'Preparing for PrEP?' A review of the current evidence for Pre-Exposure Prophylaxis (PrEP) to prevent HIV in Wales – Summary Report

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Purpose and Summary of Document:
This report provides the recommendations on Pre-Exposure Prophylaxis (PrEP) in Wales from the HIV Expert Group to the Cabinet Secretary for Health, Well-being and Sport. These recommendations are based on information available up to the end of October 2016.

An extensive report of the evidence available at this time, *'Preparing for PrEP?' A Review of the Current Evidence for Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection in Wales*, has been prepared to inform this summary report.

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

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
SWS	Sexual Health in Wales Surveillance Scheme
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organisation

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1 Key Points for Consideration

- PrEP is already being accessed via alternative means, by individuals in Wales, so, as a minimum, consideration needs to be given to providing guidance regarding dosing regimens, potential side effects, interactions and resistance. Monitoring needs to be in place 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.

- PrEP trial participants and clients of PrEP programmes generally do have high rates of STIs, but this is true at the outset before they start taking Truvada®. Most studies indicate that men at highest risk for HIV – which includes those who already do not use condoms – are most likely to seek PrEP. And in many cities where demonstration projects have taken place STI rates were on the rise well before PrEP became widely available.

- 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, needs 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 potential issue of cross border activity, particularly if England are not providing – our proposed eligibility criteria could cover this by using residency in Wales as a criterion.

2 Summary Recommendations

- Pending the outcome of the decision from the All Wales Medicines Strategy Group (AWMSG) regarding NHS provision of PrEP medication, in line with Prudent Healthcare principles, 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. If PrEP is subsequently provided through the NHS this recommendation should be extended to include all individuals accessing PrEP.

- It is of paramount importance that the services are able to provide accessible services for this client group to attend every three months for STI screening and HIV testing regardless of PrEP use. Presently, the services are under considerable pressure so will need support to be able to achieve this.

- 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 regular reviews, twelve months from initial evidence publication or on emergence of significant new evidence, whichever is earlier. Relevant updates will be provided to services and public messaging revised accordingly.

3 Background

3.1 What is PrEP?

PrEP, or Pre Exposure Prophylaxis, is the use of an antiretroviral medication by people who are uninfected to prevent the acquisition of HIV infection. Currently Emtricitabine/Tenofovir Disoproxil Fumarate (TDF/FTC) or tenofovir alone is used. The branded form of TDF/FTC is called 'Truvada®' and is licensed and used in Wales as a combination antiretroviral treatment.

3.2 Is PrEP effective?

The HIV Expert Group considered the Evidence Review published by NHS England which covered evidence up to October 2015. In addition, the Evidence Service of Public Health Wales provided a review of evidence covering the period to end October 2016. This Public Health Wales review matched the search terms of the NHS England review.

Since 2010, the efficacy of oral PrEP, commonly 'Truvada®', has been demonstrated in four key studies, iPrEx, PROUD, IPERGAY and Partner (see chapter 6 of accompanying document for full details of clinical trials).

The iPrEx study (2010) - 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® (Emtricitabine 200mg/Tenofovir Disoproxil 245mg) 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 pre-exposure prophylaxis, 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.

PROUD (2012)– 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. The trial was done 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 aimed to assess a number of other factors including who takes up the offer of PrEP and whether adherence behaviour changes over time. It 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 emtricitabine (200 mg) and tenofovir disoproxil fumarate (245 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 was 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. 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 NNT of 13.

IPERGAY (2014-2016) - 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 a non-randomised implementation study.

As with PROUD, HIV incidence in IPERGAY was higher than anticipated, and this meant that the study could prove effectiveness in what is, for a prevention study, a remarkably small number of participants, and in a short space of time. The longest anyone was in the trial before the November de-randomisation was 20 months but the median time was only nine months.

The effectiveness observed was 86% – exactly the same rate as seen in the PROUD study. This could be an under-representation of the effectiveness, as reasons for the 14% 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. The effectiveness rate was achieved on an overall pill usage of 14 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. There was no evidence of behaviour change in the study. The proportion of participants reporting at least one episode of condomless anal sex in the previous two months remained at 70%, as did episodes where the participant was the receptive partner, the number of partners remained at just under eight in the last two months, and the

number of sexual acts remained completely unchanged at ten in the last month.

