'Preparing for PrEP?'
A Review of the Current Evidence for Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection in Wales

Lead Authors: Adam Jones, Public Health Practitioner - Policy
Zoë Couzens, Principal in Public Health, Health Protection

Contributors: Welsh Independent HIV Expert Group

Date: 14th March 2017 | **Version:** 2

Publication/ Distribution:

- Public (Internet)
- NHS Wales (Intranet)
- Public Health Wales (Intranet)

Review Date: To be subject to regular updates, twelve months from publication of the review, or on emergence of significant new evidence.

Purpose and Summary of Document:
This document provides an overview of the current evidence related to the provision of Pre-Exposure Prophylaxis (PrEP) for HIV prevention, featuring an extensive review of the available evidence for specific aspects of the subject, analysis of clinical trials, the policy, regulatory and legislative context, and global perspectives.

This version of the document includes an additional Appendix, capturing developments related to PrEP globally since the submission of Version 1 of the document on 30th November 2016.

Work Plan reference:

- Strategic Priorities 5 & 6

Contents

List of Abbreviations **4**

Acknowledgements **4**

1 Introduction **5**

2 Background **5**

2.1 Summary Considerations 7

2.2 Summary Recommendations 7

3 Evidence Review **8**

3.1 Search Strategy 8

4 Key Focus Points **8**

4.1 The identification of individuals who are most at risk of HIV and would, if compliant, benefit from PrEP 8

4.2 The implications of PrEP introduction to sexual health services in Wales11

4.3 Cost-effectiveness of the introduction of PrEP to the identified most at risk group 13

4.4 Recommendations on the most prudent approach to the potential introduction of PrEP in Wales 18

5 Professional Organisations **20**

5.1 UK Organisations 20

5.2 European Organisations 20

5.3 International Organisations 20

5.4 Advocacy Groups 21

6 Lessons from Clinical Trials **22**

6.1 iPrEX Study 22

6.2 Partners PrEP Study 23

6.3 PROUD Study 23

6.4 IPERGAY Study 25

6.5 Other Clinical Trials 26

7 Other Emerging and Potential Issues **27**

7.1 Risk of Increased STI Rates 27

7.2 Online Purchasing and Access 27

7.3 Drug Interactions 27

7.4 PrEP Resistance 28

7.5 Safety of PrEP 28

8 Legislative and Regulatory Context **30**

8.1 Marketing Authorisation for Truvada® as PrEP 30

9 Horizon Scan of Future Developments **30**

10 Summary of UK Progress towards Provision of PrEP **31**

10.1 England 31

10.2 Scotland 32

11 PrEP Globally **32**

11.1 France 32
11.2 Netherlands 33
11.3 Norway 33
11.4 US 33

12 Conclusions and Recommendations 34

13 Frequently Asked Questions (FAQs) 36

14 Appendices 37
14.1 Appendix 1 – Membership of HIV Expert Group 37
14.2 Appendix 2 – Proposed Eligibility Criteria 38
14.3 Appendix 3 – 'An estimate of the incidence of HIV in men who have sex with men at high risk of HIV acquisition attending Integrated Sexual Health clinics in Wales, 2014' 39
14.4 Appendix 4 - UK rates for tenofovir and emtricitabine resistance in both naive and drug-experienced patients. 43
14.5 Appendix 5 – Examples of Proof of Residency 44
14.6 Appendix 6 – PrEP Developments Update, March 2017 45

15 References 49

List of Abbreviations

ARVs	Anti-Retroviral Medications
AWMSG	All Wales Medicines Strategy Group
AWTTC	All Wales Therapeutics & Toxicology Centre
BASHH	British Association for Sexual Health and HIV
BHIVA	British HIV Association
BNF	British National Formulary
CAI	Condomless Anal Intercourse
CDC	Centers for Disease Control and Prevention
CDSC	Communicable Disease Surveillance Centre
CHMP	Committee for Medicinal Products for Human Use
CROI	Conference on Retroviruses and Opportunistic Infections
CT	C. trachomatis
EACS	European AIDS Clinical Society
EATG	European AIDS Treatment Group
ECDC	European Centre for Disease Control
EMA	European Medicines Agency
FTC	Emtricitabine
GMC	General Medical Council
GPC	General Practitioners Committee
HIVEG	HIV Expert Group
MHRA	Medicines and Healthcare products Regulatory Agency
MSM	Men who have sex with men
NAT	National AIDS Trust
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
PEP	Post-Exposure Prophylaxis
PEPSE	Post Exposure Prophylaxis for sexual exposure
PHE	Public Health England
PHW	Public Health Wales
PiEI	PrEP in Europe Initiative
PrEP	Pre-Exposure Prophylaxis
RTU	Recommendation of Temporary Use
SWS	Sexual Health in Wales Surveillance Scheme
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organisation

Acknowledgements

The authors would like to thank the members of the HIV Expert Group (see Appendix 1 for group members) for their contributions and guidance which has helped to shape this report, Laia Fina, Epidemiologist, Public Health Wales, for the epidemiological analysis within this report (and as a whole in Appendix 3) and Isabel Puscas, Senior Evidence and Knowledge Analyst, Public Health Wales for her assistance during the evidence review.

1 Introduction

Pre-Exposure Prophylaxis (PrEP) presents a new option for the prevention of new HIV infections in Wales, though this is not without challenges; clinical, ethical and financial. In this report, we provide an impartial overview of the current available evidence and draw conclusions and recommendations aimed at supporting future commissioning decisions in Wales.

We will continue to update the evidence base underpinning this work on the emergence of vital new evidence. The document submitted to Welsh Government included data and literature that was available up to the end of October 2016. This published version has an additional appendix (Appendix 6) which captures further global developments regarding PrEP from November 2016 until publication date. Importantly, these developments have no bearing on our original recommendations, and are provided for further information only.

2 Background

There has been a steady increase in the number of people living with HIV in Wales, reflecting both an increase in survival and new diagnoses. On average, over the last six reporting years (2010-2015) [1], there have been approximately 153 new cases diagnosed annually.

The vast majority of infections diagnosed in Wales are sexually transmitted with 47.5% of new diagnoses since 2011 being attributed to men who have sex with men (MSM) whilst 31.6% of infections are recorded as acquired through heterosexual contact. Whilst these infections have been diagnosed in Wales it may, in many cases, not be the probable country of infection.

Probable exposure category and gender	2011	2012	2013	2014	2015
Sex between men	**74**	**52**	**76**	**69**	**91**
Heterosexual contact	**58**	**45**	**39**	**64**	**35**
Injecting drug use	**<5**	**<5**	**0**	**8**	**7**
Mother to child	**0**	**<5**	**<5**	**<5**	**0**
Blood/blood products	**0**	**0**	**0**	**0**	**0**
Other	**0**	**0**	**0**	**0**	**0**
TOTAL New HIV Diagnoses	**156**	**120**	**132**	**186**	**168**

- Sex between men includes men who also reported injecting drug use.
- Mother to child includes individuals born outside but diagnosed in the United Kingdom.
- All HIV positives acquired through receipt of blood/blood products diagnosed since 2002 were acquired outside of the UK.

- Totals may include individuals with probable exposure category not reported or could not be determined after follow up.

Source:PHE

Full Annual HIV and STI Trend Reports are available online [2]. The latest full reporting year was 2014, and the Public Health Wales Communicable Disease Surveillance Centre (CDSC) also publishes quarterly reports, the latest covering data to the end of December 2014.

Using the Sexual Health in Wales Surveillance Scheme (SWS) data, the estimated number of HIV negative MSM attending specialist sexual health clinics in Wales in the last calendar year was 4200. The proportion of MSM attending sexual health clinics that are diagnosed with HIV infection is 9.7%.

In recent years, the introduction of PrEP has emerged as a potential new strategy for HIV prevention, with clinical trials undertaken to ascertain effectiveness amongst high-risk populations. As these trials are still underway or awaiting final conclusions, the evidence base for the introduction of PrEP for HIV prevention has been uncertain. Certain findings from trials and from areas where PrEP has been introduced, along with anecdotal evidence, also raise concerns about the suitability and viability of PrEP for HIV prevention and, more generally, for population health.

In light of an increasing awareness of, and demand for, PrEP, Public Health Wales has been asked by Welsh Government to convene an independent HIV Expert Group (HIVEG).

In relation to PrEP, the HIVEG is expected to:

- Identify and quantify those individuals who are most at risk of HIV and would, if compliant, benefit from PrEP.
- Consider the implications of PrEP introduction to sexual health services in Wales, this to include: education of client group; monitoring of effectiveness and testing for and treating sexually transmitted infections.
- Undertake a cost benefit analysis on the introduction of PrEP to the identified most at risk group.
- Make recommendations on the most prudent approach to the potential introduction of PrEP in Wales with timescales and costs included.

This paper provides analysis of each of these aspects.

The HIVEG is comprised of practitioners representing public health protection, public health promotion, public health policy, epidemiology, pharmacy, sexual health and HIV clinical services and academia (Appendix 1).

The All Wales Medicines Strategy Group (AWMSG) is also in the process of conducting an appraisal of Truvada® for use as PrEP in Wales; this appraisal will measure the clinical effectiveness of Truvada® against the

costs. As such, our report **does not** look into the clinical effectiveness of Truvada®, and should therefore be considered alongside the report of the AWMSG.

2.1 Summary Considerations

- PrEP is being accessed online, etc by individuals in Wales already so as a minimum, consideration needs to be given to providing guidance and monitoring to ensure safe use.
- Specialist sexual health services are under significant pressure already. However, providing advice and monitoring related to PrEP will ensure that individuals whose sexual behaviour is particularly high risk are being seen as a priority.
- The most important issue to address is education – the reality of PrEP and what it can and can't do, and therefore, how it should be used in the context of wider HIV prevention.
- Staff education regarding PrEP is as important as public messaging. Staff across all sectors, including primary care, need to be aware of PrEP and the information provided needs to be consistent.
- Processes around information sharing between services regarding patient's use of PrEP will need to be agreed.
- If PrEP medication is provided through the NHS via the sexual health clinics, consideration needs to be given to the issue of cross border activity, particularly if England are not providing – eligibility criteria could cover this by using resident in Wales as a criterion.

2.2 Summary Recommendations

- Pending the outcome of the decision from the All Wales Medicines Strategy Group (AWMSG) regarding NHS provision of PrEP medication, the HIV Expert Group recommends that the specialist sexual health services provide advice and clinical monitoring to individuals who have accessed PrEP medication outside of the NHS or are considering doing so.
- Additional funding will be required for specific support and monitoring of PrEP in specialist sexual health services.
- Formal structures should be in place centrally to monitor and evaluate the use of PrEP in Wales, to include: the outcomes regarding infection (HIV and other STIs); usage of PrEP (length of use, on demand or continual); behavioural changes (perceived risk of activity and condom use).
- Information regarding PrEP should be produced centrally, in collaboration with key stakeholders, as part of a revised HIV prevention programme.
- PrEP should not be considered in isolation but be seen as part of a comprehensive package of HIV prevention. Support needs to be

given to allow for earlier diagnosis and linkage to other interventions that may reduce the incidence of STIs.
- Information regarding PrEP is constantly evolving, therefore central oversight needs to continue with updates being provided to services on a regular basis and public messaging revised accordingly.

3 Evidence Review

3.1 Search Strategy

An update to the search strategies used for the NHS England Evidence Review: Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults [3] was undertaken to capture available evidence up to the end of October 2016.

As Public Health Wales does not have access to the full range of databases used by NHS England for their Review, only Embase, Medline and PubMed were searched for this update.

Two main search questions were run – firstly, to identify studies that focus on the clinical efficacy, effectiveness and safety of pre-exposure prophylaxis to reduce incidence of HIV among populations at substantial risk (according to the World Health Organization (WHO) definition, this includes: Men who have sex with men; people who inject drugs; Sero-discordant couples; transgender women), and secondly to ascertain whether provision of PrEP to populations at substantial risk is cost effective. Both searches were global in scope and utilised keywords identified in the NHS England strategy.

Other epidemiological studies that could not be generalised to the Welsh context were excluded.

4 Key Focus Points

4.1 The identification of individuals who are most at risk of HIV and would, if compliant, benefit from PrEP

Making PrEP available to high-risk populations is recognised as best practice, and a range of definitions of 'high-risk' behaviour is evident in those areas that have already introduced PrEP as an HIV prevention tool.

In their latest guidelines [4], the **World Health Organization (WHO)** recommends that PrEP containing tenofovir disoproxil fumarate (TDF) should be offered as part of HIV prevention programmes to people at 'substantial risk of HIV infection'.

This is an update to WHO recommendations published in 2014 which recommended the use of PrEP in entire key populations, which included men who have sex with men (MSM), injecting drug users, sex workers, transgender people and prisoners. WHO explains that the revised recommendation 'enables the offer of PrEP to be considered for people at substantial risk of acquiring HIV rather than limiting the recommendation to specific populations.' They continue to highlight that the offer of PrEP could be based on local epidemiology and individual assessment.

WHO defines 'substantial risk' as 'HIV incidence around 3 per 100 person-years or higher in the absence of PrEP'. For illustration purposes, WHO highlight the fact that this incidence has been identified among some groups of MSM, transgender women and heterosexual men and women whose partners have undiagnosed or untreated HIV infection.

Perspectives

In Scotland, the **Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group** have reviewed evidence applicable to the Scottish context [5]. Within their report, the group consider that the population at highest risk of contracting HIV were MSM, with the definition of highest risk MSM being those who had had a rectal STI in the previous year and/or had participated in condomless anal intercourse (CAI) with two or more partners in the same timeframe. However, the group also believe that 'PrEP should be considered for all individuals whose circumstances places them at the highest risk of HIV acquisition in Scotland...'. This would make PrEP provision equitable to other populations, estimated at 5% or less of populations other than MSM.

The joint **British HIV Association (BHIVA) & British Association for Sexual Health and HIV (BASHH)** position statement on PrEP [6] recommends that PrEP should be made available to MSM and transgender men and women who engage in CAI, HIV-negative partners in relationships with HIV-positive partners with unsuppressed viral loads and other heterosexuals considered to be high risk.

As part of **NHS England**'s considerations, a Clinical Commissioning Policy Proposition was produced [7]. Within this document, a proposed criteria was produced [7], stating that PrEP would be made available to MSM and transgender women or men who are HIV negative and have either tested negative for HIV during the last year, report CAI in the previous 3 months and state the likeliness of repeated CAI in the next three months. The criteria is also inclusive of HIV negative partners of HIV positive persons not known to be virally suppressed, with whom CAI is considered likely, and HIV negative heterosexuals clinically assessed and known to have had condomless sex with a person with HIV within the past 3 months and are deemed likely to do so again.

