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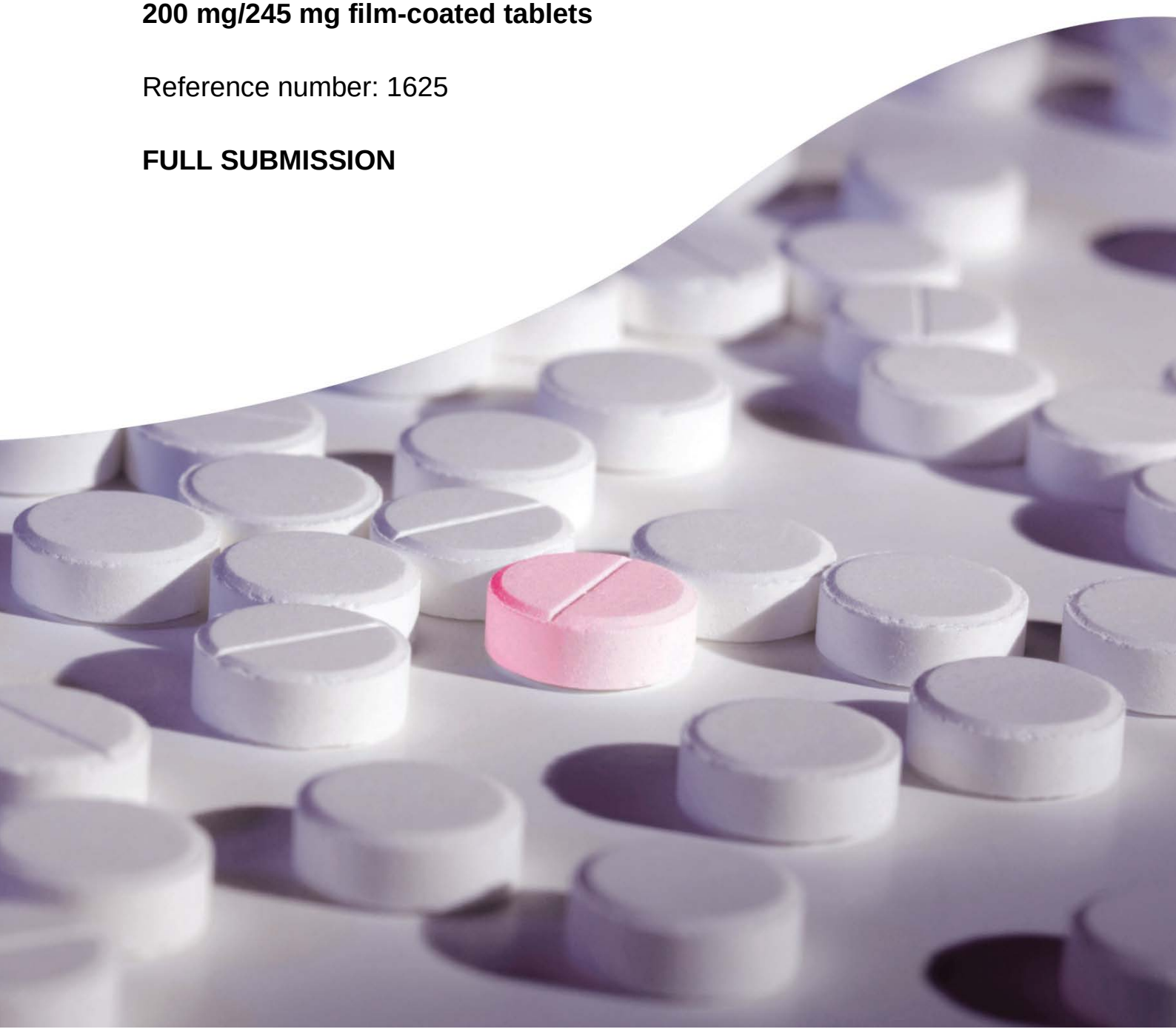
AWMSG SECRETARIAT ASSESSMENT REPORT

Emtricitabine/tenofovir disoproxil (as fumarate) (Truvada®) 200 mg/245 mg film-coated tablets

Reference number: 1625

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Emtricitabine/tenofovir disoproxil (as fumarate) (Truvada®) 200 mg/245 mg film-coated tablets

This assessment report is based on evidence submitted by Gilead Sciences Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Emtricitabine/tenofovir disoproxil fumarate (Truvada®) in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	One tablet to be taken orally once daily, preferably taken with food[2].
Marketing authorisation date	18 August 2016 (licensed for antiretroviral combination therapy for the treatment of HIV-1 infected adults on 21 February 2005)[2].

2.0 DECISION CONTEXT

2.1 Background

Human immunodeficiency virus (HIV) is a retrovirus that infects cells in the human immune system, such as $CD4^+$ lymphocytes, causing their destruction which results in the progressive suppression of the host immune system[3]. Untreated HIV is a progressive disease leading to the development of acquired immunodeficiency syndrome (AIDS)[3]. The number of people living with HIV in Wales continues to increase and new HIV diagnoses in Wales have continued with an annual average of 153 over the past six years[4]. The majority of HIV-1 infections diagnosed in Wales are sexually transmitted, with men who have sex with other men (MSM) accounting for 48% of all new HIV diagnoses since 2011 and 32% are recorded as acquired through heterosexual contact[5].