During the study, 39% of participants were diagnosed with a sexually transmitted infection.

PARTNER (2010-ongoing) - The PARTNER study 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 provide 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. These results can help serodiscordant couples assess their HIV risk and make informed decisions.

The investigators of the PARTNER study concluded that the overall risk of HIV transmission through condomless sex for couples in stable serodiscordant relationships (when the HIV-positive partner is on ARVs, 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."

4 The current situation in Wales

At the request of Welsh Government, Public Health Wales established an independent HIV expert group to review the evidence of the effectiveness of PrEP in HIV prevention and the implications for the acquisition of other sexually transmitted infections.

The review was **not** expected to measure the clinical effectiveness against the costs as this is the role of the All Wales Medicines Strategy Group (AWMSG)

The group was asked 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.

4.1 Identify and quantify those individuals who are most at risk of HIV and would, if compliant, benefit from PrEP

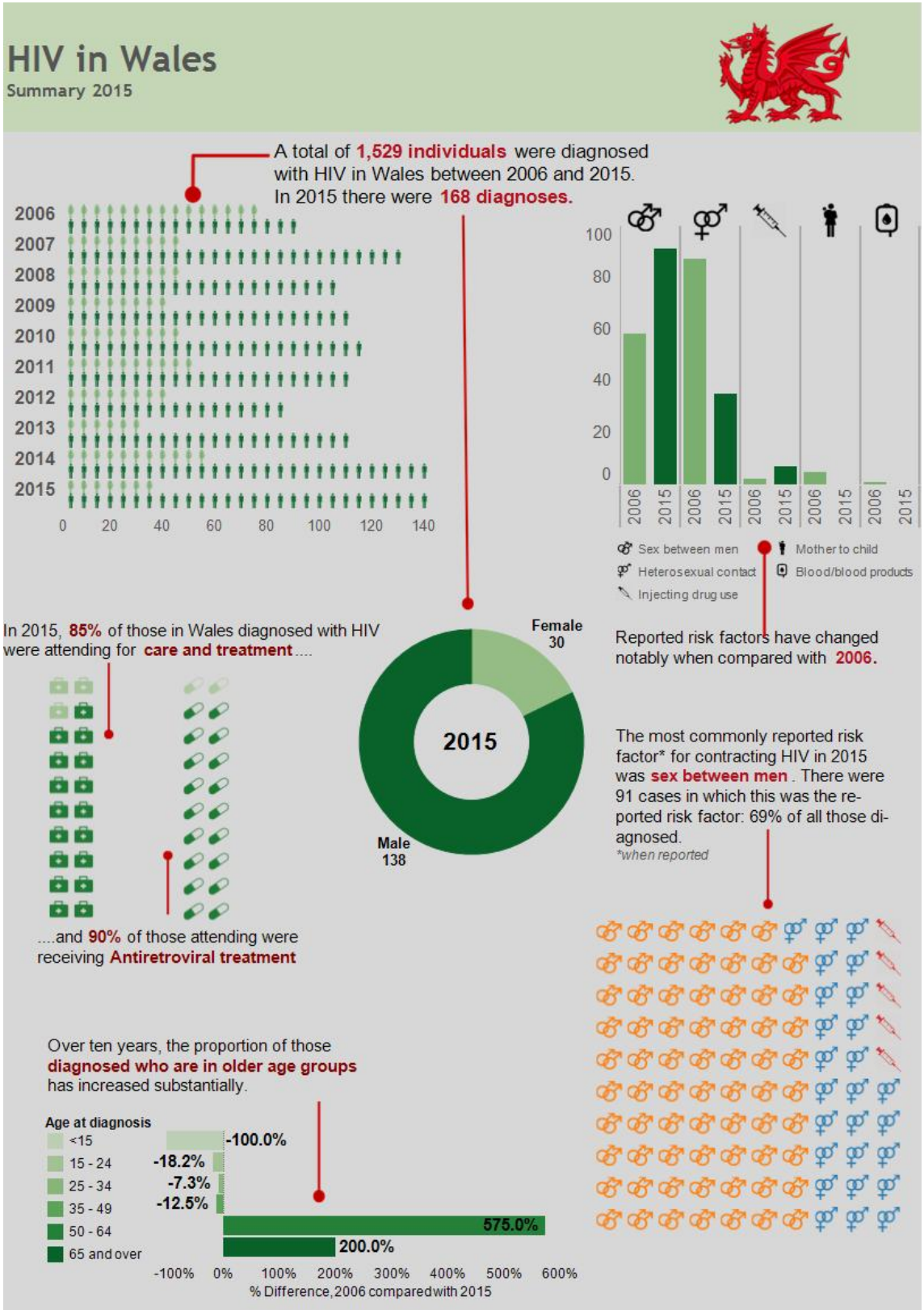
There is a steady increase in the number of people living with HIV in Wales, reflecting both an increase in survival and new diagnoses. On average, over the past six years, there have been approximately 153 new cases diagnosed annually.