Exclusion criteria are also defined within NHS England's work [7]. This includes individuals in monogamous relationships with HIV positive partners with an undetectable viral load, individuals without a current confirmed HIV negative test, and individuals under 16 years of age. In addition, criteria for starting and stopping have been developed.

The **European Centre for Disease Prevention and Control (ECDC)**'s expert meeting report [8] reflects on the discussions regarding eligibility criteria, acknowledging that any eligibility criteria within Europe may need to be adapted to reflect the epidemiological context of a given country.

The **European AIDS Clinical Society (EACS)** published their latest guidelines (Version 8.1) in October 2016 [9]. The clinical guidelines include a chapter on PrEP [10], and their recommendations are in line with the WHO guidelines, and those outlined by NHS England and HIV Scotland.

In the Welsh Context

Regarding data on the proportion of HIV negative MSM who have had CAI with two or more partners, a survey undertaken by colleagues in Scotland [11], which included respondents in Wales, gave a figure of 22.3% (range 19.8%-25.1%) reporting CAI with two or more partners. In the survey, 58.5% (226/386) of participants reported that they would be willing to take a daily pill to prevent HIV infection. If this was translated into a 'real world' situation in Wales, this suggests that approximately 560 people (range 480-620) would present should PrEP be provided in Wales.

This would need to be reviewed 12 months after implementation to provide indicative numbers for future years.

The figure seems reasonable given that Post Exposure Prophylaxis for sexual exposure (PEPSE) was given 333 times in Integrated Sexual Health (ISH) clinics in Wales, between January 2015 and June 2016, 73% of these instances were in MSM.

Recommendations

There is clearly an emerging consensus on who should be eligible for PrEP provision, and how they should receive this. Accordingly, the HIVEG's recommended eligibility criteria for access to PrEP, informed by HIV epidemiology in Wales identifying those at highest risk of acquiring HIV, and in accordance with examples from clinical trials, guidance and implementation elsewhere, are available in full in Appendix 2.

As a minimum, and in accordance with the most recent BASHH/BHIVA statement, the HIVEG strongly recommends that PrEP be made available within a comprehensive HIV prevention package to:

- MSM and transgender women who are engaging in condomless anal sex
- Heterosexual and same-sex, HIV-negative partners who are in relationships with a HIV-positive partners whose viral replication is not suppressed
- Other heterosexuals considered to be at high risk.

In addition, individuals must have tested HIV negative via a fourth generation test, are able to, and agree to, attend regular 3 monthly review for monitoring and sexual health screening including HIV testing, and are resident in Wales (and are able to provide proof of residence – see Appendix 5 for suggested acceptable proof of residency).

We also recommend that, as the definition of individuals at highest risk of HIV acquisition is subject to continual change, provision to those outside of the proposed criteria should be determined by an appropriately qualified physician.

4.2 The implications of PrEP introduction to sexual health services in Wales

Overview

Introducing a new treatment at any stage will have an impact on service delivery, and the potential introduction of PrEP provision to a sexual health service is no different.

In their position statement on PrEP [6], **BHIVA & BASHH** explain that patients taking Truvada® as PrEP should be tested every quarter with a 4th generation test, as they must know that they are HIV negative.

The report of a meeting of the **European Centre for Disease Prevention and Control (ECDC)** looks into models of service delivery for PrEP [12]. It was acknowledged that integrating PrEP provision should be 'relatively straightforward' for countries with services offering HIV/STI treatment and diagnosis and Post-Exposure Prophylaxis (PEP). The ECDC does not make Europe-wide recommendations on how best to provide PrEP, due to the differences in country contexts and health systems, though it will consider developing guidance on minimum standards and general principles.

The report goes on to consider the monitoring of people on PrEP. Issues emerging from the presentations and discussion on this subject included concerns over adherence if PrEP is not provided through health services, fears over increased STI incidences, and the need to adapt surveillance systems to monitor the use of PrEP.

Evidence presented at the **Conference on Retroviruses and Opportunistic Infections (CROI) 2016** [13–15] emphasises the importance of quarterly STI screening in the US areas where PrEP is currently provided. Of these, one paper [14] reflects on the current Centers for Disease Control and Prevention (CDC) guidelines for the provision of PrEP which recommends screening for STIs every six months. The authors of this paper found that if these guidelines had been followed, rather than screening their patients after three months of taking PrEP, then they would have delayed diagnosis and treatment for 24% of their PrEP patients, including 40 cases of rectal STI and three cases of syphilis.

Lessons from the roll-out of PrEP in France can be found in section 11.1.

Welsh Context

The All-Wales average cost for a follow up attendance at a sexual health clinic for 15/16 was £101.10. This figure is a fully absorbed cost relating to outpatient sexual health clinics, including all overheads, including test costs. As per the recommended quarterly testing requirement for people on PrEP, (including the approximate £2.75 cost for liver function tests and £2.37 for renal function tests) the cost of quarterly clinic visits for high-risk MSM per year, excluding drug costs, would equate to:

£101.10 + £2.75 + £2.37 = £106.22, x 4

= £424.88 per person.

However, these individuals would ideally be seen regardless of PrEP, so these may not be new costs for all potential recipients of PrEP, excluding the additional costs of tests for liver function and renal function, which cost £20.48 per year per patient. [16]

Using the costs from a presentation by Valentina Cambiano at the BASHH Spring Conference 2015 [17], the additional cost of monitoring people on PrEP compared to people at similar risk not on PrEP is £284 annually. This is based on 3 monthly follow up where individuals attend for HIV and STI testing and tests to assess renal function as tenofovir disoproxil fumarate can cause renal toxicity.

Therefore, based on the estimated number of individuals who are most at risk of HIV (as per section 4.1.2) and would, if compliant, benefit from PrEP, the estimated basic additional cost of PrEP advice and support for 560 people (excluding drug costs) in first year would be £159,040 across Wales, or £11468.80 (the costs of quarterly renal and liver function tests for the 560 individuals) assuming that this group of individuals should ideally be accessing services every three months for screening if they were not on PrEP. Other tests may be required on an individual basis as dictated by clinical need. These would be tests to evaluate the

medication's effect on bone, renal and liver function, beyond the basic minimum monitoring and would incur further costs.

Additional costs on top of these clinical costs would include client and staff education around PrEP (e.g. staff training, information provision) which, at this stage, is impossible to quantify without a full needs assessment.

Recommendations

Pending the outcome of the decision from the All Wales Medicines Strategy Group (AWMSG) regarding NHS provision of PrEP medication, the HIVEG recommends that the specialist sexual health services provide advice and clinical monitoring to individuals who have accessed PrEP medication outside of the NHS or are considering doing so. If PrEP is subsequently provided through the NHS, this recommendation should be extended to all individuals accessing PrEP.

Additional funding will be required for specific support and monitoring of PrEP in specialist sexual health services.

In addition, formal structures should be in place to centrally monitor and evaluate the use of PrEP in Wales, to include: the outcomes regarding infection (HIV and other STIs); usage of PrEP (length of use, 'event-based/on demand' or continual); behavioural changes (perceived risk of activity and condom use).

4.3 Cost-effectiveness of the introduction of PrEP to the identified most at risk group

Overview

At the **ECDC Expert Meeting** in April 2016 [12], two presentations from England on cost-effectiveness of PrEP among MSM in the UK were delivered, each looking at different models. These were presented alongside work from the Netherlands which highlighted that PrEP was only cost-effective when provided 'on-demand'. The presenters 'pointed out that making the public health case for an intervention such as PrEP, which has a substantial short-term budget impact but potential for substantial longer-term savings in cost and public health benefit, is challenging.'

The report from the meeting considers the evidence from these presentations, highlighting that the cost of the drugs is the 'key barrier' to free provision of PrEP. The ECDC also acknowledges that 'guidance to standardise...cost-effectiveness studies would be useful.'

Similarly, the Scottish Health Protection Network recommended that people at the "highest risk of HIV in Scotland are provided with the option

of PrEP as part of a wider targeted national prevention programme delivered by the NHS in sexual health services, subject to the delivery of the programme at a *cost effective price* and *reflecting SMC advice* where applicable." [5]

Within **NHS England**'s proposed eligibility and exclusion criteria [7, p.7], individuals whose injecting drug use is their only risk of HIV acquisition are excluded from proposed PrEP provision, on the grounds that 'current HIV incidence in this group in the UK is too low for PrEP to be cost effective'.

Cost-Effectiveness Studies

General reviews of cost-effectiveness for PrEP provision have been undertaken in recent years [18,19], along with a simulated strategy based on three separate clinical trials [20]. This study clearly demonstrated that for the provision of PrEP to MSM, strategies need to be targeted at those at high risk. Over 20 years, making PrEP available to all MSM is projected to prevent 33.5% of new HIV infections, but with a cost/QALY estimate of $1,474,000/QALY, which is considerably in excess of acceptable cost-effectiveness thresholds. However, implementing strategies in high-risk population groups at 'acceptable' cost levels, increases the likelihood that such strategies are within the bounds of what is considered to represent value for money.

This is confirmed by other studies, which have been undertaken in a number of countries and settings, including, for example, **England** [21] and the **UK** [17], the **Netherlands** [22,23], **Australia** [24], **Los Angeles** [25] and **Canada** [26]. There is no clear indication that PrEP is cost-effective, with a range of estimates being evident from the studies conducted – ranging from cost-saving to cost/QALY of 800,000CAD. Two of these studies [22,26] relate specifically to the cost-effectiveness of 'on-demand' provision.

The Netherlands study was based on mathematical modelling to predict the effectiveness and cost-effectiveness of PrEP in daily usage and on-demand. While both scenarios were shown to be cost-effective (based on a cost/QALY threshold of €20,000), the analysis showed that on-demand PrEP would be cost-saving if the price was reduced by 30-40%. Another modelling study undertaken in Canada [27] highlighted that the use of PrEP among all HIV-uninfected MSM was not cost-effective, but that targeting PrEP for the highest risk MSM is likely to improve cost-effectiveness and that maximising PrEP efficacy, by supporting adherence, in a scenario of 25% coverage of high risk MSM would result in a cost/QALY of $15,000CAD. Adherence to PrEP also featured as a determinant of cost-effectiveness in a study undertaken in Los Angeles (25). It is the case that the cost-effectiveness of PrEP is dependent on the extent of risk, the level of adherence, prevalence rates and the price

involved. The Australian study (24) demonstrated that pre-exposure prophylaxis targeted at HIV-negative MSM in a discordant regular partnership was likely to be cost-effective, but other scenarios did not generate cost-effectiveness ratios that would constitute value for money, and would result in significant budgetary impact.

In relation to the provision of PrEP to injecting drug users, a cost-effectiveness study has been undertaken in the **United States** [28], which indicated that it is unlikely to meet recognised cost-effectiveness thresholds, being highly dependent on the annual cost of PrEP and dependent on PrEP drug adherence, individual transmission risks and community HIV prevalence.

A study undertaken in Ukraine, as being a representative case for mixed HIV epidemics, suggested that oral PrEP for injecting drug users can be part of an effective and cost-effective strategy to control HIV in regions where injection use is a significant driver of the epidemic [29].

In the Welsh Context

AWMSG is the body responsible for advising Welsh Government on whether or not new medicines should be routinely available in NHS Wales. In making a recommendation to Welsh Government AWMSG considers the clinical-effectiveness, cost-effectiveness, budget impact and wider societal issues. It is the role of the AWMSG to determine the clinical effectiveness against cost for PrEP.

The HIVEG has, therefore, considered factors which may assist this, in particular by defining eligibility criteria (see 4.1 and Appendix 2) and providing, in the first instance, an estimate of the amount of Truvada® which might be prescribed in the first year.

There are a number of factors to consider when undertaking a cost-effectiveness review for PrEP:

- **Cost of Medication**

The current cost of branded Truvada®, as listed in the British National Formulary (BNF) [30], is net price 30-tab pack = £355.73. This may change in the near future as the patent is due to expire in 2017 and generic formulations are already available online. NHS Wales may have negotiated a lower price with the drug manufacturer Gilead Sciences, Inc., but due to confidentiality, any alternative costs are unavailable for this review.

The BNF cost excludes VAT - VAT will be added if medication is dispensed within the hospital setting. However, provision in the community

overcomes this and is the approach used in Wales at present for dispensing HIV treatment.

Therefore, the costs based on the net price for an annual prescription of 12 packs would be £4268.76.

- **PrEP dosing regimens**

For PrEP to be most effective, the drug needs to be at an appropriate level within the body. Suggested regimens are outlined in the latest European AIDS Clinical Society (EACS) Guidelines [9].

In line with clinical trials and the latest clinical guidelines, there are two options for taking PrEP, either daily or 'event-based/on-demand'. The best approach would depend upon individual circumstances. In both cases, as the body takes a while to absorb the treatment, PrEP needs to be taken both before sex, and for several days afterwards.

PrEP does not get into the vaginal tissues as well as it gets into rectal tissues, therefore, for vaginal sex it is necessary to take PrEP every day. It should also be taken daily for two weeks (ideally three) before sex to reach drug levels that give the highest protection.

For anal sex, daily PrEP has been proven to be most effective. However, the IPERGAY trial showed that 'event-based' (or 'on-demand') dosing was effective for MSM. This involved taking two pills before sex as a double dose and a single pill 24 and 48 hours after last sex.

When IPERGAY was originally published (See Section 6.4, IPERGAY Study for an overview of this trial) it was reported that participants used a median of 15 pills per month. In the most recent feedback from the study, two thirds of participants used event-based dosing and this resulted in a median of 18 pills per month.

This data can be used to calculate a multiplier of 18/30 = 0.6 that can be applied to provide an estimated cost of branded Truvada® per eligible person per year (ex VAT) of £2,561.

Assuming that, like the IPERGAY study, two thirds of the 560 individuals in Wales were prepared to use 'event-based/on-demand' dosing, the total annual cost of Truvada® will be:

$$(373 \times 2{,}561) + (187 \times 4268.76) = 955253 + 798258.12 = £1{,}753{,}511.12$$

However, at this time, as Truvada®, the only antiretroviral product licensed for use as PrEP in the UK, has received a marketing licence extension for once-daily use only - 'on demand' use of Truvada®, tenofovir disoproxil (Viread) alone, or with emtricitabine (Emtriva) as

separate tablets, is not licensed for PrEP. As such, and given the high risk behaviour of this client group in Wales, daily dosing would be recommended, therefore the total annual cost of Truvada® will be:

560 x 4268.76 = **£2,390,505.60**

- **Dispensing Costs**

As noted earlier, HIV medication is dispensed in the community in Wales, thereby removing the cost of VAT. Consideration will need to be given to the method used for dispensing PrEP, if the AWMSG determines that it is to be provided through the NHS, as this has the potential to incur additional cost:

If PrEP is to be dispensed via community pharmacies then there will be also be a high cost drug and a dispensing fee added to each prescription by the community pharmacy.

