7.08 TENOFOVIR with EMTRICITABINE, Tablet containing tenofovir disoproxil fumarate 300 mg with emtricitabine 200 mg, TRUVADA ®, Gilead Sciences Pty Ltd

1 Purpose of Application

1.1 A resubmission to request a Section 85 (General Schedule) Streamlined listing for tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg (TDF/FTC) for use as pre-exposure prophylaxis (PrEP) against HIV-1 in adults at medium to high risk of infection. The first submission was considered by the PBAC in July 2016.

Table 1: Key components of the clinical issues addressed by the submission

Component	Description
Population	Adults at medium to high risk of HIV-1infection
Intervention	Pre-exposure prophylaxis using TDF/FTC, one tablet, once daily with standard of care (SOC)
Comparator	SOC alone, comprising HIV testing and safer sex practices
Outcomes	HIV incidence and safety
Clinical claim	TDF/FTC + SOC is more effective than SOC alone at reducing HIV infections with similar safety

Abbreviations: SOC, standard of care; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine
Source: compiled during the evaluation

2 Requested listing

2.1 Details of the proposed listing are provided in the following table.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TENOFOVIR DISOPROXIL FUMARATE 300 MG + EMTRICITABINE 200 MG ORAL TABLET, 30	1	2	$[redacted]	TRUVADA® Gilead Sciences PTY LTD

Category / Program:	General Schedule
PBS Indication:	Pre-exposure prophylaxis against HIV in adults at medium to high risk of infection
Restriction:	Streamlined
Treatment criteria:	Must be treated by a prescriber who is registered with a PrEP Prescriber Program
Clinical criteria:	Patient must be at medium to high risk of HIV infection, as defined by updated Australian Society for HIV Medicine Guidelines. AND Patient must return a negative HIV test prior to initiating treatment AND Patient must continue to return negative HIV tests at 3 monthly intervals throughout treatment.
Population criteria:	Patient must be 18 years or older
Category / Program:	General Schedule

2.2 TDF/FTC was TGA registered for use 'in combination with safer sex practices for pre exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk' on 6th May 2016.

2.3 The proposed restriction would allow for use in a broad population, in adults at 'medium to high risk' of HIV infection according the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Guidelines. This was a change from the July 2016 submission which proposed a 'substantial risk of HIV infection'. The ASHM Guidelines also recommend use of PrEP in people who inject drugs to prevent HIV transmission associated with the sharing of injecting equipment. This is broader than the TGA registered indication (of preventing sexually acquired HIV-1). The proposal to include medium risk behaviour means that there was no longer a requirement to develop a risk calculator, as included in the July 2016 submission, to determine those who would reach the 3% "substantial risk" threshold.

2.4 The requested basis for listing was cost-effectiveness of TDF/FTC + SOC compared to SOC alone.

2.5 The recommended dose is one oral tablet, once daily. The treatment is ongoing for the life time of the participant as long as the participant is at medium to high risk of HIV infection according to the proposed restriction.

2.6 The proposed eligibility criteria rely on self-reported behaviour (derived from the ASHM Guidelines, see Table 4 below), potentially complicating their use as the basis for a restriction tool.

2.7 The PBAC noted, consistent with its advice from July 2016, the resubmission proposed listing for a broader population of individuals compared with the July 2016 submission. The PBAC considered it appropriate for the eligible population to include medium and high risk individuals as defined in the ASHM Guidelines, including people who share injecting equipment. The PBAC noted the ASHM Guidelines provided with the submission were a draft version but that the final version has subsequently been published[1].

2.8 The PBAC considered that TDF/FTC for PrEP should be listed as a General Schedule item to ensure widest access and should include provision for nurse- practitioner prescribing.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 A major submission for TDF/FTC as PrEP was rejected at the July 2016 PBAC meeting.

3.2 A summary of the key differences between the July 2016 submission and the current resubmission is provided in Table 2.

Table 2: Summary of the July 2016 submission and the current resubmission

	July 2016 submission	Current resubmission
Requested DPMQ	Section 100 (30 tablets): $[redacted]	General Schedule (30 tablets): $[redacted]
Requested PBS listing	To reduce the risk of sexually acquired HIV infection in adults at substantial risk of HIV infection.	Pre-exposure prophylaxis against HIV in adults at medium to high risk of infection. This was based on the updated ASHM guidelines.
Main comparator	Standard of care **PBAC comment: "**The PBAC agreed this was the appropriate comparator, noting however that as Truvada is intended to be used in combination with, and not as a substitute for other methods to reduce the risk of HIV transmission, the appropriate comparison is therefore: 'Truvada + SOC' versus 'SOC'".[5.2 of July 2016 Public Summary Document (PSD)]	As per July 2016
Clinical evidence	Six head-to-head RCTs comparing daily TDF/FTC to placebo: iPrEx (n=2,441), Partners	Two randomised trials, IPERGAY (n=400) comparing intermittent TDF/FTC and placebo and ADAPT (n=357)

[1] Wright, Edwina, et al. Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine - HIV Pre-Exposure Prophylaxis: clinical guidelines. Journal of Virus Eradication, 2017; 3: 168-184. Accessed 5 July 2017. Open access, available at http://viruseradication.com/journal-details/Australasian_Society_for_HIV,_Viral_Hepatitis_and_Sexual_Health_Medicine_HIV_pre-exposure_prophylaxis:_clinical_guidelines/

