3.7 Drug mutations

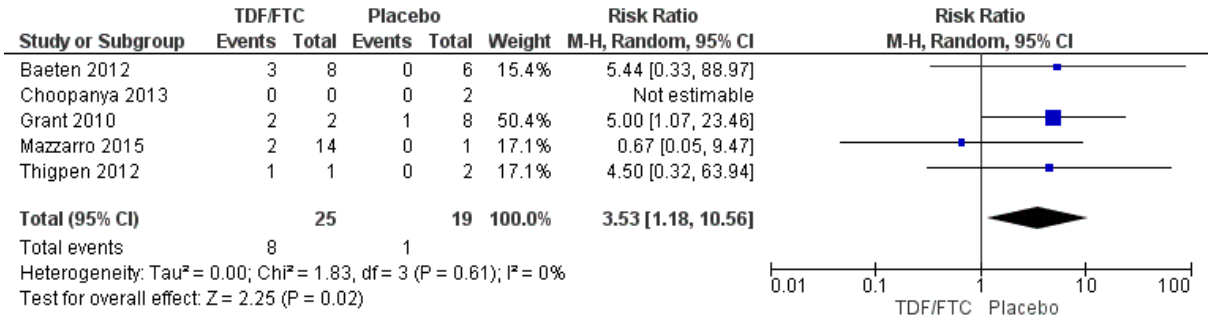
Seven placebo-controlled trials provided data on HIV mutations (to tenofovir and or

emtricitabine) among seroconverters. Seroconverters were subgrouped into those who had acute HIV infection at enrolment (unknown to study investigators) and seroconverters post-randomisation (during the follow-up period).

4.3.7.1 Acute HIV at enrolment

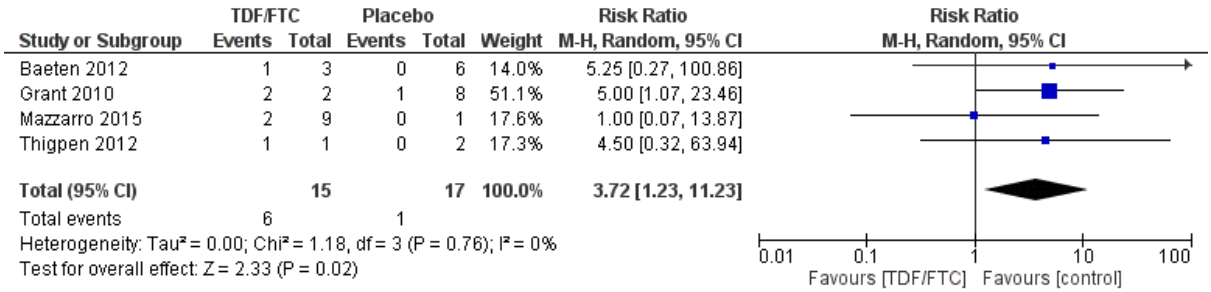
In total, there were 44 seroconversions at enrolment, 25 who received study drug and 19 who received placebo. There were nine mutations detected in total, eight among those receiving a study drug and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI: 1.18 to 10.56) (Figure 4.23).

Figure 4.23. Forest plot: any drug mutation (PrEP versus placebo)



Of the nine drug resistance mutations, seven were for emtricitabine (one in a placebo arm and six in tenofovir/emtricitabine arms). In placebo-controlled trials, the RR of emtricitabine mutation was 3.72 (95% CI: 1.23 to 11.23) in those receiving tenofovir plus emtricitabine.

Figure 4.24. Forest plot: emtricitabine mutation (tenofovir/emtricitabine versus placebo)



Tenofovir mutations were rare. Two occurred overall: one in a tenofovir-only arm and one in a tenofovir/emtricitabine arm. Due to the rarity of events, no meta-analyses yielded significant results (Figure 4.24).

4.3.7.2 HIV post-randomisation

Among participants who seroconverted postrandomisation, the development of resistant mutations was uncommon, which makes assessing relative risk difficult. Of 551 seroconverters, only seven resistance mutations were detected. One tenofovir mutation was noted in a tenofovir-only arm (k65n, a rare tenofovir resistance mutation) and six emtricitabine mutations were noted (five in tenofovir/emtricitabine arms and one in placebo).

4.4 Discussion

This systematic review and meta-analysis of 25,051 individuals encompassing 38,289 person-years of follow-up data confirms that oral PrEP to prevent HIV acquisition in populations at substantial risk is both effective and safe.

Fifteen high-quality RCTs, which were conducted in high-, middle- and low-income countries, were retrieved. Follow up ranged from 17 weeks to 6.9 years. Due to differences in mode of transmission, all analyses were stratified by risk group. Six trials enrolled men who have sex with men (MSM), two trials enrolled serodifferent couples, five trials enrolled heterosexuals and one trial enrolled people who inject drugs (PWID).

PrEP was found to be highly effective in preventing HIV acquisition in MSM with a risk reduction of 75% across all trials, rising to 86% in trials with high adherence. Two open-label extensions[33, 36] that followed the conclusion of four of these RCTs confirmed this high efficacy; one open-label extension[36] found no seroconversions in participants that took a minimum of four pills per week (of a daily dosing regimen).

Of the six trials in MSM, the PROUD Phase 3 trial,[70] conducted at 13 sexual health clinics in England, would appear highly applicable to MSM in Ireland. This is due to the similarities in background HIV prevalence (7.8% among MSM in Ireland versus 7.7% in the UK, see Chapter 3, Section 3), PrEP delivery model (provision through sexual health clinics) and by virtue of its open-label design (which may better reflect real-world situations). In this trial, a total of 23 participants became infected with HIV over the course of the study: three in the daily tenofovir/emtricitabine group and 20 in the deferred (no-PrEP) group, representing a relative risk reduction of 86% (95% CI: 53 to 96%). The number needed to treat over one year to prevent one HIV infection was 13.

PrEP was effective in preventing HIV acquisition in HIV-uninfected partners of serodifferent couples, with a risk reduction of 75%.[67, 72] Another study compared combination tenofovir/emtricitabine to tenofovir alone; no significant difference in

PrEP efficacy was noted.[73] All studies were conducted in sub-Saharan Africa. It is assumed that the biological efficacy of PrEP is likely to be identical across populations.

It is unclear if PrEP is effective in heterosexual individuals at substantial risk due to poor trial-level adherence. A meta-analysis of four identified studies showing non-significant results (RR 0.77, 95% CI: 0.46 to 1.29). PrEP was effective in preventing heterosexual HIV transmission in one trial where adherence was high (61% reduction).[64] Efficacy in this trial (by modified intention to treat) was only demonstrated in male participants; the reduction in seroconversions among females failed to reach statistical significance. Efficacy was not demonstrated in the remaining three trials, all enrolling females.[63, 65, 68] Adherence was noted to be low and all studies were conducted in sub-Saharan Africa. It is unclear if the results of these studies are transferable to Ireland where background HIV prevalence and demographic characteristics are significantly different.

PrEP was effective in preventing HIV transmission in PWID in the only high-quality trial retrieved that enrolled drug users. Risk was reduced by 49%.[62] However, this trial may not be directly applicable to the Irish context. Participants were intravenous drug users from Thailand, and stimulant drugs (such as methamphetamine) were the most commonly injected drugs. It is difficult to separate the impact of PrEP on parenteral HIV transmission from sexual transmission in PWID. The authors of the study acknowledge that, although the study was designed to measure the impact on parenteral transmission, participants may have become infected sexually.

Chemsex and slamming (the act of injecting the drugs used in chemsex) should be distinguished from injecting drug use involving heroin as the demographics of users and risk factors for HIV acquisition are different. Chemsex is frequently reported in MSM at high risk of HIV acquisition and involves drugs such as methamphetamine, methedrone and gamma hydroxybutyrate (GHB), and it significantly increases the risk of sexual HIV acquisition. In 2015, it was estimated that 7% of MSM engaged in chemsex in Ireland.[76] Opiate drug users who do not have a sexual risk factor for HIV and are at risk of HIV infection from sharing needles should ideally be offered needle exchange and opiate substitution in the first instance to minimise their risk of acquiring HIV and other blood-borne infections.

Adherence varied greatly across studies. Adherence was either recorded by self-report, pill count, structured interviews or by plasma drug monitoring. Plasma drug monitoring was considered the most objective measurement for adherence assessment; adherence by this measurement ranged from 25% to 88% across trials. Efficacy was found to be strongly associated with adherence ($p<0.01$), and adherence explained 92% of the variation in efficacy across trials. Highest efficacy

was noted in trials with highest adherence (as measured by plasma drug monitoring). In general, an interesting observation was that efficacy (in %) was consistently similar to the proportion who adhered to the PrEP regimen.

Caution should be used when generalising results from low-income to high-income countries when large sociodemographic differences exist, including background HIV prevalence. All studies that enrolled heterosexuals in this systematic review were conducted in sub-Saharan Africa, where HIV prevalence was as high as 23.1% (Botswana). By contrast, HIV prevalence in Ireland is approximately 0.2% in the general population (see Chapter 3). The only study that enrolled PWID was conducted in Thailand; drug users in Thailand have an estimated HIV prevalence of almost 20%. With the exception of one study that enrolled MSM in England, prevalence estimates among MSM were also somewhat higher (14.5% in the US, 14.9% in Canada and 14% in France compared with 7.8% in Ireland).[35]

Changes in sexual behaviour patterns were measured in a number of ways, including condom use, number of sexual partners and new STI diagnoses. The most clinically relevant outcome is STI diagnoses due to the fact that the other two indicators are self-reported and are subject to reporting bias. Unfortunately, placebo-controlled trials are not very helpful in assessing risk compensation (altering sexual behaviour due to the knowledge that PrEP is protective). One purpose of the placebo is to control for behaviour, and it is not possible to reach conclusions on the impact of PrEP on behaviour as participants do not know if they are on active drug. However, it is possible to evaluate the impact of the support provided to all participants over time (counselling on safer sex practices and provision of condoms).

Studies showed either no change in condom use over time (n=4 studies) or an increase in condom use (n=4 studies). Most studies showed no change in the number of sexual partners throughout the duration of the study (n=6 studies), four studies showed a slight reduction in number of sexual partners and one showed an increase. In the study that showed an increase, investigators noted the possibility of partner underreporting at baseline.[71] In the open-label PROUD study, in which participants knew they were taking PrEP, there was no difference between the immediate and deferred (no-PrEP) groups in the total number of sexual partners (p=0.57) in the three months prior to the one-year questionnaire, but a greater proportion of the immediate group reported receptive anal sex without a condom with 10 or more partners compared with the deferred group (21% versus 12%, p-=0.03). There was no difference in the frequency of bacterial STIs during the randomised phase (p=0.74).

PrEP was found to be safe in RCTs. However, the maximum follow-up period was

6.9 years and, therefore, long-term safety was not assessed. Not all studies defined what constituted adverse events (including serious adverse events). A high rate of adverse events was noted in some control arms, including a higher rate of serious adverse events in the placebo arm of one trial (compared with active drug). Therefore, occurrence is not evidence of causality. A meta-analysis of placebo-controlled trials demonstrated that adverse events (overall) and serious adverse events do not occur more commonly with PrEP compared with placebo, and no drug-related deaths were reported. There was no difference in adverse event rates comparing single agent tenofovir with tenofovir/emtricitabine in combination.

A transient elevation of creatinine was noted in some studies with resolution upon discontinuation of study drug. Where renal function has been affected, PrEP was associated with mild, non-progressive and reversible reductions in creatinine clearance.[10, 62, 66, 67, 70] Some trials found slight decreases in bone mineral density.[64, 68] There are no long-term data on bone health or evidence of increased fracture risk, however. Following the CDC MSM safety study, in multivariate analysis, back pain was associated with use of tenofovir and also a small decrease in bone mineral density among a subset of 184 men in the San Francisco site. However, tenofovir use was not associated with bone fractures.[32]

One risk associated with the administration of PrEP is the development of drug resistance. This could occur due to PrEP failure (considered a rare event when adherence is adequate) or due to an unrecognised acute HIV infection at enrolment. Seven placebo-controlled trials evaluated drug resistance. In total, there were 44 seroconversions at enrolment, 25 who received study drug and 19 who received placebo. There were nine mutations detected, eight among those receiving PrEP and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI: 1.18 to 10.56). Of the nine resistant mutations, seven conferred resistance to emtricitabine. Development of resistance post-randomisation was uncommon. The potential for development of resistance emphasises the need for careful participant screening, including ascertaining if the patient could be in the ‘window period’ (the time between exposure to HIV and the point when HIV testing will give an accurate result) at enrolment, to ensure the patient is HIV negative prior to commencing PrEP. This highlights the need for PrEP delivery as part of a holistic programme that incorporates HIV testing and patient counselling regarding the risk and long-term consequences of resistance if poorly adherent to PrEP.

In conclusion, high-quality evidence exists that PrEP is safe and highly efficacious in preventing HIV acquisition in populations at substantial risk, including MSM and serodifferent couples. Efficacy is strongly associated with adherence. The generalisability of trials that enrolled heterosexual participants (conducted in sub-

Saharan African countries) and PWID (conducted in Thailand) to the Irish setting is unclear, however, due to substantial demographic differences. Adverse events, including serious adverse events, did not occur more commonly in PrEP users compared with placebo in trials. Placebo-controlled trials are not sufficient to measure behaviour change associated with PrEP. However, an increase in high-risk behaviour over time was not noted and in many cases decreased, which is probably due to the risk reduction support offered to trial participants.

5 Systematic review of economic evaluations

Key points

- A systematic review of economic evaluations identified 18 studies from ten different countries, published between 2009 and 2018. The majority of studies (n=17) investigated PrEP use in gay, bisexual and other men who have sex with men (MSM) with one study focussing on people who inject drugs (PWID). Fifteen studies evaluated PrEP taken daily and three studies assessed PrEP taken 'on demand'.
- The annual cost of daily PrEP ART in MSM and PWID studies ranged from €232 to €14,659 per person (mean €6,543). Costs were lower in European compared with North American studies (mean annual PrEP cost of €6,419 versus €7,702). The mean annual cost of on-demand PrEP ART was €4,313.
- Parameter estimates for the efficacy of PrEP in reducing the risk of HIV transmission in MSM ranged from 44%-99%. In nine of the seventeen MSM studies, the efficacy was equal to or above 86%. The efficacy of PrEP was 49% in the PWID study.
- Seven studies were at risk of bias due to industry support. Four studies were at risk of bias due to conflicting or competing interests and financial disclosures were not stated in three studies.
- PrEP was considered cost saving in two studies. A further six studies reported an ICER below €45,000, the willingness-to-pay threshold commonly used in Ireland. Three studies estimated an ICER above €45,000. This is not necessarily an indication of cost-effectiveness, as countries have different willingness-to-pay thresholds.
- Risk compensation was included in the base case scenario of one study and as part of a scenario analysis in five studies. The maximum impact of risk compensation was a 30% increase in STIs.
- None of the studies could be considered directly applicable to Ireland.

5.1 Introduction

The aim of this chapter is to summarise the available evidence on the cost-effectiveness of PrEP to prevent the sexual acquisition of HIV. The applicability of studies to the Irish setting is assessed and the context and populations for which PrEP is most likely to be cost-effective are determined.

Mathematical models provide a framework to combine all the information available on PrEP (uptake, efficacy, adherence, changes in sexual behaviour and cost) to provide insights into the potential epidemiological impact, cost-effectiveness and budget impact of PrEP at a population level. A cost-effectiveness analysis compares the cost and outcomes of two or more different options and usually involves calculation of the cost of obtaining a gain in health, such as infections averted, deaths averted, additional years of life ('life years gained' [LYGs]), quality-adjusted life years (QALYs) gained or disability-adjusted life-years (DALYs) averted. The advantage of using a standardised measure such as QALYs gained is that outcomes can be compared across interventions in any disease area.

5.2 Methods

A systematic review was undertaken to summarise the cost-effectiveness literature for oral PrEP when used to prevent HIV infection. The applicability of the evidence was assessed to inform cost-effectiveness in an Irish health and social care setting.

5.2.1 Search Strategy

5.2.1.1 Search terms and database search

A search string was developed to identify relevant studies. This comprised key words pertaining to the epidemiology of HIV, PrEP treatment and economic evaluation. The search of electronic databases was conducted from 2000 until 02 October 2018. The electronic search included the following databases: PubMed, Embase, EBSCOhost (CINAHL + EconLit), University of York's CRD DARE and HTA databases and the Cochrane Library. A grey literature search was also conducted which included hand-searching of journals and disease-specific conference proceedings (for example, AIDS Research and Human Retroviruses, Journal of the International AIDS Society (JIAS), HIV Medicine). The review followed national guidelines for the retrieval and interpretation of economic literature.[77]

5.2.1.2 Criteria for inclusion of studies

Table 5.1 outlines the Population, Intervention, Comparator, Outcome, Study

(PICOS) criteria for the selection of studies.

Table 5.1 Inclusion criteria for the review of cost-effectiveness studies

Population	HIV-negative patients at high risk of contracting HIV. Subgroups include gay, bisexual and other men who have sex with men (MSM), persons who inject drugs (PWID), serodifferent couples (SDC) and heterosexual individuals at high risk.
Intervention	Oral tenofovir-containing PrEP.
Comparator	Usual care (current suite of HIV prevention strategies, such as provision of condoms, HIV testing and Treatment as Prevention [TasP]).
Outcomes	Incremental cost-effectiveness ratios (ICERs), cost per HIV infection averted, LYG, QALYs, DALYs, any measure of cost and benefits.
Study Designs	Economic evaluations (cost-utility, cost-effectiveness, partial economic evaluation studies (cost-analysis, cost-of illness) .

Key: DALY – disability-adjusted life year; HIV – human immunodeficiency virus; PrEP – pre-exposure prophylaxis; QALY – quality-adjusted life year.

Studies for which the intervention was not relevant were excluded. These included non-oral PrEP, oral PrEP that did not contain tenofovir, and PrEP that was employed as part of a wider HIV prevention strategy (such as changes to the frequency of HIV testing or the provision of anti-retroviral therapy [ART] to HIV-infected individuals in countries where ART is not universally available). Studies were also excluded in cases where the comparator was not relevant, published only as abstracts or were not in English. These included studies that compared PrEP administration with increased coverage of ART in HIV-infected individuals. These studies were considered irrelevant as early and effective ART is the standard of care for HIV positive individuals in Ireland. Finally, studies were excluded due to the study design (that is, the cost or cost-effectiveness of PrEP was not evaluated).

5.2.2 Identification of studies

Titles and abstracts retrieved were downloaded and stored in EndNote reference manager. Citations were independently screened by two reviewers per the inclusion and exclusion criteria. References obtained by hand-searching were added to the database and duplicates were removed.

5.2.3 Data extraction and management

Data were extracted using standardised data extraction templates by two independent reviewers. These data included identification information (author, year and country), key epidemiological parameters (incidence and prevalence of HIV, efficacy of PrEP and target population demographics), costing data (cost of PrEP medication, cost of PrEP delivery [laboratory investigations, follow-up appointments

etc], cost of ART in HIV-infected individuals, cost of non-ART HIV-related care and the discount rate applied), clinical outcomes (number of seroconversions, number of LYG, QALYs, DALYs) and cost-effectiveness outcomes (ICERs).Details of model design, assumptions and limitations were also extracted. All costs were inflated using the consumer price index (CPI) for health and converted to 2017 Irish Euro using purchasing power parity (PPP).

5.2.4 Applicability of included studies

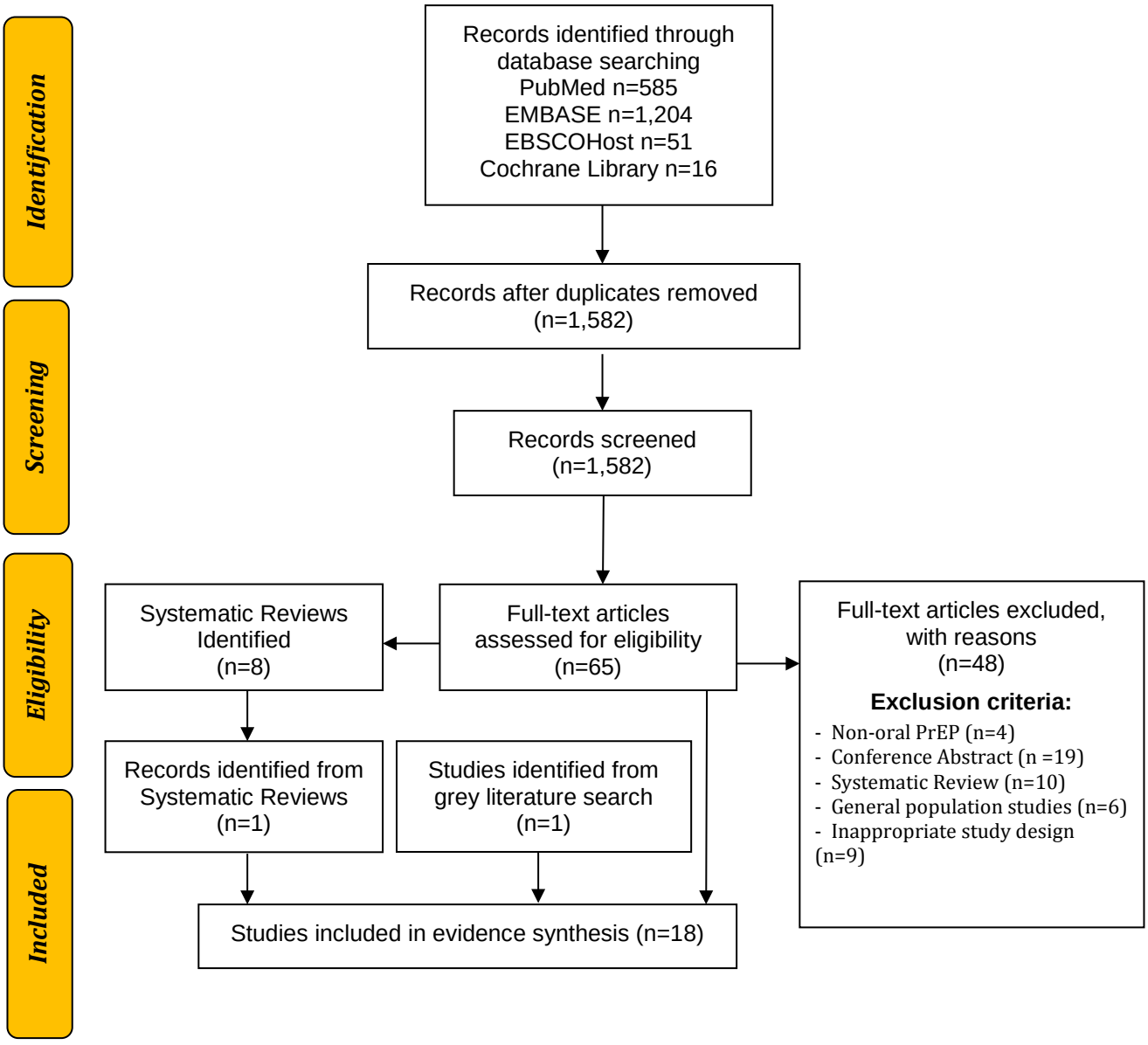
The quality, relevance and credibility of the modelling studies were assessed using the Consensus on Health Economic Criteria (CHEC) list.[78] The methodological relevance and transferability of studies to the healthcare system in Ireland were appraised by employing the International Society for Pharmacoeconomics Outcomes and Research (ISPOR) questionnaire.[79] Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted, and whether the authors had any conflicts of interest. Two reviewers independently applied the questions and any disagreements were be resolved by discussion, or if necessary, a third reviewer.

5.3 Results

5.3.1 Search results

Details of the search process are presented in Figure 5.1. In total, 1,582 records were retrieved from electronic searches (after 192 duplicate records were removed). The title and abstract were screened and 1,517 irrelevant records were removed leaving 65 studies for full text review. Sixteen relevant economic studies [80-95] met the inclusion criteria and were included. The reference lists of eight systematic reviews [96-103] identified in the full text review were screened and one additional study was identified for inclusion.[104] One additional study was identified as part of the grey literature search,[105] this brought the total to eighteen studies. Appendix 4.1 provides a full list of excluded studies (including reasons for their exclusion).

Figure 5.1. Flow diagram of studies identified and included in the review of cost-effectiveness studies



5.3.2 Quality and applicability of evidence

The population, comparator, perspective, costs and outcomes were appropriate in all studies, and the study design in all but one study.[85] The generalisability of results was low with many of the results only applicable within the context of the study. The results of four studies were considered transferable outside of the scope of the research.[89, 90, 94, 105]

A potential conflict of interest pertaining to either direct payments or funding of research was reported in four studies.[81, 87, 89, 92] This related to personal fees, direct payments and research grants to authors. Gilead provided financial support in three

cases.[87, 89, 92] In one study, no financial disclosures were made.[85] There were no conflicts of interests disclosed in one study[84] and no funding reported in one study.[93]

In regard to transferability, the target population (MSM and PWID) of included studies was relevant to this HTA. However, significant demographic differences existed between identified studies and the Irish population.

The intervention and comparator were applicable in all studies. The primary clinical outcome of HIV infections averted was reported in all studies and utility outcomes were quantified in QALYs in all but four studies. Two studies reported DALYs which is more relevant to developing countries. The other studies were cost-effectiveness analyses which reported life years saved and the cost per infection prevented.

None of the papers explicitly stated that the model used was internally or externally validated. The validity and design of 17 of the models was suitable; however, two cost prevention models appeared overly simplified to apply to other settings. The data used in the model were suitable for all studies and the analysis was adequate. Uncertainty was considered in 17 economic evaluations apart from the aforementioned cost prevention studies which only altered the discount rate as part of a sensitivity analysis. The reporting of results was consistently accurate and balanced in all studies.

The costs were presented appropriately, however the cost year was not explicitly stated in six studies. Although the costs could be identified from references it was unclear if they had been inflated or converted to a particular year or a present value when the study was published.

5.3.3 Overview of study characteristics

Of the 18 studies included in this review, six were set in the United States, five in Europe (France, Netherlands, Spain, and the UK), two in South America (Brazil and Peru), two in Canada, two in Australia and one in Thailand (see Table 5.2).

Sixteen of the eighteen economic evaluations carried out a cost-utility analysis (CUA) and two studies conducted cost-effectiveness analysis (CEA). A mathematical model was used to evaluate PrEP in 15 studies, the most common model being a dynamic transmission model (n=10), followed by a decision analytic model (n=2), state-transition Monte Carlo stimulation model (n=2) and a Bernoulli Process model (n=1). Three studies did not use a model, instead calculating the cost per infection averted (using the number needed to treat [NNT]).

Ten studies adopted the perspective of a public payer, six a societal perspective and one the perspective of a third party payer. The perspective was not stated in one study.

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at rates of 3% (n=11 studies)[80, 83, 84, 86-89, 92, 94, 95, 104], 3.5% (n=2)[81, 90] or 5% (n=1).[105] Two studies did not state a base case scenario, but reported three scenarios where discount rates of 0%, 3% and 5% were applied to costs and benefits.[91, 93] These studies reference CADTH guidelines (3rd edition) which state a discount rate of 5% should be applied.[106] This scenario was therefore considered the base case and reported in tables and figures. No discounting was applied to costs or outcomes in two studies. The studies were based on a single year of PrEP provided in the first year, so this was not discounted.[82, 85]

Sixteen studies modeled patients taking daily PrEP as the base case scenario while two studies considered 'on-demand' PrEP dosing regimens. The target population for the intervention was exclusively MSM in 17 studies and PWID in one study. No study investigated the cost-effectiveness of PrEP in heterosexuals at high risk of HIV acquisition or serodifferent couples.

All studies compared the intervention of providing PrEP free of charge against the comparator of the status quo ('No PrEP'). The infrastructure and costs for providing PrEP differed between studies due to different standards pertaining to screening, monitoring and counseling. A detailed description of each study is provided in Appendix 4.5.

Table 5.2. Study characteristics, subgroup population, perspective and discount rate

Study	Country	Type of analysis	Population	Perspective	Discount Rate
Bernard (2017)[80]	USA	CUA	PWID	Societal	3%
Cambiano (2018)[81]	UK	CUA	MSM	Public payer	3.5%
Desai (2008)[104]	USA	CUA	MSM	Public payer	3%
Durand-Zaleski (2016)[82]	France	CEA	MSM	Public payer	N/R
Gomez (2012)[83]	Peru	CUA (DALYs)	MSM	Public payer	3%
Gray (2017)[105]	Australia	CUA	MSM	Public payer	5%
Juusola (2012)[84]	USA	CUA	MSM	Societal	3%

Lin (2016)[85]	USA	CUA	MSM	Societal	N/R
Luz (2018)[86]	Brazil	CEA	MSM	Public payer	3%
MacFadden (2018)[87]	Canada	CUA	MSM	Public payer	3%
McKenney (2017)[88]	USA	CUA	MSM	Societal	3%
Nichols (2016)[89]	Netherlands	CUA	MSM	Third Party Payer	3%
Ong (2017)[90]	UK	CUA	MSM	Public payer	3.5%
Ouellet (2015)[91]	Canada	CUA	MSM	Societal	5%*
Paltiel (2009)[92]	USA	CUA	MSM	Societal	3%
Reyes-Uruena (2018)[93]	Spain	CUA	MSM	N/R	5%*
Schneider (2014)[94]	Australia	CUA	MSM	Public payer	3%
Suraratdecha (2017)[95]	Thailand	CUA (DALYs)	MSM	Public payer	3%

Key: CUA = cost-utility analysis; DALY = disability-adjusted life year; MSM = men who have sex with men; PWID = people who inject drugs; SDC = serodiscordant couples; N/R = not reported
* Three scenarios presented whereby discount rates of 0%, 3% and 5% for costs and benefits were adopted. These studies reference CADTH guidelines of 5%. This was taken as the base case scenario.

The following sections report outcomes by the population identified: MSM (5.3.3) and PWID (5.3.4).

5.3.4 MSM population

Seventeen studies were identified that assessed cost or cost-effectiveness in the MSM population [81-88, 90-95, 104, 107]. Studies were conducted in the USA (n=5), Canada (n=2), UK (n=2), Australia (n=2), and one each in Brazil, France, Netherlands, Peru, Spain and Thailand.

There was no universal definition of what constituted 'high risk' across studies.. Furthermore, there were differences in the method used to calculate this 'high risk' group.. UK and Australian studies employed data-driven methods using information collected at STI clinics to obtain a more precise estimate of the population eligible. [81, 90, 105] Other studies assigned an arbitrary figure for the proportion at high risk (for example, a third of all MSM).[95] In some studies, the cost effectiveness of PrEP for MSM at low and medium risk, as well as the whole MSM population, was considered in scenario analyses.

Six of the nine studies that used dynamic transition models to calculate the cost effectiveness of PrEP either adapted a previously developed HIV transmission model or adopted a model used in a previous cost-effectiveness study. The models adapted

were the HIV synthesis model,[108] OPTIMA model [109] and a precursor to the OPTIMA, the Prevtool model.[110] The remaining three studies developed novel dynamic transmission models for their analysis. Of the two studies using decision analytic models, one was based on a novel model while the other was adapted from a previous model. The state-transition Monte Carlo models were adaptions of the cost-effectiveness of preventing AIDS complications (CEPAC) model.[111] The Bernoulli process model was a novel approach to evaluating the cost-effectiveness of PrEP. This model stated the incremental cost per prevented case of HIV was defined as the additional unit cost of the intervention per person divided by the intervention effect.

A non-mathematical method was used in three studies (Table 5.3). These studies (Durant-Zaleski et al.[82][CEA], Ouellet et al.[91][CUA] and Reyes-Uruena et al.[93][CUA]) employed a simplified approach of multiplying the cost by the NNT (that is, the cost to avert one infection), and to estimate cost-effectiveness, dividing this by the health benefit (such as QALY gained). As these models are static, the impact of PrEP on the HIV epidemic and the onward transmission of HIV are not captured.

The NNT was stated as 17.2, 51.78 and 58.1 for Durant-Zaleski et al., Ouellet et al. and Reye-Uruena et al., respectively. The substantial difference in NNT is explained by the fact that Ouellet et al. and Reye-Uruena et al. used local incidence data (Canada and Spain, respectively) as opposed to the trial data (IPERGAY) used by Durant-Zaleski et al. The use of IPERGAY trial data is considered appropriate in this study, however, as it enrolled participants from the same population as the target population for the cost-effectiveness analysis.

Table 5.3. Economic model type and PrEP efficacy estimate used in MSM studies

Mathematical modelling studies	Description of economic model	PrEP efficacy
Cambiano (2018)[81]	Dynamic individual based stochastic model (HIV synthesis model)	86%
Desai (2008)[104]	Stochastic compartmental mathematical model	50%
Gomez (2012)[83]	Deterministic compartmental mathematical model	92%
Gray (2017)[105]	Dynamic transmission model (Prevtool)	99%
Juusola (2012)[84]	Deterministic dynamic compartmental model	44%
Lin (2016)[85]	Bernoulli process model	44%
Luz (2018)[112]	State-transition Monte Carlo stimulation model (CEPAC)	95% (43.2%)*
MacFadden (2018)[87]	Dynamic stochastic compartmental model	44%
McKenney (2017)[88]	Decision analytic model	56%
Nichols (2016)[89]	Deterministic mathematical transmission model	86%
Ong (2017)[90]	A static decision analytic model	86%
Paltiel (2009)[92]	State-transition Monte Carlo stimulation model (CEPAC)	50%
Schneider (2014)[94]	Stochastic agent-based model	95% (75%)*
Suraratdecha (2017)[95]	Dynamic transmission model (OPTIMA)	75%
Non-mathematical modelling studies	**Description of economic model**	**PrEP efficacy**
Durand-Zaleski (2017)[82]	Non-mathematical cost effectiveness analysis	86%
Ouellet (2015)[91]	Non-mathematical cost utility analysis	44%
Reyes-Uruena (2017)[93]	Non-mathematical cost utility analysis	86%

* Combined efficacy and adherence. Overall effectiveness in parenthesis.

Parameter estimates for the efficacy of PrEP in reducing the risk of HIV transmission used in the studies ranged from 44%-96%. (Table 5.2). As detailed in Chapter 4, the iPrEx trial (2010) reported an efficacy of 44% and the trial by Peterson et al. (2007) reported an efficacy of 50%. The efficacy from iPrEx was employed in four models[84, 85, 87, 91] and that of Petersen et al. in two models.[92, 104] A relative risk reduction of 75% from a 2012 study by Baetens et al. was used in the base case in two studies.[94, 95] The most recently published PrEP RCT trials, PROUD (2016) and IPERGAY (2015), reported an effectiveness of 86% for both daily and on-demand

dosing schedules in the MSM group. This estimate was used in five studies.[81, 88-90, 93] The remaining two studies used a combination of adherence and efficacy resulting in efficacies of 96%[86] and 52%.[83]

Thirteen studies used pooled utility values derived from a 2002 meta-analysis published by Tengs and Lin.[113] Time-trade-off was used to elicit utilities from patients which were estimated as a utility of 0.94 for asymptomatic HIV infection, 0.82 for symptomatic HIV and 0.7 for AIDS. Two UK studies used utility values from a study by Miners et al. that merged two UK cross-sectional surveys, the ASTRA study (2012) and the Health Survey for England (2011), to generate comparisons between HIV-infected and HIV-uninfected individuals using multivariable models.[114] The disutility values associated with HIV infection were: HIV-positive diagnosed with CD4>200 cells/mm^3 -0.1 (95% CI: -0.08; -0.12); HIV-positive diagnosed with CD4≤200 cells/mm3 -0.15 (95% CI: -0.11; -0.19). Values for HIV-positive diagnosed stage 4 (WHO) -0.55 (95% CI: -0.38; -0.71) and HIV-positive diagnosed stage 3 (WHO) -0.22 (95% CI -0.15; -0.31) were sourced from a study on the global burden of disease study.[115] The two remaining CUA papers, Gomez et al. (2012) and Suraratdecha et al. (2018), conducted in low/middle income countries, used DALYs rather than QALYs (as recommended by the WHO).[116]

Table 5.4 provides the annual cost of PrEP medication used in each study. All costs were inflated using the consumer price index (CPI) for health and converted to 2017 Irish Euro using purchasing power parity (PPP). A daily dosing regimen was the base case scenario in most studies although two studies used event-based (also known as 'on demand') dosing.[81, 82] One study calculated the average cost of PrEP for patients taking five pills per week and the other study based the cost of PrEP on patients taking a mean of 15.6 pills per month (SD: 7.2).