  - The dispensing in community will need cascading to community pharmacies throughout Wales. Liaison with Gilead Sciences will be paramount to obtaining the Truvada® at the All Wales Contract price in the community.

If the PrEP is dispensed via Homecare services then there will be a dispensing fee per delivery – this varies between supplies at £30-£60 per delivery (depending on prescription length)

  - If PrEP is to be dispensed via this service then Homecare services in hospitals will need to be contacted. These services are at full capacity, therefore any new service will need funding.

These approaches are currently used for dispensing HIV medication for treatment.

- **HIV care costs**

The additional lifetime healthcare costs due to HIV have been calculated based on the cost of an MSM aged 30 years being infected in 2013. The rate of HIV diagnosis used in the calculation was chosen to reflect the current situation observed in the UK regarding CD4 at diagnosis, including the fact that 35% are diagnosed late. People diagnosed promptly are less likely to experience morbidity associated with HIV, are likely to respond better to treatment and to achieve a suppressed viral load more swiftly, monitoring associated with PrEP would make this more likely. Based on a median life expectancy of 71.5 years, the average lifetime cost of the HIV care in the UK would be £360,800 [31]. The largest proportion of these costs (68%) is attributable to the antiretroviral drugs. If patented drugs

are replaced with generic ones, at 20% cost of patented prices, the estimated mean lifetime cost reduces to £179,000.

Recommendations

In line with the recommendations from the Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group [5], we conclude that the highest risk groups are provided with the option of PrEP, as part of a wider national prevention programme, subject to delivery of the programme at a cost-effective price and reflecting AWMSG advice.

4.4 Recommendations on the most prudent approach to the potential introduction of PrEP in Wales

Overview

Prudent Healthcare's principles of co-production, caring for those with the greatest health need first, doing only what is needed and do no harm, and reducing inappropriate variation through evidence-based approaches [32] have underpinned the development of this report and our summary recommendations. The HIVEG features both practitioners and representatives of population groups that are disproportionately affected by HIV infection.

When we consider prudent healthcare in the whole on this topic, we must acknowledge that, at this time, PrEP is not available through the NHS, and as such individuals are accessing it through alternative means. As such, we need to tailor our services and promotion campaigns to do all we can to ensure these individuals receive the appropriate testing and treatment that would ensure their continued safe use of PrEP. As examples, through anecdotal reports, we know of individuals, resident in Wales, accessing PrEP via 'informal' or 'DIY' ways, including:

- **Ordering generic PrEP online**

As described on the 'I Want PrEP Now' website [33], it is possible for people to purchase a generic version of Truvada® from online pharmacies. 'I Want PrEP Now' has ordered from a number of these providers and, before recommending the providers, has tested the supplied medication to verify that it is genuine PrEP medication [34].

All of these methods present challenges, either in terms of expense which results in inequity of access, or in terms of lack of monitoring and support or the potential for counterfeit products, all of which may result in the risk of inappropriate and unsafe use. The European AIDS Treatment Group (EATG), in their position statement on HIV Prevention [35], say that 'Self-

prescribed PrEP is clearly a second-best but if people are going to use it there should be information on how to use it safely'.

As a minimum, the HIVEG recommends that, pending the outcome of the decision from the All Wales Medicines Strategy Group (AWMSG) regarding NHS provision of PrEP medication, specialist sexual health services provide advice and clinical monitoring to individuals who have accessed PrEP medication outside of the NHS or are considering doing so.

- "**Clinic-hopping" or PEP as PrEP**

In some settings, it is possible to obtain Truvada® by presenting at clinics for PEP, then discarding the remaining regimen. A blogpost outlining this technique has been widely read and referenced by PrEP advocacy groups [36].

- **Pill-sharing**

Some people are accessing PrEP through their HIV-positive friends, who either share the Truvada® pills that are no longer needed by them for treatment, or by going back to clinics for more, stating they have lost the prescription or the bottle.

- **Accessing Overseas**

People are also asking friends who live abroad to bring Truvada® into the country for them or bringing it into the country from abroad themselves.

Recommendations

The principles of prudent healthcare include 'do only what is needed, no more no less; and do no harm' [32]. Regardless of whether PrEP is eventually provided through the NHS, it is of paramount importance that client groups accessing PrEP through other means are encouraged to attend sexual health services for quarterly STI screening and HIV testing, and that the services are supported to enable this. This, of course, should also be the case for any high-risk individual, regardless of whether they are accessing PrEP.

The HIVEG stresses that PrEP should not be considered in isolation, but be seen as part of a comprehensive package of HIV prevention. Support needs to be given to allow for earlier diagnosis and linkage to other interventions that may reduce the incidence of STIs.

In addition, as information regarding PrEP is constantly evolving, central oversight needs to continue with regular reviews, twelve months from initial evidence publication or on emergence of significant new evidence. In light of this, relevant updates will be provided to services, and public

messaging revised accordingly. What is the position of other organisations with regards to PrEP provision/ implementation?

5 Professional Organisations

5.1 UK Organisations

The **British HIV Association (BHIVA)** and **British Association for Sexual Health and HIV (BASHH)** have issued a joint position statement on PrEP in the UK [6], the latest version of which, at the time of writing, was published in May 2016. Their statement reflects on the current context of HIV in the UK, the available evidence and policy positions outlined elsewhere. The statement also provides practice and professional guidance for clinicians, including guidance on how to advise service users on taking PrEP.

In concluding their statement, BHIVA and BASHH 'strongly recommend that PrEP be made available within a comprehensive HIV prevention package' to MSM, transgender men and transgender women who are engaging in condomless anal sex, along with 'HIV-negative partners who are in sero-different heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not suppressed' and 'other heterosexuals considered to be at high risk' [6]. The authors also reflect on the outstanding research questions, particularly regarding the 'broader heterosexual community, new drugs and formulations, and the need for greater precision around the effectiveness of event-driven Truvada® in women particularly'.

5.2 European Organisations

The **European Centre for Disease Prevention and Control (ECDC)** held an expert meeting in April 2016 to discuss PrEP [8]. The meeting looked into four key areas, similar to the key focus points of this report (Specific points of reference are included in Chapter 4 of this document). The ECDC meeting report concludes by stating that PrEP 'should not be considered in isolation but as an additional option for people at substantial risk of HIV infection as one element of a combination prevention approach'. The report also considers two main obstacles for implementation – firstly, the current cost, and secondly, the 'potential impact of PrEP on risk behaviour by an already high risk population'.

5.3 International Organisations

As discussed earlier in this document, **WHO** has produced a specific guideline on PrEP, along with updated guidance on HIV prevention to incorporate PrEP [4,37]. As relevant sections of these documents are

referenced elsewhere in this document, we will not duplicate in this section. WHO have also produced a policy brief, which captures the key points of their guidance in a two-sided summary [38].

5.4 Advocacy Groups

UK-based

National AIDS Trust (NAT) has campaigned for PrEP over a number of years, culminating in the decision to refer NHS England's decision over PrEP provision in England to the High Court [39]. Alongside it's advocacy role, NAT has also produced documents including a briefing on why they believe PrEP is needed [40].

Dedicated advocacy groups campaigning for the provision of PrEP in England have emerged. These include 'Prepster' [41], 'PrEP Access' [42], 'I Want PrEP Now' [43], and their remits range from garnering community support for PrEP, providing guidance on how to access PrEP, and co-ordinating advocacy efforts.

European

The **European AIDS Treatment Group (EATG)**, in their October 2015 'Position on HIV Prevention' [35], whilst acknowledging that PrEP is 'not effective for everyone' go on to state that there are 'populations for whom PrEP is very suitable'. Their position statement declared the evidence for the effectiveness of PrEP in gay men/MSM as 'overwhelming', and calls for 'affordable PrEP (e.g. with drug price reductions)' to be available consistently throughout Europe without a restrictive criteria. Also, the EATG calls for 'much better public information about PrEP to be available in Europe' (32, p14).

The **PrEP in Europe Initiative (PiEI)** [44], a coalition of European advocacy organisations and individuals, has been formed to advocate for PrEP provision for people at high risk of HIV. The initiative aims to provide information on PrEP access in Europe, influence policy and to support other advocacy organisations. The steering committee for the PiEI includes NAT, EATG and NAM/aidsmap.

In their report 'PrEP Access in Europe' [45], PiEI provide reflection on the clinical trials and demonstration projects for PrEP that have been conducted in Europe, as well as highlighting national and European guidelines for the provision of PrEP.

6 Lessons from Clinical Trials

The recent NICE Evidence Review into PrEP for adults at high risk [46] provided an overview of four key studies into the efficacy of PrEP. In this section of the report, we look at these four studies, along with reference to other global trials underway or concluding.

6.1 iPrEX Study

Date Reported	2010
Trial Type	Double-blind RCT
Geographical Scope	Peru, Ecuador, Brazil, United States, Thailand, South Africa
Trial Subjects	HIV-negative men or transgender women who have sex with men with evidence of high-risk behaviour for HIV infection.

The first randomised controlled trial of PrEP in humans to produce a statistically meaningful result [47]. The iPrEx (Pre-exposure Prophylaxis Initiative) trial found that the HIV infection rate in HIV-negative gay men who were given a daily pill containing two HIV drugs was reduced by 44%, compared with men given a placebo.

The trial gave Truvada® (tenofovir/FTC) pills or placebo pills of identical appearance to 2499 initially HIV-negative men who have sex with men at high risk of HIV infection, in nine cities in four continents. The men were told to take one pill once a day. They were followed for an average of 14 months between July 2007 and December 2009 and 31% were followed for two years or more.

The trial subjects were told there was a 50% chance they might be taking a placebo and were therefore, in the words of the researchers, 'instructed' to maintain safer sex. The provision of safer-sex counselling and condoms was very effective in itself. At the time potential participants were screened for possible participation in the trial, the average number of sexual partners reported in the past three months was 18. By the time of trial enrolment, by which time participants had already been introduced to the trial concept, had preliminary discussions and signed a consent form, participants were reporting an average of seven partners in the last three months. During the trial itself, this went down to two partners in the previous three months. The efficacy reported for PrEP in the study was, therefore, demonstrated in a setting in which behaviour change was already reducing the risk of HIV infection relative to baseline.

Efficacy in subjects reporting unprotected receptive anal intercourse at screening was 58%; in subjects reporting no receptive sex, there was no significant efficacy, indicating that PrEP was only making a significant difference to infection risk in the highest-risk men.

Efficacy was also significantly greater than placebo in men: aged over 25 (59%); with at least secondary education (54%); who took fewer than five alcoholic drinks a day (57%); who were circumcised (77%); and who did not have HSV-2 (54%).

This was the first study to definitively prove that PrEP, as a concept, works. Under study conditions, it protected nearly half of a group of high-risk gay men who would otherwise have caught HIV. With good adherence, it's likely that efficacy would be considerably greater.

6.2 Partners PrEP Study

Date Reported	2012-2014
Trial Type	Double-blind RCT
Geographical Scope	Kenya and Uganda
Trial Subjects	Sero-discordant heterosexual couples

A longitudinal study undertaken in 2013 [48] reported a small increase in unprotected sex with outside partners was reported after the publication of preliminary results [49], though there was no significant increase in STIs.

In addition, the investigators undertaking the longitudinal analysis [48] found that the provision of PrEP may not result in substantial changes in risk-taking sexual behaviour amongst heterosexuals.

Despite this being one of the few trials focussed on heterosexual couples, due to the location of the trial (sub-Saharan Africa) the findings may not be directly relevant to the Welsh cultural context.

6.3 PROUD Study

Date Reported	2012
Trial Type	Open-label trial of once-daily Truvada®
Geographical Scope	London
Trial Subjects	HIV-negative men or transgender women who have sex with men. Randomised to start PrEP with Truvada® immediately or after deferral period.
Website	http://www.proud.mrc.ac.uk [50]

PROUD was the first-open-label randomised controlled trial of PrEP, and used a pragmatic schedule and procedures to represent how PrEP would be used in routine clinical practice. Of all of the clinical trials analysed, the PROUD trial is the closest to being applicable to the Welsh context.

The trial was undertaken at 13 sexual health clinics in England. Its primary aim was to assess whether, if participants knew they were taking PrEP, their risk behaviour would change. It also aimed to assess a number

of other factors including who takes up the offer of PrEP and whether adherence behaviour changes over time.

The trial enrolled HIV-negative gay and other men who have sex with men who had had anal intercourse without a condom in the previous 90 days. Participants were randomly assigned (1:1) to receive daily combined tenofovir disoproxil fumarate (245 mg) and emtricitabine (200 mg) either immediately or after a deferral period of 1 year. Randomisation was done via web-based access to a central computer-generated list with variable block sizes (stratified by clinical site). Follow-up appointments were arranged quarterly.

The primary outcomes for the pilot phase were time to accrue 500 participants and retention; secondary outcomes included incident HIV infection during the deferral period, safety, adherence, and risk compensation. Randomisation stopped in October 2014 and all participants in the deferred arm were offered PrEP after an interim analysis showed an 86% reduction in HIV risk [51]. Reasons for the 14% non-reduction in risk are not necessarily reflective of the treatment itself, and could include factors such as lack of patient adherence, patient already being infected with HIV and sero-converting at outset of treatment, and patients being lost to follow-up. Annual incidence in the deferred arm was 9.0% and in the immediate arm 1.2%, yielding a number needed to treat (NNT) of 13.

An analysis of the baseline data from the study has recently been published [52], providing insight into the demographics of trial participants. The median age of participants was 35, with the majority of participants of white ethnicity (81%), educated at university level (61%) and in full-time employment (72%). Participants also reported a median of 10 sexual partners in the last 90 days.

A poster presented at this year's Public Health England (PHE) looked at chemsex in the PROUD study [53]. Chemsex, defined as '*sexual activity engaged in while under the influence of stimulant drugs such as methamphetamine or mephedrone, typically involving several participants* [54]', is a high-risk behaviour, and is associated with high levels of STI, HIV and Hepatitis C transmission. Within the PROUD study, chemsex use was common in a cohort of participants who had at least one follow-up visit in PROUD's Hepatitis C sub-study. 52% of this cohort reported participating in chemsex on at least one occasion. 21% reported consistent chemsex (defined as those reporting, at every clinic visit, having participated in chemsex).

A video documentary has also been produced to provide information about the PROUD Study [55].

6.4 IPERGAY Study

Date Reported	2014-2016
Trial Type	Double-blind RCT of Truvada® or placebo taken 'on-demand', then open label phase from Nov 2014 - June 2016
Geographical Scope	France, Canada and Germany
Trial Subjects	414 high-risk men who have sex with men (MSM)
Website:	http://www.IPERGAY.fr [56]

In IPERGAY, gay men and other men and transgender women who have sex with men, and were at high risk of HIV infection, were asked to take two Truvada® pills (or a placebo) from one day to two hours before they anticipated having sex. If they actually did have sex, then they were to take another pill 24 hours after having sex and a fourth pill 48 hours after it. The period of taking PrEP would thus cover two to three days. If they continued having sex, they were told to continue taking PrEP until 48 hours after their last experience.