The principle interventions currently in use to prevent HIV-1 transmission are voluntary testing, risk counselling and the promotion of condoms. The effectiveness of these interventions has been variable and the prevalence of HIV-1 remains high[6]. The British HIV Association (BHIVA) state that a biomedical prevention tool could have a major impact on the HIV epidemic in the UK[7]. As of January 2017 emtricitabine/tenofovir disoproxil fumarate (Truvada®) is the only licensed treatment for pre-exposure prophylaxis (PrEP) of HIV-1 infection. The licence specifies adults at high risk of acquiring HIV-1 infection (which is considered best practice) and a number of definitions exist. The applicant company highlight the World Health Organisation (WHO) guidelines which state that offering PrEP should be a priority for populations with an HIV incidence of about 3 per 100 person-years or higher[1,8]. They also refer to the European AIDS Clinical Society (EACS) guidelines which highlight the following individuals:

- MSM and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment[1,9].
- HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment[1,9].

2.2 Comparators

The applicant company did not highlight a comparator in their submission; Truvada® is the first licensed medicine for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

2.3 Guidance and related advice*

- National Institute for Health and Care Excellence (NICE). Evidence summary (ES) 78. Pre-exposure prophylaxis of HIV in adults at high risk: Truvada® (Emtricitabine/tenofovir disoproxil) (2016)[10].
- BHIVA-British Association for Sexual Health and HIV (BASHH) position statement on PrEP in UK (2016)[7].
- Scottish HIV PrEP Short Life Working Group (SLWG) and Scottish Health Protection Network (SHPN). PrEP in Scotland (2016)[11].
- NHS England Specialised Services Clinical Reference Group for HIV. Clinical commissioning policy proposition: pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults – draft for public consultation (2016)[12].
- EACS. Guidelines version 8.1 (2016)[9].
- NHS England Specialised Services Clinical Reference Group for HIV. Evidence review: pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV in adults – for public consultation (2015)[13].
- WHO. WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP): policy brief (2015)[14].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of emtricitabine/tenofovir disoproxil fumarate (Truvada®) for the treatment of HIV-1 infected adults who are treatment-naive[15].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of two pivotal studies (iPrEX in HIV-1 negative MSM and Partners PrEP in serodiscordant heterosexual couples). The Partners PrEP had a third arm to evaluate tenofovir; however, the results from this arm are not relevant to the submission and will not be discussed further. Two supportive studies (PROUD in HIV-1 negative MSM, TDF2 in HIV-1 negative heterosexual adults) and one off-label supporting study (IPERGAY in HIV-1 negative MSM) were also included in the submission.

3.1 iPrEx

iPrEx was a phase III, randomised, double-blind, placebo-controlled, multicentre study, evaluating once-daily Truvada® (n = 1,251) or placebo (n = 1,248), in HIV-negative men or transgender women (male sex at birth) who have sex with men, and have evidence of high risk for acquisition of HIV infection[16]. The study was conducted in Peru, Ecuador, Brazil, the US, Thailand and South Africa. Participants also received a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms, and diagnosis and treatment of symptomatic sexually transmitted infection[16]. Follow-up was for a median of 1.2 years and a maximum of 2.8 years[10]. The primary endpoints were the incidence of HIV seroconversion and adverse events[16].

Ten participants were found to be infected with HIV at enrolment, and 100 became infected during follow-up (36 in the Truvada® group and 64 in the placebo group),

* *'Preparing for PrEP?' A review of the current evidence for pre-exposure prophylaxis (PrEP) to prevent HIV infection in Wales* was published on 21 March 2017 by Public Health Wales, after the writing of this report. Available at http://www.wales.nhs.uk/sitesplus/888/news/44336.

indicating a 44% reduction in the incidence of HIV-1 infection, compared with placebo participants (see Table 1 for results)[16]. Efficacy was strongly correlated with adherence as assessed by detection of plasma or intracellular drug levels in a case-control study. In the Truvada® group, the study drug was detected in 22 of 43 (51%) of seronegative participants and in 3 of 34 (9%) HIV-infected participants ($p < 0.001$). Self-reported sexual practices were similar in the Truvada® and placebo groups at all time points. The total number of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those who used a condom increased in both groups after enrolment in the study[16].

3.2 Partners PrEP

Partners PrEP was a phase III, randomised, double-blind, placebo-controlled study, evaluating once daily Truvada® (n = 1,583) or placebo (n = 1,586), in HIV-1 negative adults in a serodiscordant (i.e. one partner is HIV positive and the other is HIV negative) heterosexual relationship[17]. The study was conducted in Kenya and Uganda[17]. Participants also received a comprehensive package of prevention services including HIV testing, individual and couples risk-reduction counselling, condoms, sexually transmitted infection management, referral for male circumcision and post-exposure prophylaxis[10]. HIV seropositive partners were not receiving antiretroviral therapy[17]. Couples were not excluded from the study if either partner within the couple had other sexual partners; about 8% of seronegative partners reported sex with a third party (HIV status not stated)[10]. Follow-up was for a median of 23 months (interquartile range 1–36 months) [17]. After an interim review, the placebo group was discontinued and participants initially randomised to this group were re-randomised to the active group[10]. A total of 633 people from the placebo group were re-randomised to once daily Truvada®[10]. The primary endpoints were seropositivity in people previously seronegative for HIV and adverse events[17].