	July 2016 submission	Current resubmission
	PrEP (n=3,154), TDF2 (n=1,216), PROUD (n=523), FEM-PrEP (n=2,056) and VOICE (n=2,002).	comparing intermittent TDF/FTC and daily TDF/FTC. Five non randomised observation studies of TDF/FTC as PrEP. The resubmission did not represent the RCTs contained in the July 2016 submission. Four Australian PrEP Demonstration Projects were identified but no new data were provided.
Key effectiveness data	The RRR for HIV seroconversion for the six clinical trials ranged from -0.04 to 0.86. The meta-analysed efficacy estimate was 0.50 (95% CI: 0.16, 0.70). **PBAC Comment**: "Given the heterogeneity between the trials, this pooled estimate is not very informative. The meta-analysed efficacy estimate was not used in the economic evaluation." [6.7 of July 2016 PSD]	In IPERGAY (placebo controlled RCT with intermittent TDF/FTC) the RRR for HIV seroconversion from the ITT analysis was 0.82 (95% CI: 0.36, 0.97, p=0.002).
Key safety data	TDF/FTC was associated with gastrointestinal adverse events including nausea and vomiting compared to SOC. **PBAC Comment:** "The use of Truvada may lead to a de-prioritisation of other risk-mitigating practices (e.g. increased unprotected anal sex with potentially infected partners)…. decreased condom use may increase the risk of acquiring HIV as well as other sexually transmitted infections" [6.16 of July 2016 PSD]	IPERGAY (placebo controlled RCT with intermittent TDF/FTC) showed higher levels of gastrointestinal adverse events among subjects receiving TDF/FTC. These events were not associated with treatment discontinuations. No long-term safety data were presented. Some evidence of changes in risk behaviour (less condom use) and an increased incidence of STIs were reported for the RCTs and observational studies.
Economic evaluation: Model structure	Static cohort Markov model (Model 1) Population dynamic transmission model (Model 2): • Chronic HIV health states (Stage I, Stage II, Stage III). • No exogenous introduction of chronic HIV infected persons • No viral suppression status, all treated achieve viral suppression	Model 1 was excluded from the resubmission. Modified population dynamic transmission model. Structural changes include: • Additional HIV infection health state (primary infection) that is associated with a higher force of infection than chronic HIV health states (Stage I, Stage II, Stage III). • Exogenous introduction of chronic HIV infected persons • Additional partitions within HIV infection health states for viral suppression status (suppressed and unsuppressed).
Economic evaluation: Transition probabilities	Population dynamic transmission model (Model 2) with key transition probabilities: • Impact of adherence on efficacy modelled via separate factor. • HIV transmission models (adopting a gamma distribution for the individual risk multiplier and a normal distribution for individual variations of risk). • Eligibility for PrEP depends on meeting a predefined risk level. • Subjects discontinue if their risk level falls below the prespecified level.	Modified population dynamic transmission model. Changes to transition probabilities include: • The impact of adherence on efficacy was no longer modelled. • Changes to the HIV transmission models (assumed a lower SD for the gamma distribution for the individual risk multiplier and uses a uniform distribution for individual variations of risk). • Eligibility for PrEP depends on meeting a suitability threshold (gamma distribution mean 1%, SD 0.1%). • Continuation threshold removed (PrEP continuation is not dependent on risk).
ICER	Model 1 - $105,000 - $200,000 per QALY	More than $200,000 per QALY gained. Change largely

	July 2016 submission	Current resubmission
	gained Model 2 – TDF/FTC was dominant	due to the higher incremental cost associated with the assumption of continuing PrEP. While the incremental QALY gained also increased threefold, this was less than proportional to the rise in incremental costs resulting in an increased ICER.
Participant numbers	3,407 participants in Year 1 increasing to 3,970 in Year 5	8,763 participants in Year 1 increasing to 29,614 in Year 6. Change in numbers due to a broader eligible subject pool and the assumption of continuing PrEP.
Estimated net cost to PBS	$20 - $30 million in Year 1 increasing to $30 – 60 million in Year 5, for a total of more than $100 million over the first 5 years of listing.	$60 - $100 million in Year 1 increasing to more than $100 million in Year 6, for a total of more than $100 million over the first 6 years of listing. Change in PBS cost due to increase in participant numbers.

Abbreviations: ASHM, Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine

3.3 Outstanding matters of concern to the PBAC and how they were addressed by the resubmission are summarised in Table 3.

Table 3: Summary of outstanding matters of concern

Matters of concern (July 2016 submission)	How it was addressed in the re-submission (July 2017)
Requested PBS listing	
"The population eligible for treatment was restricted to those meeting a high risk criterion. The PBAC considered it would be more appropriate for a broader group of individuals with potential benefit to have access to Truvada as PrEP." [paragraph 7.9, July 2016 PSD]	The resubmission requested 'Pre-exposure prophylaxis against HIV in adults at medium to high risk of infection'. This is broader than the population requested in the July 2016 submission. The inclusion of reference to the ASHM Guidelines is broader than the TGA registered indication.
"The appropriate and likely use in clinical practice, including the possibility of intermittent use." [paragraph 7.9, July 2016 PSD]	The resubmission reiterated the approved PI use of TDF/FTC as daily dosing, and this was the basis of the economic model and financial estimates. The resubmission presented two RCTs that included intermittent dosing regimens. The impact of intermittent dosage regimens and adherence on the efficacy of PrEP was presented in the submission, but was not used in the economic evaluation.
"Details relating to the management of the 'approved PrEP service'". [paragraph 7.9, July 2016 PSD]	The resubmission suggested that ASHM could manage the PrEP Program.
Clinical effectiveness	
"The PBAC considered that the available data were not representative of the proposed PBS population. The Committee's concerns about the applicability of the trial data to the Australian setting included that a large proportion of the data were generated in communities known to have a substantially higher incidence of HIV infection (and therefore higher risk) than the Australian population. "[paragraph 7.4, July 2016 PSD]	The resubmission presented two RCTs and four international observational studies with study sites in developed countries. The results from these studies are potentially more applicable to the PBS population than those from studies from developing countries with different HIV profiles. The resubmission referred to four Australian PrEP demonstration projects. However, the baseline characteristics and results are only available for one of these projects - VicPrEP.
"Adherence with Truvada as PrEP, and the potential impact of Truvada on other preventative strategies, in clinical practice." [paragraph 7.9, July 2016 PSD] "The model assumed a high uptake of Truvada as PrEP in high risk individuals, which the PBAC considered was not reasonable since high risk patients are partly defined by low	The resubmission continued to assume high adherence with TDF/FTC as PrEP in the economic model. However, the model was modified so that the function specifying the effectiveness estimate incorporated the impact of adherence directly; it was no longer possible to vary adherence to observe the impact in the model of such a change on effectiveness. The resubmission continued to