As in PROUD, all participants also received risk-reduction counselling, were provided with condoms, had three-monthly tests for HIV and other sexually transmitted infections (STIs), and received hepatitis A and B vaccines if needed.

IPERGAY started enrolling participants in February 2012.

In November 2014, and prompted in part by the PROUD study researchers' announcement that all participants were to be offered PrEP at once because of high effectiveness, IPERGAY's Data and Safety Monitoring Board also looked at the HIV incidence data and found high effectiveness too. Like PROUD, IPERGAY continued as an open-label study [57].

The first findings from the double-blind study were published in December 2015 [58], showing that in a population of 400 MSM in France and Canada at high risk of contracting HIV, the implementation of an 'on-demand' strategy led to an 86% drop in HIV infections over a 9 month period. The study also reported on increased rates of gastrointestinal and renal adverse events for those taking PrEP.

PrEP reduced HIV risk among high-risk MSM by an average of 86% – exactly the same rate as seen in the PROUD study. This was achieved on an overall pill usage of 15 pills per month, or approximately half the number that would be used if participants had taken them daily, with good adherence. Twenty per cent of participants took over 25 pills a month, i.e. the equivalent of almost daily, and 20% less than four, i.e. less than one a week.

Participants varied their PrEP-taking according to whether they perceived themselves as being at risk.

During the study, 39% of participants were diagnosed with a sexually transmitted infection, and a significant decrease in condom use for receptive anal intercourse was reported. [59]

At the International Congress of Drug Therapy in HIV Infection, held in Glasgow in October 2016, a paper was presented on lessons learned from the implementation of PrEP in France [60]. This followed the end of the IPERGAY trial, and along with the October paper, a similar presentation was delivered at the 21st International AIDS Conference in July 2016, which is available online [61]. The investigator highlights a series of recommendations for future provision of PrEP, along with reference to the challenges faced in France.

6.5 Other Clinical Trials

PARTNER Study

The PARTNER study [62,63] is a large observational study that is following serodiscordant couples at over 70 HIV clinics in 14 European countries. All of the couples enrolled:

- are either heterosexual or gay men
- consist of one HIV-negative partner and one HIV-positive partner who is on ARVs
- do not use condoms regularly

The study began in September 2010 and is ongoing.

The preliminary results from the PARTNER study [64] provided important and encouraging new insight into the risk of transmitting HIV sexually when a person's viral load is undetectable and no condom is used.

The investigators of the PARTNER study concluded that the overall risk of HIV transmission through condomless sex for couples in stable sero-discordant relationships (when the HIV-positive partner is on ART, receives regular HIV care, and has an undetectable blood viral load) is 'extremely low, but uncertainty over the risk remains, particularly over receptive anal sex.'

A summary of all current, future and completed clinical trials related to oral PrEP is available online [57].

7 Other Emerging and Potential Issues

7.1 Risk of Increased STI Rates

In spite of the clear potential of PrEP for the prevention of HIV, there is also an opportunity for increased transmission of other STIs, impacting upon STI control efforts and management. This is a critical public health concern, particularly in an age of increasing rates of drug-resistant gonorrhoea. A number of papers have looked into the relationship between STI rates and PrEP uptake.

In a paper presented at the International Congress of Drug Therapy in HIV Infection in Glasgow recently [65], investigators reported on an increased rate of C. trachomatis (CT) infection for patients prescribed PrEP. Findings included an increase in CT infections at any site of 13% (from 13% before taking PrEP to 26% after taking PrEP), suggesting an increase in condomless sexual activity.

7.2 Online Purchasing and Access

It is not illegal for anyone to purchase generic PrEP medication from an online provider, and we know that many people in the UK, including Wales, are doing so, in lieu of PrEP being provided on the NHS. Of course, it is impossible to quantify exactly how many people are accessing PrEP through this manner, and where exactly they are purchasing PrEP from. An article provides some anecdotal evidence regarding this from London [66], as does Section 4.4 of this report.

The main source information on accessing PrEP online in the UK is the website 'I Want PrEP Now' [43]. Importantly, the drugs signposted through this website have been tested and verified as genuine PrEP through the London-based sexual health clinic 56 Dean Street, who also provide information regarding purchasing PrEP online [67].

The **European AIDS Treatment Group (EATG)**, in their position statement on HIV Prevention [35], say that 'Self-prescribed PrEP is clearly a second-best but if people are going to use it there should be information on how to use it safely'.

7.3 Drug Interactions

As with all medications, the provision of PrEP to a patient has to be considered in the context of any other medication that they are taking. However, there are few clinically important interactions between tenofovir/FTC compared to other ARVs. However, see section 7.5.1 regarding the unknown interactions between PrEP and hormonal medication for transgender populations.

7.4 PrEP Resistance

Another consideration in relation to PrEP treatment is whether a patient becomes resistant to the drug, thus increasing their risk of contracting HIV and, should they become HIV positive, removing a treatment option for them. There have been isolated incidences of patients becoming HIV positive despite reported adherence to recommended PrEP regimens in the media [68,69] and in academic literature [70].

Nevertheless, current **WHO** Guidelines [37, p.55] state that the risk of resistance to PrEP is low (0.1%), and where it did occur, it was mainly among people 'who were acutely infected with HIV when initiating PrEP', though the guidelines do go on to state that 'how implementation of PrEP on a large scale affects resistance overall is unknown'.

A study published in July 2016 [71] followed a survey of virologists concerns about drug resistance to PrEP, especially as widespread use of PrEP will not mirror the close-control of trial studies. Again, this study reported that resistance levels are expected to be small, but for those individuals who do become HIV infected despite using PrEP, it is recommended that they are 'closely monitored due to higher risk of virological failure when initiating antiretroviral treatment in the future.'

For further information regarding UK rates of resistance, please see Appendix 4.

7.5 Safety of PrEP

As PrEP is not routinely available, we know that a number of people, including people living in Wales, have resorted to buying generic versions of the treatment online. This is not illegal, though of course does raise concern of what exactly it is that people are buying. As noted in section 7.2, the main source of information about purchasing PrEP online in the UK independently tests and verifies the authenticity of the PrEP medication that it signposts to, though of course we cannot be sure of the authenticity, and thus the safety, of PrEP purchased via other providers.

The current **WHO** Guidelines [37] looked into ten randomised controlled trials that compared PrEP with placebo-presented data on any adverse events, and concluded that there was no statistical difference in rates of any adverse events across a range of subgroups (mode of acquisition, adherence, sex, drug regimen, drug dosing or age).

Some studies [72–74] have looked into declines in renal function and bone mineral density, though the WHO guidelines concluded that these 'did not result in clinical events and were not progressive over time'.

Cisgender and Transgender Women

Cisgender Women

Cisgender women (that is, women who were born into the female sex) are also at risk of contracting HIV, fundamentally from sexual partners with undiagnosed or untreated HIV infection. In the Welsh context, cisgender women are not considered a high-risk population according to the WHO definition noted earlier in this document. Nevertheless, it is important to highlight the unique issues related to the provision of PrEP for cisgender women should the situation change.

WHO's review of evidence to support their updated guidelines [37] looked into the differences in PrEP according to gender. Of the 10 randomised trials that WHO looked at, which could include oral PrEP and other forms of PrEP, cisgender women were included in six studies, and PrEP was shown as effective. Many clinical trials which have included women have been conducted in countries where the HIV incidence rate for cisgender women is considerably higher than that in Wales, and as some of these trials looked into alternative types of PrEP (non-oral PrEP) it is not entirely appropriate to draw direct comparisons in the Welsh context.

In relation to hormonal contraception, the WHO review [37] states that 'PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends towards higher rates of pregnancy among oral contraceptive users who also took PrEP'. Also, WHO found that oral PrEP was 'not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy.' This statement refers to two studies undertaken in the Kenya and Uganda [49] and Sub-Saharan African [75], so whilst this is good evidence, it is also not entirely relevant in the Welsh context.

Also, PrEP does not get into the vaginal tissues as well as it gets into rectal tissues, therefore, for vaginal sex it is necessary to take PrEP every day. It should also be taken daily at least two weeks (ideally three) before sex to reach drug levels that give the highest protection. BHIVA and BASHH, in their position statement on PrEP in the UK [6], call for further clinical research into the effectiveness of on-demand Truvada® in women.

Transgender Women

In their updated guidelines [37], **WHO**, whilst considering transgender people a population at 'substantial risk', also acknowledge that 'more information is needed about interactions between PrEP and hormone therapy used by transgender people' (ibid. p55).

A session at the 21st International AIDS Conference this year looked into transgender access to PrEP in a New York City community health centre [76]. The study demonstrated low involvement in PrEP access by

transgender clients (in the first six months, just 5 clients). In response, the clinic offered HIV screening to all new transgender clients presenting at the clinic, and the development of transgender-inclusive promotional materials. This has in turn seen the uptake of PrEP by the transgender community increase to 118 transgender clients out of 1500 in total in the first three years of the service being offered.

8 Legislative and Regulatory Context

8.1 Marketing Authorisation for Truvada® as PrEP

Truvada® has been licensed for use as post-exposure prophylaxis (PEP) in the UK for a number of years, therefore it is not a new medicine within the UK.

In July 2016, the European Medicines Agency (EMA), namely its Committee for Medicinal Products for Human Use (CHMP), recommended a license application for Truvada® to be used as PrEP within the EU [77]. This decision was considered and approved by the European Commission in August 2016, which now enables EU Member States to decide whether to commission Truvada® as PrEP in their country through its usual medicines regulatory channels.

Truvada® is the only antiretroviral product licensed for use as PrEP in the UK. The licence extension is for once-daily use: 'on demand' use of Truvada®, tenofovir disoproxil (Viread) alone, or with emtricitabine (Emtriva) as separate tablets, is not licensed for PrEP [46].

9 Horizon Scan of Future Developments

Later in 2016, **WHO** will publish comprehensive implementation guidance for PrEP. This guidance will include suggestions for implementing PrEP, looking at a variety of factors, including community engagement, coordination of services, laboratory monitoring and pharmacy services.

The **ECDC** are considering tools and guidance to support the implementation of PrEP in Europe [12]. Under consideration are the development of a model/tool to support comparable national cost-effectiveness studies, the identification of minimum standards and principles for service delivery and the monitoring of PrEP.

According to the **PiEI** report 'PrEP Access in Europe' report [45], a large non-inferiority study of a new alternative to Truvada®, Descovy®, is planned to take place in North America and Europe [78]. (A non-inferiority study is one in which a new drug is compared with an existing treatment with a view to demonstrating that it is not 'clinically worse' [79]). The efficacy for this drug as PrEP is not yet known, but as a HIV treatment it

has been shown to produce fewer bone and kidney-related side effects, and is provided in a lower dose than Truvada®.

BHIVA are due to release updated clinical guidelines for HIV in 2017, which will include the provision of PrEP. An interim set of guidelines are currently available [80].

10 Summary of UK Progress towards Provision of PrEP

10.1 England

In England, any decision over PrEP provision has been delayed by a court case, the first hearing of which was held in July 2016. Our document will not go into the details of the court case, as it has no relevance to the Welsh context, focused as it was on who had responsibility for funding and commissioning PrEP in the English healthcare system. Nonetheless, the Court of Appeal ruled that **NHS England** has the ability, but not the obligation, to fund PrEP. As such NHS England have issued an update [81], which states that it is now formally considering whether to fund PrEP, and if it does, how this will be provided. The update statement also challenges the drug manufacturer to 'reconsider it's currently proposed excessively high pricing', and states that NHS England will 'explore options for using generics'.

Prior to the court case and decision, NHS England produced substantial material to support a consultation on the subject. These included an evidence review [3], a clinical commissioning policy proposition [7], and an impact assessment report [82].

At the same time, the **National Institute for Health and Care Excellence (NICE)** have undertaken an new medicine evidence summary [46], which aimed to inform planning around the use of Truvada® for PrEP within local health systems in England. As the NICE review mainly looks into clinical effectiveness of the drug, this paper does not look at this in depth, but nonetheless it is a recommended read for those taking a final decision on the provision of PrEP.

Of interest to this document however is that, whilst acknowledging that 'there is little doubt that Truvada is effective in reducing HIV acquisition in high-risk people who are HIV-negative', the NICE review also states that it is also important to consider 'issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritisation for prophylaxis and cost-effectiveness,...especially at a population level' (ibid. p12).

10.2 Scotland

In Scotland, **NHS Scotland** will make a decision on provision of PrEP following recommendations from HIV Scotland and the medicines regulatory approval for Truvada® by the Scottish Medicines Consortium.

The **Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group** has recently published its draft policy [5]. Aspects of this document are considered earlier on in this report (Section 4.1.1) and as such are not duplicated here.

11 PrEP Globally

In this section, a brief overview is provided on global approaches towards PrEP provision, including legislative, regulatory and strategic approaches. Examples are provided where available for reference, and do not necessarily constitute best practice. The primary source for much of the information in this section is the PrEPWatch 'Country Updates' [83].

11.1 France

Following the IPERGAY trial (see Section 6.4), Truvada® for PrEP has been approved since November 2015 (effective since January 2016), though is currently recommended under an emergency Recommendation of Temporary Use (RTU) measure [84]. An RTU is granted for three years, and can be renewed.

The lead author of the IPERGAY trial, Jean-Michel Molina, spoke at The 21st International AIDS Conference (AIDS 2016) on 'PrEP Roll-Out in France' [61]. His presentation highlighted the eligibility criteria for those accessing PrEP, along with the dosing regimens and follow-up arrangements. Because of the RTU licence, clinicians in France are also expected to report through a specialist website detail of the patients characteristics at treatment initiation and how PrEP is being used (daily/on-demand), along with any acquired HIV infections or adverse events following the provision of PrEP.

Molina's presentation also highlighted the uptake between January and June 2016. Of 867 patients, the average age was 38, they were 87% French and 96.4% male – all of whom were MSM. Of the total patients, 20.8% were using psychoactive drugs, 30% had STIs in the prior 12 months, and 11.9% had used PEP in the last 12 months. 65.2% were using PrEP on-demand. In the presentation, two reported cases of HIV infection were referenced.

Challenges with the PrEP roll-out were also considered by Molina. These included the need to have dedicated nurses to provide information,

organising the outpatient clinic to meet demand (informing nurses and administrative personnel, identifying doctors to provide PrEP, and increasing the number of consultations). Lessons learned from the PrEP roll-out have included the need to increase PrEP awareness among doctors and people at risk, the need to adapt available resources to provide comprehensive sexual health care and the need to monitor and evaluate PrEP implementation.