A total of 82 HIV-1 infections occurred in seronegative participants during the study (13 in the Truvada® group and 52 in the placebo group), indicating a 75% relative reduction in the incidence of HIV-1 infection compared with placebo (see Table 1)[17]. Efficacy of Truvada® was dependent on adherence to the study regimen; 97% of the dispensed study tablets were calculated to have been taken (based on pill counts of returned, unused study medicine)[17].

3.3 PROUD

PROUD was an open-label randomised, controlled study of once-daily Truvada® started either immediately after randomisation (n = 275) or after a deferral period planned of one year (n = 269) in HIV-negative men or transgender women (male sex at birth) who have sex with men[18]. Eligible participants had reported anal intercourse without a condom in the previous 90 days and were likely to in the next 90 days. The study was conducted at 13 sexual health clinics in England[18]. Interventions to reduce risk were offered according to routine practice at the clinic[10]. The primary endpoint was the time to accrual of 500 participants and retention[18]. The secondary endpoints were confirmed HIV infection between randomisation and month 12, safety, adherence, and risk compensation[18].

At month 12, three HIV infections occurred in the immediate group versus 20 in the deferred group, indicating an 86% reduction in the incidence of HIV-1 infection compared with deferred Truvada® (see Table 1)[18]. Thirteen men (90% confidence interval [CI]: 9–23) in a similar population would need access to one year of PrEP to avert one HIV infection. Overall there was no difference between groups in the total number of sexual partners or in the frequency of bacterial sexually transmitted infections. However, a larger proportion of people in the immediate group reported having receptive anal sex with ten or more partners without a condom (21% versus 12%; $p = 0.03$). Post-exposure prophylaxis was prescribed to 12 people (14 courses) in the immediate Truvada® group and 85 people (174 courses) in the deferred group[18].

3.4 TDF2

TDF2 was a phase III randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of once-daily Truvada® (n = 611) or placebo (n = 608) in HIV-1 negative heterosexual adults who were sexually active and at high risk of acquiring HIV-1 infection[19]. Participants also received a package of prevention services including HIV testing, counselling on adherence to medication, management of sexually transmitted infections, monitoring for adverse events, and individualised counselling on risk reduction. Participants were followed for a median of 1.1 years and a maximum of 3.7 years. The study was conducted in Botswana. The primary endpoint was the rate of HIV infection[19].

During the study, nine participants in the Truvada® group and 24 in the placebo group became infected with HIV, indicating a 62.2% reduction in the incidence of HIV infection compared with placebo (see Table 1)[19]. Overall there was no difference between groups in the frequency of sexually transmitted infections. Better adherence to Truvada® correlated with higher levels of plasma drug concentrations and a reduced risk of HIV-1 infection[6].

3.5 IPERGAY

IPERGAY was a randomised, double-blind, placebo-controlled study evaluating Truvada® (n = 206) or placebo (n = 208) taken 'on demand' before and after sexual activity in high-risk men or transgender women (male sex at birth) who have sex with men[20]. Participants also received a comprehensive package of prevention services including risk-reduction counselling, condoms, and sexually transmitted infection management[10]. The study was conducted in France and Canada[20]. After an interim review, the placebo group was discontinued and all study participants were offered 'on-demand' Truvada®[10]. Follow-up was for a median of 9.3 months (interquartile range 4.9–20.6 months)[20]. The primary endpoint was the diagnosis of HIV infection[20].

At follow-up, two participants in the Truvada® group and 14 participants in the placebo group had emergent HIV infection, indicating an 86% reduction in the incidence of HIV infection compared with placebo (see Table 1)[10]. Participants took a median of 15 pills of Truvada® or placebo per month (p = 0.57)[20]. Overall, sexual practices did not change during the study period as compared with baseline in either group[20].

Table 1. Summary of results[16-20].

	Truvada®	Placebo
PROUD (MSM)		
Participants with emergent HIV infection	3 (n = 268)*	20 (n = 255)†
Incidence per 100 person-years (90% CI)	1.2 (0.4 to 2.9)*	9.0 (6.1 to 12.8)†
Relative risk reduction (90% CI)	86% (64 to 96) p = 0.0001	
IPERGAY (MSM)		
Participants with emergent HIV infection	2 (n = 199)	14 (n = 201)
Incidence per 100 person-years	0.9 (NR)	6.6 (NR)
Relative risk reduction (95% CI)	86% (40 to 98) p = 0.002	
iPrEx (MSM)		
Participants with emergent HIV infection	36 (n = 1,224)§	64 (n = 1,217)§
Incidence per 100 person-years	NR	NR
Relative risk reduction (95% CI)	44% (15 to 63) p = 0.005	
TDF2 (Heterosexual adults)		
Participants with emergent HIV infection	9 (n = 610)§	24 (n = 606)§
Incidence per 100 person-years	1.2 (NR)	3.1 (NR)
Relative risk reduction (95% CI)	62% (21.5 to 83.4) p = 0.03	
Partners PrEP (Serodiscordant heterosexual couples)		
Participants with emergent HIV infection	13 (n = 1,576)	52 (n = 1,578)
Incidence per 100 person-years (95% CI)	0.5 (NR)	2.0 (NR)
Relative risk reduction (95% CI)	75% (55 to 87) p = <0.001	

CI: confidence interval; MSM: men who have sex with men; NR: not reported.