Matters of concern (July 2016 submission)	How it was addressed in the re-submission (July 2017)
uptake of currently available 'safe sex' practices (e.g. condoms). "[paragraph 7.7, July 2016 PSD]	assume that adherence would impact on costs (cost*compliance). The impact of TDF/FTC on safer sex practices, including condom use and potential STIs was presented in the observational studies. The resubmission continued to model changes in risk behaviour using an inhibition factor multiplier applied to the infection risk, but did not model the incidence or costs associated with STIs.
Economic evaluation	
The issues with the Model 2: "Sexual contact between individuals was assumed to be random rather than assortative by risk level. This was considered unrealistic as individuals at high risk may be more likely to have contact with other high risk individuals rather than someone who is low risk. The model population was closed and hence does not allow new at-risk MSM to enter, allowing for transmission to be rapidly exhausted even in the no PrEP scenario. "[paragraph 7.7, 2016 PSD]	The individual risk distribution reflects some non-randomness in sexual contacts as it assumed that there was a small group of extremely risky individuals interacting with each other. No evidence was provided to support the distributions used for the individual risk distribution (gamma) and individual risk variation (uniform). The inhibition factor (which allows for changes in risky behaviour) was applied as a multiplier to the efficacy estimate. This does not link that multiplier to behaviour. The resubmission included the exogenous introduction of HIV-infected individuals into the model and transmission was no longer rapidly exhausted.
The issues with the Model 2: "The PBAC noted the agent based model developed by researchers at the Kirby Institute, in which individual interactions are represented over time. The PBAC noted that the results of this model suggest the price of Truvada has a strong influence on cost-effectiveness of PrEP, with the current PBS list price of Truvada only likely to be cost-effective for PrEP when used in men in a regular partnership with an HIV-discordant man." [paragraph 7.7, 2016 PSD]	The resubmission maintained the same price (on an ex-manufacturer basis) as the July 2016 submission. Results of sensitivity analyses showed that the ICER was sensitive to the price of TDF/FTC. The AFAO/Kirby report included as a reference to the resubmission estimated the annual TDF/FTC costs to achieve an ICER at the willingness to pay thresholds of $30K, $60K and $90K per QALY. Uptake rates varied across the risk groups (high risk-medium risk-low risk) and the scenarios presented in the AFAO/Kirby report that are most similar to the resubmission are Scenarios 90-60-30 (estimated overall uptake rate 48.1%) and Scenario 90-60-0 (estimated overall uptake rate 28.2%). According to these scenarios the annual cost per TDF/FTC unit would need to be $2,150 and $3,730, respectively in order to achieve an ICER of $30,000 per QALY. The ESC noted the former included the use of TDF/FTC as PrEP in individuals at low risk.
The issues with the Model 2: "The ICER was sensitive to a range of input parameters including treatment adherence, the risk level at which individuals discontinue treatment, the distribution of risk across the population and the model time horizon." [paragraph 7.7, 2016 PSD]	The resubmission removed the 2% annual risk continuation threshold at which participants discontinue PrEP. Treatment adherence was removed as an input parameter affecting efficacy in the model. No new data were presented regarding longer-term PrEP use; the results of sensitivity analyses using different time horizons were presented.
Financial implications	
"The size of the eligible patient population likely to seek access" [paragraph 7.9, July 2016 PSD]	The resubmission continued to estimate the future use of PrEP from the dynamic transmission model. This was not a purely epidemiological approach and relied on the validity of the assumptions underpinning that model. Subject numbers have increased in accordance with the broader

Matters of concern (July 2016 submission)	How it was addressed in the re-submission (July 2017)
	population included in the proposed restriction.

Abbreviations: PrEP, pre-exposure prophylaxis

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Population and disease

4.1 Infection with HIV can result in an acute illness and chronic sequelae (including but not limited to acquired immunodeficiency syndrome [AIDS]). HIV is spread through infected blood, semen or vaginal fluids. Treatment with antiretroviral therapies (ARV) is recommended for HIV-infected individuals to reduce morbidity and mortality (including AIDS related morbidity and mortality). Treatment with ARVs can impact on quality of life and mortality.

4.2 The proposed place of TDF/FTC is in the prevention of HIV infection in individuals at medium to high risk. The resubmission proposed that the medium-high risk group is defined by the updated ASHM guidelines (ASHM HIV PreExposure Prophylaxis: Clinical guidelines, 5 July 2017). The risk criteria presented were based on sexual and or drug injecting activity (based on behaviour, not identity) over the last 3 months, and likely activity in the next 3 months (indicating sustained risk). The criteria apply to men who have sex with men (MSM), trans and gender diverse people, heterosexual people and people who inject drugs (PWID). A summary of the risk criteria for MSM to identify their eligibility for PrEP from the ASHM Guidelines is presented in Table 4.

Table 4: Risk criteria for MSM to identify their eligibility for PrEP

A. High risk – recommend prescribing daily PrEP if the patient acknowledges		
Having had any of the following in the last 3 months: • At least one episode of condomless anal intercourse (CLAI) with a regular HIV+ partner (not on treatment and/or detectable viral load) • At least **one** episode of receptive CLAI with any casual HIV + male partner or a male partner of unknown status • Rectal gonorrhoea, rectal chlamydia or infectious syphilis diagnosis (during the last 3 months or at screening for PrEP) • Methamphetamine use, which may increase the risk of HIV acquisition	AND	Being likely to have in the next 3 months (indicating sustained risk): • Multiple events of CLAI, with or without sharing intravenous drug equipment
B. Medium risk – consider prescribing daily PrEP, based on case by case approach if discussion reveals		
Having had any of the following in the last 3 months • More than one episode of anal intercourse when proper condom use was not achieved (e.g. condom slipped off or broke) where the serostatus of partner was no known, or was HIV+ and not on treatment with a detectable viral load • (if patient uncircumcised) more than one episode of insertive CLAI where the serostatus of partner was not known, or was HIV + and not on treatment or with a detectable viral load	AND	Being likely to have in the next 3 months (indicating sustained risk) • Multiple events of CLAI, with or without sharing intravenous drug equipment
Case by case approach Based on a complete sexual and alcohol and other drug-using history and the personal circumstances of the patient, if the clinician is of the opinion that the patient is likely to be at high risk of HIV, then PrEP prescription may be considered despite the absence of reported high- or medium-risk factors above.		

Source: Wright, Edwina, et al. Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine - HIV Pre-Exposure Prophylaxis: clinical guidelines. Journal of Virus Eradication, 2017; 3: 168-184. Accessed 5 July 2017. Open access, available at http://viruseradication.com/journal-details/Australasian_Society_for_HIV,_Viral_Hepatitis_and_Sexual_Health_Medicine_HIV_pre-exposure_prophylaxis:_clinical_guidelines/

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The resubmission nominated SOC as the main comparator. The PBAC had previously accepted that this is the appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3), and organisations (10) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of TDF/FTC as PrEP, including greater protection from HIV, positive

changes in community perceptions of HIV, and a reduction in stigma for those living with HIV. The PBAC noted the consumer comments submitted from a social media based support group "PrEP'D For Change" which also described the benefits of PrEP and the current legal and financial challenges for patients accessing PrEP via the TGA Personal Importation Scheme.

6.3 The PBAC noted advice received from the Australian Federation of AIDS Organisations (AFAO) and National Association of People with HIV Australia (NAPWHA), which described the benefits of PrEP, including data from the IPERGAY trial which reported an 86% reduction in the risk of HIV infection among participants, and further described the efficacy of PrEP in a 'real-world' setting, and associated health benefits such as more frequent sexual health checks and patient contact with clinicians. The PBAC noted the AFAO was supportive of a General Schedule PBS listing.

The PBAC also noted the correspondence of support for the AFAO position from the following organisations:

- AIDS Council of NSW (ACON)
- AIDS Action Council of the ACT
- The Bobby Goldsmith Foundation
- Family Planning NSW
- Multicultural HIV and Hepatitis Service NSW
- Victorian AIDS Council
- Western Australian AIDS Council

Clinical trials

6.4 The resubmission did not present the six RCTs (iPrEx, Partners PrEP, TDF2, PROUD, FEM-PrEP and VOICE) for which data were presented in the July 2016 submission. However, the efficacy estimate for the model continued to be sourced from case control analysis of iPrEx and Partners PrEP studies.