Table 5.4. Estimated annual cost of PrEP used in economic evaluations converted to 2017 Ireland (€)

Study (Year)	Annual Cost of PrEP ART	Annual Cost of PrEP ART (2017 Irish €)	Annual Monitoring and Screening Costs	Annual Cost of PrEP Programme	Annual Cost PrEP Programme (2017 Irish €)
Cambiano (2018)[81]	£3,248*	€3,553	£649**	£3,897	€4,263*
Desai(2008)[104]	$11,315	€6,738	Year 1: €1,300 Subsequent years: $1,020	$12,615	€7,512
Durand-Zaleski (2016)[82]	€3,117*	€3,115	Year 1: €738 Subsequent	€4,271	€4,268*

			years: €690		
Gomez (2012)[83]	$600	€554	$230	$830	€767
Gray (2017)[105]	$10,249	€5,610	$645	$10,894	€5,963
Juusola (2012)[84]	$9,312	€9,188	$771	$10,083	€9,188
Lin (2016)[85]	$8,969	€6,318	Year 1:$1,534 Subsequent years: $1,204	$10,338	€7,282
Luz (2018)[86]	$270	€232	$22	$292	€250
MacFadden (2016)[87]	$10,012	€6,606	Initial visit: $305 Subsequent Visit: $100	$10,617	€7,005
McKenney (2017)[88]	$10,711	€7,058	$1,173	$11,884	€7,830
Nichols (2016)[89]	€7,400	€7,282	€2,335	€12,987	€12,780
Ong (2017)[90]	£4,331	€4,738	£649**	£4,507	€4,931
Ouellet (2015)[91]	$9,505*	€6,271	$2,496	$12,001	€7,918*
Paltiel (2009)[92]	$9,036	€10,301	$336	$9,372	€10,684
Reyes-Uruena (2018)[93]	€5,874	€7,238	€1,303	€7,177	€8,843
Schneider (2014)[94]	$9,597	€6,041	$765	$10,362	€6,523
Suraratdecha (2018)[95]	$14,106	€11,659	$2,985	$17,091	€14,126

* PrEP On-Demand Dosing ** Incremental cost of £176 used model. This is the estimated cost of PrEP monitoring (£649) minus the usual care cost for high risk MSM (£473).

The annual price of daily PrEP ART ranged from €232 to €11,659 and the mean cost was €6,397. The annual cost of PrEP was lowest in South American counties (Brazil [€232] and Peru [€554]) and highest in Thailand (€14,222). The annual cost of on-demand PrEP ART was €3,115, €4,738 and €6,271 (mean €4,708) in the studies that used this dose regimen as the base case.

In European studies the cost of daily PrEP ART ranged from €4,738 to €7,282; the mean cost was €6,419 (n=3). In North American studies the cost of daily PrEP ART ranged from €7,058 to €10,301 (n=6) and the mean cost was €7,702. A lower cost of PrEP, up to 80% less than the original price, was routinely varied in sensitivity analysis.

A discount rate was applied in the base case analysis to future costs and outcomes in thirteen of the seventeen papers. Only one study used a discount rate of 5%, all others studies used 3% or 3.5%. The impact of discount rate has a significant impact on cost-effectiveness as models follow patient over lifetime. The cost of PrEP is upfront, while the benefits of avoiding HIV infection are spread over the lifetime, it

is likely that a high discount rate will result in the intervention being less cost-effective. Two non-mathematical models illustrate this with a one-year PrEP intervention estimated as cost saving when undiscounted but increased to €39,734 and €192,019 at 5% discount rate.[91, 93]

As identified in Chapter 4, there is a concern that use of PrEP may be associated with an increase in risky sexual behaviour, also referred to as 'risk compensation' and 'sexual disinhibition'. Six studies included changes in condom use and the number of sexual partners to capture behaviour changes.[84, 88, 90, 94, 95, 105] No study incorporated sexual behaviour change into the base case scenario. One study included costs of STI treatment and QALY losses associated with STI diagnosis and treatment.[88] Table 5.5 outlines parameters relating to risk compensation used in the MSM studies.

Table 5.5. Sexual risk behaviour parameter values, costs and outcomes

Study	Parameter values for sexual & behavioural change	Cost & outcomes of STI & STI Testing
Gray (2018)[105]	Not modelled in base-case. Condom use decreased by: 10%, 30% and 50%	N/R
Juusola (2012)[84]	Not modelled in base-case. Appendix results: 20% increase in partners and 20% reduction in condom use	N/R
McKenney (2017)[88]	Not modelled in base-case. Scenario analysis: 25% increase in sexual encounters, STI, sexual risk & 25% decrease in condom use.	STI treatment: $180 ($99-295) STI test: $67 ($27-80) STI QALY loss: 0.02 (0.01-0.03)
Ong (2017)[90]	Not modelled in base-case. Sensitivity analysis: Risk compensation of 10%, 20% and 30% included.	N/R
Schneider (2014)[94]	Not modelled in base-case. Sensitivity analysis: 25%-75% reduction in condom use.	N/R
Suraratdecha (2017)[95]	Not modelled in base-case. Sensitivity analysis: Condom use reduced by 10% (0-20%)	N/R

N/R = not reported

The lifetime cost of HIV infection was an important parameter that varied widely across studies. To facilitate comparison, all costs were converted to 2017 Irish Euro. The annual cost of HIV infection ranged from €3,517 to €25,468 (mean €13,450), see Table 5.6. The lowest cost was used in the study conducted in Brazil, where far lower costs for ART and healthcare were observed compared with high-income countries. There were two studies for which the cost of HIV exceeded €20,000 per

year; this was attributed to high costs of ART. Three studies reported an annual cost between €10,000 and €20,000. Of the three studies reporting annual costs under €10,000, one was the aforementioned Brazilian study and the remaining two studies stated costs of €8,412 (USA) and €8,917 (USA).

Table 5.6. Estimates of annual cost of HIV used in economic evaluations

Study	Annual Cost of HIV	Adjusted Cost (2017 Euros)	Source
Desai (2008)[104]*	$14,179	€10,472	Schackman (2006)[117]
Durant (2016)	$20,000	€20,238	Sloan et al (2012)[118]
Juusola (2012)[84]**	$25,831	€25,468	Schackman (2006)[117]
Lin (2016)[85]***	$11,943	€8,412	Farnham (2012)[119]
Luz (2018)[86]	$4,100	€3,517	n/a
MacFadden (2018)[87]*	$17,059	€11,255	Krentz (2008)[120]
McKenney (2017)[88]*	$13,533	€8,917	Schackman (2006)[117]
Reyes-Uruena (2018)[93]	€13,482	€16,613	2016 GESIDA/Spanish AIDS National Plan[121]

* Lifetime cost divided by 24.2 as stated in Schackman et al (2006).
**Juusola (2012): $6181 – Symptomatic HIV treated, $15,589 – ART, $4,061 – Non-medical costs.
***Lin (2016): $418,000 lifetime cost of HIV per Appendix, divided by 35 years.

5.3.5 PWID

One US study estimated the cost-effectiveness of using PrEP to reduce HIV transmission in PWID.[80] A dynamic transmission model was adapted from a previously developed model by the same lead author.[122] All costs were presented in 2015 US dollars. When adjusted to 2017 Irish euro, the annual drug cost of PrEP was €8,579 with screening costing €686 a year. The prevalence of HIV was 9.8%. The effectiveness of PrEP in averting HIV infection for PWID was stated as 48.9%. This was based on the Bangkok tenofovir study, in which participants did not have access to needle exchange, which determined PrEP efficacy in PWID.[123] A societal perspective was taken. The utility values associated with HIV were derived from Tengs and Lin.[113] The dosing regimen was daily, the time horizon 20 years and discount rate 3%. The base case ICER for 36% coverage of PrEP was €269,366 with a budget impact of €59 billion.

5.3.6 Summary of Cost-Effectiveness Results

5.3.6.1 MSM

Cost-effectiveness results from the 17 studies focusing on the MSM population were not uniformly reported. Results are usually interpreted in the context of a

willingness-to-pay threshold; this differed by jurisdiction. In Ireland, willingness-to-pay thresholds of €20,000/QALY and €45,000/QALY are used to interpret the cost-effectiveness for medicines in Ireland.

In eight of the eleven mathematical cost-utility studies which reported QALYs, the baseline ICER was below €45,000 (see Table 5.7). Five of the studies which reported PrEP to be cost-effective used estimates of PrEP efficacy significantly lower (43%-56%) than the efficacy estimate (86%) from the more recent PROUD or IPERGAY trials. This indicates that PrEP is likely more cost-effective than stated in these studies.

Table 5.7. Baseline ICER in mathematical modelling studies reporting QALYS

Study (Year)	Country	Baseline Outcomes: ICER (€ per QALY/DALY)	Adjusted cost of Outcomes (€ Ireland 2017)
Cambiano (2018)[81]	UK	Cost saving	Cost saving
Desai(2008)[104]	USA	$31,972	€23,613/QALY gained
Gray (2017)[105]	Australia	N/R	N/R
Juusola (2012)[84]	USA	$44,556	€43,961/QALY gained
Lin (2016)[85]	USA	$58,849	€41,452/QALY saved
MacFadden (2016)[87]	Canada	$34,999	€41,367/QALY
McKenney (2017)[88]	USA	$64,000	€42,170/QALY gained
Nichols (2016)[89]	Netherlands	€7,800	<€20,000/QALY gained
Ong (2017)[90]	UK	Cost saving	Cost saving
Paltiel (2009)[92]	USA	$298,000	€339,791/QALY gained
Schneider (2014)[94]	Australia	$180,146	€113,339 Cost/QALY (10 partners, 15% coverage)

One Australian study did not report ICERs, but instead presented uptake scenarios and calculated the annual cost of PrEP for which PrEP would be cost-effective at different willingness-to-pay (WTP) thresholds. The current estimated PrEP unit cost (of $10,249) would need to fall by 26-47% for the scenarios in which PrEP is used only by high-risk MSM to be considered cost-effective. At a WTP of $30,000 (€32,708), the authors concluded that PrEP would be cost-effective in a scenario where 30% of high risk MSM take PrEP and the annual cost was less than €4,132.

The two UK-based mathematical modeling studies which found PrEP to be a cost saving intervention employed an efficacy value of 86%.[81, 90] One employed a dynamic transmission model with an 80 year time horizon and the other a decision analysis that assessed the lifelong costs and benefits following one year of PrEP

administration. Decision analytic models underestimate cost-effectiveness as, unlike dynamic transmission models, they fail to capture the prevention of onward HIV transmission ('snowball effect').

Finally, two mathematical studies reported an ICER greater than €45,000 and stated that PrEP was not cost-effective.[92-94] The highest reported costs per QALY were €339,791 (US study) and €113,339 (Australian study). The US study (2009) pre-dated the iPrEx, PROUD and IPERGAY trials and as such, employed an efficacy of 50%. Additionally, the annual cost of PrEP (€9,891) was higher than average. In a sensitivity analysis the efficacy of PrEP was increased to 90%, resulting in a cost per QALY of €121,980. The Australian study was more applicable to Ireland, using an efficacy of 95% (provided adherence was at least 75%) and the cost of ART was lower than the median €6,041.

Two of the non-mathematical studies presented least expensive (on-demand PrEP) and most expensive (daily PrEP) scenarios and used discount rates of 0%, 3% and 6% (Table 5.8). The Canadian study found PrEP to be cost-saving when undiscounted or at a discount rate of 3%. PrEP was cost-effective when a 5% discount rate was used (ICER €31,233 to €39,734). The Spanish study concluded that, when undiscounted, on-demand PrEP was cost saving and daily PrEP was cost-effective (ICER €7,740). When the discount rate was increased to 3%, on-demand PrEP was estimated to be cost-effective (ICER €20,587), but daily PrEP exceeded the Irish threshold for cost-effectiveness (ICER €70,761). When a 5% discount rate (CADTH guidelines) was applied both on-demand (ICER €53,392) and daily PrEP (ICER €192,019) far exceeded the Irish cost-effectiveness threshold.

Table 5.8. Baseline ICER in non-mathematical modelling studies

Study (Year)	Country	Baseline Outcomes: ICER (€/$ per QALY/DALY)	Adjusted cost of Outcomes (€ Ireland 2017)
Durand-Zaleski (2016)[82]	France	€75,258	€75,214 per infection averted
Ouellet (2015)[91]	Canada	$60,233	ICER €39,734 (Most expensive HIV cost, 5% discount)
Reyes-Uruena (2018)[93]	Spain	€156,830	ICER €192,019 (Daily PrEP, 5% discount)

The other non-mathematical study did not incorporate QALYs. The cost of averting one HIV infection was calculated at three prices for PrEP. The international market price (€60/30 tablets), French generic price (€180/30 tablets) and the French drug

list price (€501/ 30 tablets). These different costs of PrEP resulted in a cost per HIV infection averted of €26,771, €37,948 and €75,214.

Two studies reported cost per DALY averted, and one study cost per life year saved (LYS). LYS and DALYs are not applicable to a developed country such as Ireland for which the QALY is the gold standard used to quantify health outcomes. Furthermore, three of these studies were at the extreme ends in terms of the cost of PrEP. The annual cost of PrEP in two of the South American studies (€223-€554) was significantly below the median (€7,170) whilst the cost in the Asian study was significantly higher (€14,222). These studies are summarised in Table 5.9.

Table 5.9. Baseline ICER in mathematical studies not reporting QALYs

Study (Year)	Country	Baseline Outcomes: ICER (€ per QALY/DALY)	Adjusted cost of Outcomes (€ Ireland 2017)
Gomez (2012)[83]	Peru	€1,780	€1,644/DALY averted
Luz (2018)[86]	Brazil	$2,530	€2,170/LYS
Suraratdecha (2018)[95]	Thailand	$4,957	€4,097 Cost per DALY averted

Sensitivity Analysis

Fifteen studies conducted a sensitivity analysis. The key parameters influencing cost effectiveness were the drug cost, the effectiveness of PrEP in averting HIV infections and the incidence of HIV. The US study which reported the highest cost per QALY noted that if efficacy increased from 50% to 90%, the ICER decreased from €339,791 to €129,960. A similar reduction was observed when the annual cost of drug was reduced from €10,300 to €5,150: the ICER decreased to €121,980. A combination of a lower annual drug cost and increased efficacy would therefore potentially have made PrEP cost-effective, however, multivariate analysis was not conducted. Another US-based study found that PrEP offered to high risk MSM at an efficacy of 44% had an ICER of €43,961. When the annual cost of PrEP was reduced from €9,188 to €4,594, the ICER reduced to €24,829. The impact of increased efficacy was observed in a Canadian study when the base case scenario reported an ICER of €23,092 at 44% efficacy which was reduced to €15,021 (76% efficacy) or €10,483 (96% efficacy). A Dutch deterministic mathematical modelling study estimated that the cost per QALY gained would be less than €20,000. At 80% effectiveness, daily PrEP could be considered cost-saving if the price of PrEP is reduced by 70%, and on-demand PrEP could be considered cost-saving if the price is reduced by 30-40%.

The incidence of HIV had a marked impact on results when studied in sensitivity analysis. The UK study by Ong et al found PrEP to be cost saving in most scenarios

when considering different values for efficacy, cost of PrEP and future costs of ART for HIV. When incidence was varied, PrEP remained cost-effective in most scenarios; however it was no longer cost saving when the incidence of HIV decreased below 2.0 per 100 person-years. Sensitivity analyses in other studies also noted improved cost-effectiveness with higher PrEP efficacy estimates. Sensitivity analyses in other studies also noted improved cost-effectiveness with higher PrEP efficacy estimates.[81, 88]

5.3.6.2 PWID

The cost-effectiveness of PrEP in PWID was reported in one study. Using an uptake rate of 36%, PrEP was not found to be cost-effective (ICER of €269,366) compared with standard care.

5.4 Discussion

The systematic review identified eighteen economic evaluations of PrEP to prevent HIV infection. Evidence of cost-effectiveness was inconsistent due to differences in the study input parameters and design, with incremental cost-effectiveness ratios (ICERs) ranging from cost saving to €339,791 per Quality-Adjusted Life Year (QALY) gained. Evidence from sensitivity analyses suggests that the annual cost of PrEP and the estimate of effectiveness used are important drivers within individual studies.

The discount rate applied is also influential, with PrEP becoming less cost-effective in studies where a higher discount rate was applied. There were insufficient details available on some key parameters, for example five studies did not report the incidence of HIV. This could explain the difference in results as it is an important determinant of cost-effectiveness (PrEP is more likely to be cost-effective when background incidence is high).

Three studies, two from the UK and one from Australia, were most applicable to Ireland regarding the perspective, efficacy of PrEP (based on Chapter 4 results) and the incidence of HIV. The two UK studies (which used a discount rate of 3.5%) estimated that PrEP would be cost-saving.[5, 14] The Australian study [105] used a range of willingness-to-pay thresholds, of which $60,000 (Australian Dollars) is most closely aligned to the €45,000 used in Ireland. In this study, PrEP would only be considered cost-effective if the annual cost of PrEP (€5,587) fell by 26-47%. However, PrEP would be considered cost-effective or cost saving if generic PrEP is used, which is the case in Ireland. This study employed a 5% discount rate, which is the discount rate used for HTA in Ireland.

Of note, the perspective used in health economic evaluations has important implications for the interpretation of the results. For example, an intervention may not appear to be cost-effective when the public payer perspective is considered, but if that same intervention has benefits other than those born by the health sector, it may be cost-effective. In Ireland the perspective taken is that of the public payer, hence studies adopting a societal perspective may be less relevant to this HTA.

The systematic review identified four types of mathematical model: dynamic transmission, decision analytic, state-transition Markov, and Bernoulli process model. Three economic evaluations were also identified that did not use a mathematical model. Economic models have different properties that both affect the result and the interpretation of the results. In deterministic models, the output of the model is fully determined by the parameter values and the initial conditions whereas stochastic models possess some inherent randomness. Dynamic models, on the other hand, track the transmission of infection in the population. The model can therefore incorporate future costs and benefits such as onward transmission. This accounts for all individuals for which PrEP averts HIV infection, including those who do not directly take part in the programme. These future benefits and costs require a significant amount of detailed information on prevalence, incidence and even migration patterns. Furthermore, assumptions have to be made not only about the HIV epidemic and whether it will remain stable or fluctuate, but also the future costs of both PrEP and HIV treatment. This increasing number of assumptions is associated with a greater level of uncertainty compared with static models. The key limitation of decision analytic models is that they do not incorporate the non-linear dynamics of HIV and therefore do not quantify the impact of PrEP on the wider HIV epidemic. This limits the impact of PrEP as onward transmission is not included and as such decision analytic models are considered more conservative when assessing the impact of PrEP.

Although clinical data presented in Chapter 4 has not suggested significant increases in risky sexual behaviour in PrEP users ('risk compensation' or behavioural disinhibition), it is a factor that could influence the cost-effectiveness of PrEP. Sexual disinhibition is the concept whereby those taking PrEP may engage in more risky sexual behaviour with an increase in sexual partners and decrease in condom use. This could therefore lead to an increase in STIs in this population, causing increased costs and a decrease in utilities. This factor was incorporated into the sensitivity analysis of four studies with arbitrary increases of 10-30% modeled; however, inclusion of risk compensation had a negligible effect on the estimate of cost-effectiveness.

The three economic evaluations most applicable to the Irish healthcare system found the use of PrEP in MSM to prevent the sexual acquisition was cost-effective and cost saving at generic drug pricing. However, due to differences in the discount rates, lifetime cost of HIV and annual cost of PrEP medication used, a de novo economic evaluation using Irish data to estimate the cost-effectiveness and budget impact in the Irish health care setting was required to inform decision-making.

6 Economic evaluation

Key points

- An original discrete-time transition Markov model was developed to compare the costs and benefits of providing a national PrEP programme in Ireland.
- This cross-sectional population model tracks all HIV-negative Irish gay, bisexual and other men who have sex with men (MSM) at the outset of the simulation (2018) and follows these men over their lifetime. While a prospective PrEP programme would enrol all eligible participants and not exclusively MSM at substantial risk, only MSM are considered for the purposes of cost-effectiveness modelling due to the fact that more than 95% of participants are expected to be MSM and very limited data were retrieved on other groups.
- In the base case analysis, PrEP is cost saving, with an incremental cost-effectiveness ratio (ICER) of -€2,735 over the cohort's lifetime (95% CI: -€16,486 to €21,585). This means that providing PrEP is less costly, and more effective (in terms of quality-adjusted life years [QALYs] gained), than not providing PrEP.
- Univariate deterministic sensitivity analysis was carried out to identify how sensitive these results are to changes in the input parameters. The results are robust to considerable variations in the main assumptions and plausible parameter values.
- PrEP effectiveness was the main driver of cost-effectiveness in the model. PrEP was found to be cost saving when adherence-related effectiveness is 60% or more. At an effectiveness of 44% (reported in iPrEX, the lowest effectiveness recorded among MSM), the ICER is €4,711/QALY (highly cost-effective).
- The ICERs were also sensitive to key cost parameters, including the cost of HIV care and the cost of PrEP. However, PrEP was still considered cost saving over a range of plausible costs.
- Two-way sensitivity analysis was carried out on the proportion of MSM at high risk and the PrEP uptake rate. PrEP becomes more cost saving as either parameter increases.

- Although PrEP is currently only licensed for daily dosing, in the scenario where 50% of PrEP recipients follow event-based dosing, the ICER decreases to -€4,594 (95% CI: -€20,158 to €14,150).
- The mean number of people estimated to join a potential PrEP programme in Year 1 is 1,705 people (95% CI: 617 to 3,452).
- The incremental budget impact of the PrEP programme is €1.5m in the first year (95% CI: €0.5m to €3m) and €5.4m over 5 years (95% CI: €1.8m to €11.5m).
- In the base case analysis, an average of 173 HIV infections are estimated to be averted in the first five years.
- Extending the budget impact assessment beyond five years, the yearly incremental budget impact becomes negative after eight years and the aggregate budget impact ('break even' point) is reached after 14 years (all programme and medication costs will have been recouped).

6.1 Methods

6.1.1 Overview of economic evaluation

Chapter 5 (systematic review of prior cost-effectiveness studies) highlighted the significant variability in the cost-effectiveness of PrEP. The estimated cost-effectiveness is influenced by a number of parameters that tend to be country specific, including sociodemographic differences and differences in the cost of antiretroviral therapy (ART) used as PrEP and in the treatment of HIV. As such, a de novo economic model tailored to the Irish context is required to estimate the cost-effectiveness and budget impact of a PrEP programme in Ireland.

This chapter describes the economic model constructed and the estimated cost-effectiveness and budget impact of providing a PrEP programme in Ireland. The objective of the economic evaluation is to aid decision-making by estimating the incremental costs and benefits of funding a PrEP programme for those at substantial risk of sexual HIV acquisition.

The target population is gay, bisexual and other men who have sex with men (MSM) who are eligible for PrEP, and the setting is the Irish publicly-funded health and social care system, namely, the Health Service Executive (HSE). While a prospective PrEP programme would enrol all eligible participants and not exclusively MSM at substantial risk, only MSM are considered for the purposes of cost-effectiveness modelling due to the fact that more than 95% of participants are expected to be MSM and very limited data were retrieved on other groups. For comparison, 99% of participants in the first year of Scotland's national PrEP programme were male (n=1,855), and 99% of these were MSM (n=1,846).

6.1.2 Perspective, time horizon and discount rate

Consistent with national guidelines for the economic evaluation of health technologies, the perspective adopted was that of the HSE in Ireland. Only direct costs to the HSE were considered. The time horizon of the analysis was the cohort's lifetime. A discount rate of 5.0% was applied to both costs and benefits.

6.1.3 Choice of comparator

The comparator chosen was that of the current suite of HIV prevention strategies in Ireland (barrier protection, treatment-as-prevention [TaSP], post-exposure prophylaxis [PEP]) without access to PrEP. While there currently is no organised PrEP progrmme in Ireland, it is acknowledged that components of the proposed programme are being provided on an ad hoc basis. As illustrated in Chapter 7

Section 7.4, a number of publicly funded STI clinics have designated some of their STI clinics as PrEP clinics, where screening and monitoring of PrEP eligible patients takes place. Medications are not provided by the publicly funded system, rather patients pay for PrEP out of pocket. There is also evidence that patients are accessing PrEP through online sites. As the numbers of patients accessing PrEP, their persistence with treatment and the treatment effectiveness are unknown, for simplicity the comparator adopted in the base case analysis assumed no current access to PrEP. Additionally, as individuals currently pay for PrEP out of pocket, using the current ad hoc arrangement as a comparator would bias the analysis against adopting a HSE-funded PrEP programme due to the fact that direct costs only are considered (PrEP medications are currently obtained at no additional cost to the HSE). Table 6.1 outlines the base case for the economic evaluation.

Table 6.1. Base case

Element of technology assessment	Base case
Evaluation type	Cost-utility analysis
Perspective on costs	The publicly-funded health and social care system in Ireland (HSE)
Perspective on outcomes	All health benefits accruing to individuals
Choice of comparator	The current suite of HIV prevention strategies in Ireland (barrier protection, treatment-as-prevention [TaSP], post-exposure prophylaxis [PEP]) without access to an organised PrEP programme
Synthesis of effectiveness	Based on systematic review and meta-analysis (Chapter 4: Efficacy)
Outcome measurement	Quality-adjusted life year (QALY) gained
Discount rate	Apply an annual rate of 5.0% on costs and outcomes occurring after the first year
Sensitivity analysis	Deterministic and probabilistic sensitivity analysis

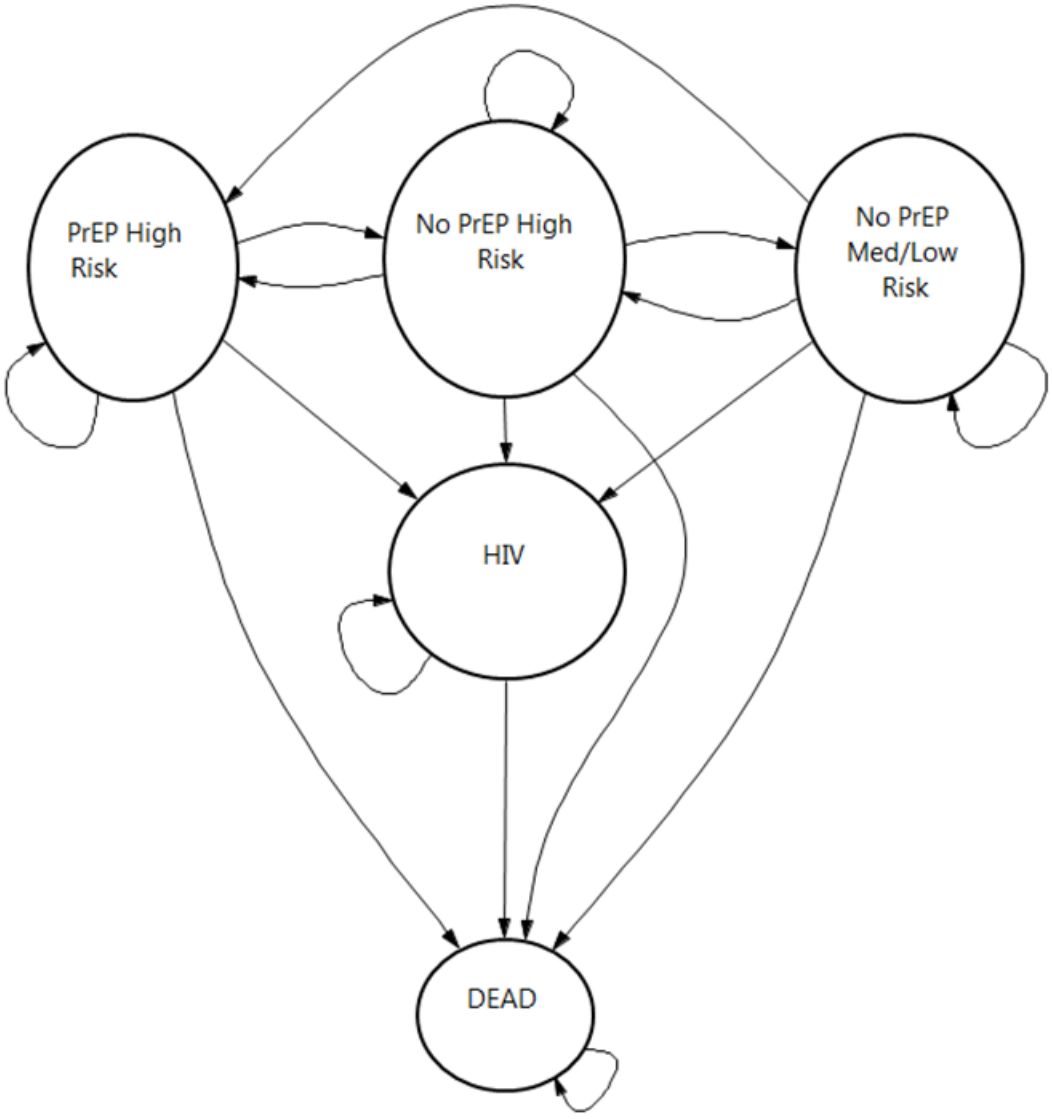
6.1.4 Model structure

An original state transition Markov model was developed to compare the costs and consequences of providing a PrEP programme in Ireland. The model is a closed cross-sectional population model that tracks the entire population of Irish HIV-uninfected MSM at the outset of the simulation (2018) and follows these men until they die.

The basic model structure is shown in Figure 6.1. In the model, the risk status of MSM is either categorised as ‘high’ or ‘medium/low’ risk. ‘High risk’ is defined by the

eligibility criteria for PrEP, as outlined in Chapter 2. All other MSM are considered 'medium/low risk'. Additionally, 'high risk' individuals may be taking PrEP ('PrEP high risk') or not ('No PrEP high risk'). It is assumed that individuals in the 'medium/low risk' group will not take PrEP as they do not meet the eligibility criteria. Individuals may move between these health states, until they acquire HIV or die.

Figure 6.1. Model structure



Key: HIV — human immunodeficiency virus; PrEP — pre-exposure prophylaxis.

6.1.5 Sensitivity analysis

Monte Carlo simulation was carried out, with each parameter being defined as a distribution based on the plausible range of values, which were then sampled over the course of 10,000 replications to take account of the uncertainty associated with the model outputs. Deterministic univariate sensitivity analysis was carried out to estimate the effect of uncertainty pertaining to individual parameter estimates.

6.2 Clinical and epidemiological parameter estimates

6.2.1 Target population

6.2.1.1 Numbers and proportions of MSM by risk group

Due to the fact that 95% or more of eligible individuals are likely to be MSM, and in the absence of data specific to other groups in Ireland, the modelled cohort comprises only MSM for the purposes of cost-effectiveness modelling. The overall number of MSM in Ireland was estimated using CSO population estimates and information from Healthy Ireland surveys.

The estimated total male population aged 16 to 80 was 1,802,395 in 2018.[42] The 2017 Healthy Ireland Survey, which is a nationally representative probability based survey, found that 4% of men had reported that their last sex was with a man.[23] This is the most recent Healthy Ireland survey that reports sexual behaviour data. A previous Healthy Ireland survey reported a higher rate of 6%.[41] To ascertain sexual orientation, the Healthy Ireland survey asked respondents what gender the last person they had sex with was. The survey, therefore, does not capture bisexual men whose last sexual encounter was with a woman.

Another survey (My World Survey National Study of Youth Mental Health, 2012) of young male and female adults and adolescents (n=14,306) noted that 4% identified as gay and 4% as bisexual.[13] An earlier study, the Irish Study of Sexual Health and Relationships (2006), reported lower rates: 1.6% of 3,188 male respondents classified themselves as homosexual and 1.1% as bisexual.[30] The range of prevalences of MSM are presented in Table 6.2.

Table 6.2. MSM prevalence

Survey	Proportion MSM
Healthy Ireland 2017	4%
Healthy Ireland 2015	6%
My World Survey National Study of	8% (male and female, young

Youth Mental Health 2012	adult and adolescent sample)
The Irish Study of Sexual Health and Relationships 2006	2.7%

Key: MSM — men who have sex with men.

As the Healthy Ireland surveys are the most recent surveys identified and consist of a nationally representative sample, older surveys were not used to estimate the MSM population. Table 6.3 outlines these estimates.

Table 6.3. MSM population

Population	Number	
Population of Ireland*	4,857,015	
Male population aged 16 to 80*	1,802,395	
Population	**Mean**	**Range**
Proportion MSM**	5%	4 to 6%
MSM population	84,713	68,491 to 101,737

*Source: CSO 2018 estimates
**Pooled analysis of Healthy Ireland surveys 2015 and 2017

As this reflects all MSM, the number of MSM that are HIV positive (7.8% of those tested, or 5% of total [see Chapter 3: Epidemiology]) is subtracted to obtain the HIV-negative MSM population. Additionally, an arbitrary increase of 5% was applied to account for the non-MSM group in the budget impact analysis. In the absence of Irish data, a 5% increase was thought to fully capture this group, keeping in mind that less than 1% of Scotland's PrEP programme consisted of non-MSM individuals.

6.2.1.2 Proportion sexually active

The question posed by the Healthy Ireland ascertained the sex of respondents' last sexual encounter and provides information on the proportion that may be MSM. However, the sexual health component of Healthy Ireland surveys excludes those who are not yet sexually active. Additionally, as it refers to prior sexual exposure, one cannot assume that the respondents are currently sexually active.

For this reason, the proportion of MSM who are currently sexually active was estimated. Information on the sexually active heterosexual population were identified in the The Irish Study of Sexual Health and Relationships (ISSHR)[(124)] and The Irish Longitudinal Study on Ageing (TILDA)[(125)] datasets and, for the MSM population, from ISSHR.[(124)] Data were pooled from older age groups (TILDA) and younger age groups (ISSHR) to estimate the proportion sexually active in a heterosexual population. Data on the proportion of the MSM population that are

sexually active was reported in the ISSHR, but due to the small number of survey respondents the results were not reported by age band. In the absence of information regarding the age distribution of the survey respondents, it was, therefore, not possible to calculate an appropriately age-weighted average proportion. The reported overall proportion that was sexually active in the MSM population was lower than for the heterosexual population. The proportion of MSM that are sexually active was conservatively estimated as the average of the figures reported for MSM and heterosexual populations and applied to the MSM age distribution of MISI 2015.

Overall, the proportion of MSM aged 16 to 80 that are currently sexually active was estimated at 63% (95% CI: 49 to 76%). The wide confidence interval reflects the uncertainty associated with these estimates. However, these surveys are relatively old (ISSHR was published in 2006) and they may not be reflective of current sexual practices.

6.2.1.3 Proportion at high sexual risk for HIV

The proportion of MSM in Ireland who are at high sexual risk of HIV is unknown. For the purpose of this HTA, 'high risk' was defined by the eligibility criteria for PrEP. As outlined in Chapter 2, Section 2.4.1, MSM are at sufficient risk to be deemed eligible for PrEP if one or more of the following conditions are met:

- reported condomless anal sex with at least two casual partners over the last six months
- documented or reported episode of an acute STI over the last 12 months (excluding anogenital warts and non-primary herpes simplex virus)
- documented or reported use of HIV post-exposure prophylaxis following sexual exposure (PEPSE) over the last 12 months
- engagement in chemsex over the last six months
- the individual is a partner of a HIV-positive person who is not stably suppressed on antiretroviral therapy.