* Truvada® started immediately after randomisation.
† Truvada® started after a deferred period of one year, no active medicine.
§ Modified intention to treat population.

3.6 Safety

Emtricitabine and tenofovir are primarily excreted by the kidneys, and renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy have been reported with the use of tenofovir disoproxil for treating HIV infection[2]. In the iPrEx study, elevated creatinine levels were seen in 2% (25/1,251) of the Truvada® group and 1% (14/1,248) of the placebo group (p = 0.08), with ten elevations (seven in the Truvada® group and three in the placebo group) in serum creatinine levels leading to discontinuation of the study drug[16]. All elevations resolved after discontinuation of the treatment[16]. Also, bone fractures were reported in 1% (15/1,251) of the Truvada® group and < 1% (11/1,248) of the placebo group (p = 0.41)[10]. Headache was the only treatment-related adverse event (AE) reported in 4% (56/1,251) of the Truvada® group (placebo: 3% [41/1,248]). No resistance to emtricitabine or tenofovir disoproxil fumarate was detected in either group in those individuals who had confirmed HIV-1 seroconversion during the study[6].

The safety data originates from studies that were not sponsored by the applicant company and due to a lack of consistency across the studies, an integration of safety data for the indication under consideration has not been possible[6]. However, the European Medicines Agency (EMA) concluded that the safety and tolerability profile of Truvada® PrEP was as expected based on the safety profile of Truvada® in the treatment of HIV-1[6]; Truvada® was generally well tolerated throughout all five studies[16-20] with a similar percentage of participants experiencing any AE compared with placebo (Truvada®: 55% to 93%; Placebo: 56% to 90%)[16,17,19,20]. AEs leading to discontinuation were low (Truvada®: 1% to 2%; placebo: 0% to 2%)[16,19,20].

3.7 AWTTC critique

- At the time of writing Truvada® is the only licensed treatment for PrEP of HIV-1 infection in the UK and is already available in some countries including the US, Norway and France. It has been recommended for use in Wales[15] as a treatment option for HIV-1 infected adults in line with BHIVA guidelines[7] since 2007 and for a number of years has been available for use as post-exposure prophylaxis (PEP).
- There is significant support for PrEP (Truvada®) from patient organisations and as detailed in the "PrEP in Scotland" report[11] it is recognised that people in the UK are already accessing PrEP. This is further supported by Welsh clinical expert opinion sought by AWTTC.
- With an increasing awareness and demand for PrEP there is an emerging consensus on who should be eligible for treatment. Truvada® is licensed for PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. As outlined in reports from Scotland, NHS England and BHIVA/BASHH[7,11,12], it is generally agreed that high risk groups should be defined 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 the company submission, the clinical effectiveness of Truvada® is based on five studies. Three involved MSM and two were conducted in heterosexual adults. Results for the reduction in incidence of HIV-1 infection range from 44% (iPrEx) to 86% (IPERGAY and PROUD) for people who received Truvada® compared to those who did not. The IPERGAY study assessed 'on demand' use of Truvada® rather than once daily use as per licence. The findings of the iPrEx, Partners PrEP, and TDF2 studies may be less relevant to the Welsh population due to the countries in which they were conducted. There is a risk that the results of the PROUD study conducted in England may be biased due to its open-label design.
- The effectiveness of Truvada® in reducing the risk of acquiring HIV is strongly correlated with adherence[2,6]. In the pivotal iPrEx study, the 44% reduction in the relative risk of acquiring HIV infection is less than that seen in other studies and less than was expected. The pill count suggested a median range of 89% to 95% use however, drug level monitoring in a pre-specified subgroup showed that emtricitabine or tenofovir was detected in only 9% of people with HIV infection and 51% of people who were HIV-negative[16]. For individuals where ≥ 90% study drug adherence was reported, the relative risk reduction for HIV-1 acquisition was 73% (95% CI: 41 to 88; $p < 0.001$)[6].
- The PROUD study was designed to mimic clinical practice should PrEP be introduced. However, as with the IPERGAY study, participants were highly sexually active and the HIV incidence in the control groups was higher than expected. In the PROUD study HIV-1 infection was reported as 9.0 cases[18] per 100 person-years in the control group whereas the national rate among MSM attending sexual health clinics in the UK is estimated closer to 1.3 cases per 100 person-years[21].
- Following the results of PROUD and IPERGAY studies a number of national and international guidelines and reports have been updated to include recommendations for the use of PrEP. BASHH and BHIVA strongly recommend that PrEP be made available within a comprehensive HIV prevention package designed to meet the needs of the most at risk individuals. A package of prevention services typically includes regular HIV testing, risk-reduction counselling, provision of condoms, and screening and treatment of sexually transmitted infection.
- Although it appears the risk is likely low, HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking Truvada®[1,2,6]. Truvada® should only be used to reduce the risk of acquiring

HIV-1 in individuals confirmed to be HIV negative and therefore, individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every three months)[1,2,6].