6.5 The resubmission presented two supplementary randomised trials, IPERGAY (n=400) comparing an intermittent TDF/FTC dosing regimen and placebo, and ADAPT (n=357) comparing two intermittent TDF/FTC dosage regimens and daily TDF/FTC dosing, as supportive clinical evidence. Five non-randomised observational studies of TDF/FTC as PrEP were also presented. These consisted of the iPrEx open label extension (OLE) study; three international demonstration studies (The Demo Project, Kaiser Permanente SF, PrEPare 2 YMSM) and one Australian demonstration study (VicPrEP). Three additional Australian demonstration programs were identified and are ongoing with no information provided in the resubmission (PrELUDE, EPIC, QPrEPd). Details of the studies presented in the resubmission are provided in Tables 5 and 6.

Table 5: Randomised trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
IPERGAY NCT: 01473472	Molina JM, Capitant C, Spire B, Pialoux G, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. Protocol for: Molina J-M, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. Sagaon-Teyssier L, Suzan-Monti M, Demoulin B, Capitant C et al. Uptake of PrEP and condom and sexual risk behaviour among MSM during the ANRS IPERGARY trial	New Engl J Med 2015; 373 (23):2237-2246. AIDS CARE 2016; 28 (S1): 48-55
067/ADAPT NCT013227651	Mannheimer S, Hirsch-Moverman Y, Loquere A, Franks J, Hughes J et al. HPTN 067/ADAPT study: a comparison of daily and intermittent pre-exposure prophylaxis dosing for HIV prevention in men who have sex with men and transgender women in New York City Holtz TH, Chitwarakorn A, Curlin ME, Hughes J et al. HPTN 067/ADAPT study: a comparison of daily and non-daily pre-exposure prophylaxis dosing in Thai men who have sex with men, Bangkok, Thailand	Journal of the International AIDS Society, 2015; 18 (Suppl 4):24-25 Journal of the International AIDS Society, 2015; 18 (Suppl 4):25-26

Source: Table B.3, p.35 of the resubmission. Table 1, p.4, 6.06, Truvada®, emtricitabine 200mg/tenofovir disoproxil fumarate 300mg, PSD July 2016

[1]The July 2016 submission reported Thigpen et al. to be published in 2015, but the article was published in 2012.

Table 6: Studies and associated reports presented in the resubmission

Study	Description	Reports
TDF/FTC		
Nonrandomised studies presented in the resubmission		
IPrEx OLE	OLE, daily dosing of TDF/FTC	Grant RM, Anderson PL, McMahan V, Liu A, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014; 14(9):820-829
The Demo Project US	Observational study in US. Daily dosing of TDF/FTC (PrEP)	Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, et al. HIV Pre-Exposure Prophylaxis Integrated with Municipal and Community Based Sexual Health Services. JAMA Intern Med 2016; 176(1):75-84 Cohen SE, Vittinghoff E, Bacon O, Doblecki-Lewis S, Postle BS, et al. High Interest in Pre-exposure Prophylaxis Among Men Who Have Sex with Men at Risk for HIV-Infection: Baseline Data from the US PrEP Demonstration Project. J Acquir Immune Defic Syndr 2015; 68(4): 439-448
Kaiser Permanente (KPSF)	Observational study in US, San Francisco. Daily dosing of TDF/FTC	Volk JE, Marcus JL, Phengrasamy T, Bleckinger D, Nguyen DP, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. HIV/AIDS CID 2015; 61(10):1601-3
PrEPare 2 YMSM	Observational study in US. Phase II safety. Daily dosing of TDF/FTC.	Hosek SG, Rudy B, Landovitz R, Kapogiannis B, Siberry G, et al. An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM. J Acquir Immune Defic Syndr 2017; 74(1):21-29
VicPrEP	Observational study in Australia, Victoria. Daily dosing of TDF/FTC for at least one year	De Wit JBF, Murphy DA, Lal L, Audsley JM, Roth N ,et al. O19.2 Pre-exposure Prophylaxis and Risk Compensation: Evidence of Decreased Condom Use at Three-Month Follow-Up Among Predominantly Gay Male Participants in the VicPrEP Study. Sex Transm Infect 2015; 91 (Suppl 2): A1-A256

Abbreviations: TDF/FTC, tenofovir disoproxil fumarate/emtricitabine
Source: Table B.3, p.35 of the resubmission

6.6 The key features of the supplementary randomised trials are summarised in Table 7.

Table 7: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome	Use in modelled evaluation
TDF/FTC intermittent dosing vs. placebo						
IPERGAY	400	R, DB, MC, Phase III, placebo-controlled, 24 months Event-driven intermittent dosing (loading dose of 2 tablets (both TDF/FTC) 2 to 24 hours before sex; 1 tablet 24 hours after 1st drug intake; 1 tablet 24 hours later.	Low	MSM (France, Canada)	Incidence of HIV-1 seroconversions.	Not used
TDF/FTC intermittent dosing vs. daily dosing						
ADAPT	357[a]	R, OL, MC, Phase II, 7.5 months Event-driven intermittent dosing: Week 0-5 1 tablet orally, once daily; Week 6 onwards 1 tablet orally, 1 tablet before and 1 tablet after sexual intercourse. Time-driven intermittent dosing: Week 0-5 1 tablet orally, once daily; Week 6 onwards 1 tablet orally, twice per week and 1 tablet after sexual intercourse. Daily dosing: Week 0-5 1 tablet orally, once daily; Week 6 onwards 1 tablet orally, once daily.	High	MSM (US, Thailand, South Africa)	Sexual exposures covered by PrEP. Pills for 100% coverage.	Not used

a. n=179 from New York, n=178 from Bangkok, participant numbers from South Africa site not specified
Abbreviations: DB, double blind; HIV, human immunodeficiency virus; MC, multi-centre; MSM, men who have sex with men; OL, open label; R, randomised.
Source: compiled during the evaluation

6.7 A summary of the evidence presented in the resubmission across the randomised and nonrandomised trials is presented in Table 8.

6.8 The information provided on the VicPrEP study in the resubmission is the same as included in the July 2016 submission. A description of the study designs was the only information provided for the three other Australian demonstration projects.

Table 8: Evidence presented in the resubmission

	Baseline characteristics	Efficacy	Safety	Adherence	Risk behaviour and STI
Randomised trials					
IPERGAY	Yes	Yes	Yes	Yes	Yes
ADAPT – New York	Yes	No	Yes	Yes	No
ADAPT – Thailand	Yes	Yes	No	Yes	No
ADAPT – South Africa	No	No	No	No	No
Nonrandomised trials					
IPrEx OLE	Yes	Yes	Yes	Yes	Yes
The Demo Project US	Yes	Yes	Yes	Yes	Yes
Kaiser Permanente (KPSF)	Yes	Yes	No	No	Yes
PrEPare 2 YMSM	Yes	Yes	Yes	No	Yes
VicPrEP –Australia	Yes	Yes	Yes	No	Yes
PrELUDE –Australia	No	No	No	No	No
EPIC-NSW –Australia	No	No	No	No	No
QPrEPd –Australia	No	No	No	No	No

Source: compiled during the evaluation

Comparative effectiveness

6.9 While not presented in the resubmission, the results of the six RCTs from the July 2016 submission are presented in Table 9. The RRR for HIV seroconversion ranged across the trials from a -0.04 to 0.86. The ESC noted the RRR assumed in the economic model was 0.90 based on case control analyses of adherent subjects in the iPrEx and Partners PrEP studies.