In the report *HIV Pre-Exposure Prophylaxis (PrEP) in Ireland: PrEP estimates for populations at risk of sexual acquisition of HIV,*[21] or the 'PrEP Cascade', compiled by the HSE, the Sexual Health and Crisis Pregnancy Programme (SHCPP) and the Health Protection Surveillance Centre (HPSC), the proportion of MSM who are at high risk was estimated based on secondary analysis of the Men who have Sex with Men Internet Survey Ireland (MISI 2015), a national online sexual behaviour study.[27] An estimated 23% (95% CI: 22.7 to 23.3%) of respondents would be considered eligible based on French PrEP eligibility criteria, or 706 out of 3,045

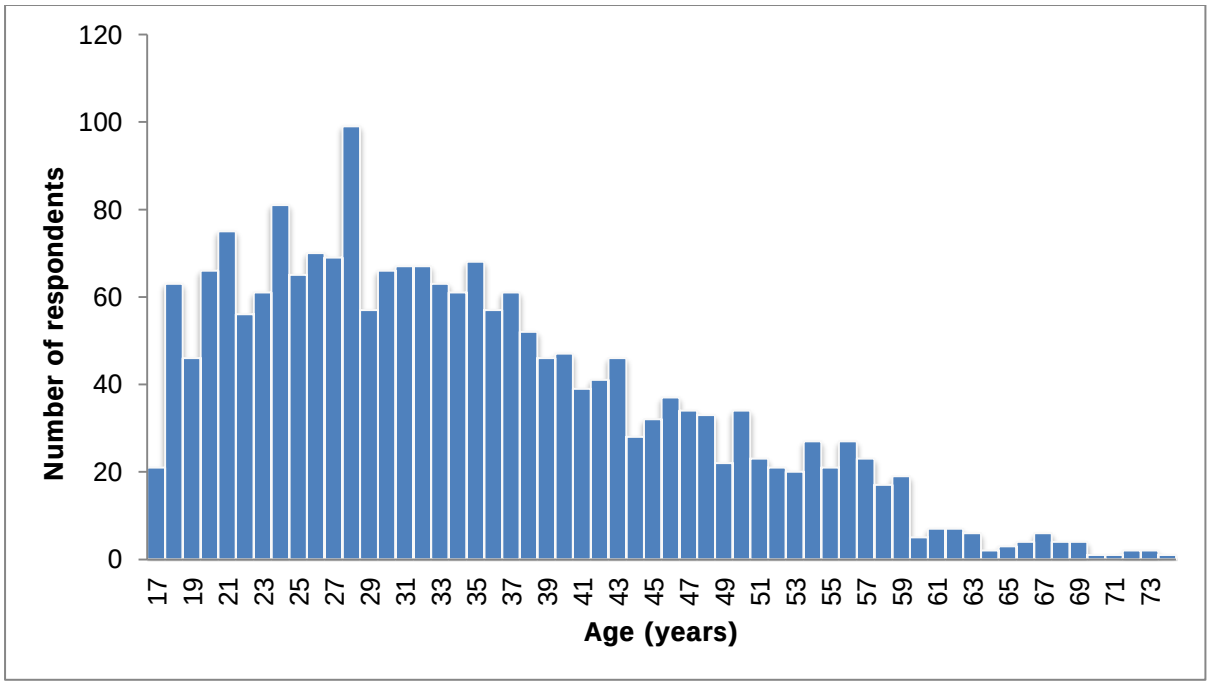
respondents. Additional information on the MISI dataset is provided in Chapter 3, Section 3.4.

Since then, in 2017, Ireland participated in a pan-European MSM survey, the European Men who have sex with men Internet Survey (EMIS 2017), the results of which are expected later this year. EMIS 2017 was an online cross-sectional behavioural surveillance survey of MSM, conducted across Europe and elsewhere, including Ireland. The overall aim of EMIS-2017 was to generate data useful for the planning of HIV and STI prevention and care programmes and for the monitoring of national progress in this area by describing the level and distribution of HIV transmission risk and precautionary behaviours.

Following discussion at the EMIS Ireland 2017 Steering committee meeting on 25 March 2019, there was agreement that the EMIS Ireland 2017 dataset should be used to provide the most up-to-date percentage of MSM at substantial risk of sexually acquired HIV and eligible for PrEP. The following results were provided to HIQA by the EMIS Ireland 2017 Steering committee.

The EMIS Ireland 2017 report included 2,083 qualifying cases of men/trans-men aged between 17 and 74 with respondents from each county in Ireland. Fewer than 1% identified as trans-men. Figure 6.2 shows the distribution of ages across the entire sample.

Figure 6.2. Age distribution of respondents (N=2,083)



Additional demographic information on EMIS Ireland 2017 respondents are presented in Chapter 3, Section 3.4.

For use in this HTA, the EMIS study authors applied Irish PrEP eligibility criteria to the Irish portion of responses to identify the proportion at substantial risk for the purpose of economic modelling. Table 6.6 shows the number and percentage of MSM at substantial risk for sexually acquired HIV and eligible for PrEP using the Irish criteria. The number eligible for PrEP based on overlapping survey responses was 647 (31%). A number of adjustments to the Irish PrEP eligibility criteria had to be made based on the EMIS Ireland 2017 dataset.

Table 6.6. Eligibility for PrEP using the EMIS Ireland 2017 dataset

Criteria used	EMIS 2017 N (%)
Aged ≥ 17 years	2,083 (100)
Man/ transman	2,083 (100)
Sexually active	2,083 (100)
Never tested for HIV/last HIV test negative	1,929 (93)
ONE of the following	
CAI with ≥ 2 non-steady partners last 12 months*	457 (24)
STI diagnosis in last 12 months	252 (13)
Ever had ≥2 treatments of PEP **	42 (2)
Use of stimulant drugs during sex last 6 months***	181 (9)
Eligible for PrEP†	**647/2083 (31)**

* Irish eligibility criteria is CAI with two or more casual partners in the past six months.
** Irish eligibility criteria is reported use of PEP over last 12 months.
***The stimulant drugs included in this definition were: ecstasy/MDMA, cocaine, amphetamine (speed), crystal methamphetamine (Tina, Pervitin), mephedrone and ketamine. Irish eligibility criteria define drugs used during sex as 'crystal meth, GHB/GBL, mephedrone and ketamine'.
† Number eligible for PrEP based on overlapping survey responses.

Note that the results of EMIS and MISI are not directly comparable, as different eligibility criteria for PrEP were used to identify the eligible population, in addition to other sociodemographic factors. It is, nonetheless, of concern that high-risk behaviour has increased in the MSM group in Ireland over a relatively short time period. The number who reported 'CAI [condomless anal intercourse] with two or more non-steady partners in past 12 months' doubled, from 12% in MISI 2015 to 24% in EMIS 2017. Smaller increases were noted for acute STI diagnoses, and there may have been an increase in chemsex use.

As both MISI and EMIS are online surveys that target sexually active MSM, it is unknown how representative respondents are of the general MSM population. One

UK study compared sociodemographic and behavioural differences between MSM participating in convenience surveys (such as EMIS 2017) and national sample surveys.[126] In this study, the national survey consisted of MSM aged 18–64 years (n=148) interviewed for Britain's third National Survey of Sexual Attitudes and Lifestyles (Natsal-3) undertaken in 2010–2012. Participants in contemporaneous convenience surveys were British male residents interviewed in the European MSM Internet Survey (EMIS 2010) (n=15,500); the London Gay Men's Sexual Health Survey (n=797) and Scotland's Gay Men's Sexual Health Survey (n=1,234). A range of high-risk behaviours were compared, such as sexual behaviours (for example, condomless anal intercourse), STI diagnoses and drug use.

Table 6.7 compares the EMIS 2010 data with the national sample (Natsal-3), for three outcomes: condomless anal intercourse, diagnosed STI and drug use. A comparison of all four studies is provided in the Appendix 5.1. These data indicate convenience samples may over-report behaviours that are considered high risk.

Table 6.7. Comparison of self-reported high risk behaviour findings from EMIS with Natsal-3

Outcome	aOR*	LCI	UCI
Condomless anal intercourse (with 2+ partners), past year	2.30	1.18	4.59
Diagnosed with STI, past year	1.91	0.85	4.30
Drug use, past year	3.62	2.33	5.61

Key: aOR — adjusted odds ratio; LCI — lower confidence interval; UCI — upper confidence interval.
*Adjusted for age, academic qualification and London residency (EMIS); age, employment and ethnicity (London-GMSHS); age and academic qualification (Scotland-GMSHS)
Source: Prah et al. 2016

Not only is it possible that respondents over-report certain behaviours in convenience surveys, it is possible that sexually active MSM are more likely to self-select to participate in sexual behaviour surveys than non-sexually active MSM, leading to a biased sample of participants. It is, therefore, reasonable to assume that datasets such as EMIS and MISI are not nationally representative samples. Also, as evidenced by Figure 6.2, it is noted that the age distribution of respondents in EMIS differs significantly from that of the general MSM population (a relatively young sample was obtained).

Due to the difficulty in ascertaining the true proportion of MSM who are at substantial sexual risk of HIV in Ireland, it was decided pragmatically to arbitrarily assign a starting mean proportion of 20% to sexually active MSM with a wide variation (95% confidence interval [CI]: 3% to 48%) and to calibrate this with observed data (see Section 6.3). This calibration exercise obviates the need for a

nationally representative survey sample to inform parameter values and ensures the model outputs are plausible with respect to the Irish HIV epidemic. A scenario analysis was also performed, using the proportion at high risk (31%) identified in the EMIS Ireland 2017 report without model calibration (see Section 6.4.2.1).

6.2.1.4 PrEP uptake

The most applicable international data to date on the actual numbers of MSM likely to avail of PrEP emanate from Scotland's experience of their first year of a national PrEP programme. Overall, 1,872 individuals were prescribed PrEP at least once in the first year of the Scottish NHS PrEP programme (Scotland's population is 5.4 million compared with 4.8 million in Ireland).[127] Very little other data were available to guide the uptake rate of PrEP in Ireland.

One online survey from 2016 of PrEP awareness and acceptability among MSM in four celtic nations (Scotland, Wales, Northern Ireland and the Republic of Ireland) found that 58.5% of respondents would be willing to take PrEP.[128] The study consisted of an online self-complete survey of HIV-negative/status unknown MSM who reported condomless anal intercourse with two or more men in the last year, recruited from gay sociosexual media. Over half of respondents (58.5%, 226/356) reported that they would be willing to use PrEP if available to them. However, only a third of men responded that they were aware of PrEP (34.5%, 132/386). The inconsistency between knowledge of PrEP and willingness to use it means that 58.5% may be an over-estimate. Additionally, as participants were recruited through sociosexual media, it is unclear if respondents are representative of the MSM group as a whole.

Separate from issues of uptake rate, the number of HIV negative MSM engaged in services (that is, attend STI clinics) in Ireland is also unknown. In the previously mentioned 'PrEP Cascade', three scenarios were examined: 15, 30 or 45% engagement in services. While engagement in services may guide the estimation of the target population, it is noteworthy that in the Scottish programme, 28% of PrEP users in the first year had not attended any public Scottish NHS sexual health clinic in the two years prior to PrEP programme implementation and almost 20% had not visited a publicly funded Scottish STI clinic in over 10 years (and possibly never). Therefore, prospective PrEP users will likely be a combination of those currently engaged and those not engaged with STI services.

Taking an approximation of engagement in services (30%), increasing this approximation by 19% to account for new STI clinic attendees (36%), and incorporating the uptake rate previously outlined (58.5%), roughly 21% of eligible MSM may avail of PrEP. Similar to the method used to estimate the proportion of

MSM who are high risk (Section 6.2.1.3), a calibration exercise was undertaken to produce plausible estimates for the uptake rate (see Section 6.3). In the calibration process, this 21% uptake was varied widely (95% CI: 14 to 30%). Uptake estimates that corresponded with a plausible number of PrEP users (based on Scottish data) and a plausible incidence of HIV were selected.

Of note, for the purposes of cost-effectiveness modelling, a cohort of MSM (with a mean age of 36.7, based on the age distribution of attendees at the Gay Men's Health Service) was followed for their lifetime. Due to the fact that the cohort is closed (new members do not join the group), the proportions in each group do not remain static over time. In contrast to the closed cohort modelled as part of the cost-effectiveness analysis, the budget impact model is an open model in the sense that new entrants (migrants and 16 year olds coming of age) can enter the model after Year 1. The number of new entrants was calculated using CSO population estimates.[129]

6.2.1.5 Movement between risk groups

It was also necessary to estimate the movement of individuals between risk groups over time (those eligible for PrEP ['high risk' in model] and those not eligible for PrEP ['Medium/Low risk' in model]). No Irish data were identified that follow MSM over time to ascertain the duration an individual remains at 'high risk' and the proportion of 'high risk' individuals that become 'medium/low risk' after a defined period.

The change in high risk behaviour over time in high risk MSM was estimated in a 2017 UK study.[130] Study authors analysed change in high risk behaviour via a longitudinal five year follow-up of high risk MSM (the proxy for 'high risk' was a diagnosis of a recent bacterial STI infection) from 2009. Data were extracted from GUMCAD, the mandatory surveillance system for STIs that collects data on all STI tests and diagnoses from all commissioned sexual health services in England. It allows pseudo-anonymised digital download of patient-level data on all diagnoses at GUM clinics. Each pseudo-anonymised record contains a clinic identifier as well as a local patient number, so data from the same individual attending the same clinic can be linked longitudinally.

Overall, the proportion of MSM identified in the initial (2009) high risk group (n=11,742) who continued to be at high risk in each of the subsequent four years (2010 to 2013) decreased rapidly over the first two years (2010 and 2011). Of the initial 2009 high risk cohort, 65.64% were **never** characterised as high risk over the subsequent four years (see Table 6.8). Following the initial high risk year, the average length of time someone was categorised as being at high risk was less than

two years. These findings, however, only apply to MSM in GUM clinics in the UK who are entered into the GUMCAD system. Therefore, generalising to high risk MSM who are not engaged in services, and generalising to MSM in jurisdictions outside England, should be done with caution. Additionally, it is not known if the proxy used for a change in high risk behaviour, that is a diagnosis of a recent bacterial STI infection, can be generalised to other high risk behaviours. Furthermore it is noted that while visits can be linked longitudinally, this is limited to attendances at the same clinic, so these data may underestimate the proportion that is subsequently categorised as high risk.

Table 6.8. Proportion of high risk MSM in 2009 subsequently categorised as high risk

High risk MSM in 2009: 11,742	
Subsequent years	Proportion high risk
Never	65.64%
1 additional year	24.14%
2 additional years	6.99%
3 additional years	2.50%
4 additional years	0.72%

1. To interpret this table, of the high risk MSM in 2009, 65.64% were not high risk in the subsequent four years; 24.13% were high risk the following year, 6.99% were high risk for the following 2 years, 2.5% for 3 years and 0.72% for 4 years.

These data suggest that roughly one third of MSM who are classified as ‘high risk’ are still classified as ‘high risk’ following the first year in English GUM clinics. Approximately 7%, 2.5% and less than 1% of those at high risk in year one were classified as high risk in years 2, 3 and 4, respectively.

These proportions were applied to MSM at substantial risk in the model. Two-thirds of the ‘high risk’ group move into the ‘medium/low risk’ group after one year. Due to the fact that the overall proportion of MSM at ‘high risk’ is unlikely to change substantially over time, to balance this movement of individuals the model allows movement of MSM from ‘medium/low risk’ to ‘high risk’ in the model.

6.2.1.6 PrEP discontinuation

It was assumed that individuals at high risk on PrEP whose risk status changes to medium/low risk would discontinue PrEP from their next three-monthly clinic visit onwards (as they no longer meet the eligibility criteria). Limited data were identified on the proportion of high risk individuals who voluntarily discontinue PrEP despite still meeting eligibility criteria. Similarly, limited data were identified on the proportion who re-start PrEP following an interruption. Some economic modelling

studies (such as a 2018 UK study[131]) applied a probability of 0.5 with a wide variation (95% CI: 0.27; 0.73) for the purpose of analyses.

In the first year of the PrEP clinic operating at the Gay Men's Health Service, there were 950 attendees; 431 were first visits and the remainder follow-up visits. It is not possible to ascertain the drop-out rate as individuals joined the programme on a rolling basis. It is also not known if those attending for first visits were new to PrEP or if they had previously access PrEP elsewhere. Additionally, it is not known whether those who discontinued did so because they no longer met the eligibility criteria (no longer considered at substantial risk) or if they discontinued for other reasons (for example, due to affordability issues or moved to another clinic).

Short-term retention rates have been published by the Welsh PrEP programme.[53] Data for all participants enrolled between 1 July 2017 and 1 December 2017 were analysed on 2 January 2018. Of 261 patients who started PrEP, 182 (70%) were still taking PrEP at the end of the five-month study period, eight stopped taking PrEP and 44 were lost to follow-up or their status was unknown. Ninety six percent of participants were MSM, with a median age of 33 years.

One-year retention rates were reported in Australia.[132] The EPIC-NSW study was an implementation cohort study which recruited high risk MSM taking PrEP in New South Wales. By the end of the 12-month follow-up period (until 31 October 2017), 7,621 participants were enrolled. The persistence of participants taking PrEP was inferred by reviewing follow-up visit attendance. After three months, 90% (n=3,259) attended the follow-up visit. This dropped to 76% (n=2,804) by the end of the twelve month follow-up visit. In total, 97% (n=3,577) participants were dispensed study drugs more than once in the year after the first date of dispensing.

In this model a 12-month retention of 76% (95% CI: 75 to 77%) based on data from the EPIC-NSW cohort in Australia has been used, as it is the cohort with complete data whose programme is most similar to that envisaged in Ireland.

In Scotland, a total of 45 individuals were coded as having stopped PrEP during the first year of their national programme (this represents 2% of the 1,872 patients who were prescribed PrEP during this time). Additional analysis, based on sequential prescription data in addition to PrEP coding, is planned to more accurately assess the numbers of individuals who may have stopped PrEP during the year.

The only other data identified relating to retention and discontinuation rates were from programmes in North America (all information presented at the Conference on Retroviruses and Opportunistic Infections [CROI], March 2018). While interpretation is complicated by a lack of detail in the study reports regarding how data were

collected and the fact that a high discontinuation was attributed to lack of health care insurance at some sites, these reports provide the longest follow-up data on PrEP use due to the fact that to PrEP was licensed by the FDA in 2012, many years before the EU/EEA (2016).

- Montreal[19]: The Actuel PrEP cohort was assessed for discontinuation and interruptions between 1 January 2011 and 1 September 2017. The cohort measured 450 consistent PrEP users (36%), 114 PrEP users (9%) who temporarily stopped and re-initiated PrEP at least once, 214 individuals who permanently discontinued PrEP (17%) and 480 individuals who were lost to follow-up (38%).

- Detroit[133]: Between July 2016 and March 2017, thirty-four (76%) interviewed patients had initiated PrEP, of whom 17 (50%) had subsequently discontinued their medication a mean of 92 days (95% CI ± 23.8) following receipt of a prescription.

- Los Angeles[134]: A longitudinal analysis of patients who initiated PrEP at the Los Angeles LGBT Center between March 2014 and February 2017 was undertaken. At the end of the analysis period, 47% (n = 809) of patients who started PrEP were active, 37% had discontinued, and 16% were lost to follow-up. By three months, 32% (n=572) discontinued, and 45% (n=802) discontinued by six months.

- San Francisco[135]: Patients receiving PrEP within the San Francisco Department of Public Health Primary Care (SFPC) clinics are included in a centralised PrEP registry to monitor metrics such as uptake and persistence. Patients receiving PrEP at any time from January 2015 to February 2016 were analysed, regardless of initiation date. The median time enrolled was 217 days, with 67% persistence at 1 year.

- Atlanta[19]: PrEP users were followed between October 2015 and March 2017. As of March 2017, only 78/201 (39%) participants remained persistent in PrEP care.

Another US study published in 2019 examined persistence with PrEP via pharmacy fill records from a national chain pharmacy to describe persistence on PrEP medication over a two-year period.[136] De-identified pharmacy fill records of 7,148 eligible individuals who initiated PrEP were followed for 24 months. Persistence was 56% in year 1, 63% in year 2 and 41% from initiation to year 2. A key limitation to this study was that data were from a single pharmacy chain and therefore individuals changing pharmacies could be persistent on PrEP, but classified as non-

persistent. Additionally its applicability may be low to the Irish context as many users had to pay a copay.

6.2.2 HIV epidemiological parameters

6.2.2.1 HIV incidence in each risk stratum

To model the effects of PrEP, the incidence of HIV in MSM at substantial risk must be ascertained, as well as the incidence in medium/low risk MSM. In Chapter 3, the notification rate of HIV, reported in Ireland by the HPSC, is described in detail. This, however, is not the same as the incidence of HIV, as diagnoses are dependent on testing.

A 2017 study estimated the incidence of HIV in 'high risk' MSM in the UK using GUMCAD, a comprehensive, pseudo-anonymised digital download of patient-level data on all sexually transmitted infection (STI) services and diagnoses provided in GUM clinics in England.[130] To assess risk group, GUMCAD data on HIV negative clinic-attending MSM for 2009 to 2013 were extracted, and the diagnosis or not of any bacterial STI in the previous year was used as a proxy to indicate recent condomless anal intercourse and to stratify the future risk of being diagnosed with HIV. Those with a bacterial STI in the previous year were labelled 'high risk' and eligible for PrEP, and those without as having 'medium risk' for HIV acquisition. A limitation of this method is that the proxy used for high risk (recent bacterial STI) only applies to a subset of MSM at high risk.

HIV incidence estimation methodology followed that used in Desai et al.[137] HIV incidence for high and medium risk MSM in England was estimated using data from 2012, the most recent year whereby complete one-year follow-up data (up to year 2013) was available. To calculate HIV incidence in 2012, MSM were followed from their first negative HIV test of the calendar year until seroconversion or their last attendance occurring within 12 months of the first test. In 2012, of the 17,429 high risk HIV negative MSM attending GUM clinics, a total of 6,239 were repeat tested for HIV, with 130 seroconversions, and an estimated HIV incidence of 3.3 per 100 person-years (95% CI: 2.8 to 4.9 per 100 person-years). Of the 68,076 medium risk HIV negative MSM attending, 19,953 repeat tested, with 194 seroconversions, and an estimated HIV incidence of 1.5 per 100 person-years (95% CI 1.3 to 1.8 per 100 person-years). HIV incidence was 2 per 100 person-years (95% CI 1.8 to 2.2 per 100 person-years) in the overall HIV negative MSM GUM attendees. From the above data, the incidence in medium/low risk combined can be calculated (0.43 per 100 person years).

Similar HIV incidence rates were estimated by Desai et al., analysing GUMCAD data for the year 2012.[138] Study authors estimated the overall incidence of HIV as 2.0 per 100 person-years in MSM and 3.2 per 100 person-years in the high risk stratum.

These annual rates were converted to yearly probabilities in the model, according to the following conversion:

$$\text{Probability} = (1-e^{-\text{rate}})$$

From the systematic review of efficacy (Chapter 4), the pooled efficacy of PrEP to prevent sexual acquisition of HIV in MSM was estimated at 75% (meta-analysis of six trials). More recent MSM trials (open-label PROUD and IPERGAY) reported a higher efficacy (86%). The PROUD and IPERGAY trials noted higher adherence than previous studies, and may be more applicable to Ireland due to the fact PrEP was administered through STI clinics in resource-rich countries. The sensitivity analysis varied the efficacy of PrEP between the lowest efficacy reported (the iPrEX trial; relative risk [RR]: 0.56 [95% CI: 0.37 to 0.84]) and the highest (pooled analysis of PROUD/IPERGAY; RR: 0.14 [95% CI: 0.06 to 0.35]). These RRs are multiplied by the rate of HIV acquisition in MSM at high risk to estimate the incidence of HIV in PrEP users.

Of note, an older cohort study in Australia recorded relatively lower incidence rates (the Health in Men study [HIM]).[139] The study recruited participants from June 2001 to December 2004. Interviews were conducted from June 2001 to June 2007. The incidence in the cohort overall was 0.78 per 100 person-years, and nine risk variables were associated with an HIV incidence of 2 per 100 PY or greater. Stepwise inclusion of these variables revealed a 'high-incidence' subgroup of men representing 24% of the total follow-up time with a combined HIV incidence of 2.71 per 100 person-years (the variables that contributed to this figure were condomless anal sex with HIV-positive partner, condomless anal sex with a casual partner and chemsex use).

6.2.2.2 All-cause mortality

Age-specific all-cause mortality rates for males in Ireland were retrieved from the Central Statistics Office (CSO).[140]

All-cause mortality for HIV positive males is not reported by the CSO in Ireland. Estimates for all-cause mortality in HIV positive individuals are available in the UK. A 2017 UK study linked cohort data collected by Public Health England (PHE) for

individuals aged 15 years and older, diagnosed with HIV in England and Wales from 1997 to 2012, to the Office for National Statistics (ONS) national mortality register.[141] In total, 88,994 people were diagnosed with HIV, contributing 448,839 person-years of follow up.

Cohort mortality was significantly higher than the general population for all causes (standardised mortality ratio [SMR] 5.7, 95% CI: 5.5–5.8), particularly non-AIDS infections (SMR 10.8, 95% CI: 9.8–12.0) and liver disease (SMR 3.7, 95% CI: 3.3–4.2). All-cause mortality was highest in the year after diagnosis (SMR 24.3, 95% CI: 23.4–25.2). All-cause mortality in males was 130 per 10,000 person years, with a SMR of 4.9 (95% CI 4.8 to 5.1). An adjustment was made for the fact that later years in their analyses recorded lower mortality than earlier years. Table 6.9 gives the hazard ratios from the Cox proportion hazards model for three time periods.

Table 6.9. Hazard ratios for all-cause mortality in HIV positive individuals

Diagnosis year	Unadjusted hazard ratio	Adjusted hazard ratio
1997–2002	1.0 [reference period]	1.0 [reference period]
2003–07	0.66 (95%CI: 0.62–0.70)	0.78 (95%CI: 0.70–0.87)
2008–12	0·65 (95%CI: 0.60–0.71)	0.55 (95%CI: 0.48–0.63)

Source: Croxford et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort, 2017.

While mortality rates in the UK and Ireland may differ slightly, it is reasonable to assume that the ratio between all-cause mortality in HIV positive individuals and the general population would be similar, due to similarities in HIV care between the two countries. The adjusted male SMRs have therefore been applied to the all-cause mortality rates in Irish men to estimate all-cause mortality in HIV positive MSM in Ireland.

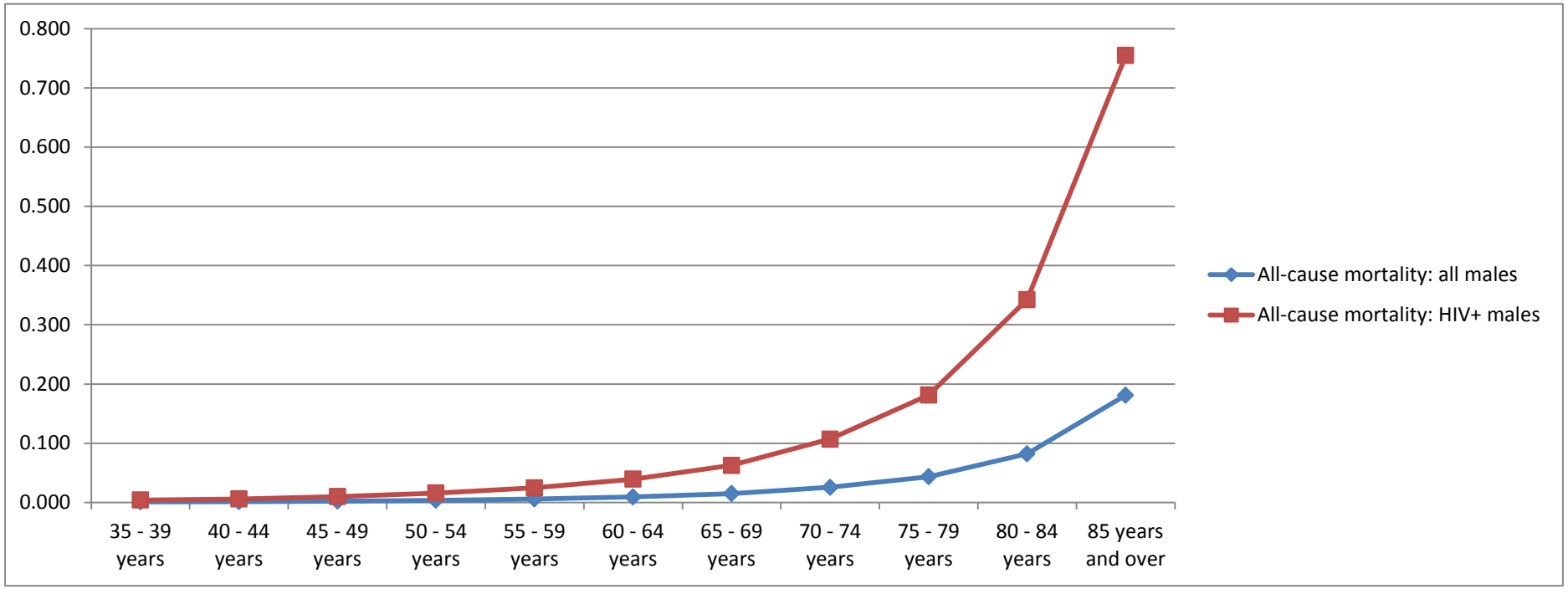
Table 6.10 and Figure 6.3, below, compare these mortality rates.

Table 6.10. All-cause mortality in all males and HIV+ males in Ireland

	All-cause mortality: all males	All-cause mortality: HIV+ males	Lower CI	Upper CI
35 - 39 years	0.001	0.004	0.004869	0.005173
40 - 44 years	0.001	0.006	0.006937	0.007371
45 - 49 years	0.002	0.010	0.011514	0.012233
50 - 54 years	0.004	0.016	0.018333	0.019478
55 - 59 years	0.006	0.025	0.028654	0.030445
60 - 64 years	0.009	0.039	0.045369	0.048205
65 - 69 years	0.015	0.063	0.072406	0.076931
70 - 74 years	0.026	0.107	0.123429	0.131143
75 - 79 years	0.044	0.181	0.209016	0.22208
80 - 84 years	0.082	0.343	0.394824	0.4195
85 years and over	0.181	0.755	0.869731	0.924089

CI – confidence interval

Figure 6.3. All-cause mortality in all males and HIV+ males in Ireland, by age

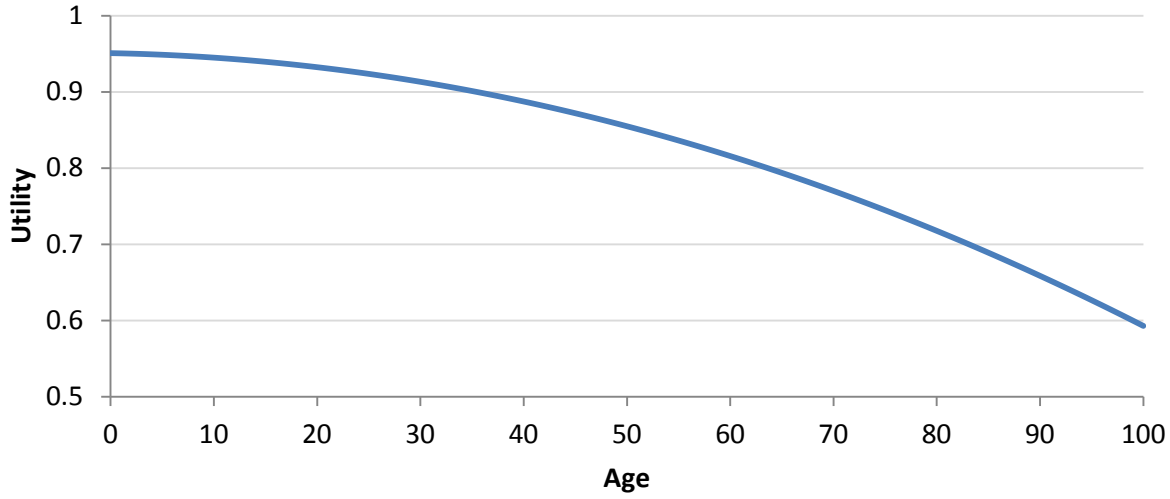


6.2.2.3 Utility parameter estimates

For the cost-utility analysis, where outcomes are expressed as cost per quality-adjusted life years (QALY) gained, it is necessary to estimate both the baseline quality of life of the population as well as the utility weights associated with having a diagnosis of HIV.

In the absence of validated Irish data, baseline quality of life for males by age (for those with no current morbidity) was taken from UK estimates for a general population based on data from the Health Survey for England (Figure 6.4).[142]

Figure 6.4. Baseline utility for a general male population



Formula for curve: General Population EQ-5D utility = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2

Utility weights for HIV positive individuals were obtained from a 2014 study.[143] In this study, two UK cross-sectional surveys were merged: the ASTRA study, which recruited participants with HIV aged 18 years or older from eight outpatient clinics in the UK between February 2011 and December 2012; and the Health Survey for England 2011, which measures health and health-related behaviours in individuals living in a random sample of private households in England. Health-related Quality of Life (HRQoL) was assessed with the Euroqol 5D questionnaire three level (EQ-5D-3L) instrument that measures health on five domains, each with three levels. Table 6.11, below, lists the utility decrements associated with HIV positivity (diagnosed) and by CD4 count and ART therapy.

Note that an assumption was made that an undiagnosed HIV positive individual did not have a utility loss.

Table 6.11. Disutilities due to HIV positivity, by health state

Health status	Disutility	95% CI	Distribution	Source
HIV+	-0.11	-0.13 to -0.10	Beta	Miners et al.
HIV+, CD4 count >200 cells per μL	-0.1	-0.12 to -0.08	Beta	Miners et al.
HIV+, CD4 count ≤ 200 cells per μL	-0.15	-0.19 to -0.11	Beta	Miners et al.
HIV+, on ART, VL ≤ 50 copies per mL	-0.11	-0.13 to -0.09	Beta	Miners et al.
HIV+, on ART, VL >50 copies per mL	-0.12	-0.15 to -0.09	Beta	Miners et al.
HIV+, stopped ART	-0.14	-0.20 to -0.07	Beta	Miners et al.
HIV+, never started ART	-0.05	-0.08 to -0.02	Beta	Miners et al.
HIV+, undiagnosed	0	Assumption		

Note: 95% range is the same as the confidence interval in the source indicated

In addition, these utilities were adjusted by age (-0.004 per additional year[143] [in addition to the normal aging decrement]). As the imprecision associated with the reported reduction in utility due to age was close to zero, a fixed value was used.

6.2.3 Cost

6.2.3.1 Cost of PrEP medication

There are a number of generic formulations of tenofovir/emtricitaine licensed and marketed for use in Ireland, for example emtricitabine/tenofovir disoproxil maleate (produced by Mylan NV) and emtricitabine/tenofovir disoproxil phosphate (produced by Teva Pharmaceutical Industries).

The wholesale cost was estimated based on reported costs of dispensed PrEP from community pharmacies. While a range of costs were identified, it was assumed that the HSE could achieve a similar wholesale cost to that obtained by large retail chains. The direct cost to the HSE was calculated using the approach outlined in the National Centre for Pharmacoeconomics (NCPE) Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluations (2018).[144]

According to these guidelines, the following adjustments should be made:

i. Apply a wholesale mark-up to the price to wholesaler
ii. Apply the pharmacy dispensing fee
iii. Deduct a rebate to PCRS (if applicable).

In our calculations, the wholesale mark-up was 8%, the average dispensing fee was €5.48 per item and a rebate of 12.5% was applied at the level of price to wholesaler. A zero rate of VAT applies to oral medicines.

6.2.3.2 Cost of PrEP care pathway

A microcosting or 'bottom up' approach was employed to determine costs. Analysis was performed from a healthcare perspective; a societal perspective was not considered, consistent with national HTA guidelines.[145] Direct health care costs were included. Productivity losses as a result of morbidity were not included. Retrospective healthcare costs were inflated to 2018 using the Consumer Price Index for health (CSO).[10]

Previously collected cost data from St James's Hospital GUIDE clinic was used to estimate the cost of providing the PrEP care pathway for each patient, as outlined in Chapter 2. St James's Hospital GUIDE clinic has previously estimated staff resource use for a typical clinic appointment by HIV positive patients in the '*Time in Motion Study'* (received with permission from Dr Saloni Surah). These times were used as a guide to estimate staff resource use for PrEP appointments. Laboratory costs were retrieved from St James's Hospital laboratory and the National Virus Reference Laboratory.

Salary costs were derived from consolidated salary scales available from the Irish Department of Health.[146] The midpoint of each scale was selected as the base salary. Per Irish guidelines,[11] the base salary was adjusted for non-pay costs: employers' PRSI (@10.75%), superannuation (4% of base salary) and overheads (25% of base salary).

The clinical management pathway for eligible PrEP recipients is described in Chapter 2. Table 6.12, below, summarises the costs associated with each visit. The cost per patient in the first year is €549 and €509 in subsequent years. See Appendix 5.2 for full itemised costs. Conservatively, the higher value (€549) is used for all years in the model.

Table 6.12. Costs associated with each visit in first year

PrEP Programme: Year 1 (per patient)		
	Unit price	Proportion patients
1st Assessment	€187.23	100%
Starting visit*	€16.12	50%
Subsequent visits in year 1	€118.07	100%
Total (1st assessment, starting visit*, 3 subsequent visits): €549.50		

*Approximately 50% of participants will require this additional visit

Cost of 'usual care' for high-risk MSM per patient

Appendix 5.2 provides the cost of 'usual care' for high-risk MSM in Ireland. Current guidelines in the UK (BASHH) and the US (CDC) recommend three-monthly STI screening for MSM at high risk (e.g., multiple anonymous partners).[12] The cost per visit is estimated at €127.

Incremental cost of PrEP programme

The incremental cost of the PrEP programme is the total cost of the programme, less the cost of 'usual care' that would theoretically be provided to high-risk MSM without a programme in place.