- Individuals should be counselled to strictly adhere to the recommended dosing schedule for Truvada®. The EMA highlight the potential for dwindling adherence to daily dosing which is already shown to clearly impact efficacy[6]. Further, it is suggested that taking PrEP may prompt more risky behaviour, including a change in condom use, which may impact on sexually transmitted infection (STI) rates. The EMA also highlight this behaviour could result in a higher rate of seroconversion despite PrEP compared to the trial settings, especially if also accompanied by dwindling adherence. However, this has not been consistently shown through the studies and the EMA also note that several studies found that those engaging in unprotected receptive anal intercourse (URAI) were more likely to be adherent and derived high levels of protection despite this behaviour. More information on very long term adherence and behavioural changes are still required.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes cost-effectiveness analyses (CEA) and a cost-utility analysis (CUA) comparing the once daily oral administration of PrEP Truvada® 200 mg/245 mg with no active therapy, in adults at high risk of contracting HIV-1 infection. In the company submission, this high-risk population can encompass a number of distinct sub-populations, including MSM, and heterosexual adults and heterosexual serodiscordant couples.

The CEAs and CUA take the form of Excel-based models, which adopt an NHS/Personal Social Service perspective. The CEAs estimate the cost per HIV-1 infection prevented, and cost per life year gained. The CUA examines the cost per quality-adjusted life year (QALY) gained, and adopts a lifetime time horizon. Given the marked heterogeneities in study designs, patient populations and baseline HIV-1 incidence across the studies evaluating Truvada® for PrEP, the data from these studies are not pooled to determine cost-effectiveness for the whole population. Instead, CEA and CUA are conducted at individual sub-population and study levels according to baseline infection risk.

For the base case analyses, the baseline infection rates used in the models are taken from five studies[16-20], which have been undertaken in a variety of countries and are focused on different high-risk patient populations. In contrast, treatment effectiveness is assumed consistent across all sub-populations at a rate of 86%, but is taken from just two studies which included the MSM population only[18,20]. AEs are not incorporated in the models, in terms of either costs or utility decrements, on the basis that a similar safety profile has been found between Truvada® and placebo.

The analyses include costs associated with drug acquisition, monitoring, and treatment of HIV-1 infection (which is avoided in the case of successful prevention). Drug acquisition costs are sourced from the Monthly Index of Medical Specialities (MIMS)[22] for the current list price of Truvada®. Monitoring costs are taken from the literature[23,24] and NHS reference costs[25]. The costs associated with lifetime treatment for HIV-1 are also sourced from the literature[26]. These lifetime costs have been estimated via a simulation model designed to project the outcomes and costs of a UK based MSM population infected with HIV in 2013 aged 30, over 10,000 simulations (based on a median life expectancy of 71.5 years). Truvada® for PrEP treatment and monitoring costs are assumed to occur in the present, and therefore have not been discounted.

However, HIV-1 lifetime costs, together with life year gains, have been discounted at a rate of 3.5%.

Life years gained through successful prevention have been guided by the literature[27]; again with a focus on the MSM sub-population, rather than the whole HIV-1 population. The estimate of a loss of 7.5 years of life on average due to HIV-1 has been derived from a stochastic model for this sub-population. Utility values for subjects with HIV-1 have been reported in the literature[28,29], and are stratified according to CD4 cell count[29]. However, the company propose that most subjects diagnosed with HIV-1 are asymptomatic if treated. Accordingly the utility for the general population in Wales (0.89)[30] is used to calculate QALYs. Utility is thus assumed to be the same for uninfected and infected subjects.

Univariate sensitivity analyses test the influence of the uncertainty of individual parameters on the robustness of the base case results. They explore the impact of varying efficacy of Truvada®, the lifetime cost of HIV-1 infection, life years gained, health state utility values and intermittent dosing of Truvada®. No probabilistic sensitivity analyses are presented.

4.1.2 Results

The results of the base case analyses are detailed in Tables 2 and 3. They suggest that PrEP with Truvada® 200 mg/245 mg is a cost saving intervention in the majority of high-risk sub-populations, with the exception of serodiscordant heterosexual couples. In contrast to the other sub-populations, the cost of preventative prophylaxis in serodiscordant heterosexual couples is not offset by the treatment cost savings achieved through reducing the infection rate of HIV-1 due to the lower baseline infection rate of 2.0 in this sub-population. Instead, the cost per HIV-1 infection prevented in this sub-population is £83,708. Similarly, the CEAs examining the cost per life year gained and the CUAs conducted all find Truvada® to be dominant in all sub-populations, except serodiscordant heterosexual couples. In this sub-population the cost per life year gained is estimated to be £44,290 and the incremental cost-effectiveness ratio (ICER) produced is £49,764 per QALY gained.

Table 2. Results of the base case analysis: cost per HIV infection prevented[1].