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


HIV in Wales
Summary 2015
A total of 1,529 individuals were diagnosed with HIV in Wales between 2006 and 2015.
In 2015 there were 168 diagnoses.
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
0 20 40 60 80 100 120 140
100
80
60
40
20
0
2006 2015 2006 2015 2006 2015 2006 2015 2006 2015
Sex between men
Heterosexual contact
Injecting drug use
Mother to child
Blood/blood products
Reported risk factors have changed notably when compared with 2006.
In 2015, 85% of those in Wales diagnosed with HIV were attending for care and treatment....
....and 90% of those attending were receiving Antiretroviral treatment
Female 30
2015
Male 138
The most commonly reported risk factor* for contracting HIV in 2015 was sex between men . There were 91 cases in which this was the reported risk factor: 69% of all those diagnosed.
*when reported
Over ten years, the proportion of those diagnosed who are in older age groups has increased substantially.
Age at diagnosis
<15
15 - 24
25 - 34
35 - 49
50 - 64
65 and over
-100.0%
-18.2%
-7.3%
-12.5%
575.0%
200.0%
-100% 0% 100% 200% 300% 400% 500% 600%
% Difference, 2006 compared with 2015

Using the SWS surveillance 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 who are diagnosed with infection is 9.7%.

However, within this group there is a subgroup of MSM who frequently request HIV testing and are, therefore, considered to be at high risk and may benefit from HIV pre-exposure prophylaxis (PrEP). 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

Regarding data on proportion of HIV negative MSM who have had condomless anal intercourse (CAI) with two or more partners the information has been taken from the 'towards preparedness for PrEP' survey which gave a figure of 22.3% (range 19.8%-25.1%) reporting CAI with two or more partners. This figure fits with the information in table 1 which estimates the number of MSM at high risk of HIV acquisition in Wales.

Like other nations the Expert Group found that there is limited data available regarding PrEP awareness and acceptability, therefore predicting the uptake of PrEP in Wales by those who are eligible is somewhat difficult. Currently the only data available that may inform this comes from an online self-completed survey of high risk (defined as reporting two or more CAI partners in the previous year) HIV negative/status unknown MSM recruited via gay socio-sexual media from the four Celtic nations, including Wales. [1]

In the survey 58.5% (226 of 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 and be eligible in the first year.

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

This 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.

4.2 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

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.

Regular engagement of individuals using or considering using PrEP is of paramount importance in order to ensure its safe use as part of a comprehensive package of HIV prevention, including regular HIV testing and counselling, provision of condoms, screening and treatment for sexually transmitted infections (STIs), designed to meet the needs of the most at risk individuals.

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 should be produced centrally, in collaboration with key stakeholders, as part of a revised HIV prevention programme.

Formal mechanisms should be implemented 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, on demand or continual); behavioural changes (perceived risk of activity and condom use).

In order for the specialist services to provide support for individuals and for effective monitoring of the outcome of PrEP use in Wales some additional funding should be provided.

4.3 Undertake a cost benefit analysis on the introduction of PrEP to the identified most at risk group.

The 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 cost-effectiveness of PrEP. The Expert Group has, therefore, considered factors which may assist this, in particular by defining eligibility criteria and providing, in the first instance, an estimate of the amount of Truvada® which might be prescribed in the first year.

4.3.1 Eligibility criteria for Wales

The criteria are informed by HIV epidemiology in Wales identifying those at highest risk of acquiring HIV.

BASHH and **BHIVA** [2] strongly recommend that PrEP be made available within a comprehensive HIV prevention package to:

- MSM and trans 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.