In the Scottish PrEP programme, based on the NaSH dataset, it was noted that more than a quarter (28%) of those prescribed PrEP had not attended a Scottish sexual health clinic in the two years before PrEP became available and that 19% had not attended a publicly funded Scottish STI clinic in at least 10 years, and possibly never. For this reason, it is assumed that approximately a quarter of participants in the Irish PrEP programme will be new to services. For the remainder, it was assumed that approximately half would attend per BASHH guidelines and half would attend at half this rate.

The estimated average incremental cost of the PrEP programme including screening, monitoring and medications is €903 per person per year. It was assumed patients would be prescribed a daily PrEP regimen and that four three-monthly prescriptions would be redeemed per year. Table 6.13 lists these incremental costs.

Table 6.13. Incremental PrEP programme costs per year

Incremental costs			
	Unit cost per visit	Proportion of cases incurring cost	Average yearly realised cost
Usual care	€126.64	25% are not engaged (no visits), 37.5% attend 4 visits per year and 37.5% attend 2 visits per year	€284.94
PrEP programme (first year)			€549.50
Incremental cost of programme			€264.56
Incremental cost of programme+PrEP medications			€903
Vary by 20%			€723 to €1,084

6.2.3.3 Cost of HIV

The lifetime and annual costs associated with HIV infection were obtained from a 2015 UK study.[147] The lifetime costs of MSM infected with HIV in a resource-rich setting were estimated using an updated version of the HIV Synthesis progression model. This model has been shown to provide a generally close fit to observed data relating to the natural progression and treatment outcomes associated with HIV. Cost and epidemiological patterns were calibrated to the UK HIV epidemic.

MSM who were infected with HIV in 2013 aged 30 were modelled over 10,000 simulations. Based on a median (interquartile range) life expectancy of 71.5 (45.0–81.5) years for MSM in such a setting, the estimated mean lifetime cost of treating one person was £360,800 ($567,000 or €480,000). With 3.5% discounting, it was £185,200 ($291,000 or €246,000). The majority, 68% (£245,200), of projected lifetime healthcare cost was attributed to ART costs. This translates to an annual cost of €11,566 per patient. Table 6.14, below, provides details of the sensitivity analysis conducted by study authors. We assumed HIV care costs in Ireland would not differ substantially from these estimates.

Table 6.14. Mean undiscounted lifetime costs under different model assumptions

Assumption in base-case analysis	New assumption	Mean lifetime costs*
Base-case analysis	-	360,800
Infected at age 30 years	Infected at age 20 years	432,400
	Infected at age 40 years	297,800
Rate of diagnosis in line with that currently observed (median CD4 count at diagnosis = 422 cells/mm^3)	Diagnosed almost immediately after infection	371,000
	Diagnosed only when symptomatic or develop AIDS	294,000
Never lost from care	5% per year loss to care rate (return to care only when symptomatic or develop AIDS)	353,440
Initiate ART when CD4 count drops below 350 cells/mm^3 (unless symptomatic)	Initiate ART when CD4 count drops below 500 cells/mm^3 (unless symptomatic)	361,800
	Initiate ART soon after HIV diagnosis (unless symptomatic)	366,100
1.5-fold increased risk of non-AIDS deaths (compared to the general population)	1.1-fold increased risk of non-AIDS deaths (compared to the general population)	387,400
	1.25-fold increased risk of non-AIDS deaths (compared to the general population)	396,400
	1.5-fold increased risk of non-AIDS deaths but 2-fold in people with unsuppressed viral load (compared to the general population)	358,600
	1.5-fold increased risk of non-AIDS deaths (compared to the general population) and 1.5-fold increased healthcare centre visit costs whilst CD4 count <200 cells/mm^3	404,500
Population distribution of adherence calibrated to data on proportion of men with suppressed viral load	Better population distribution of adherence	371,500
	Slightly worse population distribution of adherence	359,400
	Worse population distribution of adherence	241,300
Patented drugs replaced by generic versions (80% reduction in price) and population distribution of adherence calibrated to data on proportion of men with suppressed viral load	Patented drugs replaced by generic versions (80% reduction in price) and slightly worse population distribution of adherence	178,400
	Patented drugs replaced by generic versions (80% reduction in price) and worse population distribution of adherence	136,900

Healthcare centre visit costs incurred while undiagnosed are the same as those of someone who is diagnosed but with CD4 count >200 cells/mm^3	No healthcare centre visit costs incurred while undiagnosed	348,300

*All costs in 2013 £
Source: Nakagawa et al. 2015

From the above sensitivity analysis, the range of mean undiscounted lifetime HIV costs based on alternative model assumptions is between £136,900 and £432,400. The scenario *'Initiate ART soon after HIV diagnosis'* is most applicable to Ireland as that is the standard of care; this cost was used in analyses (£366,100)

Costs were inflated using the CPI for health to year 2017 (UK) and converted to Irish Euro using purchasing power parity (PPP), per Irish guidelines.[28] Table 6.15 gives the estimated mean lifetime and annual costs of HIV in Ireland.

Table 6.15. Estimated mean (undiscounted lifetime and annual costs of HIV

Model Assumption	UK (2013 £)	Ireland (2017 €)
Lifetime		
Mean	366,100	423,200
Least costly alternative	136,900	158,200
Most costly alternative	404,500	467,500
Annual		
Base case		10,200
Least costly alternative		3,800
Most costly alternative		11,300

Note: All costs rounded to nearest 100.
Mean annual cost estimated by dividing the lifetime cost with the number of years infected with HIV.

Few other studies have estimated the lifetime costs associated with HIV in the era of combined ART. Earlier studies typically reported higher lifetime costs, largely due to higher ART costs and higher HIV-related morbidity. Schackman et al., 2006, estimated that from time of entry into HIV care, an adult starting treatment with CD4 count <350 cells/mm^3 had a projected life expectancy of 24.2 years and projected lifetime cost of $618,900 in 2004 USD (approximately €544,500).[148] A study in 2012 by Sloan et al. projected a mean life expectancy of 26.5 years and lifetime cost of €535,000 (in 2010 €) for their simulated cohort with mean age 38 years who started combined ART with CD4 count <350 cells/mm3.[149] These earlier studies that report higher HIV care costs and lower life expectancies for HIV positive individuals were not deemed reflective of current HIV care in Ireland.

Costs used in other economic evaluations varied somewhat. The analysis by Cambiano et al., 2018, estimated an annual cost of between €11,200 and €13,900 (converted to 2017 €) in the UK.[131] Also in the UK, Ong et al. 2017 modelled two costs: an annual cost of €10,300 in HIV positive individuals with CD4>200 and €13,260 in individuals with CD4<200 (converted to 2017 €).

The only Irish study identified (Brennan et al. 2015[150]) estimated the cost of ambulatory HIV care in an Irish HIV clinic. In 2011/2012, the average monthly cost was between €927 and €1,019 (equivalent to €11,124 to €12,228 annually).

The estimate of €10,200 used in the base case analysis would appear to be a conservative estimate (biasing against PrEP) as it is somewhat lower than that used by other authors. This cost was varied by 20% in the model (€8,160 to €12,240)

It was assumed that ART starts immediately after diagnosis. For many, there is a delay between infection and diagnosis. A UK study estimated the average time between HIV infection and diagnosis date for high-risk MSM, identified from Public Health England HIV surveillance data for the years 2011 to 2013.[130, 151] Table 6.16, below, demonstrates the time to diagnosis in England. It estimated that 39% are diagnosed the year in which they are infected with 82% diagnosed within five years of being infected. This lag was incorporated into the budget impact model due to its short time frame (5 years), but not the cost-effectiveness model (a lifetime horizon was used).

Table 6.16. Time to HIV diagnosis (UK data)

Time (Year)	Proportion of HIV Infections Occurring in Year-1 that are Diagnosed in Year-1 or in Subsequent Years	Cumulative Proportion Diagnosed
1	39%	39%
2	12%	52%
3	11%	63%
4	10%	73%
5	9%	82%

These data are consistent with the MISI 2015 survey: the proportion of men who tested for HIV in the previous 12 months was 39%.[27] Also of note, the HPSC reports recent infections in Ireland using the Recent Infection Testing Algorithm (RITA) or a p24 antigen positive status.[38] In 2017, it was estimated that 13% of HIV diagnoses (of those tested) were likely to be recent infections (within four months), using the RITA. By probable routes of transmission, men who have sex with men (MSM) had the highest proportion of likely recent cases (16%).

6.2.3.4 Cost of Post-Exposure Prophylaxis following Sexual Exposure (PEPSE)

PEP is a HIV prevention intervention in which antiretroviral therapy is administered for prophylaxis against infection following exposure to HIV through sexual contact. Ideally it should be given as soon as possible following exposure, but may be considered for up to 72 hours. It is available following a clinical assessment of risk, and is provided to eligible patients free of charge. In Ireland, it is available at Emergency Departments, Sexual Assault Treatment Units and at STI clinics.

The British Association for Sexual Health and HIV (BASHH) have developed UK guidelines for the assessment, treatment and monitoring of an individual receiving PEPSE.[152] Three clinic visits in total are recommended. Table 6.17 outlines the management of a PEPSE patient. The recommended therapy is daily oral tenofovir/emtricitabine fixed dose combination with daily oral raltegravir for 28 days.

Table 6.17. BASHH management of PEPSE patients

Test	Baseline	14 days	8-12 weeks post-exposure
HIV	Yes		Yes
Hep B sAg	Yes		Only if not immune
Syphilis, HCV, HBV immunity		*Per local clinic policy*	
STI testing	Yes	Yes	If further unprotected sex
Creatinine	Yes	Only if abnormalities detected at baseline	
Alanine transaminase (ALT)	Yes	Only if abnormalities detected at baseline; HBV/HCV co-infected; or on Kaletra®	
Urinalysis or uPCR	Yes	Only if abnormalities detected at baseline	
Pregnancy test	Yes		
Creatine kinase		Only if symptomatic or myositis	

One course of PEPSE is estimated to cost €964. Appendix 5.2 details these costs. Local costing data was applied to BASHH's management guidelines for PEPSE, assuming PEPSE is first administered at a STI clinic as opposed to the Emergency Department. As the calculated Emergency Department visit cost was higher, we have conservatively chosen the cost of PEPSE at an STI clinic for the purpose of analyses.

In patients who are taking PrEP as prescribed, PEPSE is not indicated. This is therefore a potential cost offset in the economic evaluation.

Little is known of the frequency of PEPSE prescribing in Ireland. The MISI 2015 survey reported that of respondents not known to be HIV positive, 4% had *ever* used PEPSE, though this varied by HIV testing history.[153]. Those who had previously tested negative for HIV were significantly more likely to have used PEPSE than those who had never tested (7% versus 0.3%).

In the study by Ong et al., GUMCAD data was used to investigate PEPSE prescribing among high-risk MSM. Of the 17,429 high-risk MSM identified through GUMCAD data, 781 courses of PEPSE were prescribed to 663 individuals in the year 2012.[90] The total number of PEPSE courses is higher than the total number of individuals as some individuals had more than one course of PEPSE. By dividing the absolute number of PEPSE prescriptions over the total number of high-risk MSM, the proportion of overall PEPSE use was 4.48%.

We have therefore assumed that approximately 4% of PrEP users will avoid taking PEPSE each year. Not only is this a cost offset, it reduces the burden on STI services by reducing STI clinic visits.

6.2.3.5 Cost of STIs due to risk compensation

The impact of a national PrEP programme on the rates of STIs is unknown. Our systematic review and meta-analysis of RCTs (Chapter 4) did not demonstrate a significant increase in STIs in those taking PrEP.

There is, however, some evidence from observational studies that taking PrEP may reduce condom use and increase STI rates. One systematic review and meta-analysis of observational studies noted an increase in rectal chlamydia following the introduction of PrEP programmes (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.19-2.13).[154] A rise in gonorrhea or syphilis at any site, or chlamydia at non-rectal sites, was not noted. Table 6.18 outlines their results.

Table 6.18. Results from 2018 systematic review and meta-analysis

Pathogen	Studies	OR (95% CI)	p-value
Syphilis	6	1.12 (0.86–1.47)	0.408
Chlamydia	5	1.23 (1.00–1.51)	0.051
Rectal	4	1.59 (1.19–2.13)	0.002
Urethral	3	0.96 (0.61–1.51)	0.857
Pharyngeal	2	0.93 (0.53–1.62)	0.797
Gonorrhea	5	1.13 (0.78–1.64)	0.515
Rectal	4	1.21 (0.78–1.88)	0.397
Urethral	3	1.61 (0.45–5.78)	0.467
Pharyngeal	3	1.20 (0.88–1.64)	0.257

OR – odds ratio

Subsequent to this meta-analysis, a longitudinal study of 2,981 mostly gay and bisexual Australian men who received daily PrEP was published by the same authors on 9 April 2019.[155] After adjusting for testing frequency, the increase in incidence from one year pre-enrolment to follow-up was significant for any STI (adjusted incidence rate ratio, 1.12 [95% CI, 1.02-1.23]) and for chlamydia (adjusted IRR, 1.17 [95% CI, 1.04-1.33]), but not for gonorrhoea or syphilis.

Any future rise in STI diagnoses in Ireland following the introduction of a PrEP programme may be a result of an actual increase in STI transmission, or may simply reflect the frequent testing that is part of the programme, leading to an improved detection of STIs. NHS Scotland has released data on its first year of implementing a PrEP programme, and has not concluded that there was an actual rise in STIs among PrEP users.[127] Among those prescribed PrEP, rates of gonorrhoea (including rectal) testing and numbers diagnosed positive increased between the two 12 month periods either side of NHS PrEP introduction but rates of actual infection remained similar. Such rates were higher among those ever versus never prescribed PrEP; this observation indicates that the former are at higher risk of gonorrhea (and therefore HIV) infection and that the eligibility criteria for PrEP are likely to be appropriate.

Similar observations were recorded for chlamydia with an increase in testing and diagnoses among MSM ever prescribed PrEP but no overall change in the proportion positive pre and during the first year of NHS PrEP. The increases in gonorrhoea and chlamydia diagnoses could be attributed to either improved detection, an actual increase in the incidence of infection or a combination of both; the explanation is likely to be the “combination” one but the ratio of the contributions is uncertain.

Additionally, there has been a significant rise in the notification rate of both gonorrhea and chlamydia in Ireland in recent years (see Figure 6.5). Data specific to the MSM population show a steady rise in gonorrhea (Figure 6.6). The impact of

PrEP on STI rates would have to take into consideration this secular trend in rising notifications over time.

Figure 6.5. Trend in notification rate per 100,000 population of gonorrhoea and chlamydia[156]

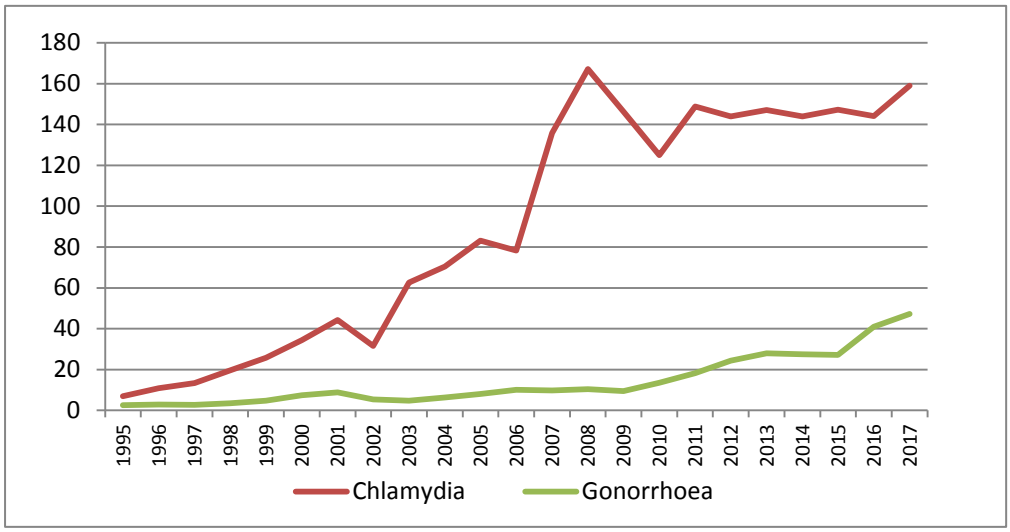
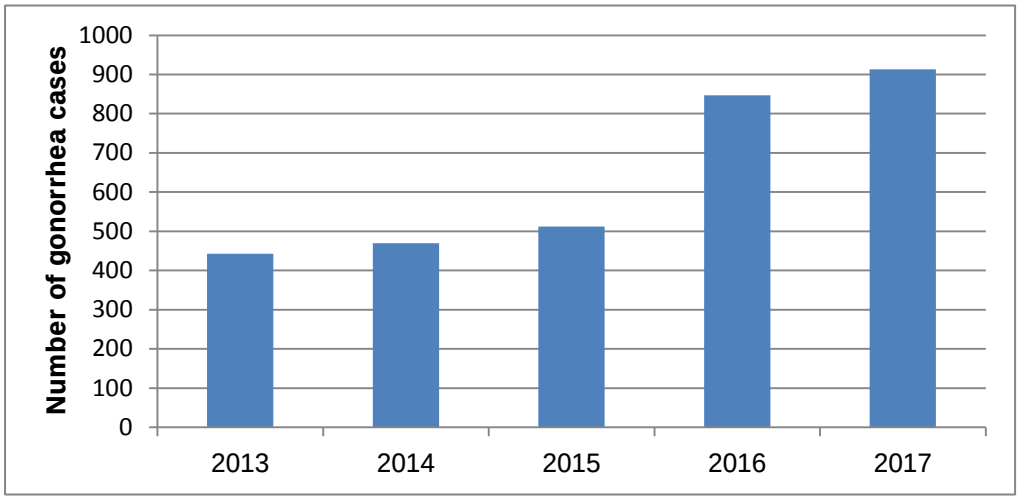


Figure 6.6. Notified cases of Gonorrhea in MSM (HPSC)[156]



Taking a conservative approach, a rise in STIs was included in the model. The increase in rectal chlamydia reported in the meta-analysis by Traeger et al.[154] was applied, whereby PrEP users experience a 33% annual increase in rectal chlamydia diagnoses (converting odds ratios to relative risks). The recommended treatment of rectal chlamydia, doxycycline 100mg twice daily for 7 days (BASHH recommendations),[157] is estimated to cost €3.48 if dispensed in a community pharmacy, based on average PCRS list costs adjusted in accordance with cost guidelines (although it is noted that most clinics dispense treatment medications

directly).[144] The total cost of treating one episode of rectal chlamydia (clinic time, investigations and treatment) is estimated to cost approximately €125 (see Appendix 5.2). A wide variation in cost was applied to account for regional variations in management.

6.3 Process for calibrating model

A number of model parameters were supported by very limited data or were based on international data that may not be directly applicable to Ireland. It is important to ensure that the model generates estimates that are reasonable based on observed data, such as the incidence and prevalence of HIV and the number of people likely to avail of PrEP.

A calibration exercise was used to explore which parameter values would lead to plausible results in the model in terms of the incidence of HIV in the MSM population and the number of people who are likely to enrol in the programme. While the incidence of HIV is unknown in Ireland, the HPSC reported 151 HIV notifications in MSM in 2017 that were new diagnoses (150 was selected as the lower bound due to the fact that a certain number of HIV infections are undiagnosed). The range of HIV incidence values was set at 150-400. In terms of the number of people likely to enrol, the Scottish PrEP programme was the first country to report national figures on their experiences in the first year of PrEP implementation. Scotland reported 1,872 people availed of PrEP in the first year (note that Ireland's population is approximately 10% smaller than Scotland's, or 4.8 versus 5.4 million). The plausible range of PrEP recipients in Ireland was set at between 1,000 and 3,000 individuals.

6.3.1 Methodology

Calibration was carried out in relation to six model parameters:

- Proportion of the male population aged 16-80 who are MSM (prop_MSM)
- Proportion of the MSM population that are currently sexually active (prop_active)
- Proportion of the MSM population that might be considered at high risk of HIV and are therefore eligible for PrEP (prop_HR)
- Proportion of the PrEP eligible population who are likely to enrol in the programme (prop_uptake)
- Rate of HIV acquisition in the MSM population at high risk of HIV acquisition (high_HIV)
- Rate of HIV acquisition in the MSM population at medium/low risk of HIV acquisition (medlow_HIV)

The mean values for the six parameters were set based on available national and international data, but defined as statistical distributions which incorporated substantial uncertainty (Table 6.19).

Table 6.19. Initial parameter values used for calibration

Parameter	Distribution	Mean	LCI	UCI
Proportion of male population aged 16-80 who are MSM **(Prop_MSM)**	beta	0.0500	0.0400	0.0600
Proportion of MSM currently sexually active **(Prop_active)**	beta	0.6304	0.4877	0.7623
Proportion of MSM population eligible for PrEP **(Prop_HR)**	beta	0.2000	0.0280	0.4827
Proportion of the PrEP eligible population who are likely to enrol **(Prop_uptake)**	beta	0.2139	0.1396	0.2991
Rate of HIV acquisition in MSM at high risk of HIV acquisition **(high_HIV)**	gamma	0.0322	0.0143	0.0573
Rate of HIV acquisition in MSM population at medium/low risk of HIV acquisition **(medlow_HIV)**	gamma	0.0043	0.0015	0.0087

UCI – upper confidence interval, LCI – lower confidence interval

Two approaches to parameter value sampling were used: Latin Hypercube and Monte Carlo. As Latin Hypercube sampling uses a stratified sampling scheme, it can improve coverage of the k-dimensional input space relative to a Monte Carlo approach. However, the trade-off is that it is more computationally intensive to generate the samples with Latin Hypercube, so there are restrictions on how large a sample can be generated. The Latin Hypercube sampling used 10,000 samples and the Monte Carlo approach was used with 1,000,000 samples.

A basic version of the economic model was developed in R version 3.5.2 (2018) that calculated the annual incidence of HIV in a 'no PrEP programme' scenario, and the number of people receiving PrEP in a 'PrEP programme' scenario. Both outcomes were calculated using the initially sampled random values for the parameters. Outcomes were considered plausible if the incidence of HIV in the MSM population was between 150 and 400 cases, and the number of people enrolling in the PrEP programme was between 1,000 and 3,000. The sampled parameter values from simulations which plausible outcome values were then used to fit new univariate distributions for the parameters. Correlations between parameters were not considered as the software being used for the modelling, TreeAge Pro 2018, only

supports correlated normal distributions and not correlated beta or gamma distributions.

Finally, the model was rerun using 10,000 simulations based on the refit parameter distributions to determine the extent to which implausible outcome values were generated.

6.3.2 Results

The proportion of initial simulations that generated plausible outcome values was 0.171 for Latin Hypercube and 0.175 for Monte Carlo sampling, respectively. As the results for both approaches were very similar, only the findings for the Latin Hypercube approach are reported here.

For the 17% of simulations that generated plausible outcome values, there were notable correlations between some parameter values (see Table 6.20). For example, the proportion high risk and the uptake were negative correlated, suggesting that when the proportion at high risk takes on high values the uptake must take on lower values to ensure the number of PrEP recipients remains plausible.

Table 6.20. Correlation between parameters in simulations with plausible outcome values based on Latin Hypercube sampling method

	Prop_MSM	Prop_active	Prop_HR
Prop_MSM	1	-0.12	-0.15
Prop_active	-0.12	1	-0.33
Prop_HR	-0.15	-0.33	1
Prop_uptake	0.04	0.04	-0.35
high_HIV	-0.12	-0.04	-0.33
medlow_HIV	-0.21	-0.23	-0.04
	Prop_uptake	**high_HIV**	**medlow_HIV**
Prop_MSM	0.04	-0.12	-0.21
Prop_active	0.04	-0.04	-0.23
Prop_HR	-0.35	-0.33	-0.04
Prop_uptake	1	0.12	0.05
high_HIV	0.12	1	-0.22
medlow_HIV	0.05	-0.22	1

After refitting, the notable changes in the parameter values were reductions in the proportion sexually active, the proportion at high risk of acquiring HIV, and the risk of acquiring HIV in the high risk group (see Table 6.21). Appendix 5.3 provides full details of all parameters used in probabilistic analysis.

Table 6.21. Refit parameter values based on Latin Hypercube sampling method

Parameter	Distribution	alpha	beta	Mean	LCI	UCI
Proportion of male population aged 16-80 who are MSM **(Prop_MSM)**	beta	83.3	1735.8	0.0458	0.0368	0.0556
Proportion of MSM currently sexually active **(Prop_active)**	beta	29.4	18.9	0.6091	0.4660	0.7369
Proportion of MSM population eligible for PrEP **(Prop_HR)**	beta	6.48	45.9	0.1221	0.049	0.2128
Proportion of the PrEP eligible population who are likely to enrol **(Prop_uptake)**	beta	31.5	83.6	0.2732	0.1984	0.3575
Rate of HIV acquisition in MSM at high risk of HIV acquisition **(high_HIV)**	gamma	100	3333.3	0.0300	0.0244	0.0358
Rate of HIV acquisition in MSM population at medium/low risk of HIV acquisition **(medlow_HIV)**	gamma	100	33333.3	0.0030	0.0024	0.0036

UCI – upper confidence interval, LCI – lower confidence interval

When the refit parameter distributions were used, 61% of simulations produced plausible results for both outcomes. Simulations were more likely to produce implausible results for the incidence of HIV (25.6%) than for numbers of PrEP recipients (18.3%). A comparison of the confidence bounds for incidence of HIV and the plausible range used shows that model simulations will be more likely to over-estimate the incidence rather than under-estimate it (see Figure 6.7). For the outcome of number of PrEP recipients, the model will not be systematically biased in over- or under-estimating numbers (see Figure 6.8). Based on the refit distributions, the outcomes were estimated as 332 (95% CI: 158 to 590) for HIV incidence and 1,697 (95% CI: 667 to 3,301) for PrEP recipients.

Figure 6.7. Estimated annual incidence of HIV using refit parameter values based on Latin Hypercube sampling method

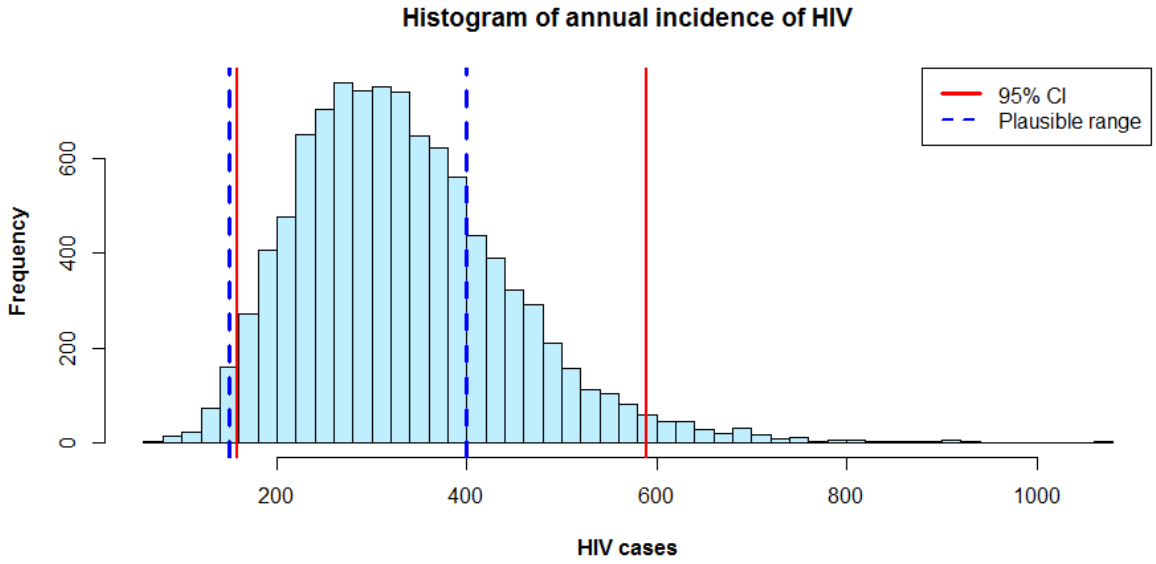
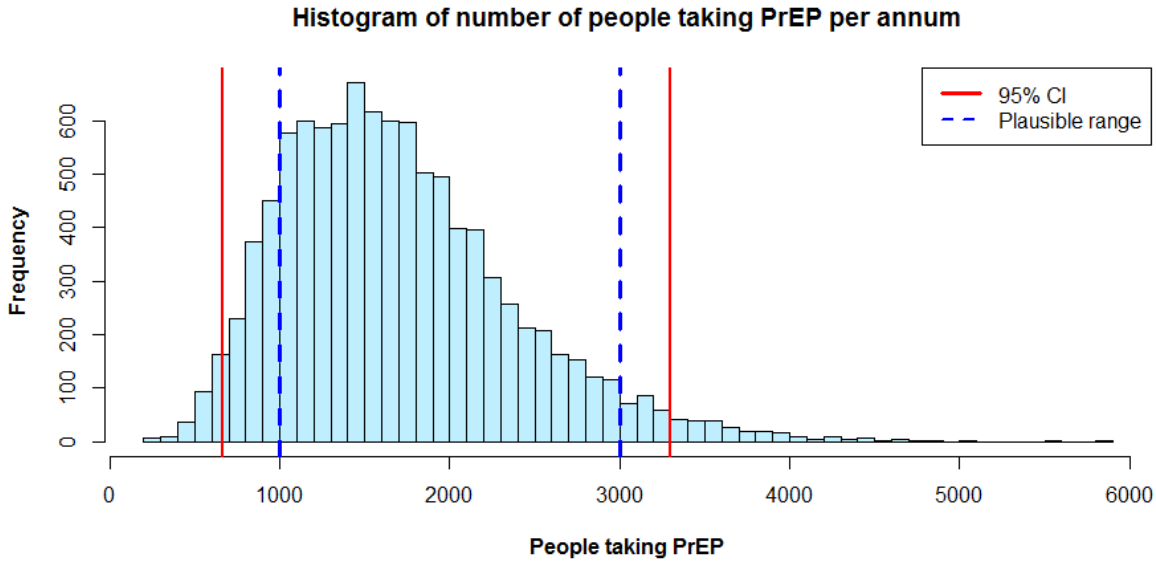


Figure 6.8. Estimated annual number of PrEP recipients using refit parameter values based on Latin Hypercube sampling method



6.3.3 Discussion

A calibration process was used to identify what parameter value distributions would result in plausible estimates for two outcomes: incidence of HIV in the MSM population and the number of likely recipients of PrEP in the first year of a

programme being implemented. Both outcomes are themselves subject to uncertainty. The estimate of 1,000 to 3,000 PrEP recipients is somewhat arbitrary, with the point estimate based on the observed number of PrEP recipients in Scotland's first year of their national programme. It is unclear how similar the MSM in population in Ireland is to the Scottish equivalent, and whether there is a similar proportion at high risk of HIV.

The incidence of HIV is also uncertain, as no study to date has estimated the true HIV incidence in Ireland. The HPSC report HIV notifications, and it was considered reasonable to assume that the lower bound for calibration would reflect HIV notifications of new cases among MSM in 2017 in Ireland. This was selected as the lower bound due to the fact that a certain number of HIV infections are undiagnosed (from Chapter 3, Section 3.3.4.1, more than a third of MISI respondents [36.7%] had never tested for HIV and 61.6% had not tested for HIV in the last year). The appropriateness of using a HIV notification rate as a proxy for incidence is dependent upon the uptake and frequency of HIV testing in a given population, however, and it is possible that the true incidence is lower than 150 if testing patterns were markedly different in 2017 compared with previous years. Model parameters were not calibrated more than what is currently presented due to the risk of over-fitting parameters values; as it stands, parameters such as the rate of HIV acquisition and the proportion at high risk are considered at their lowest plausible values.

Both sampling methods used for calibration returned similar results with almost no difference in the modelled distributions for the two outcomes of interest.

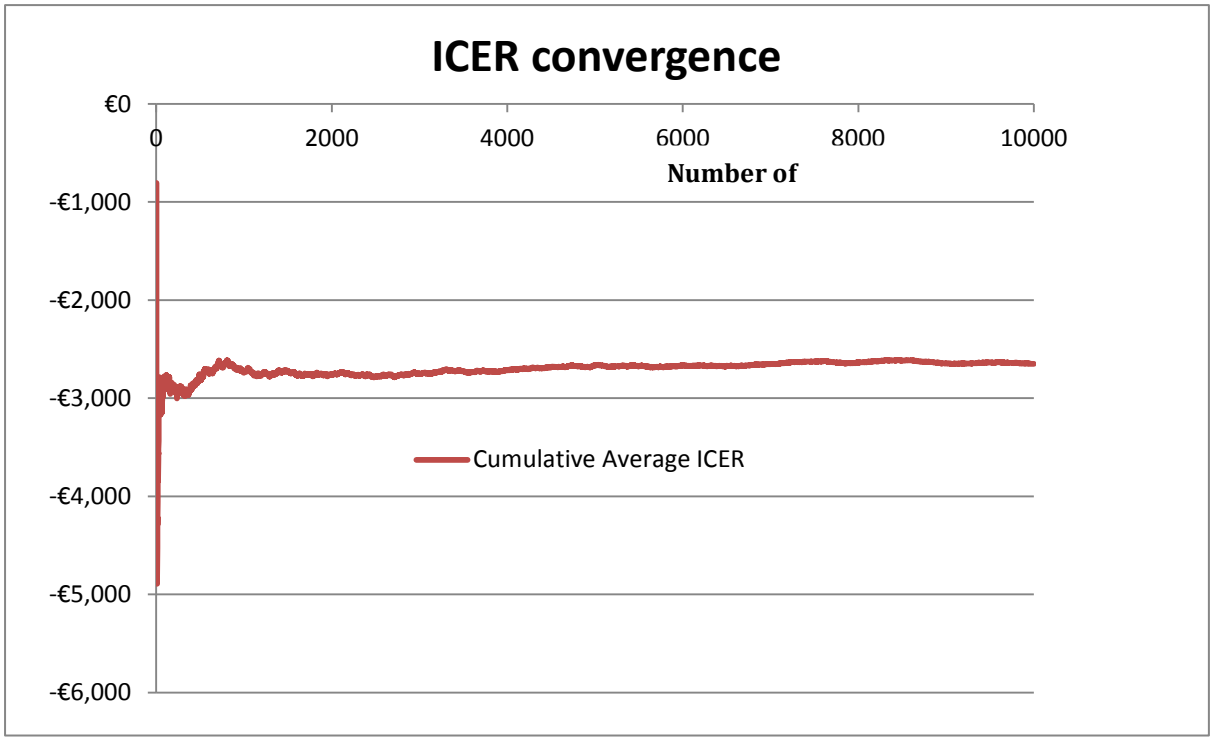
The analysis suggests that some of the distributions should ideally be correlated in the economic model to potentially improve the plausibility of the outcomes. However, there are limitations to the economic modelling software in terms of how correlated random values are generated. Failure to correlate certain values means that there will be additional uncertainty regarding the cost-effectiveness. However, the estimated correlations are not based on observed data, but only on what is necessary to ensure plausible results from the model. As such, the correlations artificially account for uncertainty in what values the parameters should take.

6.4 Cost effectiveness analysis results

6.4.1 Summary of results

Monte Carlo simulation was performed over the course of 10,000 replications to derive estimates of the costs and consequences of implementing a PrEP programme, with parameters sampled from their range of plausible values in each replication. All analyses were carried out using TreeAge Pro 2018.[158] Figure 6.9 shows that stable ICER estimates were achieved after approximately 2,000 replications. This indicates that 10,000 replications were sufficient to obtain stable results from the probabilistic analysis.

Figure 6.9. Convergence of ICER estimates



In the base case, PrEP is cost saving, with an ICER of -€2,735 over the cohort's lifetime (95% CI: -€16,486 to €21,585). This means that providing PrEP is less costly, and more effective (in terms of QALYs gained), than not providing PrEP. The cost savings can be explained by the comparatively higher cost of HIV care relative to the cost of preventing HIV infection with PrEP, over a range of plausible parameter distributions. Table 6.22 provides summary statistics of the base case analysis.

Table 6.22. Cost-effectiveness results (summary statistics)

Strategy	Costs (€)		Benefits (QALYs)		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
No PrEP programme	3,971		10.90		
PrEP programme	3,886	-85	10.93	0.03	-2,735 (Dominant)

Costs rounded to nearest euro

Figure 6.10 gives the cost-effectiveness plane; 'PrEP' dominates 'No PrEP' and is cost saving (in the fourth quadrant). Figure 6.11 gives the cost-effectiveness scatterplot at a willingness-to-pay (WTP) threshold of €45,000.