11.2 Netherlands

Despite an ongoing PrEP demonstration project [85], the Netherlands has yet to introduce PrEP. A study among 448 HIV-negative people in Amsterdam showed that overall intention to use PrEP was low, though there was a higher intention to use PrEP amongst high-risk MSM [86].

Because of the lack of PrEP provision in the Netherlands, an anonymous group of 'activist health professionals' has set up a campaign, the 'PrEP Tactical Unit' [87], to provide guidance on 'safe and reliable ways to obtain affordable PrEP'.

As cited earlier in this report, a cost-effectiveness study has shown that PrEP would only, at this stage, be cost-effective in the Netherlands if provided on-demand [23].

11.3 Norway

Norway has become the first country in the world to offer at-risk population groups PrEP free of charge [88–90]. HIV rates in Norway are closely comparable to the scale of transmission in Wales at a population level, with around 5800 people currently living with HIV in the country, and 221 newly diagnosed in 2015 [89].

11.4 US

Truvada® gained regulatory approval for use as PrEP in the United States in 2012 [91]. As a condition of the approval, Gilead Sciences, Inc. was required to collect viral isolates from individuals who acquired HIV while taking Truvada® and to evaluate these isolates for the presence of resistance. The manufacturer was also required to collect data on pregnancy outcomes for women who become pregnant whilst taking Truvada® for PrEP, and to conduct a trial to evaluate drug adherence and its relationship to adverse events, risk of seroconversion, and resistance development in seroconverters. Details of this ongoing monitoring are available on the ClinicalTrials.gov website [92].

12 Conclusions and Recommendations

PrEP has clear potential for significantly preventing the onward transmission of HIV infection, though it should not be seen as a replacement for traditional HIV prevention methods – it is an additional prevention method.

It is in high-risk population groups where we anticipate that the provision of PrEP will have the greatest impact. In line with similar reports from Scotland, NHS England and BHIVA/BASHH, we define 'high-risk' groups as MSM engaging in condomless anal sex, transgender men and women engaging in condomless anal sex, HIV-negative partners of HIV positive partners (in certain circumstances) and specific heterosexual populations. In many of these groups, we already see high levels of STIs, and therefore, while we can reasonably anticipate high or even slightly increasing STI rates for this group if PrEP is provided, we have reason to be assured that the risk of onward transmission of HIV would be substantially reduced. As we have seen earlier in this document, making PrEP available to high-risk groups is in line with guidance produced in England, Scotland, and Europe, and globally through WHO. We see no good reason to contradict their recommendations.

That said there are still a range of unknowns. Whilst evidence emerging from clinical trials has been positive, it remains to be seen how successfully patients will be in adhering to the treatment in 'real-world', uncontrolled settings. We know that PrEP becomes less and less effective the more it is misused, and we know that some people in Wales are already accessing PrEP through online purchasing and other means, and this will only continue, unmonitored, if PrEP is not provided through the NHS.

As such, it is of paramount importance that, regardless of whether PrEP is to be provided through the NHS, at the very least, the need for strengthened client and health professional education about PrEP is essential. Clients need to know that PrEP is not a solution for other STIs, and should also be informed of the potential side effects of the medication, whereas health professionals across all sectors, including primary care, need to be aware of PrEP. This information provision needs to be consistent, accessible and evidence-based. Furthermore, we believe that the need to develop new information provision for PrEP is an opportunity to update the existing HIV prevention programme to reflect the changing nature of HIV prevention efforts.

It is important to acknowledge the significant pressure that sexual health services in Wales are currently under, and we know that this will be subject to a wider sexual health services review, commencing in 2017. However, providing advice and monitoring related to PrEP will ensure that individuals whose sexual behaviour is particularly high risk are being seen

as a priority. We do however see a need for additional funding to provide specific support and monitoring of PrEP within these services. In addition, if PrEP medication is to be provided through NHS Wales' Integrated Sexual Health Clinics, consideration needs to be given to the potential issue of cross-border activity, particularly if England is not providing PrEP simultaneously – our proposed eligibility criteria could cover this by using residency in Wales as a criterion.

As this report has been developed, the authors have recognised the rapid evolution of evidence related to PrEP; therefore it is recommended that reviews of the evidence continue through central oversight, at least twelve months from initial evidence publication or on emergence of significant new evidence, whichever is earlier. In turn, relevant updates will be provided to services and public messaging revised accordingly.

13 Frequently Asked Questions (FAQs)

What is Pre-Exposure Prophylaxis (PrEP?)

PrEP requires HIV negative people to use antiretroviral medications (ARVs) regularly to reduce the risk of them becoming infected with HIV

PrEP needs to be taken regularly to be effective, though there are two alternate approaches coming to the fore from the clinical trials – 'daily PrEP' and 'PrEP on-demand'.

For this review, are we looking at a specific form of treatment?

Yes, Tenofovir disoproxil fumarate (TDF) plus Emtricitabine (FTC). This is currently recommended for use as PrEP in a single fixed dose oral combination tablet. This form of treatment is also used to treat people with HIV. Truvada® is the branded form of the drug being trialled and introduced as PrEP in various cities and countries. This is licensed as a treatment for HIV-1 infection in UK, and has been for a decade. Full pharmacological details about the medication can be viewed online [93].

Is Truvada® currently licensed for use as PrEP in the UK?

Truvada® gained licencing approval within the European Union in July 2016 [77].

Truvada® is the only antiretroviral product licensed for use as PrEP in the UK. The licence extension is for once-daily use: 'on demand' use of Truvada®, tenofovir disoproxil (Viread®) alone, or with emtricitabine (Emtriva®) as separate tablets, is not licensed for PrEP [46].

14 Appendices

14.1 Appendix 1 – Membership of HIV Expert Group

Name	***Title***	***Organisation***
Dr. Giri Shankar (Chair)	Professional Lead Consultant for Health Protection	Public Health Wales
Zoë Couzens	Principal in Public Health, Health Protection	Public Health Wales
Adam Jones	Public Health Practitioner - Policy	Public Health Wales
Sarah Andrews	Principal in Public Health, Health & Well-Being	Public Health Wales
Dr. Stephanie Perrett	Lead Nurse for Health and Justice	Public Health Wales
Dr. Matthijs Backx	Infectious Disease Consultant	Public Health Wales
Fiona Clark	HIV Specialist Pharmacist	Cardiff and Vale University Health Board
Dr. Laura Cunningham	Consultant in Sexual and Reproductive Health	Cardiff and Vale University Health Board
Dr. Ushan Andrady	Consultant in Sexual and Reproductive Health	Betsi Cadwaladr University Health Board
Dr. Carys Knapper	Consultant in Sexual and Reproductive Health	Aneurin Bevan University Health Board
Dr. Susannah Danino	Associate Specialist	Abertawe Bro Morgannwg University Health Board
Jonathan Roberts	Clinical Nurse Specialist/Health Adviser	Abertawe Bro Morgannwg University Health Board
Stewart Attridge	Clinical Nurse Specialist/Health Adviser	Cwm Taf University Health Board
Joshua Hall	Services Manager	Terrence Higgins Trust Cymru
Invited but no representative sent		GPC Wales
Jenny-Anne Bishop	Service User Representative - Transgender	Unique
Rachel Benson	Service User Representative – Young Transgender	Transform
Andrew White	Service User Representative – LGBT	Stonewall Cymru
Jonathan Ellis	Communications Officer	Public Health Wales
Nicola Price	Consultant Virologist	Public Health Wales
Rachel Jones	Consultant Virologist	Public Health Wales
Advisors		
Karen Samuels	Programme Manager	All Wales Therapeutics & Toxicology Centre (AWTTC)
Prof. Ceri Phillips	Professor of Health Economics	Swansea University

14.2 Appendix 2 – Proposed Eligibility Criteria

NOTE: This proposed criteria is provisional, based on a hypothesis that PrEP would be provided through NHS Wales Integrated Sexual Health Clinics. It is based on the proposed criteria created by NHS England [7]*. The criteria should be taken as a minimum, and should not substitute clinical judgement. It relates to someone who is already engaged in care.*

Populations	**MSM, transgender men and women**
Necessary Aspects	• A documented confirmed 4th generation HIV negative test during an earlier episode of care in the last three-twelve months • Reporting condomless anal intercourse in the previous three months • Considered likely to engage in repeated condomless intercourse in the next three months • Proof of Welsh residency provided
Further Guidance	Where available, use point of care testing (fourth generation test).
Population	**HIV negative partner of a HIV positive person**
Necessary Aspects	• HIV positive partner's viral suppression is unknown • Condomless intercourse is anticipated or has occurred within the past three months • Proof of Welsh residency provided
Further guidance	PrEP should be recommended where the treating clinician recommends and monitors treatment as part of wider risk reduction (e.g. health education, safer sex promotion) Treatment as prevention for the HIV positive partner should be considered.
Population	**HIV negative heterosexuals**
Necessary Aspects	• Known to have had condomless sex with a person with HIV within unknown viral suppression within the past three months • Anticipated to have condomless sex with person, or person of similar status, again • Proof of Welsh residency provided
Further guidance	PrEP should be recommended where the treating clinician recommends and monitors treatment as part of wider risk reduction (e.g. health education, safer sex promotion)

14.3 Appendix 3 – 'An estimate of the incidence of HIV in men who have sex with men at high risk of HIV acquisition attending Integrated Sexual Health clinics in Wales, 2014'

Introduction

Men who have sex with men (MSM) who frequently request HIV testing are considered to be at high risk and may benefit from HIV pre-exposure prophylaxis (PrEP). In order to inform the development of policy on the use of PrEP in Wales, we attempted to estimate the number of MSM at high risk of HIV acquisition, and estimate the incidence of HIV in this population group.

Aims

To estimate the number of MSM in Wales at high risk of HIV and calculate the HIV seroconversion rates in this group, in order to inform policy on Pre-exposure prophylaxis.

Methods

Data on clinic attendances, diagnoses and services, and patient characteristics were extracted from the Sexual Health in Wales Surveillance Scheme (SWS). This is a pseudo-anonymised patient-level dataset containing information on all STI diagnoses and sexual health activities reported by Integrated Sexual Health (ISH) clinics in Wales. Patient identifiers are anonymised so that patients can only be longitudinally linked and followed within clinics using a unique clinic identification number.

Clinics in South Hywel Dda did not report to SWS during the study period and therefore are not included in the analysis.

We used a method developed by Public Health England (Holly Mitchell, personal communication) to calculate HIV seroconversion among a population of MSM aged 16 years of age or over who had at least two HIV tests within a one year period ("repeat testers"). MSM who tested HIV negative at any ISH in 2014 and had another HIV test 43-365 days later at the same clinic were included in the analysis. Any HIV test within 42 days of the first test was considered to belong to the same testing episode and was therefore excluded. MSM were followed from the date of their earliest HIV test in 2014 for up to one year until they either seroconverted or until their last attendance in the year after their first test (Figure 1).

Observations were censored at the last attendance within the year, whether a test was performed or not. Where there were subsequent attendances after the second test within the year, we assumed that the

patient was still HIV negative at the last attendance (even if not tested). This was because we assumed that any new risk exposure since the previous test would trigger a further HIV test. A seroconversion was a new HIV diagnosis occurring within a year of their earliest HIV test in 2014.

HIV seroconversion was calculated for specific sub-groups of the MSM cohort considered at higher risk, based on prior attendances at the same clinic. Higher risk individuals were those in any of the following sub-groups, listed below along with their rationale.

Risk subgroup	**Rationale**
MSM who had also tested for HIV in the previous year (prior HIV test 43-365 days before their first attendance in 2014).	Prior HIV test indicates higher risk – same as NHS England PrEP eligibility criteria
MSM with bacterial STI diagnosis at first attendance in 2014 or in any of previous 365 days (including chlamydia, gonorrhoea, syphilis, LGV, NSGI, donovanosis, and chancroid; any site)	Indication of sex without condoms in past year. Again proposed criterion for PrEP in NHS England
MSM who had taken post exposure prophylaxis after sexual exposure to HIV (PEPSE) anytime in the days 1-365 before their first attendance in 2014.	PEPSE indicates risk exposure

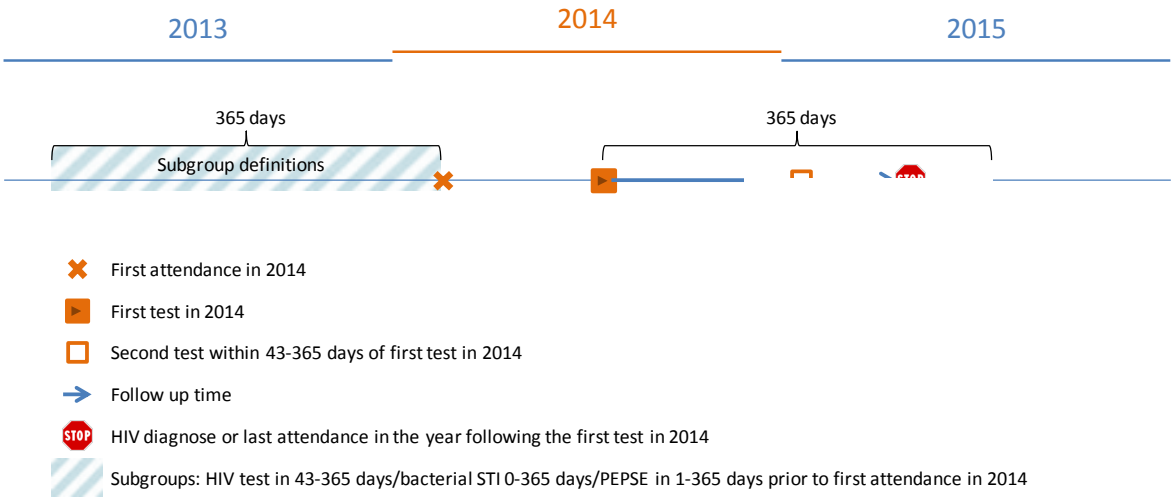
Annual HIV seroconversion rates (number of new HIV diagnoses divided by the total person-time at risk and expressed per 100 person-years) were calculated in Stata/SE 14.1 using the *stptime* command, which provides 95% Confidence Intervals calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.

Denominator: Person-time was calculated as the number of days from the first test date in 2014 to HIV diagnosis or to the last attendance in the following 365 days, whichever was first.

Outcome: Outcome was assumed to be no seroconversion, unless there was a HIV diagnosis in the year following the first test in 2014.

Exposures: Any higher risk subgroup; risk subgroups as defined in the table above.

Figure 1. Study timeline



Results

Among 582 MSM over 15 years old who were tested in 2014 and retested within one year, 5 seroconverted, giving an incidence rate of 1.3 per 100 person years (95%CI 0.6-3.2) (Table 1).

There was no statistically significant difference in the incidence in the individual risk sub-groups. Persons in any of the risk sub-groups had an incidence of 1.8 per 100 person years (95%CI 0.6-5.7), compared to an incidence of 0.9 per 100 person years (95%CI 0.2-3.7) in people not in any risk sub-group.