Table 9: Results of HIV seroconversion events at the primary efficacy timepoint assessment across the direct randomised trials, modified intention to treat (Presented in July 2016 submission)

Trial ID	TDF/FTC + SOC n with event/N	SOC n with event/N	Risk estimate (95% CI)	RRR (95% CI)	p-value
iPrEx	36/1,224	64/1,217	HR = 0.56 (0.37, 0.85)	0.44 (0.15, 0.63)	0.005
Partners PrEP	13/1,576	52/1,578	HR = 0.25 (0.13, 0.45)	0.75 (0.55, 0.87)	<0.0001
TDF2	9/610	24/606	NR	0.62 (0.22, 0.83)	0.03
PROUD	3/268	20/255	NR	0.86 (0.64, 0.96)	NR
FEM-PrEP	33/1,024	35/1,032	HR = 0.94 (0.59, 1.52)	0.06 (-0.52, 0.41)	0.81
VOICE	61/994	60/1,008	HR = 1.04 (0.73, 1.49)	-0.04 (-0.49, 0.27)	0.81

Abbreviations: HR, hazard ratio; NR, not reported; RRR, relative risk difference.
Source: Table 3, p.11 6.06 Truvada®, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, Gilead Sciences Pty Ltd, PSD, July 2016

6.10 The results of HIV-1 seroconversions for IPERGAY are presented in Table 10. The resubmission noted that the two cases of HIV seroconversion in the PrEP group were due to low adherence. In reporting on IPERGAY, Molina et al. (2015) noted that these two participants were non-adherent with 58/60 and 60/60 pills returned at the scheduled visits and the plasma samples returned at the time of HIV-1 diagnoses not containing the study drug. The modified intention to treat analysis removed one patient in the PrEP group and two patients in the placebo arm as they had seroconverted after randomisation but before the enrolment into the study.

Table 10: Results of HIV-1 seroconversion across the supplementary randomised trial

Trial ID	TDF/FTC + SOC n with event/N	SOC n with event/N	Risk estimate (95% CI)	RRR (95% CI)	p-value
IPERGAY ITT	3/206	16/208	NR	82% (36%, 97%)	0.002
IPERGAY mITT	2/199	14/201	NR	86% (40%, 98%)	0.002

Note: TDF/FTC intermitted event driven dosing regimen: loading dose of 2 tablets (both TDF/FTC) 2 to 24 hours before sex; 1 tablet 24 hours after 1st drug intake; 1 tablet 24 hours later.
Abbreviations: CI, confidence interval; ITT, intention to treat; mITT, modified intention to treat; RRR, relative risk reduction; SOC, standard of care.
Source: p.2241, Molina JM, Capitant C, Spire B, Pialoux G, et al. On-Demand Pre-exposure Prophylaxis in Men at High Risk for HIV-1 Infection. New Engl J Med 2015; 373 (23):2237-2246

6.11 For the ADAPT study, the conference abstract for the New York site did not specify whether any HIV conversions were reported; the conference abstract for the Bangkok site reported no HIV infections after 24 weeks.

6.12 The following results for HIV seroconversion were reported for the observational studies:

- iPrEx OLE: HIV seroconversions occurred in 13 participants not on PrEP (2.6 infections per 100 person-years, 95% CI: 1·5–4·5) and 28 participants on PrEP (1.8 infections per 100 person-years, 95% CI: 1·3–2·6). Of those receiving PrEP, HIV incidence was 49% (95% CI: –1 to 74) lower than among those who did not use PrEP after adjusting for the higher risk sexual practices at baseline among PrEP users, and 36% lower before adjustment (95% CI: –24 to 67%). In iPrEx (Grant et al. 2014) there were no HIV infections for persons who had at least 4 or more doses of PrEP per week. The ESC noted that self-reported compliance in the iPrEx trial was 93% at week 8; however that compliance measured by blood serum analysis of PrEP indicated compliance of 53%[2].
- The Demo Project: Two participants acquired HIV infection during follow-up, yielding an HIV incidence of 0.43 infections per 100 person years (95% CI: 0.05-1.54). The dried blood spot results indicated that tenofovir disoproxil levels were consistent with less than 2 doses/week at the time of seroconversion.
- Kaiser Permanente (KPSF): No HIV diagnoses during the 388 person-years on PrEP use with mean follow-up duration of 7.2 months.
- PrEPare 2 YMSM: Four HIV seroconversions occurred during the study (one each at weeks 4, 32, 40, and 48) for an HIV incidence rate of 3.29 per 100 person-years (95% CI: 0.07 to 6.52). None of the participants who seroconverted had detectable levels of TFV-DP in the blood sample drawn closest to the seroconversion date.
- VicPrEP: No incident HIV seroconversions reported during the 6 months of follow-up. The ESC noted that there has been one seroconversion reported

[2] Van der Straten, Ariane, *et al.* Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS, 2012, 26: F13-F19. doi: 10.1097/QAD.0b013e3283522272

for a participant in VicPrEP but it is as yet unclear if this was associated with poor adherence or viral resistance.

6.13 The PBAC noted the results of the IPERGAY trial supported the effectiveness of intermittent dosing of PrEP (RRR of 82-86%), however the reduction in risk was less than that observed in the iPrEx and Partners PrEP trials for individuals adherent with the daily dosing regimen (RRR of 90%, paragraph 6.9).

6.14 The PBAC noted that limited data from the Australian PrEP demonstration projects were available at the time of the resubmission.

Comparative harms

6.15 A summary of the adverse events for TDF/FTC in the supportive RCTs is presented in Table 11.

Table 11: Summary of key adverse events in the supplementary randomised trials

Trial ID	TDF/FTC (daily) n event/N (%)	TDF/FTC (time) n event/N (%)	TDF/FTC (event) n event/N (%)	Placebo n event/N (%)	P-value
IPERGAY					
Gastrointestinal AE	NA	NA	28/199(14)	10/201 (5)	0.002
Elevated plasma creatinine			35/199 (18)	20/201 (10)	0.03
Number discontinued			23/199 (11)	26/201 (13)	NR
Number died			0/199 (0)	0/201 (0)	1.00
ADAPT (New York site)[a]					
Neurologic (e.g. headache, dizzy and lightheaded)	24/59 (41)	20/60 (33)	18/60 (30)	NA	0.64
Gastrointestinal (nausea, vomiting, diarrhoea, bloating, gas)	39/59 (66)	18/60 (30)	28/60 (47)	NA	0.51

Abbreviations: AE, adverse event; NA, not applicable; NR, not reported; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine

[a]The conference abstract did not present individual adverse events, but rather aggregated events.