Figure 6.10. Cost-effectiveness plane

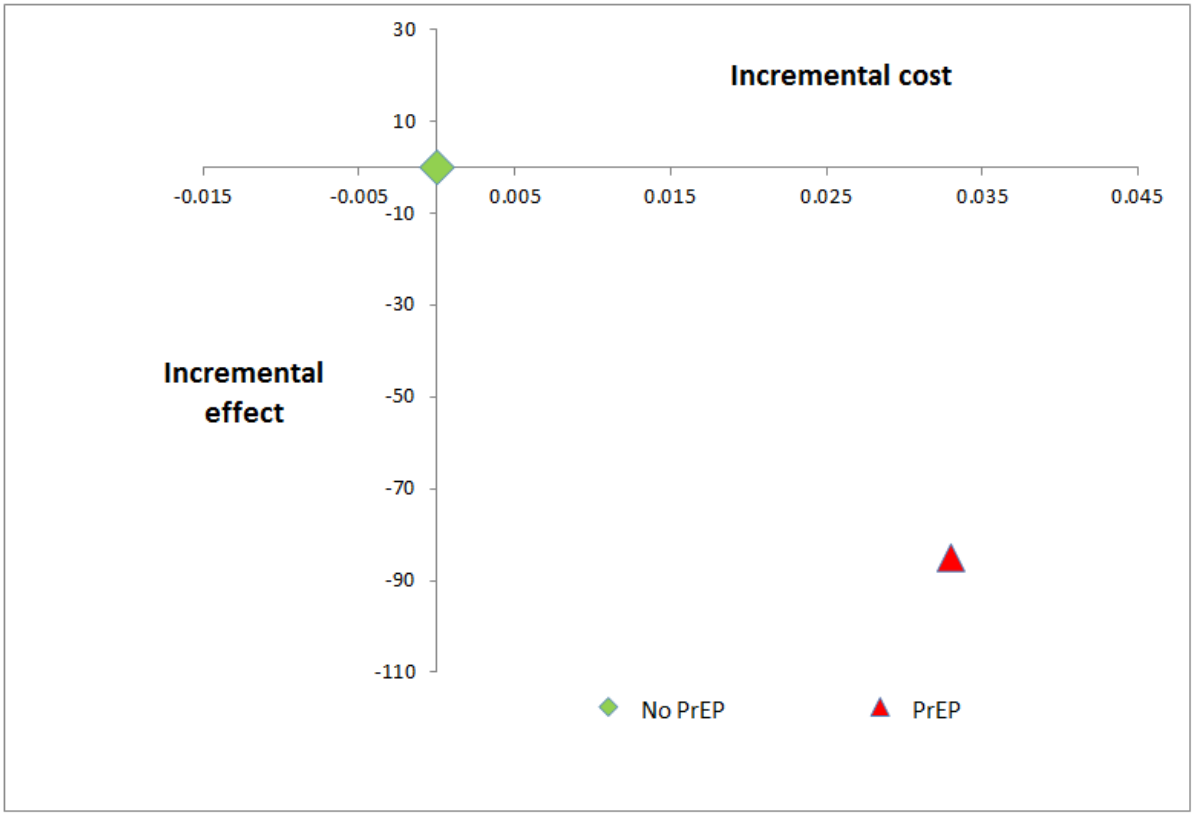
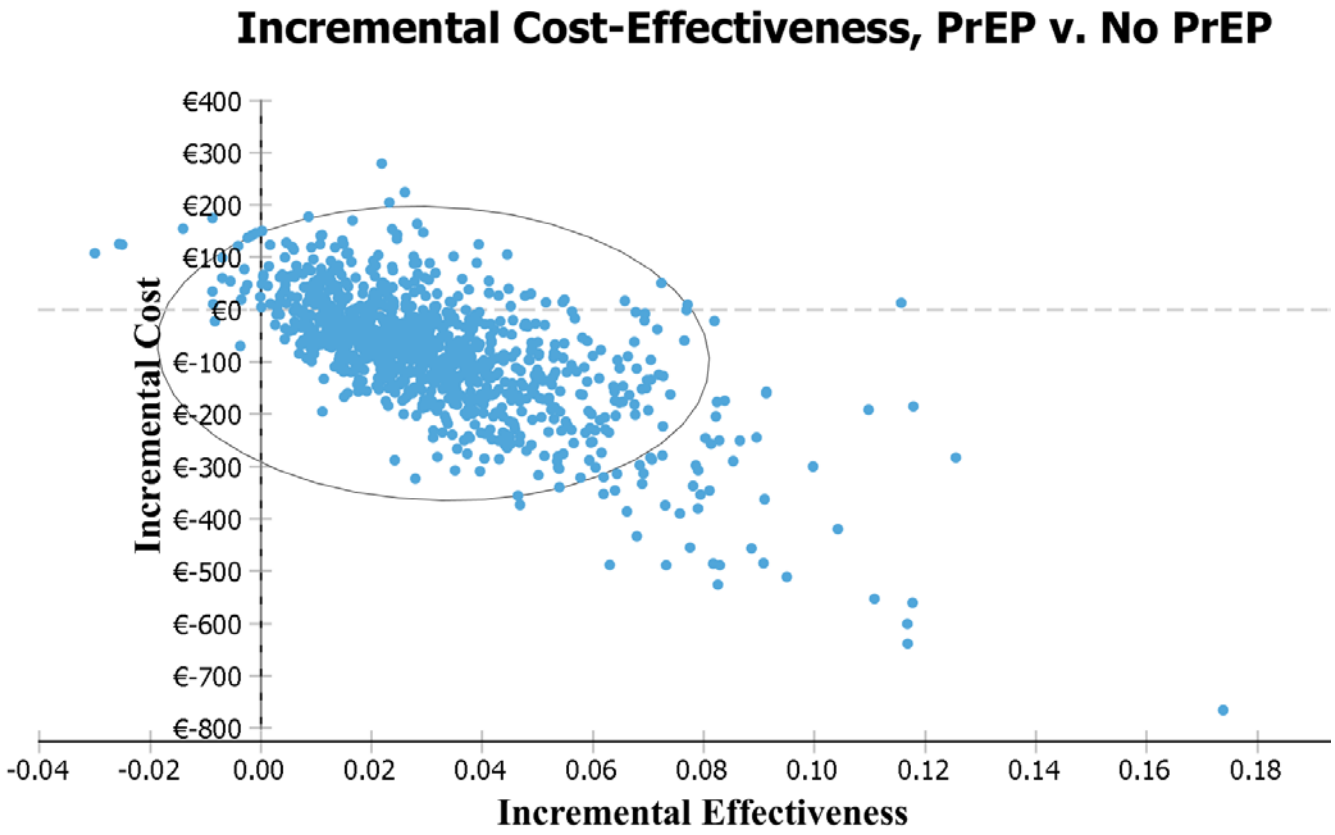


Figure 6.11. Incremental cost-effectiveness scatterplot

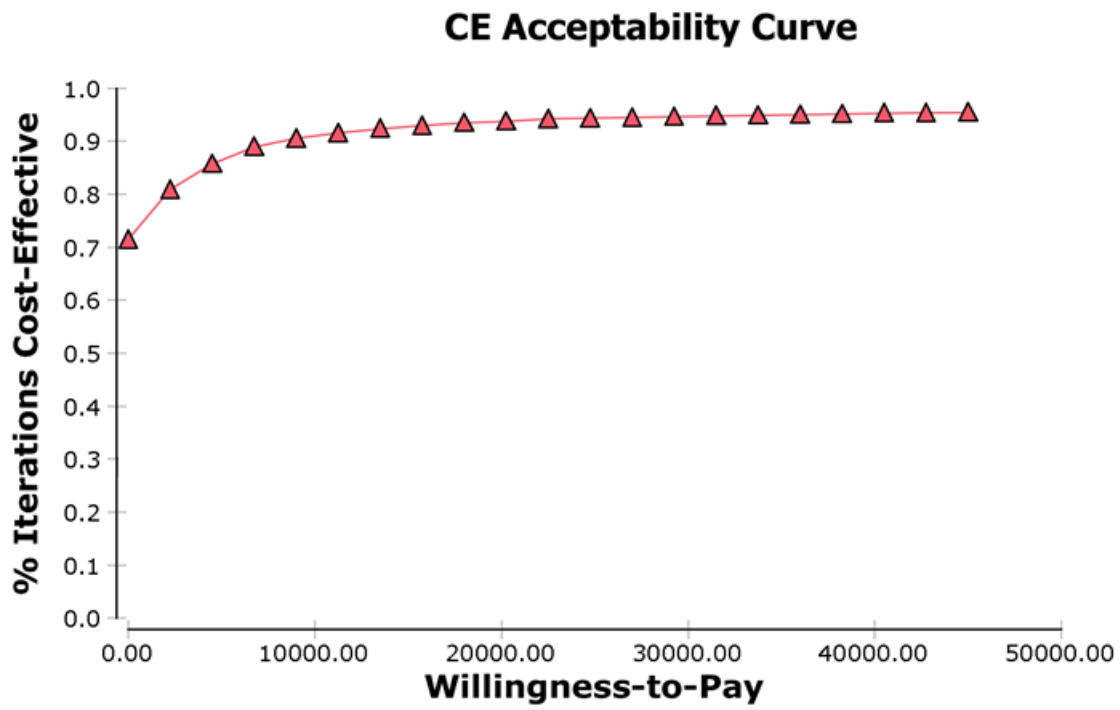


Notes:

- WTP – willingness to pay threshold (€45,000 per QALY gained).
- Each dot represents an individual simulation of the Monte Carlo analysis.
- Encircled is the 95% ellipse

Figure 6.12 gives the cost-effectiveness acceptability curve (CEAC) for the intervention. PrEP has an 87% probability of being considered cost-effective at a WTP threshold of €5,000 per QALY gained, a 94% probability at a WTP of €20,000 per QALY gained and a 95% probability of being considered cost-effective at a WTP of €45,000 per QALY gained, the agreed threshold by the Irish Pharmaceutical Healthcare Association (IPHA) and the Department of Health for pharmaeucticals to be reimbursed through the community drugs scheme.

Figure 6.12. Cost-effectiveness acceptability curve



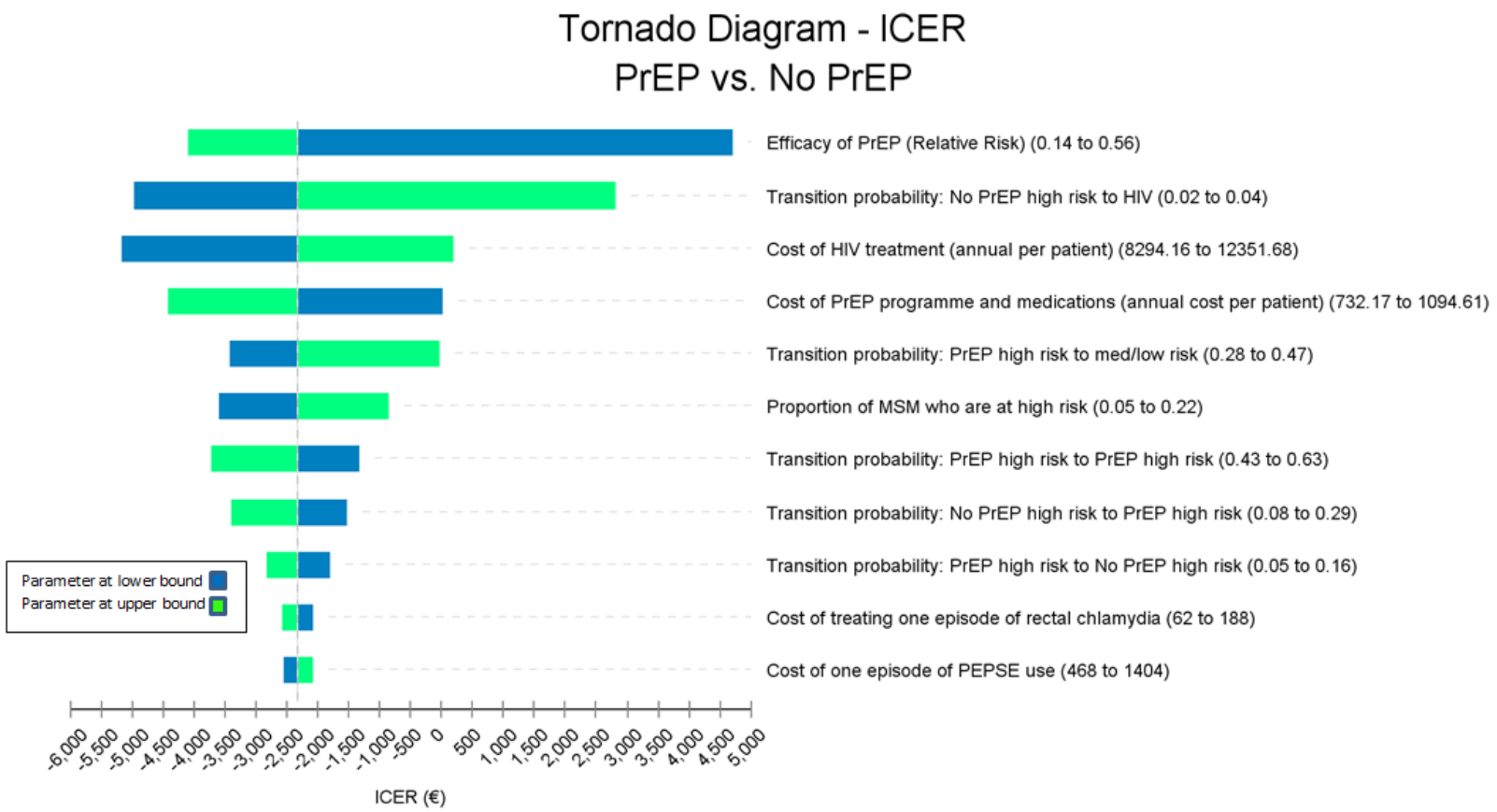
6.4.2 Sensitivity analysis

6.4.2.1 Univariate sensitivity analysis

Univariate deterministic sensitivity analysis was carried out to demonstrate how much uncertainty in the outcome (in this case, the ICER) is induced by uncertainty in individual parameters. In this type of analysis, the model is run with each of the input parameters held at their upper and lower bound, while all the other parameters were assigned their mean value, to ascertain what effect it has on the ICER for a given comparison. Figure 6.15 provides the Tornado plot of the findings (note that parameters that had less than a 5% impact on ICERs are not shown). In this analysis, costs are varied by 20% and the efficacy of PrEP ranges from the lower efficacy noted in iPrEX (44%) to the higher noted in PROUD and IPERGAY (86%). Also varied are the proportion eligible, incidence of HIV, transition probabilities between risk groups, disutility and mortality associated with HIV, and the discount rate .

In Figure 6.13, most ICERs are negative – this means that they are cost saving (in the fourth quadrant of the cost-effectiveness plane). The efficacy of PrEP and the incidence of HIV among individuals at high risk (represented by the transition probability of moving from 'high risk' to 'HIV-positive') had the greatest impact on the cost-effectiveness (see Section 6.4.5 for further analysis). The results were also sensitive to the costs associated with the PrEP programme and the treatment of HIV. The effect of varying the discount rate had little impact; increasing the discount rate from 2% to 6% resulted in ICERs decreasing from -€2,365 to -€2,774.

Figure 6.13. Univariate sensitivity analysis

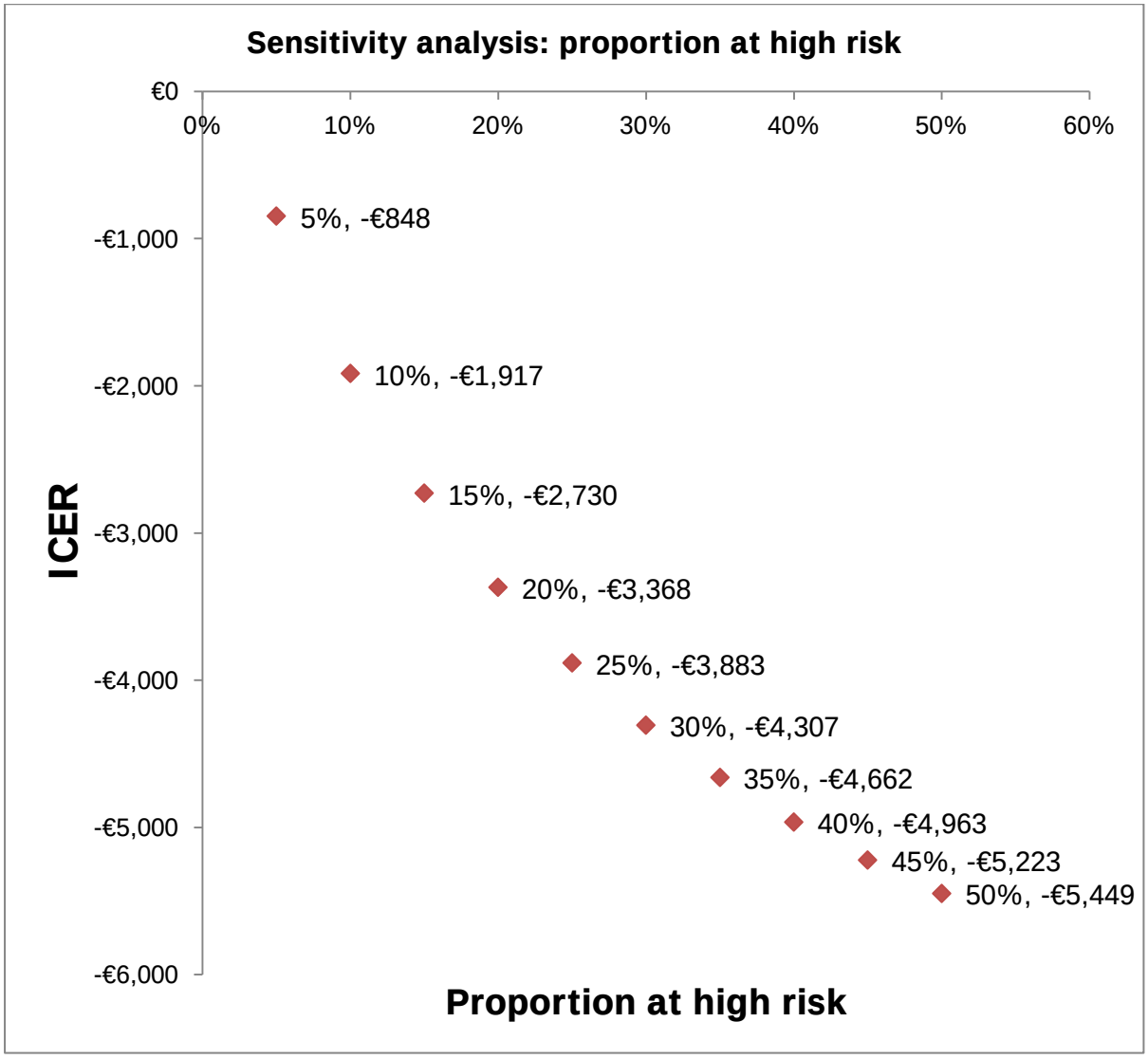


Note – Blue indicates the effect of increasing the value of the base case and red indicates decreasing the value of the base case.
In the base case, the ICER is cost saving.
WTP = willingness-to-pay threshold

6.4.2.2 Variation in eligible proportion and uptake

As outlined in Section 6.2.1.3, provisional data from EMIS 2017 indicate that the proportion eligible for PrEP may have increased in recent years. A sensitivity analysis was carried out whereby the proportion of MSM eligible for PrEP was varied, between 5% and 50% [in the base case, the proportion eligible is approximately 12%, based on model calibration]. Figure 6.14 outlines these results; the intervention becomes more cost saving as the proportion eligible increases.

Figure 6.14. Sensitivity analysis of increasing proportion of eligible MSM



A two-way sensitivity analysis was also performed whereby the uptake rate and eligible proportion were simultaneously varied, between 5% and 50%. Figure 6.15 demonstrates the resulting ICERs over this range; ICERs are negatively associated with both variables.

Figure 6.15. Two-way sensitivity analysis: uptake and proportion at high risk

ICERs		High risk									
		5%	10%	15%	20%	25%	30%	35%	40%	45%	50%
Uptake	5%	-€170	-€812	-€1,341	-€1,785	-€2,162	-€2,488	-€2,771	-€3,019	-€3,239	-€3,435
	10%	-€329	-€1,080	-€1,687	-€2,188	-€2,609	-€2,967	-€3,275	-€3,544	-€3,780	-€3,988
	15%	-€483	-€1,335	-€2,011	-€2,560	-€3,015	-€3,399	-€3,726	-€4,009	-€4,256	-€4,473
	20%	-€633	-€1,578	-€2,315	-€2,905	-€3,388	-€3,791	-€4,132	-€4,425	-€4,679	-€4,901
	25%	-€780	-€1,811	-€2,601	-€3,225	-€3,730	-€4,148	-€4,500	-€4,799	-€5,057	-€5,283
	30%	-€922	-€2,033	-€2,870	-€3,522	-€4,046	-€4,475	-€4,834	-€5,137	-€5,398	-€5,624
	35%	-€1,061	-€2,245	-€3,123	-€3,800	-€4,338	-€4,775	-€5,138	-€5,444	-€5,706	-€5,932
	40%	-€1,197	-€2,449	-€3,363	-€4,060	-€4,609	-€5,052	-€5,418	-€5,724	-€5,985	-€6,210
	45%	-€1,329	-€2,644	-€3,590	-€4,304	-€4,861	-€5,308	-€5,675	-€5,981	-€6,241	-€6,464
	50%	-€1,458	-€2,831	-€3,805	-€4,533	-€5,096	-€5,545	-€5,912	-€6,217	-€6,475	-€6,695

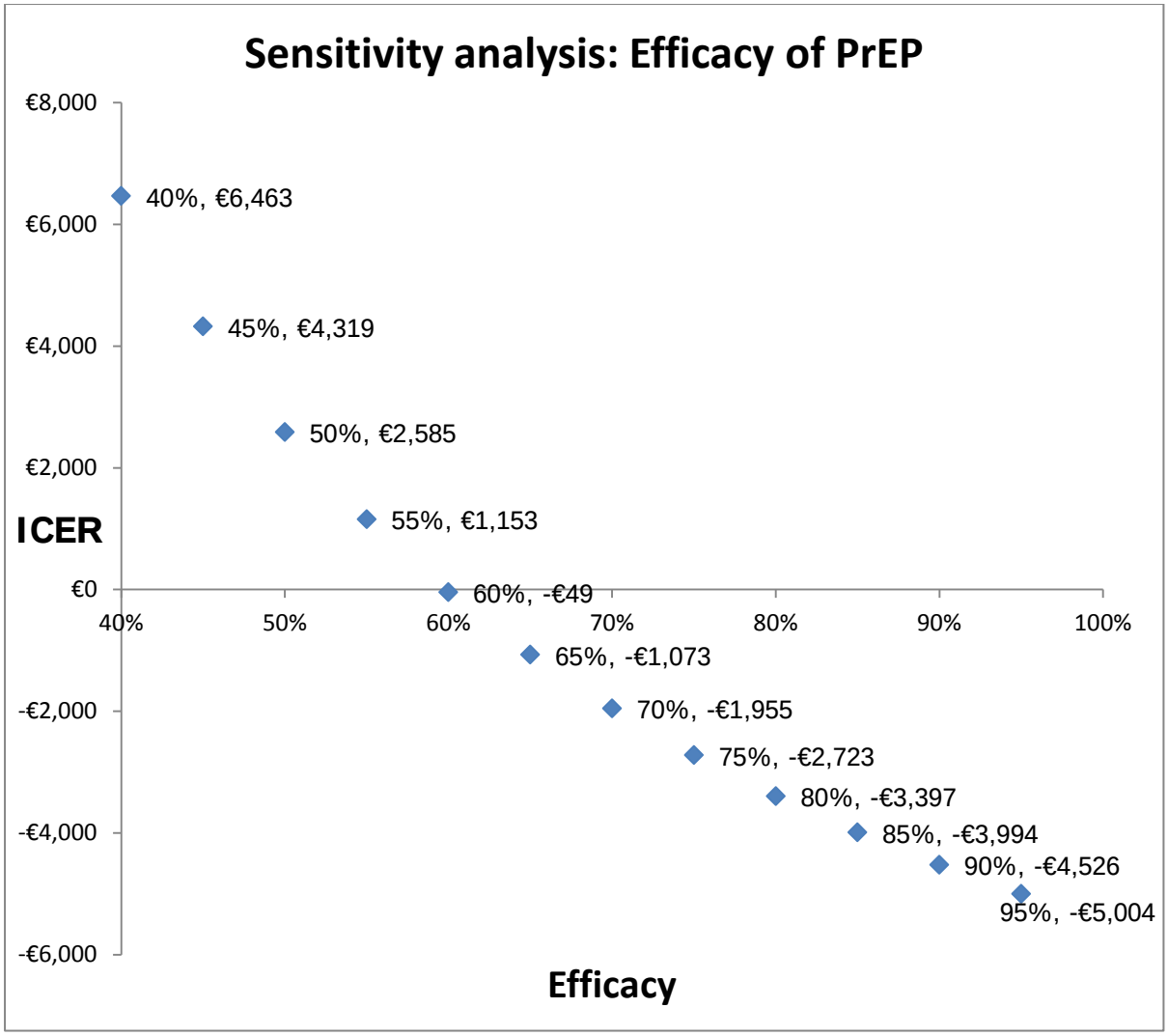
ICER – incremental cost-effectiveness ratio
Note – negative values indicate cost saving (less costly and more effective) relative to standard care

6.4.2.3 Efficacy

As the efficacy of PrEP was a significant driver in the model, a range of efficacy values was investigated to investigate their effect on the cost-effectiveness of PrEP.

In Figure 6.16 below, efficacy values ranging from 40% to 95% are presented. PrEP is cost saving at all efficacy values above 60%. At an efficacy of 44% (the lowest recorded efficacy in MSM [iPrEX trial]), the ICER is €4,711/QALY. This ICER would be considered highly cost-effective and is far below the WTP threshold for pharmaceuticals in Ireland (€45,000/QALY).

Figure 6.16. Sensitivity analysis: efficacy of PrEP



ICER – incremental cost-effectiveness ratio

6.4.3 Scenario analysis

6.4.3.1 EMIS Ireland 2017 provisional data

In the preceding sections, sensitivity analysis on both the uptake and proportion at high risk demonstrated that, intuitively, PrEP becomes more cost saving as these parameters increase in value.

A scenario analysis incorporating provisional EMIS Ireland 2017 data, the most recent data collected on the risk behaviour profile of sexually active MSM in Ireland, was undertaken. In this scenario, parameter calibration was not performed and the high risk group followed the responses of participants in the EMIS Ireland 2017 report. As described in Section 6.2.1.3, 647 of 2083 respondents fulfilled Irish eligibility criteria for PrEP in this survey (31% of total). Monte Carlo analysis was carried out over 10,000 simulations whereby the high risk group is defined by the parameter distribution beta (647, 1436).

The ICER decreases to -€5,288 (95% CI: -€12,535 to €7,289) in this scenario, that is, it becomes even more cost saving relative to usual care.

However, while the EMIS 2017 survey provided useful information on the sexual behaviour of its respondents, it is unknown how representative this sample is of the overall MSM group in Ireland. To investigate how plausible this scenario is, the 'No PrEP' group was followed for five years. Table 6.23 provides these results and compares them to the base case analysis. By the end of the first year an estimated 630 cases of HIV would be expected to occur. This falls well outside the calibration range for HIV cases previously described (150 to 400 cases maximum).

Table 6.23. Markov cohort tracing ('No PrEP' group)

Stage	All MSM	Sexually Active HIV-negative MSM	EMIS-2017 data		Base case analysis	
			MSM at high risk	Cumulative HIV cases	MSM at high risk	Cumulative HIV cases
Outset	77,755	48,986	15,216	0	5,904	0
Year 1	76,623	48,272	10,979	630	5,705	302
Year 2	75,545	47,593	8,552	1,131	5,563	592
Year 3	74,432	46,892	7,145	1,545	5,450	868
Year 4	73,244	46,144	6,312	1,894	5,349	1,125
Year 5	71,949	45,328	5,798	2,187	5,249	1,358

6.4.3.2 Event-based dosing

A scenario analysis was performed where the PrEP regimen followed 'event-based' dosing. In the only trial that investigated the efficacy of event-based oral PrEP in MSM (IPERGAY[29], with an identical efficacy as daily PrEP trials with correspondingly high adherence), a median of 15 pills per month were taken by participants.

Monte Carlo simulation was performed for three scenarios:

- 50% of PrEP users follow event-based and 50% follow daily dosing
- 75% of PrEP users follow event-based and 25% follow daily dosing
- 100% follow event-based dosing.

Table 6.24 outlines the ICERs and 95% CI's associated with these scenarios. As expected, event-based dosing is associated with a lower ICER, that is, it is more cost saving.

Table 6.24. Event-based PrEP

Scenario	ICER	95% CI Lower	95% CI Higher
50% event-based, 50% daily	-€4,594	-€20,158	€14,150
75% event-based, 25% daily	-€5,562	-€20,665	€11,012
100% event-based	-€6,258	-€22,245	€8,052

6.4.3.3 Delay in HIV treatment costs

Due to the long time horizon, average lifetime treatment costs were applied uniformly in the 'PrEP' and 'No PrEP' groups (modelled costs are applied immediately after infection). In reality, there is a delay between infection, diagnosis and treatment. In the budget impact analysis (next section), the delay between infection and diagnosis was incorporated in the model due to the short (five year) time horizon, according to the proportions described in Section 6.2.3.3 (see Table 6.16).

If this delay were included in the cost-effectiveness model, the ICER would increase to €1,226, which has a 95% probability of being considered cost-effective at a willingness to pay threshold of €20,000/QALY. With heightened focus on early diagnosis and treatment, however, the delay between infection, diagnosis and initiation of ART is likely to decrease in future years.

6.5 Budget impact analysis

6.5.1 Methods

Whereas an economic analysis addresses the additional health benefit gained from investment in a technology, such as the cost per QALY gained, budget impact analysis (BIA) addresses the affordability of the technology. For example, it outlines the net annual financial cost of adopting the technology over a defined period, typically five years. Although BIA and cost-effectiveness analysis have many similar data and methodological requirements, there are some important distinctions between the two approaches.

Budget impact analysis:

- reports costs only
- reports the costs for each year in which they occur
- is concerned with costs over a short time horizon
- incorporates Value Added Tax (VAT) where it applies
- does not incorporate discounting
- calculates net costs for the entire patient population.

In general, the BIA model used the same approach as the cost-effectiveness model, however it adopted a shorter time horizon (five years), allowed new entrants to join the initial cohort after the first year (it was an open as opposed to closed model), and took the delay between HIV infection and diagnosis into account (see Section 6.2.3.3). The incremental costs in the BIA include medication costs and all staff and resource use costs associated with PrEP clinic visits that are additional to 'usual care' (as described in Section 6.2.3.2). Not included in the incremental costs are staff shortages and infrastructural issues relating to current STI service demand that is currently unmet, unrelated to PrEP. The model incorporated the potential increase in STI diagnoses and cost offsets: the reduction in PEPSE use in PrEP users and the reduction in HIV care costs associated with averted HIV cases due to PrEP.

Scotland's first year of a national PrEP programme enrolled 1,872 individuals.[127] This number of PrEP participants was used to guide our estimates of the number of individuals who are likely to enroll in an Irish programme (note that Ireland's population is approximately 10% smaller than Scotland's; 4.8 versus 5.4 million). The model was therefore calibrated to assume a plausible range of 1,000 to 3,000 individuals joining the programme in Year 1 (the calibration process is described in Section 6.3). The same care pathway and distribution parameters outlined in the cost-effectiveness analysis were applied. Note that the total number of MSM was

decreased by 5% to obtain the HIV-negative population (as 5% of respondents in MISI 2015 were noted to be HIV-positive), which was balanced by an arbitrary increase of 5% to capture all individuals who are not MSM but who would be considered eligible for PrEP (in the absence of Irish data on this group).

The number of participants likely to enroll in the programme was therefore determined by the following parameters:

- Proportion of men who are MSM
- Proportion of MSM who are sexually active
- Proportion of sexually active MSM who are at substantial risk (eligible)
- Uptake rate among eligible MSM.

Following calibration, the mean number of people who are estimated to join the programme in Year 1 is 1,705 people (95% CI: 617 to 3,452). The distribution parameters are described previously (see Table 6.21).

This initial cohort of participants is followed according to the same pathway outlined in the state transition Markov model used in the cost-effectiveness analysis, whereby individuals may discontinue and resume PrEP over time (see Figure 6.1). In contrast to the closed cohort modelled as part of the cost-effectiveness analysis, the budget impact model is an open model in the sense that new entrants can enter the model after Year 1. New entrants consist of migrants entering the system and 16 year olds coming of age. The net inward male migration was 18,200 individuals in the year ending April 2018. Additionally, there were 32,550 males who became 16 years of age in 2018.[(129)] Applying the same four distribution parameters as before, a mean of 48 new migrants/16-year olds coming of age join the PrEP programme each year (95% CI: 17 to 98). The cycle length was set at one year intervals for convenience.

As per the cost-effectiveness analysis, all BIA results are based on probabilistic sensitivity analysis, with each parameter being defined as a distribution based on the plausible range of values. These parameters are sampled over the course of 10,000 Monte Carlo replications to take account of the uncertainty associated with the model outputs. Due to the short (five year) time horizon, the delay between infection and diagnosis/treatment with ART was incorporated in the model, according to the proportions previously described (see Table 6.16).

Sensitivity and scenario analyses were also carried out. First, a deterministic univariate sensitivity analysis was performed where all distribution parameters were varied between their lower and upper limits (Section 6.6.3). Second, the proportion eligible for PrEP was increased to that recorded in the EMIS Ireland 2017 dataset

(Section 6.6.4). Third, due to the fact that efficacy was found to be the main driver of cost-effectiveness, scenarios were carried out where the efficacy values noted in iPrEX and PROUD (the lowest and highest efficacy values recorded among daily MSM oral PrEP users) (Section 6.6.5). Fourth, a two-way sensitivity analysis was performed, simultaneously varying PrEP uptake and the eligible proportion of MSM and assessing the effect on the budget impact.

6.5.2 Results of base case analysis

The mean number of people who are estimated to join the programme in Year 1 is 1,705 people (95% CI: 617 to 3,452). The number of individuals on PrEP over the first five years is provided in Table 6.26.

Table 6.26. PrEP participants over time

Year	Mean	95% CI Lower	95% CI Higher
Year 1	1,705	617	3,452
Year 2	1,654	602	3,326
Year 3	1,634	689	3,121
Year 4	1,628	709	3,055
Year 5	1,635	688	3,123

The incremental budget impact of the PrEP programme is almost€1.5m in the first year (95% CI: €0.5m to €3m) and €5.4m over five years (95% CI: €1.8m to €11.5m). The incremental cost takes into consideration the potential increase in STIs [rectal chlamydia] and cost savings due to averted HIV infections and the reduction in PEPSE use in PrEP users. Table 6.27 and Figure 6.17 provide the incremental cost in each year following the introduction of the programme. Note that approximately 71% of total PrEP programme costs relate to PrEP medication costs.