Table 1. HIV seroconversion rates per 100 person-years in HIV negative MSM over 15 years old tested in 2014 and retested within one year, Wales

Category		Subjects	Person-years	HIV Diagnoses	HIV rate per 100 py	95% CI
MSM over 15 years old tested in 2014 and retested within one year		582	378.3	5	1.3	0.6-3.2
HIV test 43-365 days prior to first attendance in 2014	**Yes**	158	108.0	2	1.9	0.5-7.4
	No	424	270.3	3	1.1	0.4-3.4
Bacterial STI in previous year and/or at first attendance in 2014	**Yes**	140	86.7	2	2.3	0.6-9.2
	No	442	291.5	3	1.0	0.3-3.2
Received post-exposure prophylaxis in year prior to first attendance in 2014	**Yes**	5	3.8	0	0.0	0.0-97.4*
	No	577	374.5	5	1.3	0.6-3.2
Any of the above risk groups	**Yes**	249	162.5	3	1.8	0.6-5.7
	No	333	215.8	2	0.9	0.2-3.7

*one-sided, 97.5% Poisson confidence interval

Limitations

The sample was relatively small. For better precision the analysis could be done with a longer recruitment and/or follow up periods.

Study population and subgroups could be defined in reference to first test in 2014, thus simplifying interpretation.

SWS can only be used to follow up individuals within clinics and not between clinics. This could impact the results in three ways: underestimating the number of MSM who have at least two HIV tests within a year if they have them in different clinics, or overestimating it if they have multiple tests in multiple clinics. HIV incidence estimates may also be underestimated if MSM at higher risk of HIV acquisition are also more likely to attend more than one ISH for HIV testing.

The analysis only includes HIV tests and diagnoses in ISH clinics reporting to SWS. Clinics in South Hywel Dda did not report to SWS during the study period and therefore are not included in the analysis. Test and diagnoses may also be carried out in GPs and hospitals.

References

Personal communication: this analysis is largely based in unpublished work by Holly Mitchell, Public Health England.

S Desai *et al*, "O13 HIV incidence in an open national cohort of MSM attending GUM clinics in England", Sex Transm Infect 2012;88:A5, http://sti.bmj.com/content/88/Suppl_1/A5.2?trendmd-shared=1

NHS England "Clinical Commissioning Policy Proposition: Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults", Reference: NHS England F03X06, https://www.engage.england.nhs.uk/consultation/specialised-services/user_uploads/f03x06-policy-proposition.pdf

14.4 Appendix 4 - UK rates for tenofovir and emtricitabine resistance in both naive and drug-experienced patients.

% tests with low-high level resistance to TDF/FTC, according to Stanford drug susceptibility scores, 2010-2014

		Year of sample				
Treatment status	**ART**	**2010**	**2011**	**2012**	**2013**	**2014**
Naïve	TDF	1.16	0.58	0.77	0.81	1.15
Naïve	FTC	0.58	0.65	0.53	0.58	0.74
Experienced	TDF	7.13	6.66	6.97	5.55	5.42
Experienced	FTC	14.43	14.00	14.71	14.44	13.12

The above information was provided by Professor Dunn along with two papers [94,95] on TDR. The paper (88) attempts a weighted analysis of resistance rates in naïve and experienced patients given that most HIV transmission is thought to come from naive patients.

14.5 Appendix 5 – Examples of Proof of Residency

Examples of proof of Welsh residency could include:

- Driver licence
- Evidence of local address on Health Board hospital systems, inc. Previous appointment
- Latest Council Tax bill
- Latest bank statement (within 3 months)
- Using Myrddin to confirm Welsh address/GP (if not from same Health Board area)

14.6 Appendix 6 – PrEP Developments Update, March 2017

This appendix provides an in-brief summary of the latest developments (from November 2016 until publication date) regarding Pre-Exposure Prophylaxis (PrEP) from a global perspective. Full abstracts or further information are available via the references at the end of this document.

CROI 2017

The annual Conference on Retroviruses and Opportunistic Infections (CROI) [96] brings together top basic, translational, and clinical researchers from around the world to share the latest studies, important developments, and best research methods in the ongoing battle against HIV/AIDS and related infectious diseases, and in 2017 was held between 13th-16th February 2017, and featured presentations relating to PrEP demonstration trials and other emerging evidence from areas where PrEP has already been implemented.

In their poster 'STI Incidence among MSM Following HIV Pre-exposure Prophylaxis: A Modelling Study', Jenness et al. [97] hypothesise that increasing uptake of PrEP, alongside successful treatment for STIs after routine screening could lead to 'strong and sustained declines in neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) incidence and prevalence in MSM.' In addition, 'PrEP-related screening would result in early detection of many more asymptomatic rectal cases'. The authors do reflect on previous papers which state that bi-annual STI screening, as recommended in the CDC PrEP Clinical Guidelines, may miss 40% of infections, and consider that performing STI screening at quarterly intervals 'would result in a further 50% reduction in incidence.'

A poster presentation from Selinger et al. [98] looks at 'Anticipated Adherence, Efficacy and Impact of Weekly Oral Pre-Exposure Prophylaxis'. The authors contemplate the introduction of week-long orally delivered anti-retroviral drugs, and the impact that this could have with PrEP provision. A random effects meta-analysis was performed to estimate the most likely impact of weekly PrEP on efficacy, concluding that a weekly oral PrEP treatment 'has the potential to substantially increase PrEP efficacy and population-level impact relative to daily oral PrEP'.

McMahan et al. [99] contemplated 'Knowledge about PrEP Among MSM and Trans Methamphetamine Users in Seattle' in their poster presentation. Acknowledging that MSM using crystal meth are at particularly high risk of HIV infection, and are also under-represented in PrEP programs in Seattle, the authors surveyed this population to garner their knowledge of PrEP and any potential barriers to its use. The results highlighted that a considerable number had heard of PrEP, but only 7 out of the 213 respondents who knew about PrEP had actually used it. 88 respondents

who had concerns about using PrEP stated their reasons for being concerned; nearly half of them (47.7%) believed that PrEP wouldn't prevent HIV, with 31.8% also concerned that their meth use may impact PrEP efficacy.

Jean-Michel Molina, one of the scientists leading the French IPERGAY study, presented a paper on the 'provision of doxycycline along with on-demand PrEP' [100]. In this trial, participants from the ANRS IPERGAY trial were randomised 1:1 to take either two pills of doxycycline (100mg per pill) within 72h after condomless sexual intercourse (without exceeding 6 pills per week) or no PrEP. All subjects received risk-reduction counselling and condoms, and were tested every 8 weeks for HIV and STIs with serologic assays for HIV and syphilis and PCR assays for Chlamydia trachomatis and Neisseria gonorrhoeae in urine samples, oral and anal swabs. The primary study endpoint was the time to a first bacterial STI: gonorrhoea, Chlamydia infection or syphilis. The authors conclude that 'on demand PrEP with doxycycline reduced the incidence of chlamydia infection and syphilis in high risk MSM and has an acceptable safety profile. The long-term efficacy of this strategy and its impact on antibiotic resistance needs to be assessed.'

Of particular note at CROI 2017 was a case of an individual contracting HIV during a PrEP demonstration project in Amsterdam, despite consistent adherence to PrEP, which was presented by Hoornenborg and de Bree [101]. In their poster and oral presentation 'Acute Infection With a Wild-Type HIV-1 Virus in PrEP User With High TDF Levels', the case of a 50 year old MSM taking daily PrEP was considered. The individual was HIV negative at the outset, and after screening at one, three and six months. The individual participated in chemsex involving amphetamine, cocaine, GHB/GBL, mephedrone and ketamine, and reported 141 condomless anal sex (CAS) partners and 200 CAS episodes within the first 24 weeks of being on PrEP, with symptoms of fever and dysuria appearing eight months after commencing PrEP, with HIV detected three weeks later. The individual had reported excellent adherence to PrEP. The authors acknowledge that the 'underlying mechanism [for HIV infection] remains speculative', considering whether it was due to 'high repeated HIV exposure and/or mucosal damage' or 'lower levels of TDF and/or FTC in rectal mucosa'.

Ongoing Trials

Findings from trials globally continue to be published.

Based in Northern California, the **Kaiser PrEP trial**, seen as the largest trial to date conducted of PrEP use in clinical practice, reported its latest findings in the Journal of Acquired Immune Deficiency Syndromes [102,103]. This latest analysis of the trial shows that adherence to PrEP amongst the 972 trial participants was high (92%), with incidences of

gonorrhoea and Chlamydia being high, again highlighting the need for quarterly testing, rather than the bi-annual testing as per current CDC Guidelines. As NAM / aidsmap report:

'O*f the 972 users, 342 (35%) were diagnosed with at least one STI during follow-up; 173 people had multiple STIs (including a person with 19 diagnoses). A total of 771 STIs were diagnosed, for a rate of 90.7 per 100 person-years.'*

'After 12 months on PrEP, cumulative incidence rates were 42% for any STI, 27% for any rectal STI, 26% for chlamydia, 23% for gonorrhoea and 7% for syphilis. Rectal chlamydia and urethral gonorrhoea increased significantly over time. The researchers suggested that the rise in STIs could be attributable to changes in sexual behaviour after starting PrEP or changes in testing frequency.'

The Netherlands' **AMPREP** demonstration study has reported high Hepatitis C infection in participants tested for it at baseline [104,105]. In a presentation at the HepHIV2017 Conference in Malta, Maria Prins of the Academic Medical Center said that '*phylogenetic mapping suggested that the explanation might lie in study participants being more likely to have condomless sex with men of HIV-positive or unknown status, amongst whom HCV prevalence was higher than other HIV-negative men*'[104].

Aidsmap have provided an extensive review of the **US National HIV PrEP Summit**, which occurred in December 2016. Unfortunately, many of the papers from this summit are unavailable, though it is worth looking at Aidsmap's coverage for insights into ongoing developments with US demonstration studies and trials for PrEP [106].

UK Developments

<u>England</u>

NHS England and Public Health England have announced a large scale clinical trial in 2017/2018 on PrEP [107]. This is following advice from Public Health England, highlighting significant outstanding implementation questions that should be answered prior to using PrEP in a sustained way on a substantial scale in England. The clinical trial will seek to answer the following questions:

1. What proportion of genitourinary medicine (GUM) clinic attendees will be assessed as eligible for PrEP?
2. How to identify, engage and maintain other eligible PrEP users?
3. What proportions of the eligible will accept PrEP and will choose daily or intermittent dosing?
4. For how long will those beginning at high risk stay on PrEP?
5. What impact will PrEP have on HIV incidence?

6. What impact will PrEP have on STI incidence?

At least 10,000 trial participants will be recruited over the next three years, with Gilead (manufacturers of Truvada®) and other generic manufacturers invited to submit proposals to participate in the trial. Public Health England has been working with St Stephen's AIDS Trust to develop the trial proposals.

Also in England, four London clinics reported preliminary data suggesting significant drops in HIV infection amongst MSM during 2016. One of the reasons suggested for this is the number of participants of the PROUD trial, which is based in London, whilst another is improved monitoring of patients who are accessing generic PrEP from non-NHS sources [108].

International Developments

In early March 2017, New Zealand became the latest country to approve access to Truvada® as PrEP [109]. Prescriptions for the treatment can now be received at GPs and sexual health clinics in New Zealand.

Also in Australasia is the news of a trial commencing in South Australia from April 2017 called PrEPX-SA [110].

Other Research

Researchers at **DeMontfort University** have looked into the perceptions of PrEP amongst HIV-negative and HIV-positive MSM [111,112].Three main themes emerged from their findings:

1. uncertainty and fear,
2. managing relationships with others, and
3. stigma and categorization.

According to the study's abstract [111], *'HIV-negative interviewees generally perceived PrEP as a risky solution for "high risk" individuals, while HIV-positive individuals regarded it as potentially enhancing interpersonal relations between serodiscordant partners. Social stigma overwhelmingly underpinned individuals' perceptions of PrEP. This might inhibit access to PrEP among those who might benefit most from it, thereby undermining HIV prevention efforts.'*

Amongst the findings of this study were participants stating that they would not use condoms consistently while taking PrEP, whilst the concept of 'high-risk' was debated; many said that being considered 'high risk' by qualifying to take PrEP was a stigma in itself, whilst there was also a general lack of understanding about what constituted high-risk activities noted.

15 References

1. Public Health England HIV: annual data tables. GOV.UK. 2016. Available at: https://www.gov.uk/government/statistics/hiv-annual-data-tables (Accessed: 8 November 2016)

2. Public Health Wales Health Protection Division Public Health Wales Health Protection Division - Sexual Health Reports for Wales. Public Health Wales. 2016. Available at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=457&pid=27846 (Accessed: 8 November 2016)

3. NHS England Specialised Services Clinical Reference Group for, HIV, NHS England Evidence Review: Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults [Evidence Review]. NHS England; October 2015 p. 85. Available at: https://www.engage.england.nhs.uk/consultation/specialised-services/user_uploads/f03x06-evidnc-rev.pdf (Accessed: 4 November 2016)

4. World Health Organization (WHO) Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. Geneva, Switzerland: World Health Organization; July 2014 p. 184. Available at: http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1 (Accessed: 4 November 2016)

5. Nandwani R., Valiotis G. PrEP in Scotland. Scottish HIV Pre-Exposure Prophylaxis Short Life Working Group; 2016. Available at: http://www.hivscotland.com/downloads/1477409732-Scotland%20PrEP%20report%20October%202016.pdf (Accessed: 4 November 2016)

6. McCormack S., Fidler S., Waters L., Azad Y., Barber T., Cairns G., et al. BHIVA–BASHH Position Statement on PrEP in UK - Second Update, May 2016. British HIV Association (BHIVA) / British Association for Sexual and Reproductive Health (BASHH); 2016. Available at: https://www.bashhguidelines.org/media/1071/bhiva-bashh-position-statement-on-prep-in-uk-may-2016.pdf (Accessed: 1 November 2016)

7. NHS England Specialised Services Clinical Reference Group for, NHS England Clinical Commissioning Policy Proposition: Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults. NHS England; Available at: https://www.engage.england.nhs.uk/consultation/specialised-services/user_uploads/f03x06-policy-proposition.pdf (Accessed: 4 November 2016)

8. Noori T., Pharris A. Meeting report: Pre-exposure Human Immunodeficiency Virus Prophylaxis in the EU/EEA: Challenges and Opportunities, Stockholm April 2016. Eurosurveillance. 23 June 2016; 21(25). Available at: DOI:10.2807/1560-7917.ES.2016.21.25.30263 (Accessed: 9 October 2016)