Note: ADAPT trial compared three TDF/FTC dosage regimens, daily dosing and two intermittent dosage regimens (event-driven dosing and time-driven dosing)

Source: Table 2, p.2245, Molina JM, Capitant C, Spire B, Pialoux G, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. New Engl J Med 2015; 373 (23):2237-2246 and Mannheimer S, Hirsch-Moverman Y, Loquere A, Franks J, Hughes J et al. HPTN 067/ADAPT study: a comparison of daily and intermittent pre-exposure prophylaxis dosing for HIV prevention in men who have sex with men and transgender women in New York City, Journal of the International AIDS Society, 2015; 18 (Suppl 4):24-25

6.16 The PBAC had previously noted that '[g]astrointestinal adverse events (in particular nausea and vomiting) were more common in subjects receiving Truvada compared with placebo, but most events occurred in the first month and resolved with continued exposure' (p.13, 6.06 Truvada®, tablets, emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, Gilead Sciences Pty Ltd, PSD, July 2016).

6.17 The following safety issues were reported for the observational studies:

- IPrEx OLE: Seven people had discontinued PrEP for more than two months and subsequently seroconverted:
  - four of these were due to side-effects (separately: 1. hypersensitivity; 2. gastritis; 3. dizziness, nausea and flatulence; 4. weight-gain).

  - three were due to other reasons with loss to follow-up in one participant and the remaining two due to participant preference.
- The Demo Project: Discontinuation in three participants owing to elevated creatinine levels. However, therapy was restarted in these three participants before the end of the study.
- PrePARE YMSM: Discontinuation in 22 participants of 200 enrolled (median time on PrEP 0.35 years) due to personal choice or side-effects including gastrointestinal discomfort. There was a significant decline in hip and whole body BMD Z score, but not for spine between baseline and Week 24; between Week 24 and 48, hip BMD Z score continued to significantly decline but not for spine and whole body.
- VicPrEP: Two serious adverse events were reported up to month 6: 1. death due to suicide; and 2. HIV seroconversion after study entry but prior to commencing PrEP.

6.18 The resubmission presented STI rates for IPERGAY. However, these data were non-comparative, as they were reported for the overall study populations and not by treatment arm. Within IPERGAY, 81 participants (20%) acquired chlamydia infections during follow-up, 88 (22%) gonorrhoea, 39 (10%) syphilis, and 5 (1%) hepatitis C virus. It was not reported if these events occurred in separate individuals, but these data suggest the incidence of any STI could be as high as 53%. At baseline, 28% of participants had been diagnosed with an STI at screening.

6.19 STI rates in the observational studies were:

- iPrEX OLE: Syphilis incidence was similar among PrEP recipients and non-recipients (7·2 infections per 100 patient-years vs 5·4 infections per 100 patient-years, HR 1·35, 95 CI 0·83–2·19).
- The Demo Project: Overall, 26% of participants had early syphilis, gonorrhoea, or chlamydia at baseline, and 51% were diagnosed with ≥1 STI during follow-up.
- Kaiser Permanente SF: After 12 months of PrEP use, 50% of PrEP users were diagnosed with any STI (95% CI, 43%–56%), 33% with a rectal STI (95% CI, 27%–39%), 33% with chlamydia (95% CI, 27%–39%), 28% with gonorrhoea (95% CI, 23%–34%), and 5.5% with syphilis (95% CI, 3.3%–9.1%). Baseline STI rates were not reported in Kaiser Permanente SF, therefore comparisons cannot be made.
- The PrEPare 2 YMSM study reported 22% of participants with an STI at baseline. The overall STI incidence rate on study was 66.44/100 person-years (95% confidence interval: 50.53/100 person-years to 82.35/100 person-years), with higher STI incidence in the first 24 weeks of study (76.48/100 person-years) than the latter half of the study (60.99/100 person-years).
- VicPrEP reported that at baseline 12% (12 people out of 99) had 13 STIs, and at month 6, 24% (23 people out of 91) had 26 STIs.

6.20 These data suggest that in all studies, there was an increase in the observed incidence of STIs, in some to at least 50% of PrEP users (reported in The Demo

Project, KPSF and PrEPare 2 YMSM studies, and estimated for IPERGAY). This high rate is tempered to the extent that a pre-existing STI diagnosis was a criterion for PrEP eligibility for some of the studies. Nonetheless, evidence from three of the studies (IPERGAY, VicPrEP and The Demo Project) suggests that there is a doubling of baseline STI risk. Given the potentially large pool of individuals who might use PrEP this represents a substantial risk to individual health, public health and increase in health care expenditure.

6.21 The ESC noted the reported increase in STIs in the clinical studies and considered that an increase may be observed in clinical practice with the use of PrEP. The ESC considered that the monitoring and management of other STIs was an important consideration for a PrEP Prescriber Program, and noted that the requirement for 3-monthly visits for access to PrEP provides an opportunity for regular monitoring of overall sexual health.

6.22 The PBAC noted the increase in the reported cases of STIs in the clinical studies and considered in clinical practice the requirement of a medical practitioner visit every 3 months to obtain a prescription for TDF/FTC is likely to increase monitoring for STIs and result in earlier diagnosis.

6.23 The PBAC previously noted that the 'Long-term safety of Truvada as PrEP is unknown. Concerns include the long term impact on bone loss and renal function', (p.14, 6.06 Truvada, emtricitabine 200mg/tenofovir disoproxil fumarate 300mg, PSD, July 2016). The PBAC noted this was not addressed in the resubmission.

6.24 The ESC noted that flare of hepatitis B infection in individuals using TDF/FTC as PrEP is a matter of concern and was not represented in the clinical trials as it was an exclusion criterion at recruitment. The ESC considered that monitoring for hepatitis B was an important factor in determining eligibility for PrEP as disease flare was likely to have a significant impact on compliance for some patients.

6.25 The ESC considered that low adherence to PrEP could lead to an increased level of resistance to TDF/FTC, which forms the backbone of many anti-retroviral therapy regimens in HIV infection, and considered this risk would need to be managed in the context of any PrEP program.

Benefits and harms

6.26 There was insufficient information available on the use of TDF/FTC as PrEP to determine its benefits and harms in the prevention of HIV infection. This is because the efficacy and safety of TDF/FTC as prevention are dependent on adherence and the treatment regimens (daily vs. intermittent regimens). Adherence, and the treatment regimens used varied across the multiple studies presented to date for TDF/FTC. Moreover, it is unclear how TDF/FTC (PrEP) would be used in Australian

clinical practice and how such use might translate into HIV cases avoided or the associated harms of TDF/FTC as PrEP.