Study Sub-population	Truvada® for PrEP efficacy	Infection rate per 100 person-years			Cost per 100 person-years (£)			Cost per HIV-1 infection prevented (£)
		Baseline	Truvada®§	Difference	Truvada® annual cost*	Offset costs, HIV-1 prevention	Total cost	
MSM								
PROUD	86%	9.0	1.3	−7.7	£462,522	−£1,433,448	−£970,926	**Dominant**
IPERGAY†	86%	6.6†	0.9	−5.7	£462,522	−£1,051,195	−£588,673	**Dominant**
iPrEx	86%	4.3	0.6	−3.7	£462,522	−£684,870	−£222,347	**Dominant**
Heterosexual adults								
TDF2	86%	3.1	0.4	−2.7	£462,522	−£493,743	−£31,221	**Dominant**
Serodiscordant heterosexual couples								
Partners PrEP	86%	2.0	0.3	−1.7	£462,522	−£318,544	£143,978	**£83,708**

HIV-1: human immunodeficiency virus-type 1; PrEP: pre-exposure prophylaxis.

***** This includes medicine acquisition costs of £433,101 and monitoring costs of £29,421.
† Intermittent dosing was used instead of the licensed daily dosing in this study. However, for the base case costs it is assumed that the licensed dose is administered. Intermittent doses are explored in sensitivity analyses.
§ Calculated by applying the 86% risk reduction from the IPERGAY and PROUD studies to the baseline infection rate.

Table 3. Results of the base case analysis: cost per life year gained and cost per QALY[1].

Study Sub-population	Truvada® for PrEP efficacy	Infection rate per 100 person-years			Total cost	Life years gained	Cost per life year gained	QALYs gained	ICER (£/QALY gained)
		Baseline	Truvada®†	Difference					
MSM									
PROUD	86%	9.0	1.3	−7.7	−£970,926	14.63	Dominant	13.02	**Dominant**
IPERGAY*	86%	6.6*	0.9	−5.7	−£588,673	10.73	Dominant	9.55	**Dominant**
iPrEx	86%	4.3	0.6	−3.7	−£222,347	6.99	Dominant	6.22	**Dominant**
Heterosexual adults									
TDF2	86%	3.1	0.4	−2.7	−£31,221	5.04	Dominant	4.48	**Dominant**
Serodiscordant heterosexual couples									
Partners PrEP	86%	2.0	0.3	−1.7	£143,978	3.25	£44,290	2.89	**£49,764**

HIV-1: human immunodeficiency virus-type 1; ICER: incremental cost-effectiveness ratio; PrEP: pre-exposure prophylaxis; QALY: quality-adjusted life year.

* Intermittent dosing was used instead of the licensed daily dosing in this study. However, for the base case costs it is assumed that the licensed dose is administered. Intermittent doses are explored in sensitivity analyses.
† Calculated by applying the 86% risk reduction from the IPERGAY and PROUD studies to the baseline infection rate.

The univariate sensitivity and scenario analyses conducted by the company reveal no change in the dominance findings for the MSM sub-population. The most notable changes to the base case findings relate to the other two sub-populations of interest. These are detailed in Table 4, together with explorations of plausibility. The sensitivity analyses further suggest that intermittent dosing of Truvada® results in dominance in all sub-populations. However, such dosing is not currently licensed in the UK. Consequently, intermittent dosing scenarios do not represent a plausible alternative to the base case at this time. Table 4 also includes an AWTTC scenario which is deemed a plausible alternative to the base case.

Table 4. Results of the sensitivity analyses[1].

Scenarios	Cost per HIV-1 infection prevented	ICER (£/QALY gained)	Plausibility
Lower background HIV-1 infection rate of 1.3 for the MSM population in line with Welsh clinical opinion and published reports[21].	£228,205	£135,845	The lower infection rates used in the scenario are derived from Welsh clinical opinion and national estimates. This scenario offers a plausible alternative to the base case in terms of background infection rate, but retains the limitation of using the efficacy rate from the PROUD and IPERGAY studies. If the efficacy rate is lowered to 44% in line with the iPrEX study, this increases the ICER further to £370,611. A weighted average of 55.6% risk reduction from the three MSM trials produces an ICER of £270,319 per QALY gained.
Lower Truvada® efficacy of 75% a) TDF2: heterosexual adults b) Partners PrEP: serodiscordant heterosexual couples	a) £13,734 b) £123,148	a) £8,165 b) £73,211	Given that the relative risk reduction in the Partners PrEP study was 75%, these analyses could be considered a more plausible alternative to the base case in this population. In TDF2 the relative risk reduction was even lower at 62%, thus the cost per HIV-1 infection and ICER for this sub-population may be higher still. There is considerable uncertainty surrounding this parameter.
Higher discounted lifetime cost of HIV-1 infections (+20% of baseline) Partners PrEP: serodiscordant heterosexual couples	£46,668	£27,744	It is uncertain whether the lifetime costs are the same for the various sub-populations. If average age of diagnosis and life expectancy differ then this has implications for these estimates. Without evidence to support higher, lower or equivalent costs for this sub-population, it is difficult to assess the plausibility of this scenario.
Lower discounted lifetime cost of HIV-1 infections (−20% of baseline) a) TDF2: heterosexual adults b) Partners PrEP: serodiscordant heterosexual couples	a) £25,329 b) £120,748	a) £15,058 b) £71,784	The above plausibility statement applies. Without evidence to support higher, lower or equivalent future costs, it is difficult to assess the plausibility of these scenarios.
Lower discounted life years gained of 1.512 years Partners PrEP: serodiscordant heterosexual couples	£83,708	£62,205	Life years gained are calculated by applying various assumptions to rate of diagnosis and age of diagnosis for example. There is uncertainty surrounding these data inputs. Clinical expert opinion supports the proposition that it may be a plausible alternative to the base case.
Lower utility value of 0.82 Partners PrEP: serodiscordant heterosexual couples	£83,708	£54,012	This lower utility value was reported for patients with HIV/AIDS by Sakthong et al[28]. Consequently, this scenario offers a plausible alternative to the base case.
Lower efficacy (-20%) due to non-adherence Partners PrEP: serodiscordant heterosexual couples	£149,961	£89,151	Non-adherence and behavioural disinhibition have been shown to have an impact on cost-effectiveness in the MSM population[31]. However, the PROUD study and a meta-analysis of 18 PrEP studies[32] demonstrated no behavioural compensation in PrEP recipients. It is therefore uncertain whether this can be considered a plausible alternative to the base case.