9. Battegay M., Lundgren JD., Ryom L. (eds.) EACS Guidelines version 8.1, October 2016. 8.1. European AIDS Clinical Society (EACS); 2016. 96 p. Available at: http://www.eacsociety.org/files/guidelines_8.1-english.pdf (Accessed: 3 November 2016)

10. Battegay M., Lundgren JD., Ryom L. (eds.) Pre-Exposure Prophylaxis. 8.1. European AIDS Clinical Society (EACS); 2016. p. 17. Available at: http://www.eacsociety.org/files/guidelines_8.1-english.pdf (Accessed: 3 November 2016)

11. Frankis JS., Young I., Lorimer K., Davis M., Flowers P. Towards preparedness for PrEP: PrEP awareness and acceptability among MSM at high risk of HIV transmission who use sociosexual media in four Celtic nations: Scotland, Wales, Northern Ireland and The Republic of Ireland: an online survey. Sexually Transmitted Infections. June 2016; 92(4): 279–285. Available at: DOI:10.1136/sextrans-2015-052101 (Accessed: 23 May 2016)

12. European Centre for Disease Prevention and Control (ECDC) PrEP in the EU-EEA - challenges and opportunities. Stockholm: European Centre for Disease Prevention and Control (ECDC); April 2016. Available at: http://www.eatg.org/gallery/174250/PrEP%20in%20the%20EU-EEA%20-%20challenges%20and%20opportunities.pdf (Accessed: 6 August 2016)

13. Cohen S., Vittinghoff PhD E., Philip, MD, MPH SS., Doblecki-Lewis, MD S., Bacon, MD, MPH O., Chege, MD, MPH W., et al. Quarterly Screening Optimizes STI Detection Among PreP Users in the Demo Project [Poster]. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2016; 22 February 2016; Boston, Massachusetts. Available at: http://www.croiconference.org/sites/default/files/posters-2016/870.pdf (Accessed: 9 June 2016)

14. Golub SA., Pena S., Boonrai K., Douglas N., Hunt M., Radix A. STI Data From Community-Based PrEP Implementation Suggest Changes to CDC Guidelines [Poster]. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2016; 22 February 2016; Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/sti-data-community-based-

prep-implementation-suggest-changes-cdc-guidelines-0 (Accessed: 16 November 2016)

15. Golub SA. It's Complicated: Renal Function and STIs in PrEP Users [Oral]. Oral presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2016; 22 February 2016; Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/sti-data-community-based-prep-implementation-suggest-changes-cdc-guidelines-0 (Accessed: 16 November 2016)

16. Email Correspondence with Cardiff and Vale University Health Board Finance Department. 2016.

17. Cambiano V., Miners A., Dunn D., McCormack S., Ong K., Gill N., et al. Is PrEP for HIV prevention cost-effective in MSM in the UK? Glasgow: University College London; 2015.

18. Chen A., Dowdy DW. Clinical Effectiveness and Cost-Effectiveness of HIV Pre-Exposure Prophylaxis in Men Who Have Sex with Men: Risk Calculators for Real-World Decision-Making. Garcia-Lerma JG (ed.) PLoS ONE. 6 October 2014; 9(10): e108742. Available at: DOI:10.1371/journal.pone.0108742 (Accessed: 28 October 2016)

19. Hankins CA. Untangling the cost–effectiveness knot: who is oral antiretroviral HIV pre-exposure prophylaxis really for? Expert Review of Pharmacoeconomics & Outcomes Research. April 2014; 14(2): 167–170. Available at: DOI:10.1586/14737167.2014.887447 (Accessed: 28 October 2016)

20. Ross EL., Cinti SK., Hutton DW. Implementation and Operational Research: A Cost-Effective, Clinically Actionable Strategy for Targeting HIV Preexposure Prophylaxis to High-Risk Men Who Have Sex With Men. JAIDS Journal of Acquired Immune Deficiency Syndromes. July 2016; 72(3): e61–e67. Available at: DOI:10.1097/QAI.0000000000000987 (Accessed: 28 October 2016)

21. Ong KJ., Desai S., Desai M., Nardone A., Hoek AJ van., Gill ON. Cost and cost-effectiveness of an HIV pre-exposure prophylaxis (PrEP) programme for high-risk men who have sex with men in England: results of a static decision analytical model. The Lancet. 13 November 2015; Available at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)00854-5.pdf (Accessed: 28 October 2016)

22. Nichols B. PrEP is Only Cost-Effective Among MSM in the Netherlands When Used on Demand. Conference on Retroviruses and Opportunisitc Infections (CROI) 2016; 25 February 2016; Boston, Massachusetts. Available at:

http://www.croiconference.org/sites/default/files/posters-2016/1052.pdf

23. Nichols BE., Boucher CAB., van der Valk M., Rijnders BJA., van de Vijver DAMC. Cost-effectiveness analysis of pre-exposure prophylaxis for HIV-1 prevention in the Netherlands: a mathematical modelling study. The Lancet Infectious Diseases. September 2016; Available at: DOI:10.1016/S1473-3099(16)30311-5 (Accessed: 28 October 2016)

24. Schneider K., Gray RT., Wilson DP. A Cost-effectiveness Analysis of HIV Preexposure Prophylaxis for Men Who Have Sex With Men in Australia. Clinical Infectious Diseases. 4 January 2014; 58(7): 1027–1034. Available at: DOI:10.1093/cid/cit946 (Accessed: 28 October 2016)

25. Drabo EF., Hay JW., Vardavas R., Wagner ZR., Sood N. A Cost-effectiveness Analysis of Preexposure Prophylaxis for the Prevention of HIV Among Los Angeles County Men Who Have Sex With Men. Clinical Infectious Diseases. 23 August 2016; : ciw578. Available at: DOI:10.1093/cid/ciw578 (Accessed: 30 September 2016)

26. Ouellet E., Durand M., Guertin JR., LeLorier J., Tremblay CL. Cost Effectiveness of 'On Demand' Hiv Pre-Exposure Prophylaxis for Non-Injection Drug-Using Men Who Have Sex with Men in Canada. Canadian Journal of Infectious Diseases and Medical Microbiology. 2015; 26(1): 23–29. Available at: DOI:10.1155/2015/964512 (Accessed: 28 October 2016)

27. MacFadden DR., Tan DH., Mishra S. Optimizing HIV pre-exposure prophylaxis implementation among men who have sex with men in a large urban centre: a dynamic modelling study. Journal of the International AIDS Society. 23 September 2016; 19(1). Available at: DOI:10.7448/IAS.19.1.20791 (Accessed: 29 November 2016)

28. Bernard CL., Brandeau ML., Humphreys K., Bendavid E., Holodniy M., Weyant C., et al. Cost-Effectiveness of HIV Preexposure Prophylaxis for People Who Inject Drugs in the United States. Annals of Internal Medicine. 5 July 2016; 165(1): 10. Available at: DOI:10.7326/M15-2634 (Accessed: 28 October 2016)

29. Alistar SS., Owens DK., Brandeau ML. Effectiveness and Cost Effectiveness of Oral Pre-Exposure Prophylaxis in a Portfolio of Prevention Programs for Injection Drug Users in Mixed HIV Epidemics. Yazdanpanah Y (ed.) PLoS ONE. 28 January 2014; 9(1): e86584. Available at: DOI:10.1371/journal.pone.0086584 (Accessed: 29 November 2016)

30. British National Formulary (BNF) Truvada®: British National Formulary. 2016. Available at: https://www.evidence.nhs.uk/formulary/bnf/current/5-infections/53-antiviral-drugs/531-hiv-infection/nucleoside-reverse-transcriptase-inhibitors/tenofovir-disoproxil/with-emtricitabine/truvada (Accessed: 8 November 2016)

31. Nakagawa F., Miners A., Smith CJ., Simmons R., Lodwick RK., Cambiano V., et al. Projected Lifetime Healthcare Costs Associated with HIV Infection. Beck EJ (ed.) PLOS ONE. 22 April 2015; 10(4): e0125018. Available at: DOI:10.1371/journal.pone.0125018 (Accessed: 6 October 2016)

32. Public Health Wales NHS Trust, 1000 Lives Improvement Prudent healthcare – setting out the prudent principles. Making prudent healthcare happen. 2015. Available at: http://www.prudenthealthcare.org.uk/principles/ (Accessed: 17 November 2016)

33. I Want PrEP Now Buy PrEP Now. I Want PrEP Now. Available at: http://www.iwantprepnow.co.uk/buy-prep-now (Accessed: 7 November 2016)

34. I Want PrEP Now TDM results generic PrEP. I Want PrEP Now. Available at: https://drive.google.com/file/d/0B37FNlyZFahOdWl5bHVaSWRRNFU/view?usp=sharing&usp=embed_facebook (Accessed: 7 November 2016)

35. European AIDS Treatment Group (EATG) Position on HIV Prevention. 2015. Available at: http://www.eatg.org/wp-content/uploads/2015/09/EATG-Position-Paper-on-Prevention-October-2015.FINAL_.pdf (Accessed: 1 November 2016)

36. Gregowenblog Clinic hopping – gregowenblog. 2015. Available at: https://gregowenblog.wordpress.com/tag/clinic-hopping/ (Accessed: 6 November 2016)

37. World Health Organization Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. World Health Organization; 2016. Available at: http://www.who.int/hiv/pub/guidelines/keypopulations/en/ (Accessed: 8 June 2016)

38. WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP) - Policy brief. World Health Organization; 2015. Available at: http://apps.who.int/iris/bitstream/10665/197906/1/WHO_HIV_2015.48_eng.pdf?ua=1 (Accessed: 8 June 2016)

39. BBC News Aids charity to take fight over Prep drug to court. BBC News. 2015. Available at: http://www.bbc.co.uk/news/health-36464289 (Accessed: 7 June 2016)

40. National AIDS Trust Why is PrEP Needed? National AIDS Trust; 2016. Available at: http://www.nat.org.uk/sites/default/files/Why%20is%20PrEP%20needed.pdf (Accessed: 11 November 2016)

41. Prepster Prepster. Prepster. Available at: http://prepster.info/ (Accessed: 3 November 2016)

42. PrEP Access PrEP Access. PrEP Access. Available at: http://www.prepaccess.org.uk (Accessed: 13 June 2016)

43. I Want PrEP Now I Want PrEP Now. I Want PrEP Now. n.d. Available at: http://www.iwantprepnow.co.uk/ (Accessed: 9 June 2016)

44. PrEP in Europe Initiative (PiEi) Prep in Europe. Facebook. Available at: https://www.facebook.com/Prep-in-Europe-1459917834306555/ (Accessed: 17 November 2016)

45. PrEP in Europe Initiative (PiEi) PrEP Access in Europe. 2016. Available at: http://www.eatg.org/wp-content/uploads/2016/10/PrEP-access-in-Europe-PrEP-in-Europe-Initiative-PiEi.pdf (Accessed: 9 October 2016)

46. National Institute for Health and Care Excellence (NICE) Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil) [Evidence summary: new medicine]. Manchester: National Institute for Health and Care Excellence (NICE); October 2016. Report No.: esnm78. Available at: https://www.nice.org.uk/guidance/esnm78/resources/preexposure-prophylaxis-of-hiv-in-adults-at-high-risk-truvada-emtricitabinetenofovir-disoproxil-1502681172406981 (Accessed: 28 October 2016)

47. Grant RM., Lama JR., Anderson PL., McMahan V., Liu AY., Vargas L., et al. Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. New England Journal of Medicine. 30 December 2010; 363(27): 2587–2599. Available at: DOI:10.1056/NEJMoa1011205 (Accessed: 6 October 2016)

48. Mugwanya KK., Donnell D., Celum C., Thomas KK., Ndase P., Mugo N., et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. The Lancet Infectious Diseases. December 2013; 13(12): 1021–1028. Available at: DOI:10.1016/S1473-3099(13)70226-3 (Accessed: 7 November 2016)

49. Baeten JM., Donnell D., Ndase P., Mugo NR., Campbell JD., Wangisi J., et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. New England Journal of Medicine. 2 August 2012; 367(5): 399–410. Available at: DOI:10.1056/NEJMoa1108524 (Accessed: 7 June 2016)

50. PROUD. PROUD. Available at: http://www.proud.mrc.ac.uk (Accessed: 5 November 2016)

51. McCormack S., Dunn DT., Desai M., Dolling DI., Gafos M., Gilson R., et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet. January 2016; 387(10013): 53–60. Available at: DOI:10.1016/S0140-6736(15)00056-2 (Accessed: 9 June 2016)

52. Dolling DI., Desai M., McOwan A., Gilson R., Clarke A., Fisher M., et al. An analysis of baseline data from the PROUD study: an open-label randomised trial of pre-exposure prophylaxis. Trials. December 2016; 17(1). Available at: DOI:10.1186/s13063-016-1286-4 (Accessed: 7 November 2016)

53. Desai M., White E., Vora N., Gafos M., Apea V., Brady M., et al. Chemsex in the PROUD study [Poster]. Poster presented at: Public Health England Annual Conference 2016; 13 September 2016; Warwick, England.