Clinical claim

6.27 The resubmission described TDF/FTC plus SOC as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over SOC. This was unchanged from the July 2016 submission.

6.28 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.29 The PBAC reaffirmed its previous advice that it considered the claim of non-inferior comparative safety was not strongly supported by the available data, however given the duration of experience with TDF/FTC for the treatment of HIV, the claim of non-inferior comparative safety was probably reasonable. The PBAC noted there was an increase in adverse events over SOC in the IPERGAY trial, including gastrointestinal events and increased serum creatinine levels. The PBAC also considered long-term use of TDF/FTC may be associated with bone loss and reduced renal function.

Economic analysis

6.30 The resubmission presented the population dynamic transmission model from the July 2016 submission with modifications. The static cohort Markov model presented in the July 2016 submission was not represented.

Table 12: Summary of model structure and rationale

	July 2016 submission, model 2	Resubmission
Time horizon	20 years in the model base case versus median ~2 years of use in the trials.	As per July 2016
Outcomes	The model presented a range of interim clinical outcomes (infections and HIV cases), culminating in an estimate of the cost per QALY gained.	As per July 2016
Methods used to generate results	Monte Carlo simulation	Monte Carlo simulation
Cycle length	1 month	As per July 2016.
Transition probability: HIV Susceptible	Model entry in one of the four health states based on epidemiological data	Model entry in one of the five health states based on epidemiological data
Transition probability: HIV Acquisition	Infection risk: function of population incidence risk (determined by currently "infectious" population), various individual risk factors, whether or not they take TDF/FTC in that cycle, efficacy, adherence and an inhibition factor.	Infection risk: function of population incidence risk (determined by currently "infectious" population), various individual risk factors, whether subjects are on PrEP in that cycle, efficacy and an inhibition factor. Adherence/compliance was removed as an input parameter from the efficacy function in the model, and the gamma distribution defining the individual risk factor has changed. The removal of adherence/compliance as an input from the model is inappropriate.
Transition probability: HIV progression/ Improvement	HIV progression and improvement: based on previous Australian modelling.	As per July 2016. For primary/incident HIV infection, the model used 0 rate/year for improvement if treated and progression if untreated.
Transition probability: Mortality, all cause	Background mortality: age- and gender-specific all-cause mortality sourced from the ABS 2014.	As per July 2016.
Transition probability: HIV related mortality	Disease specific mortality: based on literature.	As per July 2016.
Discount rate	5% for costs and outcomes	As per July 2016.

Source: Section D.3, D.4 of the July 2016 submission and compiled during the evaluation
Abbreviations: ABS, Australian Bureau of Statistics; AIHW, authoritative information and statistics to promote better health and wellbeing; GRIM, general record of incidence of mortality; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; QALYs, quality adjusted life years.

6.31 The July 2016 submission applied a 90% efficacy rate based on case control analyses of adherent subjects from two RCTs (iPrEx and Partners PreP). This was subsequently multiplied by a separate adherence input parameter of 0.90 in the model to derive a base case efficacy estimate of 81%. The resubmission continued to apply an efficacy estimate of 90% for TDF/FTC but assumed a given level of high adherence (90%). This was no longer applied as an input parameter, but assumed that it was incorporated in the efficacy of 90% used in the model. With an underlying adherence of 90%, a final efficacy parameter of 90% relies on an assumption of 100% efficacy in adherent subjects, namely: 90%*100%=90%. The model continued to apply an adherence factor of 90% to the cost of TDF/FTC.

6.32 The results of the economic evaluation are presented in Table 13.

Table 13: Results of the economic evaluation

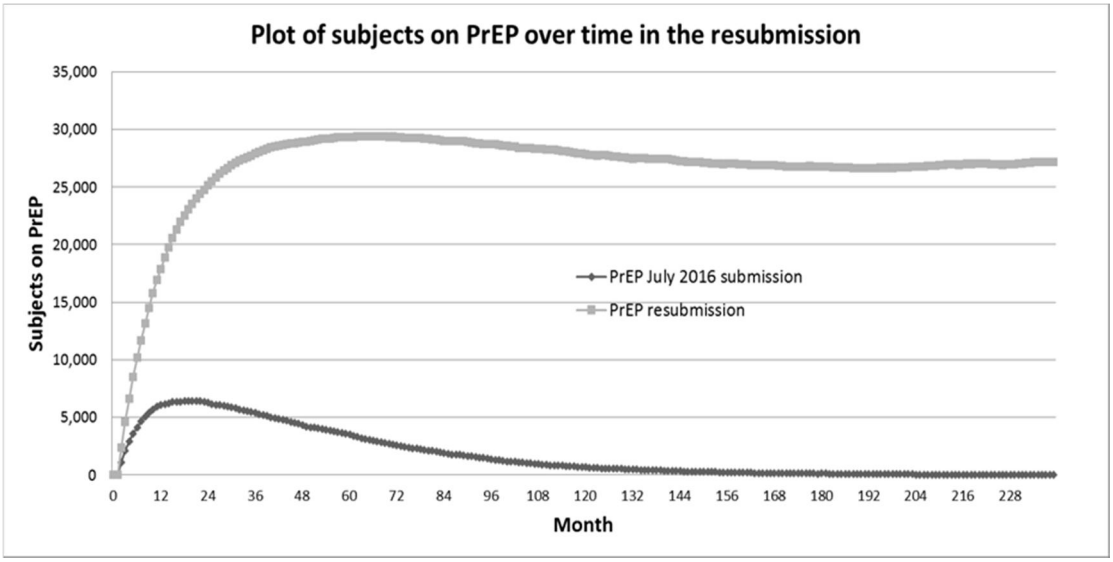
Component	TDF/FTC + SOC	SOC	Increment
July 2016 Model 2			
Costs, undiscounted	$ [redacted]	$ [redacted]	-$ [redacted]
QALY, undiscounted	2,561,806	2,556,491	5,315.60
Incremental cost/extra QALY gained, undiscounted			-$28,759
Incremental cost/extra QALY gained, discounted			-$1,143
Resubmission			
Costs, undiscounted	$ [redacted]	$ [redacted]	$ [redacted]
QALY, undiscounted	2,645,687	2,629,156	16,531
Incremental cost/extra QALY gained, undiscounted			$ [redacted]
Incremental cost/extra QALY gained, discounted			$ [redacted]

Source: Tables D-21 pp 176 of the July 2016 submission. Table D.19, D.20, P.94-95 of the resubmission
Abbreviations: QALY = quality-adjusted life year, SOC = standard of care.