Table 6.27. Incremental budget impact by year

Year	Incremental cost of PrEP (programme+drug costs)	95% CI Lower	95% CI Higher
Year 1	€1.48	€0.52	€2.98
Year 2	€1.29	€0.49	€2.65
Year 3	€1.11	€0.31	€2.42
Year 4	€0.90	-€0.03	€2.31
Year 5	€0.65	-€0.48	€2.16
5-year total	€5.44	€1.77	€11.46

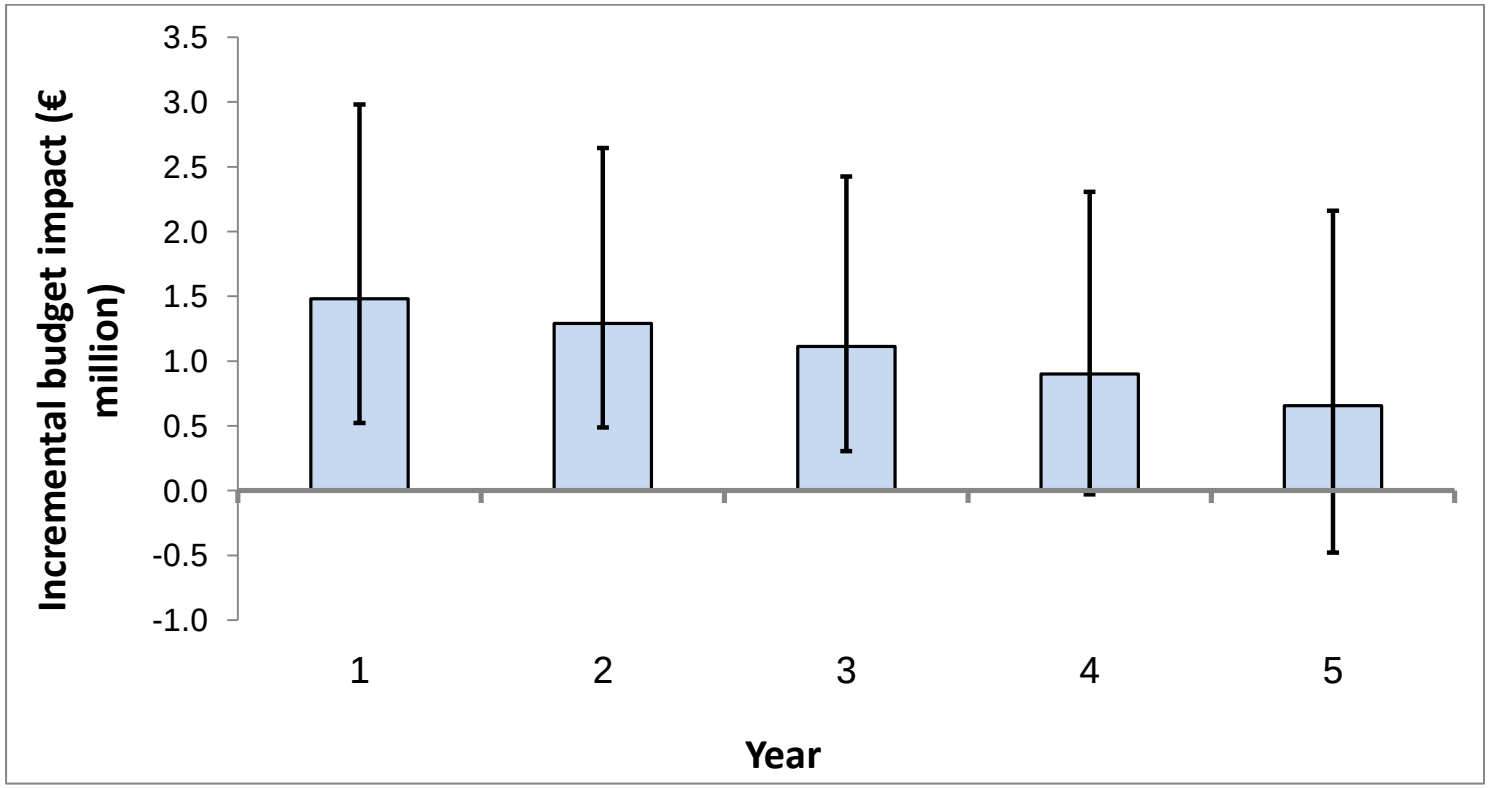
All costs in millions

In terms of incremental programme-only costs (excluding drug costs), the mean cost associated with STI clinic visits in the first year is €451,075 (95% CI: €163,234 to €913,261).Also modelled was the number of HIV infections estimated to occur with and without a PrEP programme in place (see Table 6.28). Overall, 173 HIV infections are estimated to be averted over the course of five years.

Table 6.28. HIV cases averted by PrEP programme

	PrEP programme		No PrEP		Cases averted	
	New cases	Cumulative cases	New cases	Cumulative cases	Annually	Cumulative
Outset	-	-	-	-	-	-
End-Year 1	286	286	323	323	38	38
End-Year 2	276	561	311	634	35	73
End-Year 3	277	839	311	945	34	106
End-Year 4	279	1,118	313	1,258	33	140
End-Year 5	282	1,400	315	1,573	33	173

Figure 6.17. Incremental budget impact by year



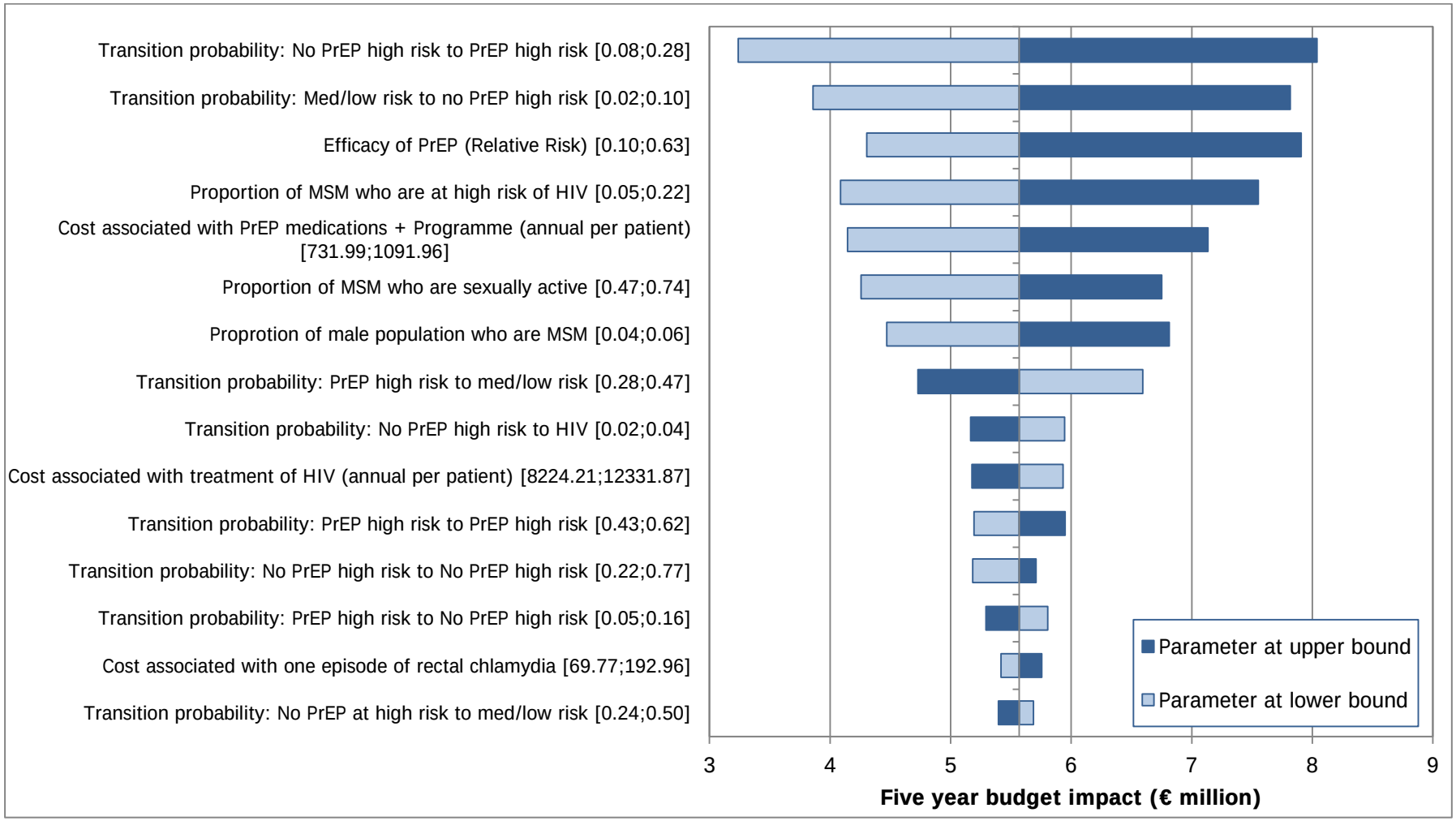
Note – overlapping bars indicate the 95% confidence interval associated with incremental costs

6.5.6 Sensitivity analysis

6.5.6.1 Univariate sensitivity analysis

A deterministic sensitivity analysis was performed where all distribution parameters were varied between their lower and upper limits. Figure 6.18 illustrates these results in the form of a Tornado diagram (only parameters that had a 5% or greater impact on the incremental budget impact are listed). The parameters that had the greatest impact on the budget were those that influenced the number of participants in the programme, such as the proportion eligible for PrEP and the transition probabilities between health states that favoured a larger proportion in the PrEP group. Also influential were the efficacy of PrEP and the cost associated with the PrEP programme and in the treatment of HIV, similar to that noted in the cost-effectiveness sensitivity analysis (see Section 6.4.2).

Figure 6.18. Tornado diagram



6.5.6.2 Two-way sensitivity analysis (uptake and proportion eligible)

As previously discussed, there is evidence to suggest that high risk behavior may be increasing in the MSM group. Any increasing trend of risky sexual behavior is of concern and will influence future cost estimates. In tandem with the proportion eligible, the uptake rate similarly affects the budgetary requirements and affordability of PrEP. A two-way sensitivity analysis was carried out whereby the proportion of MSM eligible for PrEP and the uptake rate were varied, up to 50% eligible and 40% uptake rate (in the base case, the proportion eligible is approximately 12.4% and uptake is 27.4%, based on model calibration). Figure 6.19 illustrates these results.

Figure 6.19. Two-way uptake/eligible proportion sensitivity analysis

Incremental BIA (5-year)		High risk									
		5%	10%	15%	20%	25%	30%	35%	40%	45%	50%
Uptake	5%	€4.00	€4.90	€5.80	€6.70	€7.60	€8.50	€9.40	€10.30	€11.20	€12.10
	10%	€4.00	€5.00	€5.90	€6.80	€7.70	€8.60	€9.60	€10.50	€11.40	€12.30
	15%	€4.10	€5.00	€6.00	€6.90	€7.80	€8.80	€9.70	€10.70	€11.60	€12.60
	20%	€4.10	€5.10	€6.00	€7.00	€8.00	€9.00	€9.90	€10.90	€11.90	€12.80
	25%	€4.10	€5.10	€6.10	€7.10	€8.10	€9.10	€10.10	€11.10	€12.10	€13.10
	30%	€4.10	€5.20	€6.20	€7.20	€8.20	€9.30	€10.30	€11.30	€12.30	€13.40
	35%	€4.20	€5.20	€6.30	€7.30	€8.40	€9.40	€10.50	€11.50	€12.60	€13.60
	40%	€4.20	€5.30	€6.30	€7.40	€8.50	€9.60	€10.70	€11.70	€12.80	€13.90
	45%	€4.20	€5.30	€6.40	€7.50	€8.60	€9.70	€10.90	€12.00	€13.10	€14.20
	50%	€4.20	€5.40	€6.50	€7.60	€8.80	€9.90	€11.00	€12.20	€13.30	€14.40

All costs in millions

6.5.7 Scenario analysis

6.5.7.1 EMIS Ireland 2017 provisional data

Provisional data from EMIS Ireland 2017 is described in detail in Section 6.2.1.3. Briefly, the number eligible for PrEP based on overlapping survey responses was 647 out of 2,083 respondents, or 31%.

Monte Carlo analysis was carried out over 10,000 simulations whereby the group at high risk is defined by the parameter distribution beta (647,1436). Under this scenario, an estimated 4,253 individuals (95% CI: 2,633 to 6,301) join the programme in Year 1. Unsurprisingly, this scenario is significantly more costly. The 5-year incremental budget impact is €7.6m (95% CI: €3m to €15m). Table 6.29 lists the yearly incremental costs under this scenario.

Table 6.29. Incremental budget impact – EMIS 2017 data

Year	Incremental cost of PrEP (programme+drug costs)	95% CI Lower	95% CI Higher
Year 1	€1.56	€0.54	€3.16
Year 2	€1.59	€0.62	€3.16
Year 3	€1.56	€0.59	€3.15
Year 4	€1.49	€0.44	€3.18
Year 5	€1.38	€0.23	€3.24
5-year total	€7.58	€2.97	€15.05

All costs in millions

6.5.7.2 Efficacy

Due to the fact that efficacy was the major driver of cost-effectiveness, probabilistic scenario analyses where the lowest and highest efficacy values for PrEP among MSM were undertaken to investigate the difference in results. From Chapter 4, Section 4.3.4.1, the range of efficacy values for daily oral PrEP in MSM was as follows:

- Lowest (iPrEX study): Relative risk of HIV acquisition = 0.56, SD 0.12, 95% CI 0.37 to 0.84
- Highest (PROUD study): Relative risk of HIV acquisition = 0.14, SD 0.11, 95% CI: 0.04 to 0.47

Table 6.30 compares these results. The difference in the incremental budget impact is modest in the first year (€1.5m in PROUD versus €1.6m in iPrEX). The five-year total incremental BIA is €4.7m (PROUD scenario) compared with €7.6m (iPrEX scenario).

Table 6.30. Highest and lowest efficacy scenarios

	PROUD study (86% effectiveness)			iPrEX study (44% effectiveness)		
Year	Incremental cost	95% CI Lower	95% CI Higher	Incremental cost	95% CI Lower	95% CI Higher
Year 1	€1.46	€0.51	€3.00	€1.56	€0.54	€3.16
Year 2	€1.19	€0.44	€2.50	€1.59	€0.62	€3.16
Year 3	€0.96	€0.22	€2.20	€1.56	€0.59	€3.15
Year 4	€0.70	-€0.22	€2.04	€1.49	€0.44	€3.18
Year 5	€0.40	-€0.78	€1.80	€1.38	€0.23	€3.24
5-year total	€4.72	€1.38	€10.34	€7.58	€2.97	€15.05

All costs in millions

6.5.8 Years to budget neutrality

As demonstrated in the cost-effectiveness analysis, PrEP was found to be cost saving over the modelled cohort's lifetime. Budget impact analysis typically reports costs over a much shorter time period, however, which overcomes much of the uncertainties relating to future changes in epidemiological and cost parameters.

However, if the budget impact model is continued beyond five years according to the methods previously described, the yearly incremental budget impact becomes negative (cost saving) by Year 8 (-€0.2m; 95% CI: -€2m to €1.7m). In terms of the aggregate budget impact, the 'break even' point is reached in Year 14 (all programme and medication costs will have been recuperated). It must be stressed, however, that changes in epidemiological parameters (such as changing patterns of migration) may significantly alter these findings. Table 6.31 provides the incremental budget impact and its probability of being budget neutral by year.

Table 6.31. Budget impact over 25 years and probability of cost saving

Year	Mean	95% CI lower	95% CI upper	Probability cost saving	Aggregate BIA
1	€1.5	€0.5	€3.0	0	€1.5
2	€1.3	€0.5	€2.6	0	€2.8
3	€1.1	€0.3	€2.4	0	€3.9
4	€0.9	-€0.1	€2.3	0.03	€4.8
5	€0.7	-€0.5	€2.2	0.14	€5.4
6	€0.4	-€1.0	€2.1	0.29	€5.8
7	€0.1	-€1.5	€1.9	0.45	€5.9
8	-€0.2	-€2.1	€1.7	0.59	€5.7
9	-€0.5	-€2.6	€1.5	0.71	€5.3
10	-€0.8	-€3.2	€1.4	0.79	€4.5
11	-€1.1	-€3.9	€1.2	0.85	€3.4
12	-€1.4	-€4.5	€1.1	0.89	€2.1
13	-€1.7	-€5.2	€0.9	0.92	€0.4
14	-€2.0	-€5.9	€0.8	0.94	-€1.6
15	-€2.3	-€6.6	€0.7	0.95	-€4.0
16	-€2.7	-€7.4	€0.5	0.95	-€6.6
17	-€3.0	-€8.1	€0.4	0.96	-€9.6
18	-€3.3	-€8.9	€0.3	0.97	-€12.9
19	-€3.6	-€9.7	€0.2	0.97	-€16.6
20	-€4.0	-€10.4	€0.1	0.97	-€20.6
21	-€4.3	-€11.2	-€0.0	0.98	-€24.9
22	-€4.6	-€12.1	-€0.1	0.98	-€29.5
23	-€5.0	-€12.9	-€0.2	0.98	-€34.5
24	-€5.3	-€13.7	-€0.3	0.98	-€39.8
25	-€5.6	-€14.5	-€0.5	0.98	-€45.4

All costs in millions
BIA – budget impact analysis; CI – confidence interval

6.6 Discussion

Discussion of main findings

PrEP was found to be cost saving in the first cost-effectiveness and budget impact analysis of a targeted PrEP programme tailored to the Irish HIV epidemic. Modelling the entire HIV-negative MSM population of Ireland in 2018 over a lifetime horizon, a national PrEP programme is expected to provide significant health benefits associated with a substantial reduction in HIV incidence and lead to cost savings in as little as eight years.

The movement of individuals between risk groups was tracked in an economic model and the time horizon (60 years) was adequate to capture all costs and consequences accrued over the cohort's lifetime. The key strength of this analysis was its simplicity of design requiring relatively fewer assumptions, transparency and ease of interpretation for decision makers. Consistent with national HTA guidelines, a conservative approach was adopted that would bias against PrEP. The results are robust to considerable variations in the main assumptions and variation of parameter values within plausible ranges. The model assumes adequate adherence and correspondingly high clinical effectiveness, as PrEP effectiveness was the main driver of cost-effectiveness in the model. The ICERs were also sensitive to the incidence of HIV in MSM at high risk of sexual acquisition. Nonetheless, the ICER did not exceed €5,000/QALY gained in any scenario investigated. ICERs were less sensitive to variations in key cost parameters, including the cost of HIV care and the cost of PrEP (PrEP remained cost saving over a range of plausible values).

Despite the strength of the evidence, one of the residual concerns about the introduction of PrEP is risk compensation and the potential spread of other STIs and the cost of their treatment. Trial evidence to date has not demonstrated an increase in STIs while on PrEP. Observational data is typically subject to confounding, such as differences in the frequency of testing between pre- and post-PrEP time periods, so that limited conclusions can be made. One meta-analysis of 18 observational studies noted an increased odds of rectal chlamydia,[(154)] but not of any other pathogen or chlamydia at other anatomic sites. Conservatively, it was decided to incorporate this increase in rectal chlamydia cases in analyses. It was found to have a negligible impact on the cost-effectiveness of PrEP. In any case, the early detection and treatment of STIs minimises the consequences and onward transmission, and the cost of treatment is low due to the availability of low-cost generic antimicrobials relative to the cost of HIV treatment. Even if there is a substantial increase in STIs, it would be unlikely to impact the findings of cost effectiveness analysis.

It is important to note that the comparator used in the model is all HIV-negative MSM in 2018, followed for their lifetime, without access to a PrEP programme. The assumption here is that PrEP is not available, whereas in reality it is known that there are individuals who pay for PrEP out-of-pocket at pharmacies, and others who buy PrEP online in Ireland. Including these individuals in the comparator ('No PrEP' group) was not considered appropriate, as the HSE does not incur medication costs for these people. Due to the fact that the perspective is all direct costs to the public health and social care system (HSE), this comparison would bias the cost-effectiveness analysis in favour of the 'No PrEP' group. In any case, there is little data on the actual number of individuals taking PrEP, and in the case of online ordering of PrEP, it is unknown if the eligibility criteria are met, ongoing monitoring is in place, and there is no data on adherence in this group.

A number of other economic evaluations of PrEP have been conducted in other countries employing a range of economic models. Few investigated PrEP as part of a holistic programme, and fewer still assessed the budget impact of a national programme that would provide PrEP to all eligible individuals. Most prior studies modelled PrEP over a short time horizon, failing to capture the lifelong consequences of HIV infection. In general our findings are consistent with published studies that modelled generic priced PrEP and used HIV treatment cost estimates similar to those seen in Ireland, that is, that PrEP is cost-effective or cost-saving relative to usual care. Similar to other economic evaluations, ICERs were found to be to be highly sensitive to PrEP adherence-related effectiveness, incidence of HIV and costs of antiretroviral drugs. On the other hand, ICERs in this analysis were not very sensitive to the discount rate used, unlike other analyses.

Scenario and sensitivity analyses

Scenario and sensitivity analyses were used to explore the impact of different assumptions in the model, particularly in relation to parameter uncertainty. Scenario analyses facilitate the incorporation of an alternative set of assumptions to determine the impact on the estimated cost-effectiveness and budget impact. An important feature of scenario analyses is to consider whether the decision-maker has any control over the underlying assumption. For example, a decision-maker may be unable to influence the effectiveness of PrEP, but they may be in a position to negotiate a lower price and implement strategies that increase PrEP uptake and improve medication adherence. As such, some scenario analyses illustrate the impact a different set of assumptions has on decision-making, while others may give practical guidance on the scope to improve the cost-effectiveness.

The effectiveness of PrEP was the main driver of cost-effectiveness and was varied extensively through sensitivity analysis. Effectiveness estimates were derived from a

systematic review of the international evidence (Chapter 4) and were considered applicable to Ireland. PrEP was found to be cost saving at all effectiveness values above 60%. At an effectiveness of 44%, the lowest recorded value in MSM where adherence was sub-optimal (the iPrEX trial), the ICER was €4,711/QALY. This ICER would still be considered highly cost-effective and is far below willingness to pay thresholds used for pharmaceuticals in Ireland (e.g., €45,000/QALY).

From a health policy and decision-making perspective, the scenario where the PrEP regimen followed event-based dosing is of interest. Assuming event-based PrEP remains as effective as daily PrEP in future studies, the cost would reduce substantially if participants adopted this dosing schedule. If all participants took event-based PrEP, it is estimated that the ICER would decrease from -€2,735 to -€6,258/QALY gained, that is, treatment would become even more cost saving relative to usual care. However, as PrEP is only licensed for daily use, event-based dosing cannot yet be recommended as first line treatment.

The proportion of MSM eligible for PrEP and the uptake of PrEP in these individuals, and hence the size of the PrEP programme, are both crucial parameters and were subject to significant uncertainty. Two-way sensitivity analysis investigated both the cost-effectiveness and budgetary requirements across a range of these parameter values. Intuitively, PrEP is more cost saving as the size of the programme increases. Due to the lag between programme implementation and cost savings, however, promotion of PrEP and programme scale-up must be balanced with budgetary constraints.

Limitations

The present study was subject to a number of limitations. As with any economic modelling exercise, the applicability of the findings is dependent on the assumptions underpinning the model structure and on the quality of the parameter values used.

Model structure

As with all mathematical models, this discrete-time transition Markov model is a simplification of reality, whereby individuals are stratified by risk status and all individuals within a particular health state are assumed to behave the same. While movement between risk groups is permitted in the model, individuals in any particular health state are treated as a homogenous group regardless of prior risk status. Also, for the association between behavioural risk and incidence of HIV to be valid, the assumption must hold that PrEP eligible individuals are correctly identified, as PrEP use in medium/low risk individuals would reduce the effectiveness and cost-effectiveness of the programme.

A limitation of the model's design is that it does not incorporate dynamic transmission elements, which would allow the quantification of the benefit of PrEP on the wider HIV epidemic in Ireland, including the benefits for those not given PrEP. Therefore, there is an underestimation of the total benefit. Nevertheless, as only 2% of Irish MSM were given PrEP in this model, the likely indirect impact of the PrEP programme would be limited. Dynamic transmission models typically note that the indirect impact of PrEP is relatively modest. One analysis of Dutch MSM using a dynamic model showed only a 13 to 16% decrease in the ICER when indirect effects were included.[159] However, while the effects on ICERs are typically small, the indirect health benefits can be large if PrEP coverage over a long period is maintained. A UK dynamic transmission analysis noted that 58% of averted infections over 80 years following PrEP introduction would be due to the indirect prevention of onward transmission.[131] Overall, while the addition of a dynamic component to the model would enhance PrEP's health benefits and cost savings through capturing the indirect effects of PrEP, it would introduce uncertainty and require simplifying assumptions that would reduce confidence in our findings. As with other assumptions in the model, and consistent with best practice, a conservative approach was adopted, biasing the results against PrEP, so that the model will have underestimated rather than overestimated the cost-effectiveness of PrEP

A cohort model was adopted for the cost-effectiveness analysis, unlike the BIA, and fluctuations in population parameters such as the birth rate and migration were not accounted for. Certain model parameters could be significantly altered by migration. It was decided *a priori* not to model long-term migration patterns as they are highly unpredictable. The very significant uncertainty associated with changes relating to migration would, if included in the model, dwarf the uncertainty in relation to our knowledge of the existing situation. In other words, the model reflects the best estimate of what is known currently rather than what might be known in the future. If migration patterns were to result in a higher proportion of MSM eligible for PrEP, however, this would likely make PrEP even more cost saving, as evidenced by the sensitivity analysis in which the size of the programme was increased. However, an increase in the size of the programme would increase in the BIA in the short-term.

Parameter uncertainty

There was substantial uncertainty around a number of the key parameters used in the probabilistic sensitivity analyses. The parameters used in the model were derived from a wide variety of sources based on Irish and international data, and in situations where reliable data were lacking, calibration to observed data was necessary to produce plausible estimates.

A key limitation relating to epidemiological parameters used was the reliance on sources outside Ireland, such as HIV incidence data. While the HPSC accurately reports HIV notifications in Ireland, it is not possible to ascertain the overall incidence of HIV or the incidence of HIV by risk category. UK epidemiological data were extensively used,[130] due to broadly comparable HIV prevalence, completeness and accuracy of data collected (through electronic GUM clinic records) and similarities in risk stratification in both jurisdictions (for example, similar eligibility criteria for the provision of PrEP).

In terms of quantifying the eligible population, it is not yet possible to estimate these parameters with any degree of certainty. A calibration approach was undertaken to retrieve plausible estimates for parameters relating to the eligible proportion and uptake. While sexual behaviour data has been gathered in convenience surveys, the extent to which they represent the overall MSM group in unknown. Provisional data from the European Men who have sex with men Internet Survey (EMIS) 2017, based on 2,083 Irish responses, reported a high proportion of MSM eligible for PrEP. While the estimates of the number of individuals eligible for PrEP do not alter the cost-effectiveness conclusions, they affect the budget impact. Additionally, many factors will undoubtedly influence the eventual PrEP uptake rate in the eligible population. In the absence of reliable data on future uptake, published data from Scotland's first year of their national PrEP programme were relied upon to guide our estimates.

Uncertainty also exists relating to HIV care costs. A reduction in the cost of HIV-related care would reduce the cost-effectiveness of PrEP. Future reductions in the cost of antiretroviral therapy may occur if additional generic medications enter the market, however this is impossible to predict. Also, in line with national guidelines, this evaluation did not incorporate any indirect costs relating to HIV care. Other evaluations have included indirect costs, particularly in relation to lost productivity due to HIV. In the Irish setting, a societal perspective would also entail including out-of-pocket treatment costs that accrue to patients. If the societal cost of HIV were included, however, PrEP would only be considered more cost saving.

Conclusion

Taking into account the model assumptions and data uncertainty, our analysis has shown that the introduction of a publicly funded national PrEP programme would be cost saving over the medium to long-term and provide significant health benefits relative to current care, with a high likelihood of becoming budget neutral over a relatively short time period.

Future directions

There are a number of questions that cost-effectiveness analysis cannot answer. If implementated, ongoing programme monitoring and evaluation should aim to answer the following questions:

- how many enrolled in the programme, and how many started PrEP?
- what proportion of PrEP users were new to STI services?
- how many people interrupted or discontinued PrEP once started?
- will was PrEP be taken up by those in whom PrEP is clinically recommended?
- what was their level of adherence, and how was this be measured?
- will did PrEP affect STI rates?

The finding that PrEP is cost saving is in the context of the model assumptions that underpinned this analysis. Going forward, there are two model assumptions that must be borne in mind. First, it was assumed that PrEP will be taken by eligible participants. If access to a PrEP programme is provided to individuals at medium or low risk, the population-level effectiveness and resulting cost-effectiveness of the programme will decrease, possibly substantially. Regular clinical risk assessment to ensure only those at continuing substantial risk stay on PrEP is required to maintain cost-effectiveness and ensure equitable access based on clinical need.

Second, the model assumed a HIV incidence based on clinical risk of HIV that was static over time, and that the PrEP programme would continue for the cohort's lifetime. Once incidence declines sufficiently, PrEP may no longer be necessary and would be unlikely to be considered a cost-effective public health intervention. To maintain cost effectiveness, a practical way to pause PrEP initiation when the HIV incidence drops sufficiently should be explored. While HIV incidence is not monitored in Ireland, the HIV notification rate may serve as an acceptable proxy for secular trends in HIV transmission. While only a very modest uptake of PrEP was modelled in this analysis (2% of all MSM), a myriad of HIV prevention strategies are available and a combination approach may decrease or halt transmission in the medium to long term. For example, the recommendation that all newly infected individuals immediately start ART is underpinned by very strong evidence that viral suppression prevents onward HIV transmission. Major unforeseen changes occurring in HIV treatment or prevention will likely affect the presented results.

On a final note, a range of scenarios were explored that highlight areas for potential cost savings. While not currently a licensed indication, event-based PrEP may be preferentially used to minimise costs and toxic effects, assuming that the effectiveness of daily versus event-based PrEP remains the same in future studies. Additionally, the finding that high PrEP uptake results in additional health benefits

and increases cost savings in the long run highlights the importance of promoting PrEP to eligible individuals, within current budgetary constraints.

7 Organisational issues

Key Points

- PrEP is available in at least 49 countries worldwide, with 12 countries providing PrEP through national programmes.
- Scotland was the first country to publish data from a national PrEP programme. In the first year of the Scottish programme, which commenced in July 2017 and provides free access through sexual health clinics, 1,872 individuals were prescribed PrEP at least once of which 99% were gay, bisexual and other men who have sex with men (MSM).
- In Ireland, there is no formal national PrEP programme. Access to components of the proposed programme is currently provided on an ad hoc basis through public sexually transmitted infection (STI) clinics and primary care providers. PrEP medications are paid for out of pocket and sourced through community pharmacies or online.
- There are 23 public STI clinics in 16 counties in Ireland. The Gay Men's Health Service (GMHS) is responsible for the majority of PrEP prescriptions and subsequent monitoring to date in Ireland. Current demand at GMHS exceeds the available capacity.
- The primary barriers to introducing a PrEP programme are staffing and infrastructural issues. Staff shortages were cited by all 18 public STI clinics that responded to a PrEP preparedness survey. Many services also cited time limitations and a lack of clinical space.
- A significant investment in STI services is required for a national PrEP programme to ensure a safe, sustainable and holistic service. STI services are needed to assess PrEP eligibility and to provide screening and ongoing monitoring. These are outlined in the national standards and monitoring framework.
- PrEP medication could be dispensed through community pharmacies, hospital pharmacies or on-site at STI clinics. These options differ in the level of infrastructure investment required to support a PrEP programme and in the accessibility of the services, with the widest geographical access provided by community pharmacies.
- Without investment in STI services, sub-optimal delivery of a PrEP programme could result in inequitable access to care and poor medication adherence and monitoring, as well as disruption of core STI clinic services and increased wait time for non-PrEP attendees.

7.1 Introduction

This chapter outlines the expected organisational requirements of a PrEP programme in Ireland.

A number of countries have initiated PrEP programmes, which are outlined in Section 7.2. Details of pilot studies and regional and national PrEP programmes are presented in Section 7.3. These sections provide an insight into the acceptability and feasibility of PrEP in other countries and regions. In particular, uptake and retention rates provide valuable information for a prospective programme in Ireland, such as the number of individuals likely to enrol.

Section 7.4 outlines current access to PrEP in Ireland, including existing access through sexually transmitted infection (STI) clinics. An overview of locations with potential capacity to provide PrEP is also provided.

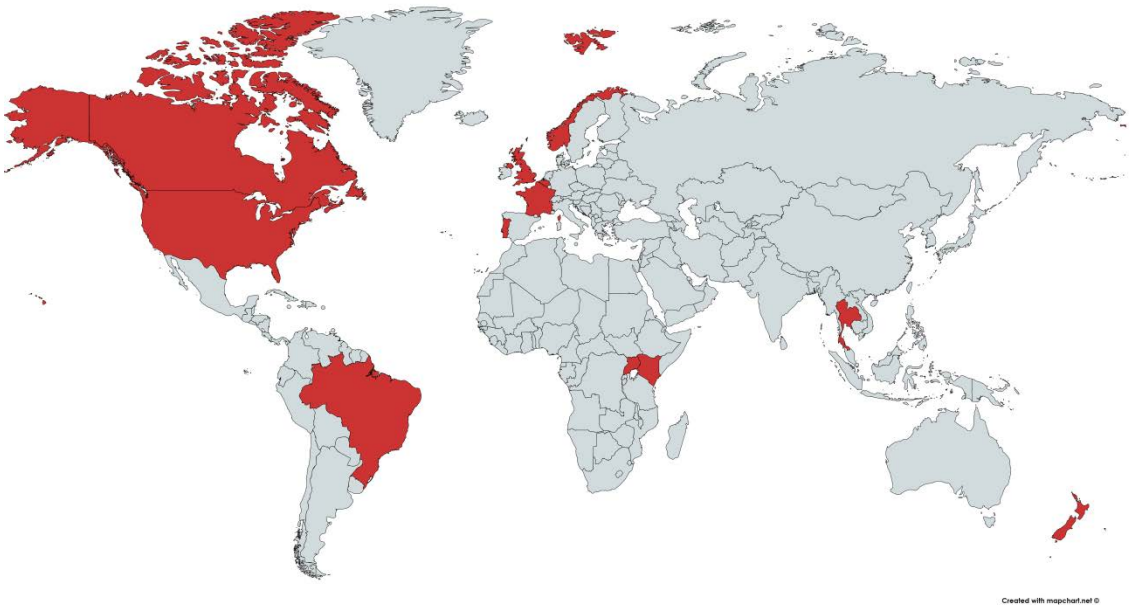
Information on current services was used to inform Section 7.5, which discusses specifications for a potential national programme. This section outlines organisational options for a PrEP programme that provides equitable access to a quality service, including PrEP medications. The potential impact of a PrEP programme on other STI services is discussed in Section 7.6. The requirements for an information and awareness campaign, should a decision be made to provide a national programme, are outlined in Section 7.7.

7.2 International PrEP programmes

PrEP is licensed in all EU/EEA member states by the European Commission (2016) and in the US by the FDA (2012).[160, 161] Many countries have offered PrEP through dedicated programmes, such as national programmes, or through initial demonstration projects, implementation projects and clinical trials. At the time of writing of this HTA, PrEP is available in at least 49 countries worldwide through one or more of these initiatives.

Twelve countries provide PrEP through national programmes and, at the time of writing, four countries were planning to introduce national programmes (see Table 7.1 and Figure 7.1). France became the first country in Europe to offer PrEP through its public health system in 2015. This was done through an 'emergency recommendation for temporary use', which became permanent in April 2017. Other European countries with national programmes in place include Belgium, Norway, Portugal and Scotland. Northern Ireland introduced a pilot PrEP clinic based in the Belfast Trust in August 2018.

Figure 7.1. Worldwide national PrEP programmes



National programmes include ongoing or pilot programmes. Countries are: Belgium, Brazil, Canada, France, Kenya, Norway, New Zealand, Thailand, Portugal, Uganda, Scotland & Northern Ireland (UK), and USA

Table 7.1. Countries with ongoing or planned national PrEP programmes

Country	Guideline or policy document
Belgium	HIV plan 2014–2019 Belgium[16]
Botswana	Planned
Brazil	Clinical Protocol and Therapeutic Guidelines for Management of HIV Infection in Adults (2018)[17]
Canada	Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational post-exposure prophylaxis[18] Guidance for the use of PrEP in British Columbia (2016)[19]
France	ANSM Pre-exposure Prophylaxis Guidelines (2017)[162]
Kenya	Framework for the Implementation of Pre-Exposure Prophylaxis of HIV In Kenya (2017)[21]
New Zealand	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines[22]
Northern Ireland	Pilot clinic commenced August 2018
Norway	No guideline documents identified
Portugal	No guideline documents identified
Scotland	Scottish NHS Programme[127]
Thailand	Thailand National Guidelines on HIV/AIDS Treatment and Prevention 2017[24]
Uganda	National HIV AND AIDS Strategic Plan 2015/2016 - 2019/2020[25] Consolidated Guidelines for Prevention and Treatment of HIV in Uganda (2016)[26]
USA	National HIV/AIDS Strategy for the United States: Updated to 2020[163]

Wales	Preparing for PrEP full report 2017[28]
Vietnam	No guideline documents available

Scotland was the first country to publish data from a national PrEP programme. Results were based on data from the National Sexual Health System (NaSH) a dataset of all specialist sexual health services provided in genitourinary medicine (GUM) clinics in Scotland.[127] Free-of-charge access to PrEP was introduced by the NHS in Scotland in July 2017. In the first year of the programme, 1,872 individuals were prescribed PrEP at least once, of which 1,855 (99%) were gay, bisexual and other men who have sex with men (MSM). This represents 16% of the total MSM (n=11,472) that attended sexual health services for any reason during the analysed time period. In terms of eligibility, 78% of participants were eligible due to a history of condomless anal sex with two or more partners, 18% had a documented bacterial rectal STI in the previous 12 months and 2% had a partner who was HIV-positive with a detectable viral load.