54. Oxford Dictionaries chemsex - definition of chemsex in English. Oxford Dictionaries | English. Available at: https://en.oxforddictionaries.com/definition/chemsex (Accessed: 7 November 2016)

55. Feustel N. The PROUD Study: a video documentary [Documentary]. MRC Clinical Trials / georgetown media; 2015. Available at: https://vimeo.com/132412294 (Accessed: 13 June 2016)

56. IPERGAY. IPERGAY. Available at: http://www.ipergay.fr (Accessed: 5 November 2016)

57. AVAC - Global Advocacy for HIV Prevention PrEP Ongoing Planned Oral Studies - as of October 2016. 2016. Available at: http://www.avac.org/sites/default/files/resource-files/PrEP_ongoing_planned_oral_studies_Oct2016.pdf (Accessed: 11 July 2016)

58. Molina J-M., Capitant C., Spire B., Pialoux G., Cotte L., Charreau I., et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. New England Journal of Medicine. 3 December 2015;

373(23): 2237–2246. Available at: DOI:10.1056/NEJMoa1506273 (Accessed: 13 June 2016)

59. Molina J-M., Charreau I., Spire B., Cotte L., Chas J., Capitant C., et al. Efficacy of on demand PrEP with TDF-FTC in the ANRS IPERGAY open-label extension study. Durban, South Africa; 2016. Available at: http://programme.aids2016.org/Abstract/Abstract/2564 (Accessed: 7 November 2016)

60. Molina J-M. Lessons from implementation in France. Glasgow, UK: Journal of the International AIDS Society; 2016. Available at: http://www.jiasociety.org/index.php/jias/issue/view/1485 (Accessed: 28 October 2016)

61. Molina J-M. PrEP Roll-Out in France. Durban, South Africa; 2016. Available at: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0ahUKEwjPpu71h5fQAhXKDMAKHVooAaMQFggkMAI&url=http%3A%2F%2Fprogramme.aids2016.org%2FPAGMaterial%2FPPT%2F5839_3168%2FPrEP%2520Roll%2520Out%2520France.ppt&usg=AFQjCNFrkuWUtjCbPi2hbiApKzMo6InC4A&sig2=-9N0OQBwN7wlzqwi2rnNlg&cad=rja (Accessed: 7 November 2016)

62. Centre of Excellence for Health, Immunity and Infections (CHIP) CHIP.DK > Studies > PARTNER > Q and A. Centre of Excellence for Health, Immunity and Infections (CHIP). Available at: http://www.chip.dk/Studies/PARTNER/Q-and-A (Accessed: 7 November 2016)

63. Centre of Excellence for Health, Immunity and Infections (CHIP) CHIP.DK > Studies > PARTNER > PARTNER 2. Centre of Excellence for Health, Immunity and Infections (CHIP). Available at: http://www.chip.dk/PARTNER-2 (Accessed: 7 November 2016)

64. Rodger AJ., Cambiano V., Bruun T., Vernazza P., Collins S., van Lunzen J., et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA. 12 July 2016; 316(2): 171. Available at: DOI:10.1001/jama.2016.5148 (Accessed: 7 November 2016)

65. Nguyen V-K., Trottier H., Tossa HG., Charest L., Longpré. D., Stéphane Lavoie, et al. Increased rate of C. trachomatis infection after being prescribed PrEP. Glasgow, UK: Journal of the International AIDS Society; 2016. Available at: http://www.jiasociety.org/index.php/jias/issue/view/1485 (Accessed: 28 October 2016)

66. Kale S. Gay and Bi Men Are Resorting to Desperate Measures to Get HIV Prevention Meds. Broadly. Available at: https://broadly.vice.com/en_us/article/gay-and-bi-men-are-resorting-to-desperate-measures-to-get-hiv-prevention-meds (Accessed: 30 September 2016)

67. 56 Dean Street 56 Dean Street - PrEP. GetPrEP.uk - PrEP Clinic London. Available at: https://getprep.uk/ (Accessed: 3 November 2016)

68. Straube T. Positive on PrEP. POZ. 2016. Available at: https://www.poz.com/article/positive-prep (Accessed: 8 June 2016)

69. Straube T. Meet the Man Who Got HIV While on Daily PrEP. POZ. 2016. Available at: https://www.poz.com/article/meet-man-got-hiv-daily-prep (Accessed: 8 June 2016)

70. Knox DC. HIV-1 Infection With Multiclass Resistance Despite Preexposure Prophylaxis (PrEP). Conference on Retroviruses and Opportunisitc Infections (CROI) 2016; 25 February 2016; Boston, Massachusetts. Available at: http://www.croiconference.org/sessions/hiv-1-infection-multiclass-resistance-despite-preexposure-prophylaxis-prep (Accessed: 8 June 2016)

71. Dimitrov DT., Boily M-C., Hallett TB., Albert J., Boucher C., Mellors JW., et al. How Much Do We Know about Drug Resistance Due to PrEP Use? Analysis of Experts' Opinion and Its Influence on the Projected Public Health Impact. Apetrei C (ed.) PLOS ONE. 8 July 2016; 11(7): e0158620. Available at: DOI:10.1371/journal.pone.0158620 (Accessed: 20 October 2016)

72. Liu AY., Vittinghoff E., Sellmeyer DE., Irvin R., Mulligan K., Mayer K., et al. Bone Mineral Density in HIV-Negative Men Participating in a Tenofovir Pre-Exposure Prophylaxis Randomized Clinical Trial in San Francisco. PLOS ONE. 29 August 2011; 6(8): e23688. Available at: DOI:10.1371/journal.pone.0023688 (Accessed: 17 November 2016)

73. Solomon MM., Lama JR., Glidden DV., Mulligan K., McMahan V., Liu AY., et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis: AIDS. March 2014; 28(6): 851–859. Available at: DOI:10.1097/QAD.0000000000000156 (Accessed: 17 November 2016)

74. Martin M., Vanichseni S., Suntharasamai P., Sangkum U., Mock PA., Gvetadze RJ., et al. Renal Function of Participants in the Bangkok Tenofovir Study—Thailand, 2005–2012. Clinical Infectious Diseases.

9 January 2014; 59(5): 716–724. Available at: DOI:10.1093/cid/ciu355 (Accessed: 17 November 2016)

75. Van Damme L., Corneli A., Ahmed K., Agot K., Lombaard J., Kapiga S., et al. Preexposure Prophylaxis for HIV Infection among African Women. New England Journal of Medicine. 2 August 2012; 367(5): 411–422. Available at: DOI:10.1056/NEJMoa1202614 (Accessed: 7 November 2016)

76. Radix A., Carneiro P., Stephanos S., Mosher S., Meacher P., Belkind U., et al. Transgender patients at risk: ensuring access to PrEP in a NYC community health centre. Durban, South Africa; Available at: http://programme.aids2016.org/Abstract/Abstract/8512 (Accessed: 30 September 2016)

77. European Medicines Agency (EMA) First medicine for HIV pre-exposure prophylaxis recommended for approval in the EU. European Medicines Agency (EMA). 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002578.jsp&mid=WC0b01ac058004d5c1 (Accessed: 3 November 2016)

78. U.S. National Institutes of Health Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection. ClinicalTrials.gov. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02842086?term=NCT02842086&rank=1 (Accessed: 17 November 2016)

79. NHS Research Design Service Non-Inferiority Trials. NHS National Institute for Health Research. Available at: http://www.rds-sc.nihr.ac.uk/planning-a-study/study-design/quantitative-studies/clinical-trials/non-inferiority-trials/ (Accessed: 17 November 2016)

80. British HIV Association (BHIVA) BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). British HIV Association (BHIVA); 2016. Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf (Accessed: 29 November 2016)

81. NHS England Update on PrEP. NHS England. 2016. Available at: https://www.england.nhs.uk/2016/11/update-on-prep/ (Accessed: 10 November 2016)

82. NHS England Integrated Impact Assessment Report for Clinical Commissioning Policies - Clinical Commissioning Policy Proposition:

Pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults. NHS England; Available at: https://www.engage.england.nhs.uk/consultation/specialised-services/user_uploads/f03x06-impact-assessment.pdf (Accessed: 4 November 2016)

83. PrEPWatch Country Updates. PrEPWatch. Available at: http://www.prepwatch.org/scaling-up/country-updates/ (Accessed: 17 November 2016)

84. Country Updates. PrEPWatch. Available at: http://www.prepwatch.org/in-country-introduction/country-updates/ (Accessed: 17 November 2016)

85. GGD Amsterdam Eén jaar Amsterdam PrEP project [webpagina]. GGD Amsterdam. Available at: http://www.ggd.amsterdam.nl/nieuwsoverzicht/een-jaar-amsterdam-p/ (Accessed: 28 October 2016)

86. Bil JP., Davidovich U., van der Veldt WM., Prins M., de Vries HJC., Sonder GJB., et al. What do Dutch MSM think of preexposure prophylaxis to prevent HIV-infection? A cross-sectional study. AIDS (London, England). 15 May 2015; 29(8): 955–964. Available at: DOI:10.1097/QAD.0000000000000639

87. Unit PT. PrEP Tactical Unit. PrEP Tactical Unit. Available at: https://ptu.nu/en/ (Accessed: 6 November 2016)

88. Weller C. Norway just became the first country to offer the leading HIV prevention drug for free. Business Insider. 21 October 2016; Available at: http://uk.businessinsider.com/norway-offers-hiv-drug-prep-free-2016-10 (Accessed: 29 November 2016)

89. Avert Norway provides PrEP for free to all those at risk of HIV. Avert. 2016. Available at: https://www.avert.org/news/norway-provides-prep-free-all-those-risk-hiv (Accessed: 29 November 2016)

90. HIVNorge PrEP til folket. 2016. Available at: https://hivnorge.no/Nyheter/Okt-2016/PrEP-til-folket (Accessed: 28 October 2016)

91. U.S. Food and Drug Administration (FDA) Press Announcements - FDA approves first drug for reducing the risk of sexually acquired HIV infection [WebContent]. 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm (Accessed: 29 November 2016)

92. ClinicalTrials.gov [US] A Prospective, Observational, Drug Utilization Study of Subjects Taking Truvada for Pre-exposure Prophylaxis in the

USA - Full Text View. ClinicalTrials.gov. 2016. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01865799 (Accessed: 29 November 2016)

93. European Medicines Agency (EMA) Truvada. European Medicines Agency (EMA). 2016. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000594/human_med_001113.jsp&mid=WC0b01ac058001d124 (Accessed: 4 November 2016)

94. Tostevin A., White E., Dunn D., Croxford S., Delpech V., Williams I., et al. Recent trends and patterns in HIV-1 transmitted drug resistance in the United Kingdom. HIV Medicine. July 2016; Available at: DOI:10.1111/hiv.12414 (Accessed: 18 November 2016)

95. Dolling D., Phillips A., Delpech V., Pillay D., Cane P., Crook A., et al. Evaluating the extent of potential resistance to pre-exposure prophylaxis within the UK HIV-1-infectious population of men who have sex with men: PrEP resistance in UK HIV-infectious MSM. HIV Medicine. May 2012; 13(5): 309–314. Available at: DOI:10.1111/j.1468-1293.2011.00968.x (Accessed: 18 November 2016)

96. Conference on Retroviruses and Opportunistic Infections (CROI) CROI 2017: Seattle | CROI Conference. 2017. Available at: http://www.croiconference.org/ (Accessed: 17 February 2017)

97. Jenness SM., Weiss K., Goodreau SM., Gift T., Chesson H., Hoover KW., et al. STI Incidence among MSM Following HIV Preexposure Prophylaxis: A Modeling Study [Poster]. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2017; February 2017; Seattle, Washington. Available at: http://www.croiconference.org/sites/default/files/posters-2017/1034_Jenness.pdf (Accessed: 17 February 2017)

98. Selinger C., Kirtane A., Abouzid O., Langer R., Traverso CG., Bershteyn A. Anticipated Adherence, Efficacy and Impact of Weekly Oral Pre-Exposure Prophylaxis [Poster]. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2017; February 2017; Seattle, Washington. Available at: http://www.croiconference.org/sites/default/files/posters-2017/1035_Selinger.pdf (Accessed: 17 February 2017)

99. McMahan V., Martin A., Garske L., Baeten J., Banta-Green C., Stekler J. Knowledge about PrEP Among MSM and Trans* Methamphetamine Users in Seattle [Poster]. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2017; February 2017; Seattle, Washington. Available at:

http://www.croiconference.org/sites/default/files/posters-2017/967_McMahan.pdf (Accessed: 17 February 2017)

100. Molina J-M., Charreau I., Chidiac C., Pialoux G., Cua E., Delaugerre C., et al. On Demand Post-Exposure Prophylaxis with Doxycycline for MSM Enrolled in a PrEP Trial [Oral Presentation]. Oral Presentation presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2017; February 2017; Seattle, Washington. Available at: http://www.croiconference.org/sessions/demand-post-exposure-prophylaxis-doxycycline-msm-enrolled-prep-trial (Accessed: 17 February 2017)

101. Hoornenborg E., de Bree GJ. Acute Infection With a Wild-Type HIV-1 Virus in PrEP User With High TDF Levels [Poster Presentation]. Poster Presentation presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2017; February 2017; Seattle, Washington. Available at: http://www.croiconference.org/sites/default/files/posters-2017/953_Hoornenborg.pdf (Accessed: 17 February 2017)

102. Highleyman L. No new HIV infections in Northern California Kaiser PrEP programme, but STI rates rising. Available at: http://www.aidsmap.com/No-new-HIV-infections-in-Northern-California-Kaiser-PrEP-programme-but-STI-rates-rising/page/3113188 (Accessed: 26 January 2017)

103. Marcus JL., Hurley LB., Hare CB., Nguyen DP., Phengrasamy T., Silverberg MJ., et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. JAIDS Journal of Acquired Immune Deficiency Syndromes. December 2016; 73(5): 540–546. Available at: DOI:10.1097/QAI.0000000000001129 (Accessed: 27 January 2017)

104. Cairns G. High hepatitis C prevalence seen in Amsterdam PrEP study participants. NAM aidsmap. 2017. Available at: http://www.aidsmap.com/High-hepatitis-C-prevalence-seen-in-Amsterdam-PrEP-study-participants/page/3115254 (Accessed: 6 February 2017)

105. Prins M. PrEP Implementation: Viral Hepatitis C Testing Required? [Oral Presentation]. Oral Presentation presented at: HIV in Europe HepHIV2017; 1 February 2017; Malta. Available at: http://newsite.hiveurope.eu/Conferences/HepHIV-2017-Conference/Presentations/Special-Session-on-PrEP-Influence-of-PrEP-and-new-treatment-paradigms-on-testing-pathways (Accessed: 19 February 2017)

106. Cairns G. Hope overshadowed – the US PrEP Summit. NAM/aidsmap. 2017. Available at: http://www.aidsmap.com/Hope-overshadowed-the-US-PrEP-Summit/page/3114118 (Accessed: 6 February 2017)

107. NHS England NHS England announces major extension of national HIV prevention programme with Public Health England and funding for ten new specialised treatments. NHS England. 2016. Available at: https://www.england.nhs.uk/2016/12/hiv-prevention-pregramme/ (Accessed: 20 February 2017)

108. Collins S. Four London clinics report dramatic drops in HIV incidence in gay men: PrEP, early testing and early ART likely to be key. HIV Treatment Bulletin (HTB). Volume 18 Number 1/2. London; February 2017; : 28. Available at: http://i-base.info/htb/wp-content/uploads/2017/02/HTB-Jan-Feb-2017e.pdf (Accessed: 15 March 2017)

109. EndingHIV.org.nz NZ PrEP Study Launches + Improved Access to Generics. EndingHIV.org.nz. 2017. Available at: http://endinghiv.org.nz/blog-events/milestone-nz-prep-study-launches-improved-access-to-generics (Accessed: 8 March 2017)

110. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) HIV Prevention Study to Commence April 2017. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). 2017. Available at: http://www.ashm.org.au/Pages/HIV-Prevention-Study-to-Commence-April-2017.aspx (Accessed: 8 March 2017)

111. Jaspal R., Daramilas C. Perceptions of pre-exposure prophylaxis (PrEP) among HIV-negative and HIV-positive men who have sex with men (MSM). Lee A (ed.) Cogent Medicine. 4 November 2016; 3(1). Available at: DOI:10.1080/2331205X.2016.1256850 (Accessed: 26 January 2017)

112. DeMontfort University New HIV prevention treatment can only work if perception improves - DMU experts. DeMontfort University. 2017. Available at: http://www.dmu.ac.uk/about-dmu/news/2017/january/new-hiv-prevention-treatment-can-only-work-if-perception-improves-dmu-experts.aspx (Accessed: 26 January 2017)