HIV-1: human immunodeficiency virus-type 1; ICER: incremental cost-effectiveness ratio; PrEP: pre-exposure prophylaxis; QALY: quality-adjusted life year.

4.1.3 AWTTC critique

The model submitted takes a simplistic, pragmatic approach to economic evaluation. Consequently, the CUA produces crude ICER estimates. The model inputs for efficacy, baseline rate of infection, costs and utility values, which are key model drivers, are subject to notable uncertainty. Caution is thus required when interpreting the results of the analyses. These limitations, together with an overview of other key strengths and weaknesses are explored below.

Strengths

- The submission provides a transparent account of data sources used to inform the model.
- Some limited sensitivity analyses have been conducted to test the robustness of the model to key model parameter changes.

Limitations

- The CUA does not capture cumulative risk over time. This is a prophylaxis therapy which requires ongoing administration to remain effective. In the model, treatment reduces the risk of being infected by HIV-1, and this is associated with an avoidance of lifetime HIV-1 treatment costs. However, it is currently unclear what length of time a person may be considered high risk, and how any changes in risk over time are accounted for. For example, if 100 people receive PrEP for one year, the model implies that 1.72 persons fewer will be infected when treated with Truvada® in that one year and are accordingly associated with HIV treatment cost savings of £318,544. However, if the model cohort patients continue to exhibit high risk behaviour in the future, they will either require further Truvada® administration to maintain risk reduction (and thus be associated with higher treatment costs) or may subsequently be infected by HIV-1 (which would then negate the majority of lifetime savings achieved through prior preventative treatment). Ideally, a discrete event simulation would have explored cohort effects over time.
- The background infection rates used in the model are taken from five studies[16-20]. AWTTC sought clinical expert opinion and published reports[21] suggest a lower background HIV infection rate, namely 1.3[21] and 2.4[33], which considerably reduces cost-effectiveness (see Table 4).
- The efficacy rates used in the model are taken from just two studies, which report the highest efficacy for Truvada® in the MSM population (PROUD and IPERGAY). These were not the pivotal studies on which the licence was issued. Furthermore, in the IPERGAY study intermittent dosing was used instead of the licensed daily dosing. This has implications in terms of the association between costs and effects. This, together with the fact that the efficacy rates obtained in the MSM population are higher than those observed in the heterosexual population studies (clinical evidence indicates this may be due to lower tenofovir concentrations in vaginal/cervical tissues than rectal tissues) introduces the potential for bias in the model, i.e. cost-effectiveness estimates may be overestimated in the heterosexual population.
- Efficacy results from the pivotal iPrEx MSM study were considerably lower than those observed in the PROUD and IPERGAY studies and no analysis has been undertaken using 95% confidence interval efficacy ranges for any of the MSM studies. The company are of the opinion that efficacy rates obtained in the PROUD and IPERGAY studies are more generalisable to the Welsh population, in terms of non-adherence tendencies and usual standards of care. If the iPrEx study efficacy rates of 44% are applied alongside the iPrEx baseline rate of infection, this results in a cost per infection prevented of £59,262, and an ICER of £35,231 per QALY gained.
- The AWTTC scenario analyses, reproduced by the company, indicate that applying efficacy data from the PrEP and TDF2 studies alongside the study

baseline rates of infection has a notable impact on the corresponding ICERs. For the heterosexual population (TDF2 study), Truvada® no longer dominates and the ICER becomes £32,503. For serodiscordant heterosexual couples (PrEP study) the ICER increases to £73,211. However, as stated above the company are of the opinion that the higher efficacy rate of 86% is a better representation of expected efficacy in Wales.