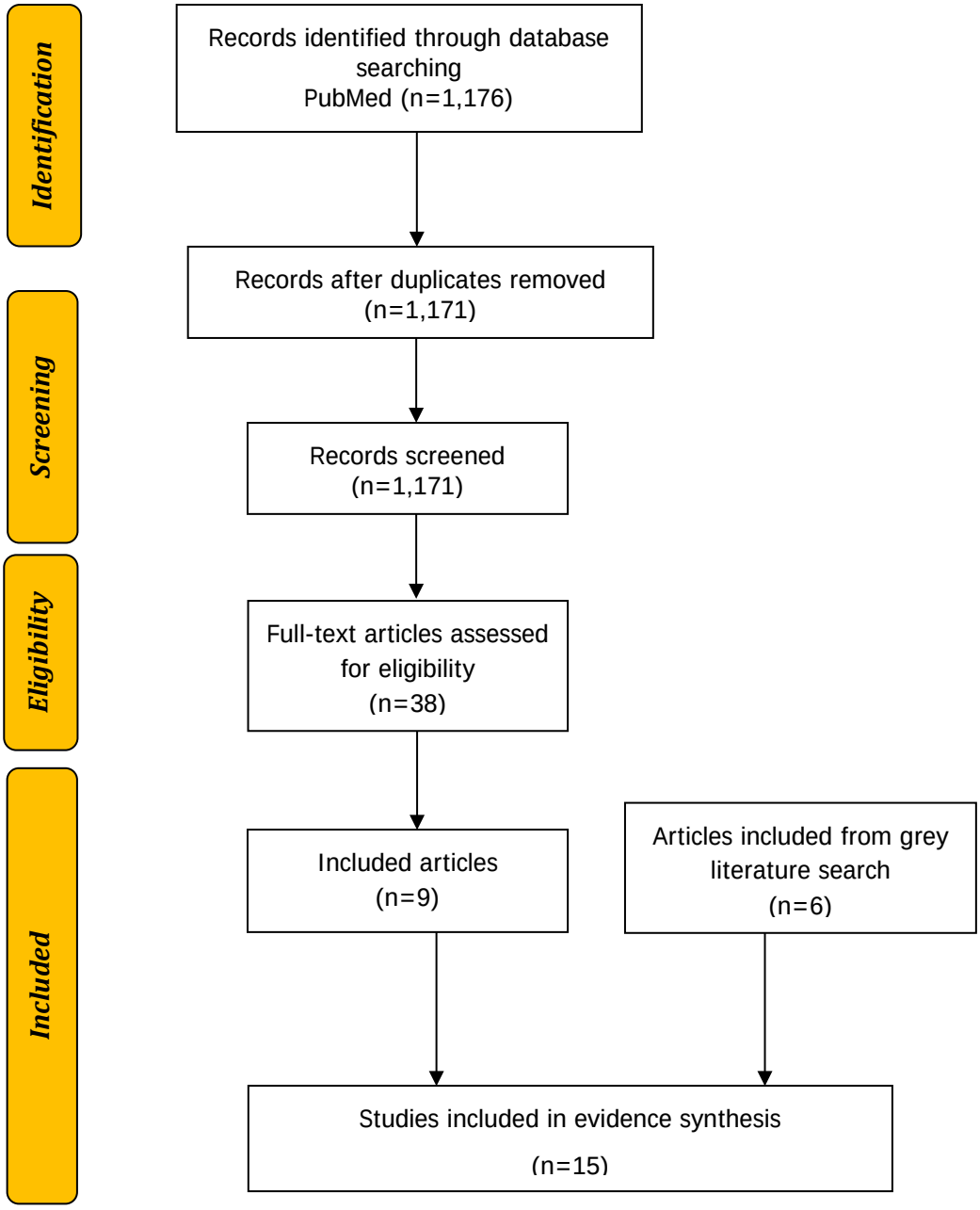
The majority of participants (74%) were prescribed a daily rather than event-based regimen. Over a quarter (28%; n=531) of those prescribed PrEP in the period analysed had not attended a GUM clinic in the two years before the PrEP programme became available. Furthermore, almost one fifth (19%; n=356) of those prescribed PrEP had no previous record on NaSH, indicating that these individuals had not attended any Scottish sexual health services since completion of the dataset's roll out in 2011.

7.3 PrEP programme performance

The results of pilot studies and regional and national PrEP programmes provide valuable information regarding acceptance and feasibility of these programmes. This information includes uptake or retention rates which may be useful to inform the implementation and organisation of a prospective national PrEP programme in Ireland.

To identify acceptability and feasibility studies for PrEP, a systematic search of the literature was conducted. The search was limited to studies published post 2010 (prior to PrEP licensure in the EU and the US). A total of 1,171 study titles were screened and 38 potentially relevant studies were identified. After screening, nine studies were found to be relevant for inclusion. These nine studies were combined with the results of a grey literature search, which identified six additional studies (Figure 7.2).

Figure 7.2. Flow chart for studies included in review of PrEP programme



The studies identified are presented in Table 7.2. Only four studies reported the dosing regimen used, with daily dosing the most common (range 57 to 100%). PrEP uptake varied from 55 to 90%. Analysis of retention rates, which ranged from 39% to 88%, was complicated by differences in the length of follow up between studies.

Table 7.2. Uptake, retention and dosing schedules in published PrEP pilot studies, and from regional and national programmes

Country		Participants	Uptake	Retention	Dosing regimen
Australia (PrELUDE)[164]		363	90% (n=327)	67% (n=243)	Daily (88.5%)
Australia (EPIC-NSW)[132]		3,700*	N/R	76% (n=2,804)	N/R
Belgium[165]		1,385	N/R	N/R	Daily (57%)
Brazil[166]		738	61% (n=450)	83% (n=375)	N/R
Canada[167]		86	60% (n=52)	88% (n=46)	N/R
France[168]		5,352	N/R	N/R	N/R
United Kingdom	**England**[169]	7,000+	N/R	N/R	N/R
	Scotland[127]	1,872	N/R	N/R	Daily (74%)
	Wales[170]	516	57% (n=296)	66% (n=203)	Daily (100%)
United States of America	**Atlanta**[171]	367	55% (n=201)	39% (n=78)	N/R
	Chicago[172]	197	N/R	67% (n=132)	N/R
	Detroit[173]	34	N/R	50% (n=17)	N/R
	Los Angeles[174]	1721	N/R	47% (n-809)	N/R
	Rhode Island Mississippi St. Louis[175]	267	N/R	60% (n=160)	N/R
	San Francisco[176]	344	78% (n=268)	62% (n=213)	N/R

*Enrolment ended 31 October 2016, but recruitment continued during 12-month follow-up. Total participants 7,621 by October 2017.

Differences in healthcare funding may limit the relevance of a number of these studies to the Irish healthcare setting. Access to PrEP in the US is influenced both by access to health insurance and coverage of PrEP by the insurer; these factors were noted to affect both PrEP uptake and retention rates.[177] A cost barrier was not an issue in other countries where PrEP is provided for free-of-charge or at a minimal cost (for example, Belgium where there is maximum charge of €11.90 for 30 tablets).[165] The identified programmes that are most similar to the proposed PrEP programme in Ireland are those implemented in Scotland and Australia (New South Wales), both of which provide universal access to free HIV screening and testing through STI clinics along with the provision of PrEP medications free of charge.

7.4 Current service delivery

In Ireland, there is currently no defined national PrEP programme through which HIV negative individuals can access PrEP services. As part of their existing service, a number of STI clinics provide free initial screening and subsequent monitoring to individuals who are attending for STI services or who present for the purpose of accessing PrEP medications.

STI clinics do not dispense PrEP, rather individuals are provided with a prescription which can be redeemed in a community pharmacy. As with any other licensed medication, a prescription for PrEP can also be obtained from other registered medical doctors, including general practitioners (GPs). In primary care, unless the patient is a Medical Card or GP Visit Card holder, the patient is responsible for the cost of the appointment. If subsequent screening and monitoring is undertaken in a GP's surgery, this would also be paid for by the patient.

No medication indicated for use as PrEP is listed as a reimbursable item through the HSE Primary Care Reimbursement Service (PCRS). Therefore, PrEP cannot currently be dispensed through any of the existing PCRS schemes. Patients attending for PrEP through primary or secondary care present prescriptions to community pharmacies and pay for the medication privately. As noted in Chapter 2, there are also reports that patients are sourcing PrEP through online sites.

In 2018, the HSE Sexual Health and Crisis Pregnancy Programme (SHCPP) published a report of the current STI and contraception services in Ireland.[178] The survey collated information about service provision by public and private STI clinics, non-governmental organisations, private contraception services and student health clinics. While not specific to PrEP, this survey provides useful background information on the location, capacity and constraints of the current STI services in Ireland.

Twenty three public STI clinics in 16 counties were identified (Figure 7.3). These clinics were based in hospital, community and primary-care settings. Details on the number of patients seen per week and the annual capacity are shown in Table 7.3. The survey responses suggest that a total of 80,000 patients are seen each year in public clinics through, on average, a total of 53 clinic sessions per week.

Table 7.3. Access and service availability of public STI services, by county

Clinic	Number of clinic sessions / week	Estimated number of patients seen per clinic session	Estimated annual capacity	Are clinics cancelled due to annual leave?
Carlow	0.5	18	465	Yes

Clare	1	14	728	No
Cork A	5	50	13,000	No
Cork B	2	20	2,080	No
Donegal	1	20	1,039	Yes
Dublin A	7	75	16,380	No
Dublin B	4	62	12,896	No
Dublin C	3	12	1,872	N/A
Dublin D	3	16	2,496	No
Galway A	1	8	415	Yes
Galway B	5	30	7,800	No
Kerry	0.5	20	520	No
Laois	1	25	1,300	No
Limerick	4	25	5,200	No
Louth A	2	18	1,872	No
Louth B	0.5	14	364	No
Mayo	1	12	624	No
Monaghan	1	16	832	No
Sligo	2	25	2,596	Yes
Tipperary A	0.5	17	440	Yes
Tipperary B	1	10	517	Yes
Waterford	6	19	5,916	Yes
Westmeath	1	12	624	No

Source: Extracted from: Sexual Health Services in Ireland: A Survey of STI and Contraception Services[178]
Key: N/A = Not applicable.

As noted, not all counties have a public STI clinic. Based on the survey results, the ten counties without public STI clinics are Cavan, Kildare, Kilkenny, Leitrim, Longford, Meath, Offaly, Roscommon, Wexford and Wicklow.

These public STI services, which receive direct public funding, are provided at no cost to patients. Public STI services are not funded from a single budget; some receive funding from primary care, some from public health and some from the acute hospitals division. There are no validated national STI clinic data that capture the number of patients attending public STI clinics.

A “Preparedness for PrEP” report is currently being undertaken by researchers at the Royal College of Surgeons in Ireland (RCSI).[179] The preliminary finding of the report is that all clinics identified issues with current staffing and or resources at STI clinics. These constraints impact service provision to varying degrees and potentially represent a major barrier to meeting the proposed national standards for a PrEP

programme.[180] Staff shortage was cited by all 18 clinics interviewed, with a particular focus on the shortage of specially qualified staff. There was feedback that positions had been advertised for a significant period of time with no applicants. Similar to that noted in the 2018 survey,[178] the inability of some clinics to find suitably qualified personnel led to temporary closure when a member of staff was on annual leave. The inability of recruit staff is a critical factor as it means that, even with an increase in funding, it may still be difficult to provide the necessary resources for a PrEP programme at certain clinics.

Many services are limited due to the lack of availability of clinic space and time. The operation of some clinics is determined by the availability of rooms in outpatient departments. The survey highlighted that there are instances where there are sufficient staff to see additional patients but clinics are unable to do so due to a lack of space for consultations.

Administrative constraints were identified as an issue for some clinics which operate without dedicated clerical cover. In those instances, the administrative work burden added to the workload of clinical staff. The introduction of a PrEP programme would increase administrative work, putting a strain on current resources and ultimately impacting on service provision.

Clinics with limited resources had concerns about the additional clinical care that PrEP patients would require. They identified that the additional support and time required for PrEP patients would likely put a substantial strain on current resources, noting that providing PrEP within a general STI clinic would have a detrimental impact on existing services.

It is clear from the feedback from the clinics that in the event of a decision to provide a national PrEP programme, additional staffing and resources will be required to ensure that it is safe and sustainable. Adequate numbers of appropriately trained staff is critical not only in the initiation but also in the monitoring and surveillance of PrEP as outlined in the national standards and monitoring framework.[181] Staffing issues were not confined to clinical members of STI clinics, and increased funding may be required for clerical staff, particularly with the increased workload required for PrEP patients.

There was a willingness of staff to provide PrEP, with all but three clinics responding to the RCSI survey that they would be 'very willing' to provide PrEP. Half of the clinics interviewed (9/18) also stated they would like more support from the HSE. This included topics such as training, policies and procedures, standardised databases, patient information leaflets, pro formas and patient survey templates.

The willingness of clinical staff to provide PrEP is substantiated by results of a cross-sectional survey on the attitudes and practice among healthcare providers in HIV and STI care in Ireland.[182] This work was undertaken to inform the work of the HSE Sexual Health and Crisis Pregnancy Programme (SHCPP). There was a high awareness of PrEP (100%); 83% agreed, or strongly agreed, with a statement that PrEP should be available in Ireland to individuals at high risk for HIV with 91% noting that they were likely or very likely to recommend PrEP to individuals at high risk of HIV acquisition. However, there was a strong agreement (>90%) that PrEP should only be provided as part of an overall HIV prevention programme. Concern was also expressed that access to PrEP could cause patients to engage in riskier behaviours (approximately 60% agreement), contribute to ART resistance (approximately 35% agreement) and result in less funding for general health services (approximately 35% agreement).

As noted earlier, elements of the proposed PrEP programme are offered on an ad hoc basis in current STI clinics. Specifically, clinicians may discuss PrEP and provide screening and monitoring consistent with the requirements of the proposed programme for eligible patients that present at STI clinics (for example, those treated with post-exposure prophylaxis following sexual exposure [PEPSE]).

Currently the majority of PrEP patients attending through public services are thought to access care through the Gay Men's Health Service (GMHS) in Dublin. It runs a dedicated PrEP monitoring clinic which operates every Thursday from 10am until noon.[183] The GMHS initially screens patients using a rapid HIV test (in addition to the gold standard fourth generation HIV test, which take up to five working days to report). Those meeting the eligibility criteria for PrEP and whose rapid test is negative are provided a prescription for three months of PrEP that they can redeem at a community pharmacy.

7.5 National PrEP programme specifications and funding

The HSE Sexual Health and Crisis Pregnancy Programme (SHCPP) has responsibility for implementing PrEP in Ireland. To inform its work, the SHCPP convened a multisectoral working group to develop recommendations in relation to the use of HIV PrEP in Ireland (the PrEP Working Group). This group, with community representation, developed clinical guidance documents and national standards in relation to the use of PrEP in Ireland. The standards represent best practice and outline the responsibilities of services, service managers, service providers and healthcare professionals, as well as establishing the expectations of service users. The standards are in line with the goals of the National Sexual Health Strategy regarding sexual health services, specifically 'Equitable, accessible and high quality sexual health services, which are targeted and tailored to need'. The PrEP Working

Group has also developed a PrEP monitoring framework document that fulfills PrEP Standard 2.3: Surveillance, monitoring and evaluation. Further details of the national standards set out by the SHCPP are provided in Chapter 2.

It is proposed that a national PrEP programme would be delivered at any site that has the expertise and capacity to deliver PrEP in line with the national standards. It is anticipated that, conditional on there being adequate resources, this would include delivery through established public STI services. Certain STI clinics, such as the Gay Men's Health Service, have already introduced targeted services for PrEP users. The roll-out of PrEP services to other STI clinics should take into consideration the geographical need for PrEP and the capacity of these clinics to provide all essential components of the monitoring programme.

From the budget impact analysis (Chapter 6, Section 6.5), an estimated 1,705 people (95% confidence interval [CI]: 617 to 3,452) may access PrEP in the first year of a national programme in Ireland. As indicated in Section 7.4, a proportion of these are already receiving care through STI services. In the first year of the PrEP monitoring clinic operating at the Gay Men's Health Service, there were 950 attendances; 431 were first visits and the remainder follow-up visits.

As highlighted in Section 7.2, 28% of individuals prescribed PrEP in the first year of the Scottish NHS PrEP programme had not previously attended any public Scottish STI clinic in at least two years, while 19% had not attended in more than 10 years, and perhaps never before. The potential increase in numbers attending STI clinics in Ireland would need to be considered in the context of the results of the 2018 survey of current STI and contraception services in Ireland undertaken by SHCPP.[178] This suggests that, on average, approximately 80,000 patients are seen each year in public STI clinics. These public STI clinics are located in 16 counties and are reported to provide, on average, 53 public STI clinics each week (see Table 7.3). These clinics are noted to be already overstretched with constraints in staffing levels and resources noted to be the primary barriers to the implementation of a national PrEP programme (as outlined in Section 7.4).

The results of Chapter 4 highlighted the strong correlation between adherence and efficacy. Any national PrEP programme must provide patients with levels of support and access to treatment that ensures an environment that promotes high adherence to PrEP. The implementation of a national programme would present a good opportunity to restructure how PrEP is currently provided.

A possible solution to staff shortages, particularly in rural areas, would be to develop and use an integrative system based on a 'hub-and-spoke' model which would create collaboration with regional teams. In this approach, the initial eligibility assessment,

screening and testing would be provided by a designated hub, that is, a larger STI service or possibly a dedicated PrEP clinic. Once initiated, subsequent quarterly monitoring and screening would be provided by the patient's local STI clinic. Such an approach could provide a patient-centred, efficient and sustainable means to improve access to PrEP. However, as with any integrated care model, clearly defined protocols would be required to facilitate seamless transitions and navigation for patients and providers and to ensure mutually understood and agreed-upon provider responsibilities. For example, prescriptions are legally valid for up to six months; however, given the requirement for quarterly screening and that patients have a documented negative HIV test before starting or continuing PrEP medications, consideration would need to be given to the logistical arrangements between the hub and any satellite screening clinic to minimise any disruption to care while also ensuring governance standards are maintained.

Access to PrEP medication

As noted in Section 7.4, no medication indicated for use as PrEP is currently listed as a reimbursable item through the PCRS. Therefore, PrEP cannot be dispensed through any of the existing PCRS schemes, rather patients are provided with private prescriptions for redemption at a community pharmacy and pay for PrEP out of pocket.

A core tenet of the proposed national PrEP programme is that there would be equitable access to PrEP services, with PrEP medication provided free of charge. This would ensure consistency with current public health policy to limit onward transmission of infectious diseases. The Infectious Disease Regulations 1981 provide for the prevention, diagnosis and treatment of notifiable infectious diseases and removal of conditions which favour the spread of infection. The schedule of diseases to which the Regulations apply was amended in 2011 to include HIV. Regulation 13(1)a states that the HSE 'shall, if required by the Minister…purchase and keep a supply of such agents…as may be approved by the Minister for…increasing resistance or for producing immunity from infection with any infectious disease'. PrEP may meet these criteria on the basis of evidence from Chapter 4 that confirms it is safe and effective at preventing the acquisition of HIV by individuals at high risk of its sexual acquisition.

Currently, treatment for a range of notifiable STIs, including HIV, is dispensed free-of-charge to patients irrespective of their means at the point of care in hospital-based HIV clinics and in selected STI clinics. Similarly, under the Infectious Disease Regulations 1981, all aspects of tuberculosis (TB) care, including medications, are provided free of charge. Depending on the region, TB medications are dispensed through satellite hospital pharmacies attached to specialist TB clinics on behalf of the

HSE or via community pharmacies with direct reimbursement of the pharmacy by the PCRS. This approach ensures timely access to medications. The National Immunisation Schedule also identifies vaccinations to prevent a range of infectious diseases which are provided free of charge to at-risk individuals in a range of primary and secondary care settings.

Three potential mechanisms through which PrEP medications could be dispensed were identified: community pharmacies, hospital pharmacies and at STI clinics. These mechanisms are discussed briefly below. In all cases, it is assumed that all other requirements for screening and monitoring outlined in the national standards in the context of a holistic PrEP programme (Chapter 2.4.2) would be provided by the existing clinical services. The base case analysis in the economic evaluation assumed that PrEP would be made available free-of-charge to patients (that is, no co-pay or cost sharing) through community pharmacies. The method used to estimate the direct cost to the HSE of PrEP dispensed through community pharmacies is outlined in Section 6.2.3.1. Costs were varied by 20% to reflect any potential difference in cost to the State if the medication was dispensed instead through public hospitals or STI clinics. This reflects the additional staffing or extra workload affecting the efficiency of existing staff.

Community pharmacy

Dispensing through community pharmacy could be considered the optimal approach to facilitate timely local access to medications. The PCRS operates a number of schemes which allow patients access to listed medications either free of charge (Long Term Illness Scheme [LTI]), for a defined co-pay (Medical Card holders) or through cost-sharing mechanisms (Drugs Payment Scheme or High Tech Scheme). As HIV is not listed as one of the sixteen specified diseases or disabilities covered by the LTI scheme, the scheme is not relevant to this discussion. As noted in Section 7.4, no medication indicated for use as PrEP is currently listed as a reimbursable item through the PCRS; therefore, in the first instance, approval would be required for their inclusion.

As noted above, the 1947 Health Act provides for the diagnosis and treatment of infectious diseases, the prevention of infectious diseases, the prevention of the spread of infectious diseases and for removing conditions which favour the spread of infection. Under the Infectious Disease Regulations 1981, all related care and treatment of the condition is provided free of charge. The provision of PrEP to prevent the acquisition and onward spread of HIV could also be considered within the terms of the Regulations, although clarification of this may need to be sought by the Department of Health.

If PrEP medications are dispensed through community pharmacies, a mechanism would be required for integration and coordination of care with the clinical services, to support the requirements for quarterly screening and monitoring outlined in the proposed national standards for a PrEP programme. There is precedence of the PCRS restricting access to certain medications through online pre-authorisation systems. Individual patient reimbursement requests must be submitted for selected medicines, with the medication reimbursed subject to certain conditions being satisfied. These systems have included one-off initial approval for a medication and time-restricted approval. Consideration could be given, therefore, to linking individual patient reimbursement requests with quarterly monitoring appointments at PrEP clinics. Following review at the clinic, an approved prescriber could issue a prescription and at the same time submit an online request for three months of medications to be dispensed to eligible patients.

Development and implementation of such a pre-authorisation system would incur one-off IT costs for the PCRS and would be conditional on the existing commitments of the PCRS ICT department in terms of scheduling any such work. Careful consideration of the design of the scheme would be required to minimise the administrative burden for prescribers and pharmacies and to ensure seamless care for patients. This would include consideration of the requirements and preparedness of the various stakeholders (including, for example, the acute services and approved prescribers within private or non-public health services) to engage with an electronic system. However, by capturing dispensing data (date and amount dispensed), use of such a scheme could provide a mechanism to audit national uptake and persistence on PrEP medications through an existing high-quality online transaction service. As noted, this mechanism has been used for other medications to manage access and reduce inappropriate prescribing.

Irrespective of the reimbursement scheme used and or the potential use of an online pre-authorisation scheme by the PCRS, patients are not restricted in terms of the location of the pharmacy in which they choose to redeem their prescription and may, therefore, select the pharmacy of their choice based on convenience, desire for anonymity or personal preference. It is noted though, that for any medication to be reimbursed through the PCRS, a community identifier must be provided. That is, the patient must provide an assigned scheme number (for example, their General Medical Scheme, GP Visit Card or Drugs Payment Scheme number) or, in the absence of an assigned scheme number, their Personal Public Service Number is required.

As noted in Chapter 2, there are a number of generic alternatives marked in Ireland in addition to the branded PrEP formulation. If a decision is made to list PrEP on the PCRS so that it can be dispensed by community pharmacies through a designated

PCRS scheme, there is potential for the HSE to achieve cost control and efficiencies through use of generic substitution and reference pricing. Products must first be designated as being interchangeable; if done at a national level, this assessment is the remit of the Health Products Regulatory Authority. Once designated as interchangeable, under the Health (Pricing and Supply of Medical Goods) Act 2013, the HSE can establish a reference price it will pay. The pharmacist can then offer a version of the medicine that is at or below the reference price. If the patient's preference is for a specific brand rather avail of the generic or alternative version, they can pay the difference between the reference price and their preferred brand.

Dispensing PrEP through community pharmacies would facilitate an efficient roll-out of the service for the HSE as, apart from the development of software for PCRS pre-authorisation, substantial changes to infrastructure are not required. Finally, empowering patients to select where they collect their prescriptions affords individuals a convenient and flexible service which may promote improved adherence and remove barriers for accessing medication.

Sexual health clinics

Another potential mechanism to provide PrEP would be for STI clinics to store and dispense medication for patients on-site, in compliance with legal requirements and guidance for the storage and supply of medicines. This option would provide immediate access to medications to eligible patients, ensuring seamless care.

Dispensing PrEP onsite at STI clinics would require significant infrastructural investment. The RCSI report highlighted issues STI clinics have in regard to both staffing and resources. Dispensing medication through STI clinics is dependent on clinics having the required storage space and facilities, including IT, to manage large quantities of medication. Many clinics do not have a dedicated space and use hospital outpatient rooms; therefore, this would not be an option at these locations. If a clinic does possess the clinic space for a storage facility, secure medication cupboards may need to be installed to ensure adherence with legal requirements for the storage of prescription medications.

The recruitment of suitably qualified staff to manage and dispense medication may prove difficult for such a specialised role with irregular, limited or anti-social hours. If specialised staff were not hired to manage an onsite dispensary, additional administration and record keeping requirements would put a strain on current services and may compromise other services delivered at STI clinics.

Hospital pharmacy

Some STI clinics are linked to hospital pharmacies, for example, St. James's Hospital is linked to an onsite pharmacy through which medications to treat STIs and HIV are dispensed free of charge for patients attending its services. Medications are typically dispensed on the day the patient is seen at the clinic, ensuring immediate access to treatment. These pharmacies have staff with the necessary professional expertise required to dispense PrEP. In addition, hospital pharmacies have the infrastructure and record keeping procedures in place to ensure adherence to information governance standards. This option will have an opportunity cost in terms of the time demand on dispensary staff and pharmacists. Although a potential option through which PrEP could be dispensed, access would be limited to those patients attending hospital-based STI services with attached pharmacies. Given that there are only a few such hospital clinics, all in major urban areas (Dublin, Cork, Galway and Limerick), a PrEP service restricted to this option would provide a very limited national coverage.

It was noted previously that given its electronic submission and reimbursement arrangements, the PCRS has a means to capture national-level data on medications dispensed through the schemes it operates. There is no such national equivalent for medications dispensed through hospital pharmacies; therefore, alternative means of collecting dispensing data would be required should this be considered necessary for audit purposes.

7.6 STI rates and risk compensation

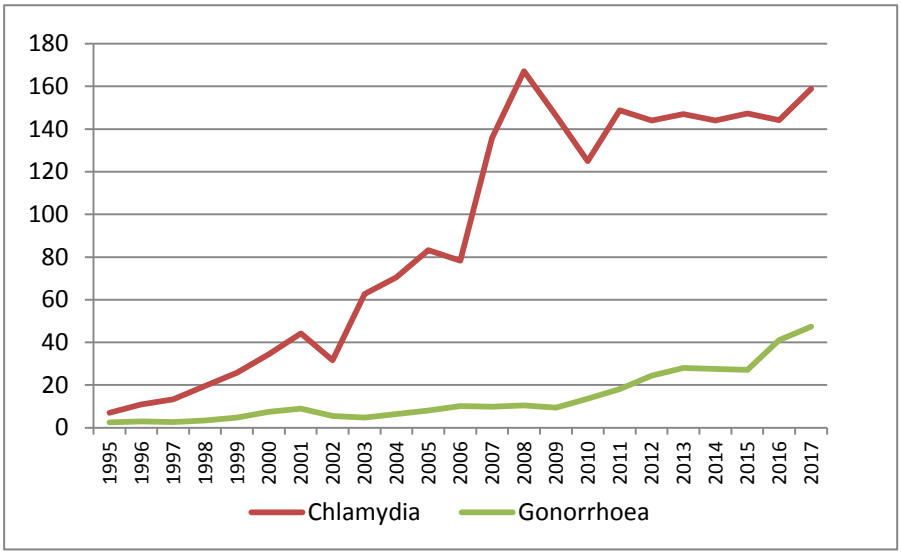
In some jurisdictions, a rise in STI diagnoses has been noted following the introduction of a PrEP programme. This increase in STI notifications may be due to an actual increase in infections or simply an increase in STI detection (testing individuals who were previously not engaged in services or more frequent testing of individuals already engaged). While 'risk compensation' (an increase in risky sexual behaviour due to the knowledge of the protective effect of PrEP) has not been observed in clinical trials, this phenomenon cannot be excluded.

The structure of the proposed PrEP programme is that everyone enrolled must be screened at three-monthly intervals. This includes testing for HIV and a range of other STIs, including chlamydia, gonorrhoea and syphilis. Best practice, per BASHH/BHIVA guidelines, is to test all individuals engaging in risky sexual behaviour every three months.[33] While this should represent current practice for high-risk individuals currently engaged with services, it is possible that not all of these would have attended four times a year; therefore, so there may be an increase in attendance and testing in those currently engaged with services. Additionally, based

on Scottish data, there is also evidence that some individuals not previously engaged with services will present for PrEP.[127] Overall, there will be a logistical burden associated with this additional testing.

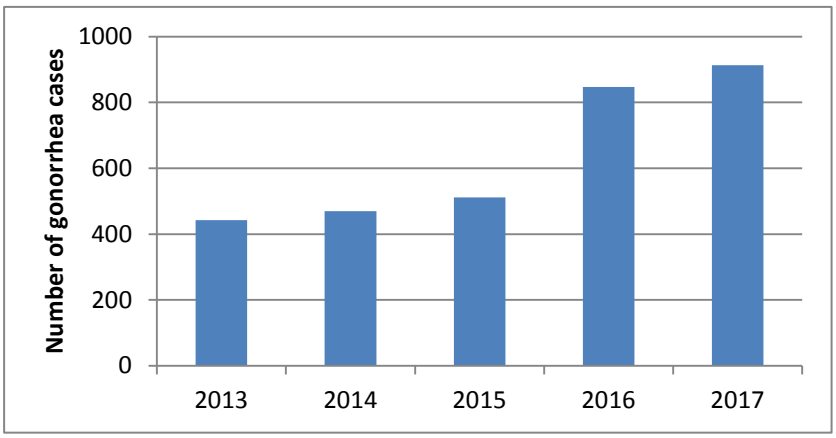
If risk compensation is suspected, this would have to be assessed in the context of underlying trends in STIs. There has been a significant rise in the notification rate of both gonorrhoea and chlamydia in Ireland (Figure 7.3).

Figure 7.3. Trends in gonorrhoea and chlamydia notifications (rate per 100,000)[156]



Data specific to the MSM population show a steady rise in gonorrhoea (Figure 7.4). This increase is in part attributable to increased testing and improved detection in the last ten years. The impact of PrEP on risk compensation would, therefore, have to be considered within the current context of an increasing background incidence of STIs.

Figure 7.4. Gonorrhoea notifications in MSM (HPSC)[156]



7.7 Information and awareness campaign to support PrEP rollout

The success of a national PrEP programme relies on appropriately targeting individuals at sufficiently elevated risk. This requires a campaign to ensure individuals are aware of their potential eligibility and are well enough informed to attend a clinic. It also requires education of clinical staff both within the STI services and in other settings to ensure referral of patients (for example, patients presenting to the emergency department for PEPSE) that may meet the eligibility criteria for PrEP.

The GMHS automatically offers PrEP to all prospective recipients (for example, those they treat with PEPSE). They also promote PrEP via posters and leaflets displayed in their clinic. Providing literature about PrEP at all STI clinics would help raise awareness nationally. The HSE have previously distributed leaflets for PrEP in Portuguese to remove the language barrier for Portuguese-speaking individuals in Ireland.

A possible route of engaging high-risk MSM who have yet to engage in STI services in Ireland may be through liaising with advocacy groups who would further increase public knowledge of PrEP. Almost one in five individuals who enrolled in Scotland's PrEP programme had not previously engaged in services. A partnership with advocacy groups could aid in the recruitment of these individuals with the dissemination of PrEP related material via less traditional means, such as through social media.

Information to support other stakeholders involved in the provision of PrEP such as community pharmacies or those involved in the care of patients taking PrEP (GPs and community pharmacies) will be required to ensure that they have access to reliable information in relation to the components of the programme to facilitate high-quality care of these patients.

7.8 Discussion

The HSE SHCPP's National Standards and Monitoring Framework provides the foundations and aims of a national PrEP programme. The standards focus on access, service configuration and structure, clinical assessment and management, managing results, information governance and public and patient engagement. The monitoring framework covers topics regarding outcomes and audit.

The preliminary findings from RCSI's survey 'Preparedness for PrEP' highlighted the key areas where current service provision is inadequate to support a PrEP programme and the resources required. The main barriers to the implementation of a

national PrEP programme were staff shortages and a lack of suitable training, clinic space and time. One of the biggest concerns among staff was the impact of increasing numbers of PrEP patients on current service provision. There was a widely held belief that once PrEP becomes subsidised the significant prohibitive barrier of cost to the patient would be removed and the numbers seeking PrEP would increase significantly. In addition to this, the increased awareness of PrEP could also drive an increase in patients seeking PrEP.

Other countries have noted a rise in STI diagnoses following the introduction of PrEP programmes. This increase in STI notifications may be due to an actual increase in infections or simply an increase in STI detection (for example, testing individuals who were previously not engaged in services or more frequent testing of individuals already engaged). While 'risk compensation' (an increase in risky sexual behaviour due to the knowledge of the protective effect of PrEP) has not been observed in clinical trials, this phenomenon cannot be excluded. If risk compensation occurs, an increase in the transmission of STIs is likely. This reinforces the need for a holistic programme that includes safer sex counselling. The resources required to screen and treat these additional STIs will need to be considered in the context of an average of approximately 80,000 STI clinic visits currently provided each year in public STI clinics.

There are a number of mechanisms through which PrEP medications could be provided to patients. To be consistent with the care and management of other infectious diseases and to prevent the acquisition and onward spread of HIV, it is proposed that PrEP medications provided through a PrEP programme would be provided free of charge. The mechanism of reimbursement of PrEP will depend on how patients will obtain the medication, either directly from clinicians at PrEP clinic appointments, from hospital pharmacies linked to PrEP clinics and or from community pharmacies. The feasibility of these alternatives will need to be explored within the context of the existing legislation. Ensuring that the system of dispensing PrEP is safe, sustainable and convenient for patients will promote an environment which supports good adherence. High adherence to PrEP was identified in Chapter 4 as having a direct correlation to the effectiveness of PrEP in averting cases of HIV and is, therefore, crucial to the success of a PrEP programme.

8 Ethical and social issues

Key points

- PrEP is efficacious at preventing HIV acquisition and has a favourable safety profile. Due to the fact that PrEP is a prevention strategy typically used by healthy individuals, careful consideration of the risk/benefit profile is necessary. With careful selection of participants who are at substantial risk, however, the benefits of PrEP are thought to far outweigh the potential harms.
- Of concern is the potential rise in sexually transmitted infections (STIs) (other than HIV) due to 'risk compensation' in PrEP users. This risk can be addressed within a holistic HIV prevention programme which incorporates frequent testing for other STIs and education of patients in relation to safer sex and adherence.
- For some individuals, the benefits of PrEP extend beyond physical health to relief from the burden of fear of HIV infection and greater autonomy in relation to one's sexual health.
- Many of the individuals who stand to benefit most from PrEP are from vulnerable groups who have unique healthcare needs and are subject to stigma and discrimination. Stigmatisation of PrEP users may serve as a barrier to uptake in certain individuals.
- Other barriers to PrEP uptake include a low perceived risk of contracting HIV, a lack of awareness of PrEP, reluctance to take medication and concerns about side effects and the opportunity cost and inconvenience of follow-up visits. A further barrier to the implementation of PrEP may be a lack of training of healthcare workers in relation to how to discuss sexual health with patients from sexual minority groups.
- Information about PrEP needs to be available and accessible to individuals who are most at risk of sexual acquisition. Informed consent must be obtained prior to PrEP initiation and the administration of PrEP in paediatric patients in Ireland must comply with *Children First: National Guidance for the Protection and Welfare of Children*.
- A recognition of the psychological dynamics of risk perception, sexual decision-making and treatment adherence in education programmes is necessary to enable healthcare professionals to encourage patients to take charge of their sexual health.

8.1 Introduction

Preceding chapters examined the epidemiology of HIV infection and established the clinical and cost-effectiveness of introducing a pre-exposure prophylaxis (PrEP) programme for populations at substantial risk of sexually acquired HIV in Ireland. The purpose of this chapter is to examine the ethical issues arising from the proposed implementation of a PrEP programme. The framework for the ethical analysis is based on the European Network of HTA (EUnetHTA) core model.[184] The following sections discuss PrEP in the context of:

- Benefit—harm balance
- autonomy and vulnerability
- justice and access
- professional values.