A summary of our proposed eligibility criteria, based on the BASHH and BHIVA Statement and NHS England's review [3] is available below. This proposed criterion is provisional, based on a hypothesis that PrEP would be provided through NHS Wales Integrated Sexual Health Clinics. 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)

4.3.2 Cost of PrEP support, excluding drug costs

The All Wales average cost for a follow up attendance at a sexual health clinic for 15/16 was £101.10.

Fully absorbed cost of clinic visits for MSM at high risk per year 101.10 per visit @ 4 visits = £404.40

However, these individuals would ideally be seen regardless of PrEP. The additional tests required for PrEP monitoring (renal and liver function) would cost approximately £20.48 per year (communication with HB finance [4]). 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.

However, using the costs from the presentation by V Cambiano [5], 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 can cause renal toxicity.

Therefore, based on the estimated number of individuals who are most at risk of HIV and would, if compliant, benefit from PrEP, given previously in this paper 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 using Cambiano's figures or £11,468.80 assuming that this group of individuals should ideally be accessing services every three months for screening if they were not on PrEP. Therefore, the only additional cost should be renal and liver function test.

However, it is of paramount importance that the services are able to provide accessible services for this client group to attend every three months for STI screening and HIV testing regardless of PrEP use. Presently, the services are under considerable pressure so will need support to be able to achieve this. Further, consideration must also be given to the additional cost of staff and client education regarding PrEP.

4.3.3 Drug costs

The current cost of branded Truvada®, as listed in the British National Formulary (BNF) [6], 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.

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 for dispensing HIV treatment already.

Therefore at the current cost an annual prescription of 12 packs would cost **£4268.76**.

4.3.4 PrEP dosing regimens

For PrEP to be most effective, the drug needs to be at an appropriate level within the body.

There are two options for taking PrEP, either daily or 'event-based', depending on individual circumstances. As the body takes a while to absorb drugs, this means 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 the most evidence. However, the IPERGAY showed that event based 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 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 dosing the total annual cost of Truvada® will be:

(373 x 2,561) + (187 x 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.**

4.3.5 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.

4.3.6 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 [7]. 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.

4.4 Make recommendations on the most prudent approach to the potential introduction of PrEP in Wales with timescales and costs included.

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 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, it is possible for people to purchase a generic version of Truvada® from online pharmacies. The UK HIV information website, i-Base, recommends www.aidsdrugs-online.com, www.alldaychemist.com and www.unitedpharmacies.com.

- **"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.

- **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 from 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.

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.

As a minimum, the Expert Group recommends that pending the outcome of the decision from the AWMSG regarding NHS provision of PrEP medication, 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.

Further, although studies of gay and bisexual men have shown that Emtricitabine 200mg/Tenofovir Disoproxil 245mg (Truvada®) PrEP reduces the likelihood of HIV infection by 86% if used consistently. A common concern is that PrEP will lead people to stop using condoms, putting them at risk for other STIs. This "risk compensation" was not seen in clinical trials that led to approval of Truvada® for HIV prevention, but it has been reported in some PrEP demonstration projects and real-world use.

PrEP trial participants and clients of PrEP programmes generally do have high rates of STIs, but this is true at the outset before they start taking

Truvada®. Most studies indicate that men at highest risk for HIV – which includes those who already do not use condoms – are most likely to seek PrEP. And in many cities where demonstration projects have taken place STI rates were on the rise well before PrEP became widely available.

Therefore, it is of paramount importance that this client group is encouraged to attend sexual health services regularly (every three months) for STI screening and HIV testing regardless of PrEP and that the services are supported to enable this.

5 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
Dr. Nicola Price	Consultant Virologist	Public Health Wales
Dr. 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

6 Appendix 2 – 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.

6.1.1 CROI 2017

The annual Conference on Retroviruses and Opportunistic Infections (CROI) [8] 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. [9] 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. [10] 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. [11] 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' [12]. 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 [13]. 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'.

6.1.2 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 [14,15]. 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 [16,17]. 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*'[16].

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 [18].

6.1.3 UK Developments

<u>England</u>

NHS England and Public Health England have announced a large scale clinical trial in 2017/2018 on PrEP [19]. 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 [20].

6.1.4 International Developments

In early March 2017, New Zealand became the latest country to approve access to Truvada® as PrEP [21]. 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 [22].

6.1.5 Other Research

Researchers at **DeMontfort University** have looked into the perceptions of PrEP amongst HIV-negative and HIV-positive MSM [23,24].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 [23], *'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.

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