- Lifetime costs for HIV-1 treatment are taken from a single source which is focused on the MSM population. It is uncertain how these costs compare to the other high risk sub-populations.
- The QALY calculations are potentially overly simplistic, as explored above. Also, whilst it is reasonable to use the Welsh general population utility value, given that it is lower than that reported in the literature for asymptomatic HIV-1 infection, the model does not take into account utility decrements associated with worsening CD4 cell count and symptomatic infection.
- The QALY calculations are based on an expected increased life extension of 7.5 years per infection avoided. This life extension originates from the assumption that patients present with a median CD4 cell count at diagnosis (351 cells/mms). If the majority of patients present earlier, then it is possible that the QALY calculations overestimate the potential gains of avoiding infection. Likewise, if the majority of patients present later, then QALY gains may be underestimated.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified a CUA conducted in the UK focused on the MSM population which found that at 86% effectiveness the administration of PrEP resulted in an ICER of £26,300, when compared with no PrEP[33]. Applying a more conservative assumption of 64% effectiveness resulted in an ICER of £54,500. The ICER was highly sensitive to year one HIV incidence, PrEP effectiveness, PrEP drug costs, and potential changes in antiretroviral treatment cost upon patent expiry. Notably, the background HIV infection rate used in this model was 2.4 per 100 person-years. This is considerably lower than the rate of infection used for the MSM population in this submission. Another study conducted in the US focused on the same high-risk population estimated a QALY gain of 6.95 per HIV infection prevented[34].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company's budget impact analysis has been based on an estimated number of eligible people by scaling the number of people eligible for HIV PrEP treatment in Scotland by the ratio of the total population of Wales and Scotland. A survey of high-risk MSM with HIV negative or status unknown found that 58% of participants would be willing to take a daily pill to prevent HIV infection[11]. The company have used this ratio as the uptake in Wales, together with forecasts of the total population, to estimate the number of people eligible for treatment with Truvada® each year for the next five years, as shown in Table 5. It is assumed that, while new patients will initiate PrEP in each year and some of those on PrEP will discontinue treatment, the overall number of treated patients will remain relatively constant. The company consider this to be a conservative approach, and suggest an average treatment duration is likely to be 7.2 months[35]). Sensitivity analyses explore the impact of: intermittent dosing of 18 tablets per month, and varying the number of people treated by +/−20%.

5.1.2 Results

The base case budget impact analysis reveals an expected cost of £2,581,282 in year 1 and £2,589,944 in year 5. The sensitivity analyses reveal that varying the number of

people who receive treatment by +/−20% results in estimated annual net medicine costs of £3,096,672 million and £2,065,892 million, in year 1 respectively.

Table 5. Company-reported costs associated with use of Truvada® for the prophylactic treatment of HIV[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible people (indication covered in this submission)	1,027	1,028	1,029	1,030	1,031
Uptake of new medicine (%)	58	58	58	58	58
Number of people receiving new medicine	596	596	597	597	598
Costs					
Total medicine acquisition costs in a market without Truvada®	£0	£0	£0	£0	£0
Total medicine acquisition costs in a market with Truvada®	**£2,581,282**	**£2,581,282**	**£2,585,613**	**£2,585,613**	**£2,589,944**
Net medicine acquisition costs	**£2,581,282**	**£2,581,282**	**£2,585,613**	**£2,585,613**	**£2,589,944**
Cumulative medicine acquisition costs	**£2,581,282**	**£5,162,564**	**£7,748,177**	**£10,333,790**	**£12,923,734**

5.1.3 AWTTC critique

- The company submission gives a detailed account of the methods used to estimate budget impact.
- It is unknown whether the proportion of people eligible for PrEP in Wales is the same as that in Scotland; which creates uncertainty surrounding these estimates.
- The proportion of people eligible for PrEP is taken from a survey conducted among the high risk MSM population. Data on the proportion of individuals eligible to receive PrEP in Scotland in non-MSM high risk groups is limited but estimated to be 5% or less[11]. The proportion of eligible patients willing to take PrEP in the high-risk MSM group (58%)[11] has been applied across all high risk sub-populations, but even if the proportion of people willing to take PrEP varies in the non-MSM high-risk groups, such preferences are unlikely to significantly alter the expected number of people treated.
- The budget impact model assumes that the number of patients receiving treatment will remain constant each year. There is no evidence to support this assumption. Furthermore, the company estimate of 7.2 months average treatment duration, which has been informed by the Volk *et al* study[35], may be considered shorter than expected. The study design indicates that not all treatment duration data is captured. Therefore budget impact estimations may be underestimated.
- The company highlights via sensitivity analyses a potential reduction in net medicine acquisition cost based on intermittent dosing. However, such dosing is not licensed for PrEP[10].

5.2 Comparative unit costs

PrEP Truvada® 200 mg/245 mg is currently the only HIV-1 prophylaxis licensed in Wales. The annual associated acquisition cost is £4,331 per patient. At this time there are no alternative treatments to enable comparisons of unit costs.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, emtricitabine/tenofovir disoproxil fumarate (Truvada®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that emtricitabine/tenofovir disoproxil fumarate (Truvada®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

There are a number of ongoing investigator-led studies on Truvada® for PrEP; however, these studies are not sponsored by Gilead and the time scale for availability of their results is unknown. There are no Gilead-sponsored trials for Truvada® for PrEP being performed in Wales.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 15 December 2016.
Date range of evidence search: No date limits were applied to database searches.

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