8.2 Benefit—harm balance

8.2.1 Burden of disease

HIV infection raises significant concerns from a public health perspective. The overall goal of providing a PrEP programme, as part of a combination HIV prevention approach which includes HIV testing and post-exposure prophylaxis (PEP), is to halt the transmission of HIV. The eligibility criteria for PrEP and the essential components of a PrEP programme are summarised in Chapter 2.

Infection with HIV results in significant morbidity (for example, reduction in health-related quality of life[143]) and increased mortality,[141] even in resource-rich settings. The notification rate and prevalence of HIV in Ireland are discussed in detail in Chapter 3. In summary, there were 492 diagnoses of HIV notified in Ireland in 2017, representing a rate of 10.3 per 100,000 population. Just over half (53%) were among gay, bisexual and other men who have sex with men (MSM). The prevalence of HIV in Ireland is not known, but was estimated in 2017 to be 7,205 people. The notification rate has remained fairly stable in recent years (10.1 to 10.5 per 100,000). It is, therefore, clear that the current range of HIV prevention strategies (promotion of barrier protection and safer sex, treatment-as-prevention [TaSP], post-exposure prophylaxis [PEP] and prevention of mother-to-child transmission) is not sufficient to halt the transmission of HIV in Ireland.

8.2.2 Benefits and harms for individuals

Due to the fact that PrEP is a prevention strategy that is typically prescribed for healthy individuals, the benefit—harm balance must be considered carefully to ensure only those truly at risk of HIV obtain PrEP. Since the intervention, although

safe, is not risk-free, individuals who are not genuinely at risk may potentially be harmed by the intervention.

In those at substantial risk, the evidence of efficacy is compelling. The systematic review and meta-analysis of efficacy and safety (Chapter 4) retrieved data from 15 randomised controlled trials (RCTs) involving a total of 25,051 participants from four distinct patient populations. PrEP was found to be highly effective in preventing HIV acquisition when used appropriately. A meta-analysis of six studies investigating the efficacy of PrEP in MSM demonstrated a 75% reduction in the risk of acquiring HIV, rising to 86% when trial-level adherence exceeded 80%. PrEP was also found to be effective in preventing HIV acquisition in HIV-uninfected partners of serodifferent couples, with a risk reduction of 75%. In the small number of trials examining the efficacy of PrEP in preventing heterosexual transmission of HIV, adherence was poor, although PrEP was shown to be effective in participants who did adhere to treatment. A single study involving people who inject drugs found a 49% reduction in HIV acquisition. There is a clear link between PrEP efficacy and treatment adherence. PrEP was found to be safe: there was no statistically significant difference in 'any' adverse event, serious adverse event or death comparing PrEP with placebo across trials.

Tenofovir/emtricitabine fixed dose oral combination is licensed across the EU for the prevention of sexually acquired HIV in adults and adolescents (see Chapter 2) and has a favourable safety profile. Similar to our systematic review of efficacy and safety (Chapter 4), another meta-analysis of 13 RCTs of combined tenofovir/embitricitabine published in 2018 found no evidence of an association between oral PrEP and an increased risk of serious adverse events.[185] The World Health Organization estimates that roughly 10% of people taking PrEP will have mild, short-term side effects, including headaches, dizziness and gastrointestinal problems, but these usually last only a few days and are almost always resolved within a month.[186] Some studies have shown a slight decrease in bone mineral density in the spine and hip in individuals taking PrEP in the first six months, but this is reversed after discontinuing PrEP. PrEP may be contraindicated in a very small number of people who have kidney problems. Serum creatinine levels will be elevated in approximately one in every 200 PrEP users; however, this will either be transient or will resolve after discontinuing PrEP.

8.2.3 Benefits and harms for others and for society in general

While early discussions of PrEP focused on clinical efficacy, safety and cost-effectiveness, increasing attention is now being devoted to 'normative' issues such as users' attitudes towards condom use, freedom from the fear of acquiring HIV and the need to strike a balance between preventing HIV infection and avoiding a rise in

other sexually-transmitted diseases.[187] More recently, concerns have been raised about a potential increase in risk compensation behaviours among people taking PrEP, particularly among MSM. Risk compensation behaviours may negate or undermine the efficacy of the PrEP programme.[188] Some fear that PrEP use will result in a reversal of the success of other HIV prevention strategies at a population level.[189] Since PrEP only prevents HIV infection, a decline in condom use may lead to an increase in other STIs or an increase in HIV transmission when PrEP is used incorrectly.

Underlying secular trends in STI diagnoses must also be taken into consideration when determining changes in STI rates associated with PrEP use, and a longer run of data pre- and post-implementation of a PrEP programme may be required to determine if there is a true effect. Additionally, it must be noted that an increase in STI diagnoses may simply reflect increased testing as opposed to an actual increase in infections.

The systematic review of efficacy (Chapter 4) concurs with other recent systematic reviews of PrEP trials and demonstration projects that found no conclusive evidence of an increase in risk compensation behaviours, that is, no significant change in condom use and no reported increase in sexual partners, among PrEP users compared with non-PrEP users.[190, 191] However, many of these early studies were randomised controlled trials and participants were unaware whether they were receiving PrEP or a placebo, resulting in continued perception of susceptibility to infection.[188] Additionally, data from clinical trials may not be entirely representative of behaviours among the wider population since recruited participants are generally motivated and health-conscious and often receive counselling or other supportive behavioural interventions during the course of participation.

One systematic review and meta-analysis of 17 observational studies published in 2018 found an increase in rectal chlamydia in PrEP users but no significant increase in gonorrhea or syphilis.[154] Additionally, chlamydia diagnoses did not increase at other anatomic sites (urethral/pharyngeal). It is notable that the primary study that reported the largest rise in chlamydia diagnoses in the meta-analysis did not compare pre- and post-PrEP periods but rather increases in the year following PrEP implementation.

An increase in risky behavior was reported in behavioural surveillance studies carried out between 2013 and 2017 in Melbourne and Sydney and involving 16,827 participants.[188] A large increase in PrEP use occurred during this period, accompanied by an increase in MSM reporting condomless sex with casual partners. Although increased use of PrEP coincided with large annual reductions in new HIV diagnoses in these jurisdictions, the long-term effect of an increase in PrEP use and a

decrease in condom use on the rate of new HIV diagnoses remains unknown. Although there has been a gradual decline in consistent condom use by gay and bisexual men in high-income countries in the last 15 years, commentators have found the rapid reduction in condom use reported in Sydney and Melbourne between 2016 and 2017 notable.

These data may indicate that the availability of PrEP may have an impact on community norms and behaviours, leading to 'community-level risk compensation'.[188] As PrEP use increases, non-PrEP users may perceive condomless sex as less risky because they assume that their partner is using PrEP. A further concern is that individuals may no longer feel that open discussion of their HIV status is necessary if their partner is taking PrEP.[192] The increased prevalence of STIs detected in more recent studies suggest increased trust in the HIV-protective effect of PrEP, potentially leading to situations in which PrEP will in time become 'normalised' for HIV prevention.[154]

While it is likely that the high degree of protection provided by PrEP when taken appropriately will outweigh the increased risk of acquiring HIV as a result of an increase in risk taking, further data is needed about the actual real-world behaviours of PrEP users.[193] Discussions of risk compensation need to take into account users' understandings of sexual risk taking and community-level changes in behaviour. It is possible that the introduction of PrEP in settings in which condom use is high might result in a decline in levels of condom use and increased rates of sexually transmitted infections, with an attendant additional burden on sexual health services.[188] However, it should be noted that an increase in STIs predated the introduction of PrEP[194] and risk compensation may be most pronounced among MSM who already engage in high-risk behaviours which place them at risk of HIV infection.[154]

Further research is needed to examine patterns of sexual behaviour change among PrEP users outside of trial settings; however, policy makers should be aware that risk compensation fears may reinforce opposition to PrEP, thereby preventing those who stand to benefit from PrEP from accessing it.[193] Such fears need to be balanced against the significant preventative effect of PrEP and the long-term impact of greater PrEP coverage.[154] Risk may be further contextualised by acknowledging that individuals who acquire HIV infection require lifelong antiretroviral treatment and may suffer significant HIV-related morbidity and mortality.[141, 143]

A final concern raised in relation to PrEP use is the possibility of medication resistance. A meta-analysis of five RCTs (Chapter 4) noted a significantly increased risk of resistance mutations developing to PrEP in patients randomised to receive PrEP who had acute HIV at enrolment. In most of these cases, the resistance was to emtricitabine. This highlights the importance of a robust screening process in

determining HIV status, the value of monitoring, and the need for counselling in relation to the association between resistance and poor adherence to PrEP. However, provided that PrEP is not administered to persons with an undiagnosed HIV infection, the potential of PrEP to prevent HIV infection 'far exceeds the risk of resistance that could occur with its use'.[195] Fear of resistance should not impede the implementation of PrEP as a strategy to prevent HIV infection. However, PrEP implementation strategies should be carefully designed and should incorporate education and counselling for individuals considered to be at substantial risk of sexually acquiring HIV, not only to inform them fully of the benefits and risks associated with PrEP (including the potential for risk compensation behaviours) but also to empower them to take charge of their sexual health.

8.3 Autonomy and vulnerability

Many of the individuals who stand to benefit most from PrEP in terms of reduced risk of HIV transmission are gay, bisexual and other men who have sex with men and transgender women. Both of these groups are vulnerable because both groups experience stigma and discrimination based, respectively, on sexual orientation and gender identity. While research involving transgender women is limited, some studies have drawn attention to stigma as a potential barrier to PrEP implementation among MSM. Stigma is a social process in which particular behaviours or attitudes are 'devalued, treated with contempt by others or used to create a social distinction'.[196] The 'societal and structural stigma'[192] which surrounds non-normative sexual practices can limit access to both healthcare and prevention strategies.[197]

HIV has been stigmatised for decades, in part because of its associations with sex work, homosexuality, promiscuity and drug misuse, and in part due to the features of the disease itself.[197] Within the gay community itself, shaming and stigma are built on associations between PrEP use and high-risk sexual activity. Stereotypes of PrEP users as promiscuous, insufficiently responsible to use condoms or as concealing a diagnosis of HIV have been reported as deterrents to PrEP uptake.[198, 199] The infamous phrase 'Truvada whores' was coined in a Huffington Post article from 2012 to refer to what its author referred to as "gay men who prefer to engage in unsafe sexual practices".[200] Early PrEP users in a recent Canadian study associated stigma with both condomless sex and with sex with a person living with HIV.[192] Fear of rejection and stigmatisation based on negative associations between PrEP use, perceived promiscuity and sexual risk taking may reduce the motivation of potential PrEP users to seek PrEP or to continue using it, thereby serving as a barrier to access for those who stand to benefit most from it.[193] Stigmatisation of marginalised at-risk groups at a societal level may also undermine the political will to make PrEP available to these populations.[185] It is important to ensure that sex-negative messaging does not 'cloud the judgement' of policy-makers, healthcare professionals or potential PrEP

users, resulting in limited access and reduced uptake.[193]

PrEP is not merely a pharmacological intervention, but should be viewed in biopsychosocial terms: social, psychological, cultural, and structural factors all contribute to the success or failure of the intervention.[197] Whether or not PrEP is seen as effective, socially acceptable or a viable tool for reducing risk of HIV infection depends on an understanding of the interaction between these factors. In pluralist societies, perceptions of risk and benefit are relative. Phenomena such as HIV infection or other STIs may be perceived as posing greater or lesser risk because one's 'perceptions of actions, events and phenomena are embedded in local ways of thinking, social conventions and practices'.[189] Individuals prioritise risk differently, and people will take more risks only in situations in which they have the opportunity to do so and perceive value in increased risk taking.[193] While some MSM adopt a 'moralising attitude' towards condom use and prevention practices, others regard fluid exchange and condomless sex as more intimate, fulfilling and pleasurable.[198] For many, the benefits of PrEP extend beyond physical health to relief from the burden of fear of HIV infection, greater autonomy in relation to one's sexual health and increased sexual pleasure.[192, 193]

A PrEP programme incorporates antiretroviral medication and other prevention methods, including education about safer sex practices, risk reduction counselling and regular screening for HIV and other STIs, with recommended follow-up visits every three months (see Chapter 2). Offering PrEP to persons identified as at substantial risk provides an opportunity for these individuals to access sexual healthcare, testing, treatment and counselling which they may not have accessed otherwise.[190] Because there is no evidence that PrEP itself or behaviour changes related to PrEP use result in a significant public health harm,[194] unwillingness to offer PrEP to people who engage in condomless sex may be viewed as running counter to the goals of public health. To penalise patients for making choices based on their values and specific life circumstances in the interests of benefitting the broader population undermines patient autonomy and conflicts with the professional obligation of clinicians to act in the best interest of their patients.[194]

8.4 Justice and access

In addition to stigma, other barriers to PrEP uptake among MSM include a low perceived risk of contracting HIV, a lack of awareness of PrEP, reluctance to take medication and concerns about side effects, the cost and inconvenience of follow-up visits and the need for HIV testing prior to receiving a new prescription.[198] The lack of training of healthcare professionals in relation to how to discuss sexual health with patients from sexual minority groups may be a further barrier to the implementation of PrEP. In a survey commissioned by the Kaiser Family Foundation in 2014, of the 7

in 10 MSM in the US who had a regular GP, 61% reported that they rarely or never discussed HIV with their doctor and 56% reported that their doctor had never recommended a HIV test.[201] Only one third of respondents were aware that HIV infections were on the rise.[201] Almost half of respondents admitted that they had never discussed their sexual orientation with a doctor. Similarly, participants in a recent Canadian survey reported feelings of discomfort related to discussing PrEP, gay sexuality or sexual risk with doctors.[192] Lack of communication between patient and doctor may, therefore, be a barrier to both HIV testing and effective prescribing of PrEP.

8.5 Professional values

Given the significant burden of HIV in Ireland, information about PrEP needs to be available and accessible to individuals who are most at risk of sexual acquisition, including those from other jurisdictions whose first language is not English. In 2017, a PrEP information leaflet has been published in Portuguese by the HSE.[202]

While there is international evidence that awareness of and access to PrEP are currently limited among members of socially marginalised groups and reluctance to promote PrEP to members of these groups may in part be value-driven,[194] there is no evidence for a reluctance to promote PrEP in marginalised groups in Ireland. In terms of HIV testing, inequalities were noted in Ireland in the MSM Internet Survey Ireland 2015 survey: untested men were more likely to be aged 18–24 years, live outside Dublin, have a lower level of education, be born in Ireland, identify as bisexual, be out to fewer people and not have had sex with a man in the previous 12 months.[203] If the levels of engagement with services for PrEP is similar to that of HIV testing, it may be the case that young, Irish-born MSM outside Dublin will be an under-served group.

Primary care providers have an important role to play in promoting access to and uptake of PrEP.[197] Clinicians need to be knowledgeable about PrEP as a tool for preventing sexually-transmitted HIV infection and be able to identify individuals who would be likely to benefit from it.

It is crucial that healthcare professionals obtain informed consent from prospective users prior to PrEP initiation. Informed consent is the authorisation of an intervention or the agreement to receive a service, following a process of communication about the proposed intervention or service. For consent to be valid, the service user must have decision-making capacity, must have received sufficient information about the nature, purpose, risks and benefits associated with the intervention/ service, must have understood the information provided and must have voluntarily agreed to receive the intervention or service.[204]

Since PrEP is licensed for adolescent use from the age of 13 upwards, special consideration should be given to the question of the treatment of minors, particularly in relation to issues of consent and assent. When a child is under 16, a parent or legal guardian is required to provide consent to treatment (excluding treatment for mental illness). However, the capacity of minors to participate in healthcare decision-making develops as they grow older and they should be involved in decision-making to the fullest extent possible.[205] In exceptional cases, a minor may wish to make a decision without the consent of a parent or guardian and in such situations healthcare providers may decide to provide the intervention without the knowledge of parents or guardians, depending on a number of factors, such as the level of maturity of the child, the stability of his or her values, his or her best interests and other considerations relating to his or her welfare.[206]

In Ireland, the principle that the welfare of the child is paramount informs the constitution and is reflected in a number of statutory instruments. Under the Children First Act (2015),[207] if any mandated health professional believes that a child is at risk of harm or has a concern about a child's welfare they must make a report to Tusla, the Child and Family Agency, in accordance with the National Guidance for the Protection and Welfare of Children (2017).[208]

The effectiveness of PrEP at both individual and public health levels is contingent upon adherence, and adherence may be compromised in situations where PrEP users feel the need to conceal their PrEP use.[197] Clinicians have a responsibility to educate potential candidates for PrEP about the importance of taking the medication appropriately. While healthcare professionals may perceive prescribing PrEP as enabling sexual disinhibition and increased risk taking, their obligations are 'to their patients' health, not to their own sexual morality'.[209] Although public health concerns about an increase in sexual risk taking and the rising prevalence of STIs are legitimate, these may be offset by the recognition that limiting access to PrEP could prevent a net reduction in HIV risk even in individuals who increase sexual risk taking.[193] An understanding of the stigma experienced by MSM and members of other sexual minority groups should inform a sensitive approach to communication relating to sexual practices and risky behaviours. Healthcare providers should provide patients with comprehensive information relating to the relative effectiveness of PrEP and condoms so that they can make conscious and informed decisions about their sexual health based on their own evaluation of harms and benefits.[194]

Education programmes which integrate epidemiological evidence with a recognition of the 'psychological dynamics of risk perception, sexual decision-making, and treatment adherence' are necessary to enable healthcare professionals to engage patients in taking charge of their sexual health.[210] Important factors to take into account in designing and implementing these programmes include cultural

perspectives, socioeconomic diversity among individuals at risk and experienced health disparities among members of sexual minority communities.[210]

8.6 Discussion

As with any new technology, there are many ethical issues to consider prior to the implementation of a PrEP programme.

Based on RCT and observational data, the benefits of PrEP to reduce sexual acquisition of HIV in populations at substantial risk are thought to far outweigh the potential harms when participants are correctly identified. However, as this is a prevention tool for uninfected and typically healthy individuals, the benefit/harm considerations are slightly different. Without careful screening of eligible participants, certain individuals will only suffer the harms of PrEP without gaining a benefit.

Of concern to clinicians and public health professionals is the potential rise in STIs (other than HIV) due to risk compensation (increases in risky behaviours such as condomless sex based on a decreased perception of the likelihood of acquiring HIV) in PrEP users. Risk compensation behaviours may have an impact on the efficacy of PrEP and may lead to a rise in other STIs due to the fact that PrEP offers no protection to STIs other than HIV. Although the trial evidence to date (Chapter 4) does not suggest PrEP induces risk compensation; however, observational studies have suggested otherwise. Also of concern is the development of resistance mutations in individuals who start PrEP with unrecognised HIV infection at baseline or in those who acquire HIV while not properly adherent to PrEP. The risks of increasing STI rates and drug resistant mutations can be mitigated by careful screening for HIV at baseline and follow-up, frequent testing for other STIs and advice on safer sex.

Many of the individuals who stand to benefit most from PrEP are from vulnerable groups who have unique healthcare needs and are subject to stigma and discrimination. Stigmatisation of PrEP users may serve as a barrier to uptake in certain individuals. Other barriers to PrEP uptake include a low perceived risk of contracting HIV, a lack of awareness of PrEP, reluctance to take medication and concerns about side effects and the opportunity cost and inconvenience of follow-up visits.

A further barrier to the implementation of PrEP may be a lack of training of healthcare workers in relation to how to discuss sexual health with patients from sexual minority groups. A recognition of the psychological dynamics of risk perception, sexual decision-making and treatment adherence in education programmes are necessary to enable healthcare professionals to engage patients in

taking charge of their sexual health. Important factors to take into account in designing and implementing these programmes include cultural perspectives, socioeconomic diversity among individuals at risk and experienced health disparities among members of sexual minority communities. Finally, information about PrEP needs to be available and accessible to individuals who are most at risk of sexual acquisition, including those from other jurisdictions whose first language is not English.

9 Summary and conclusions

9.1 Key findings

9.1.1 Description of technology

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy that uses antiretroviral medications to protect HIV-negative people from acquiring HIV. Once-daily oral tenofovir/emtricitabine, as a fixed dose combination tablet, has been licensed and available for use as PrEP in Ireland since 2016. Clinical guidance documents and national standards for PrEP use in Ireland were subsequently developed. These recommend that PrEP medications should be provided as part of a holistic programme that includes frequent monitoring for adherence and side effects, testing for HIV and other sexually transmitted infections (STIs), and counselling and advice on safer sex practices.

In this assessment, all populations who are at substantial risk of sexual acquisition of HIV and, therefore, eligible for PrEP are considered. In the cost-effectiveness analysis, the modelled cohort comprises only MSM due to the fact that this group is expected to make up more than 95% of programme participants and due to the lack of data on other groups. In the budget impact analysis, the size of the cohort is increased by 5% to account for non-MSM participants.

9.1.2 Epidemiology

HIV infection remains a significant public health threat in Ireland. HIV is a notifiable disease and all new diagnoses notified in Ireland are reported nationally by the Health Protection Surveillance Centre (HPSC). There were 492 diagnoses of HIV notified in 2017, representing a rate of 10.3 per 100,000 population. Following a large increase between 2014 and 2015, the HIV notification rate remained relatively stable between 2015 and 2017. A change in the case definition used by the HPSC (whereby confirmatory HIV testing required only one sample as opposed to two) and a rise in HIV testing may partly explain the increase in 2014 and 2015. Gay, bisexual and other men who have sex with men (MSM) are disproportionately affected: just over half of diagnoses in 2017 were in this group.

Migration plays an important role in the changing epidemiology of HIV in Ireland. Overall, 63% of the notifications to the HPSC in 2017 were for individuals born outside Ireland (compared with 26% born in Ireland and 11% with an unknown country of birth). In the MSM group, 61% of the notifications received in 2017 were for individuals born outside Ireland, with the highest number from Latin America. Additionally, there has been an increase in the proportion of notifications in people

who were previously diagnosed HIV positive abroad: in 2017, these comprised 39% of all notifications. A majority of these had transferred their care to Ireland (88%). The proportion of MSM previously diagnosed HIV positive before arrival in Ireland has increased from 16% of cases in 2012 to 42% in 2017. Of those previously diagnosed HIV positive abroad in 2017, 91% were transferring their care to Ireland.

Significant work was undertaken in 2018 to estimate the prevalence of HIV in Ireland, which included modelling undertaken by UNAIDS (in collaboration with the HPSC and HSE's Sexual Health and Crisis Pregnancy Programme) and a comprehensive national treatment audit. In summary, 7,205 (95% confidence interval [CI]: 6,456 to 8,056) people are estimated to be living with HIV in Ireland; 87.1% of whom are aware of their HIV status and 83.3% have initiated ART (UNAIDS 2018 data). Of these, 95.4% are virally suppressed (2018 treatment audit). UNAIDS has set a target of 90% for each of these three measures. While not achieving this target for the first two goals, Ireland compares favourably to the WHO Europe region as a whole.

9.1.3 Clinical effectiveness and safety

A systematic review undertaken to assess the clinical effectiveness and safety of oral PrEP retrieved 15 randomised controlled trials (RCTs) that compared PrEP with placebo, delayed PrEP or another PrEP medication or dosing schedule. Four distinct patient populations were assessed: six RCTs enrolled MSM, five enrolled heterosexual participants, three enrolled serodifferent couples and one enrolled people who inject drugs. Included studies involved 25,051 participants encompassing 38,289 person-years of follow-up data. Of the 15,062 participants that received active drug in the intervention arms of trials, 8,239 (55%) received combination tenofovir/emtricitabine fixed dose combination and 6,823 (45%) received single agent tenofovir.

PrEP was found to be highly effective in preventing HIV acquisition in MSM with a risk reduction of 75% across all trials (RR 0.25, 95% CI: 0.1 to 0.61). In trials with adherence above 80%, risk was reduced by 86% (RR 0.14, 95% CI: 0.06 to 0.35). Included in this analysis was one trial that investigated event-based dosing (also known as 'on demand' dosing; here, PrEP is taken during high-risk periods as opposed to daily use). Risk was reduced by 86% in this trial.

PrEP was also found to be effective in preventing HIV acquisition in HIV-uninfected partners of serodifferent couples, with a risk reduction of 75% (RR 0.25, 95% CI: 0.14 to 0.46). Evidence for effectiveness was not demonstrated in a meta-analysis of all trials that enrolled heterosexuals, likely due to poor adherence. Evidence of effect was found, however, in one trial where adherence was more than 80% (RR 0.39, 95% CI 0.18 to 0.83).

PrEP was found to be effective in preventing HIV transmission in people who inject drugs in the only trial retrieved that enrolled drug users, which was conducted in Bangkok. Risk was reduced by 49% (RR 0.51, 95% CI: 0.29 to 0.92). This trial may not be directly applicable to the Irish context due demographic differences and the high prevalence of HIV in people who inject drugs in Thailand. Additionally, it is difficult to separate the impact of PrEP on parenteral HIV transmission from sexual transmission in people who inject with drugs, and the authors of the study acknowledge that, although the study was designed to measure the impact on parenteral transmission, participants may have become infected sexually.

Overall, the RCTs were judged to have a low risk of bias. Adherence varied greatly across studies. Plasma drug monitoring was considered the most objective measurement for adherence assessment; adherence by this measurement ranged from 25% to 88%. Trial-level adherence greater than 80% was selected a priori as 'high' adherence for the purpose of analyses. A meta-regression found that efficacy was strongly associated with trial-level adherence ($p<0.001$). On average, an increase in adherence of 10% increased efficacy by 13%.

PrEP was found to be safe. PrEP did not increase the risk of 'any' adverse event (RR 1.01, 95% CI: 0.99 to 1.03), serious adverse events (RR 0.91, 95% CI 0.74 to 1.13) or death (RR 0.83, 95% CI: 0.6 to 1.15) compared with placebo. Minor adverse events were common in trials (78% of patients reporting 'any' adverse event), while serious adverse events and deaths were rare. A reduction in creatinine clearance was noted in some trials that returned to baseline upon discontinuation of study drug. No deaths occurred that were attributable to PrEP.

Eleven trials measured changes in sexual behaviour. Studies showed either no change in condom use throughout the duration of the study (n=4 studies) or increases in condom use (n=4 studies). There was no difference in condom use between intervention and control arms. Six studies showed no change in the number of sexual partners throughout the duration of the study, four studies showed a slight reduction in number of sexual partners and one showed an increase. There was no difference between intervention and control arms.

Five studies recorded changes in the incidence of STIs; no studies reported an increase in STIs or a between-group difference in STI diagnoses. Therefore, it cannot be concluded from RCT evidence to date that PrEP is associated with an increased risk of STIs. Of note, findings from placebo-controlled trials of PrEP do not permit conclusions to be drawn regarding the effect of PrEP on sexual behaviour. One open-label trial demonstrated no difference between the immediate and deferred arms in total number of sexual partners or the incidence of STIs, which were high in both groups prior to enrolment and during the trial.

In a meta-analysis of five trials, patients randomised to receive PrEP who had an unrecognised acute HIV infection at enrolment were at increased risk of developing resistance mutations to the study drug (RR 3.3, 95% CI: 1.17 to 8.27). Most conferred resistance to emtricitabine. This finding highlights the need for careful screening of PrEP participants at baseline, with a requirement for a negative 4th generation HIV test prior to PrEP initiation.

9.1.4 Cost-effectiveness and budget impact

A systematic review was conducted to gather the available evidence on previous cost-effectiveness studies. Seventeen studies were identified. Overall, the evidence demonstrated that when PrEP is targeted at MSM at substantial sexual risk of HIV acquisition, it has the potential to be cost-effective and potentially cost-saving, provided medication adherence is high. In general, estimates of cost-effectiveness were dependent on the efficacy of PrEP, incidence of HIV, the cost of PrEP and lifetime cost of HIV. Due to substantial sociodemographic and cost differences between countries, no study was directly applicable to the Irish setting. Additionally, many studies investigated the cost-effectiveness of PrEP medication alone and not as part of an overall holistic programme. Therefore, a de novo economic evaluation was necessary to estimate the cost-effectiveness and budget impact of introducing a PrEP programme in Ireland.

An original state transition Markov model was developed to compare the costs and consequences of providing a PrEP programme in Ireland compared with no PrEP being available. The model is a closed cross-sectional population model that tracks the entire population of Irish HIV-uninfected MSM at the outset of the simulation (2018) and follows these men for their lifetime.

Monte Carlo simulation was performed over the course of 10,000 replications to derive estimates of the costs and consequences of implementing a PrEP programme, with parameters sampled from their range of plausible values in each replication. In the base case, PrEP is cost saving, with an incremental cost-effectiveness ratio (ICER) of -€2,735 (95% CI: -€16,486 to €21,585) per quality-adjusted life year (QALYs) gained over the cohort's lifetime. A PrEP programme dominates not having a PrEP programme; that is, it is more effective and less costly. The negative value arises due to PrEP being cost saving relative to not having a PrEP programme.

Univariate deterministic sensitivity analysis was carried out to identify how sensitive these results are to changes in the input parameters. The results are robust to considerable variations in the main assumptions and plausible parameter values. PrEP effectiveness was the main driver of cost-effectiveness in the model. PrEP is cost saving when adherence-related effectiveness is 60% or more. At an

effectiveness of 44% (reported in the iPrEX RCT, the lowest effectiveness recorded among MSM), the ICER is €4,711/QALY (highly cost-effective).The ICERs were also sensitive to key cost parameters, including the cost of HIV care and the cost of PrEP. However, PrEP was still considered cost saving over a range of plausible costs.

Two-way sensitivity analysis was carried out on the proportion of MSM at high risk and the uptake rate for PrEP. PrEP becomes more cost saving as either parameter increases. PrEP also becomes more cost saving when event-based dosing is used. In the scenario where 50% of PrEP recipients follow event-based dosing, the ICER decreases to -€4,594 (95% CI: -€20,158 to €14,150).

The key strength of this analysis was its simplicity in design, transparency and ease of interpretation by decision-makers. Additionally, the movement of individuals between risk groups was tracked, and the time horizon (60 years) was adequate to capture all costs and benefits accrued over the cohort's lifetime. Extensive sensitivity and scenario analyses were used to test a range of model assumptions and parameter uncertainties; in no case did the uncertainty alter the interpretation of the findings. In general, consistent with the approach advocated in HTA guidelines, conservative values were adopted for parameters, that is, values that bias against PrEP. It is, therefore, likely that the ICER may be lower than estimated here.

However, a limitation of this design is that it does not incorporate dynamic transmission elements, which would allow the quantification of the benefit of PrEP on the wider HIV epidemic in Ireland, including the benefits for those not given PrEP (the reduction of onward transmission of HIV). Therefore, there is an underestimation of the total benefit. Nevertheless, as only 2% of Irish MSM were given PrEP in this model, the likely indirect impact of the PrEP programme would be limited.

An open Markov cohort model was developed to assess the incremental budget impact of introducing a national PrEP programme over a time horizon of five years. The mean number of people estimated to join the programme in year one is 1,705 people (95% CI: 617 to 3,452) based on model calibration to the observed number who enrolled in Scotland's national programme. The incremental budget impact of the PrEP programme is €1.5m in the first year (95% CI: €0.5m to €3m) and €5.4m over five years (95% CI: €1.8m to €11.5m).

Approximately 71% of the total programme costs relate to PrEP medication costs. On average, 173 HIV infections are estimated to be averted over the course of the first five years in the base case analysis. Deterministic sensitivity analysis revealed that the parameters that determined the number of participants in the programme (such as PrEP eligibility and uptake rate) had the greatest impact on the incremental

budget.

Extending the budget impact analysis beyond five years, the yearly incremental budget impact becomes cost saving by Year 8 and the aggregate budget impact becomes cost saving ('break even' point) by Year 14 (all programme and medication costs will have been recouped) relative to no PrEP.

9.1.5 Organisational and ethical issues

PrEP is available in at least 49 countries worldwide, with 12 countries providing PrEP through national programmes. In Ireland, there is no formal national PrEP programme. Access to components of the proposed programme (that is, screening, testing and counseling) is currently provided on an ad hoc basis through public STI clinics and primary care providers. PrEP medications are paid for out-of-pocket and sourced through community pharmacies or online.

There are a number of mechanisms through which PrEP medications could be provided to patients. To be consistent with the care and management of other infectious diseases and to prevent the acquisition and onward spread of HIV, it is proposed that PrEP medications provided through a PrEP programme would be provided free of charge. The mechanism of reimbursement of PrEP will depend on how patients will obtain the medication, either directly from clinicians at PrEP clinic appointments, from hospital pharmacies linked to PrEP clinics and or from community pharmacies. The feasibility of these alternatives will need to be explored within the context of the existing legislation. Ensuring that the system of dispensing PrEP is safe, sustainable and convenient for patients will promote an environment which supports good adherence.

There are 23 public STI clinics in 16 counties in Ireland. The primary barriers to introducing a PrEP programme are staffing and infrastructural issues. Staff shortages were cited by all 18 public STI clinics in a recent survey, with many services also limited due to the lack of availability of clinic space and time. A significant investment in STI services is required for a national PrEP programme to ensure a safe and sustainable service. Without investment in STI services, sub-optimal delivery of a PrEP programme could result in inequitable access to care and poor medication adherence and monitoring, leading to treatment-resistant HIV infections and disruption of core STI clinic services with increased wait time for non-PrEP attendees.

As with any new technology, there are many ethical issues to consider prior to the implementation of a PrEP programme. Of concern to clinicians and public health professionals is the potential rise in STIs (other than HIV) due to 'risk compensation' (an increase in condomless sex based on a decreased perception of the likelihood of acquiring HIV) in PrEP users. Also of concern is the development of resistance

mutations in individuals who start PrEP with unrecognised HIV infection at baseline or in those who acquire HIV while not properly adherent to PrEP. The risk and impact of increasing STI rates and drug resistance mutations can be mitigated by careful screening for HIV at baseline and follow-up and frequent testing for other STIs along with advice on safer sex.

Many of the individuals who stand to benefit most from PrEP are from vulnerable groups who have unique healthcare needs and are subject to stigma and discrimination. Stigmatisation of PrEP users may serve as a barrier to uptake in certain individuals. Additionally, stigmatisation of marginalised at-risk groups at a societal level may also undermine the political will to make PrEP available to these populations. Other barriers to PrEP uptake include a low perceived risk of contracting HIV, a lack of awareness of PrEP, reluctance to take medication and concerns about side effects and the opportunity cost and inconvenience of follow-up visits. A further barrier to the implementation of PrEP may be a lack of training of healthcare workers in relation to how to discuss sexual health with patients from sexual minority groups. Recognition of the psychological dynamics of risk perception, sexual decision-making, and treatment adherence in education programmes are necessary to enable healthcare professionals to engage patients in taking charge of their sexual health.

9.2 Summary

- High quality RCT evidence was retrieved that demonstrated PrEP is safe and highly effective at preventing HIV infection in MSM and in HIV-uninfected partners of serodifferent couples. PrEP effectiveness is highly dependent on adherence.

- Trial evidence does not suggest that PrEP alters sexual behaviour or leads to a rise in STI diagnoses. Findings from placebo-controlled trials of PrEP do not permit conclusions to be drawn regarding the effect of PrEP on sexual behaviour, however. One open-label trial demonstrated no difference between the immediate and deferred arms in total number of sexual partners or the incidence of STIs, which were high in both groups prior to enrolment and during the trial.

- An original economic model was developed to estimate the costs and consequences of providing a holistic national PrEP programme comprising daily oral PrEP administration. PrEP was found to be more effective and less costly than not providing PrEP. The results are robust to considerable variations in the main assumptions and plausible parameter values.

- The mean number of people estimated to join a potential PrEP programme in Year 1 is 1,705 people (95% CI: 617 to 3,452).
- The incremental budget impact of a national PrEP programme is €1.5m in the first year (95% CI: €0.5m to €3m) and €5.4m over five years (95% CI: €1.8m to €11.5m). Approximately 71% of the total programme costs relate to PrEP medication costs. In the base case analysis, 173 HIV infections are estimated to be averted over the course of the first five years.
- Extending the BIA beyond five years, the yearly incremental budget impact becomes cost saving by Year 8 and the aggregate budget impact becomes cost saving ('break even' point) by Year 14.
- The primary barriers to introducing a PrEP programme are staffing and infrastructural issues. Staff shortages were cited by all 18 public STI clinics in a recent survey with many services also limited due to the lack of availability of clinic space and time.
- A significant investment in STI services is required for a national PrEP programme to ensure a safe, sustainable and equitable service.

9.3 Conclusion

The successful implementation of a national PrEP programme would be safe, effective and cost-saving over the medium to long term in Ireland.

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