6.33 The model in the resubmission produced an ICER of more than $200,000 per QALY gained. This compares with TDF/FTC + SOC being dominant over SOC in the July 2016 submission. The main reasons for the difference in the ICER were as follows:

- Incorporating a broader population of medium to high-risk individuals with removal of the 3% annual risk eligibility criteria, resulted in higher PrEP uptake. This had the effect of increasing costs more than proportionately to be offset by improved efficacy through broader PrEP use (resulting in a higher ICER).
- Removal of the continuation threshold, therefore, resulting in no minimum risk eligibility for continuation of PrEP. The removal of the continuation threshold allowed more participants who initiate PrEP to continue to receive PrEP in subsequent cycles compared to the July 2016 submission (see Figure 1). This may not be reasonable given the potential for the use of intermittent dosing of TDF/FTC as PrEP. The increase in the proportion of individuals remaining on TDF/FTC throughout the duration of the model contributed to a higher cost of TDF/FTC. The corresponding increase in QALYs due to higher uptake was proportionately less than the cost increase, resulting in an increase in the ICER.
- The overall occurrence of HIV infections increased as a result of the change in the eligible population and the modelling of HIV transmission that removed the rapid exhaustion of HIV transmission. HIV infections avoided increased by more than 6 times in the resubmission compared to the July 2016 submission (yet the eligible population increased by less than 4 times) (see Table 14). Thus, while the total QALYs gained increased, the increase (due to the population expansion) was less than proportional to the increase in costs, resulting in a worsening of the ICER.
- TDF/FTC is proposed for listing as a Section 85 benefit item, resulting in a higher per unit cost and higher treatment costs overall.
- Reduction in the frequency of HIV and other testing in the SOC arm, reducing the SOC associated costs and resulting in a higher incremental cost for TDF/FTC.

Figure 1: Subjects receiving PrEP over time



Source: Excel spreadsheet of the resubmission 'Section D Workbook "PrEP, column Q" and July 2016 submission "Truvada PrEP Section D Simulation Results 3 – Base Case, "Susceptible PrEP, column J"

6.34 The PBAC noted the economic model included in the resubmission assumed that individuals essentially remain on PrEP indefinitely and considered that this was not reflective of the way PrEP would be used in practice, however the impact of adherence could not be tested in the model.

Table 14: Incident HIV infections and death

	July 2016 submission (Model 2)	Resubmission
Susceptible subjects	134,000	135,750
Eligible subjects	8,944 (criteria eligible)	32,999 (initiation risk)
HIV infections with no PrEP (SOC alone)	5,842	19,614
HIV infections with PrEP	3,873	6,064
HIV infections avoided	1,969	13,550
Deaths with no PrEP (SOC alone)	2,807	3,058
Deaths with PrEP	2,725	2,600
Deaths avoided	82	458

Abbreviations: NR, not reported

Source: Table D.18, p. 173 of the July 2016 submission and Excel spreadsheet of the July 2016 submission 'Truvada PrEP Section D Simulation Results 3 –Base Case', sheet 'PrEP' and 'SOC' and Excel spreadsheet Section D Workbook of the resubmission 'Incidence'.

6.35 A summary of the key drivers of the model is presented in the table below. The key drivers from the July 2016 submission of time horizon, assumptions regarding continuation and the individual risk distribution remain the same.

Table 15: Key drivers of the model

	July 2016 submission	Resubmission	
Description	**Method/Value**		**Impact**
Initiation/Suitability	3% initiation threshold	Initiation at 3% replaced with suitability threshold	High, increases ICER ICER with 3% initiation: $[redacted]
Continuation threshold	2%; assumed while the proposed PBS listing does not include continuation criteria	Removed continuation threshold (0%)	High, biases against TDF/FTC ICER with 1% continuation threshold: $[redacted]
Force of infection	0.136; estimated from Australian Surveillance Report	Primary = 0.80; Chronic = 0.08; estimated from Australian Surveillance Report and literature (equivalent to an aggregate force of infection of 0.097)	High, favours SOC ICER with 0.136 force: $[redacted]
Time horizon	20 years, assumed from ~ 2 years trial duration	20 years, assumed from ~ 2 years trial duration	High, favours TDF/FTC ICER at 10 years: $[redacted]
Individual risk distribution	Gamma distribution (mean 1, SD 2.0).	Gamma distribution (mean 1, SD 0.5).	High, favours SOC ICER with wider SD: $[redacted]

Source: compiled during the evaluation (reference sections/tables/spreadsheets within the submission)

6.36 The results of the univariate sensitivity analyses in the resubmission show that the ICER was most sensitive to the time horizon of the analysis, the force of infection applied to primary and chronic infections, the mean suitability threshold and the price of TDF/FTC.

Table 16: Results of univariate sensitivity analyses presented in the resubmission

Parameter (base case value)	Description	Peak uptake	ICER
Base case as presented in the resubmission	Seed 1	29,659	$ [redacted]
Discount rate (5%)	3.5	29,659	$ [redacted]
	7	29,659	$ [redacted]
Time horizon (20 years)	30	29,659	$ [redacted]
	10	29,659	$ [redacted]
Currently treated patients (73.4%)	80	27,897	$ [redacted]
Force of infection (cases/year: chronic=0.08; primary=0.80)	chronic=0.1; primary=1.0	33,944	$ [redacted]
	chronic=0.05; primary=0.5	20,024	$ [redacted]
Individual risk distribution (form=gamma; SD=0.5)	form=gamma, SD=2	16,773	$ [redacted]
	form=uniform, lower bound=0.5; upper bound =1.5	31,543	$ [redacted]
Hard risk thresholds (initiation ≈ 1%; continuation=NA)	initiation=3; continuation=1	12,263	$ [redacted]
Uptake (rate/year) 60%	80	31,873	$ [redacted]
	40	26,060	$ [redacted]
Discontinuation (0.1 rate/year)	0.2	26,355	$ [redacted]
	0.01	41,622	$ [redacted]
Compliance (90%)	70	29,659	$ [redacted]
	100	29,659	$ [redacted]
Effectiveness (90%)	100	29,394	$ [redacted]
	80	29,575	$ [redacted]
Inhibition factor (multiplier = 1)	0.9	29,456	$ [redacted]
	1.1	29,404	$ [redacted]
HIV testing (rate/year: PrEP=4; Primary infection = 0.5; SOC: 0-2; low risk =0.1)	PrEP=4; Primary infection = 1; SOC: 2; low risk =0)	29,207	$ [redacted]
	PrEP=4; Primary infection = 0; SOC: 1; low risk =0.5)	29,086	$ [redacted]
Treatment uptake (rate/year: Stage I=0.1; Stage II=0.2; Stage III=0.4)	Stage I=0.2; Stage II=0.4; Stage III=0.6	33,220	$ [redacted]
	Stage I=0; Stage II=0.1; Stage III=0.2	27,436	$ [redacted]
Mean suitability threshold (0.01)	0.03	13,053	$ [redacted]
	0.05	8,168	$ [redacted]
	0.07	4,708	$ [redacted]
	0.1	1,925	$ [redacted]
Total TDF/FTC PrEP cost ($827.24/month)	$500	26,659	$ [redacted]
	$400	26,659	$ [redacted]
	$300	26,659	$ [redacted]
	$200	26,659	$ [redacted]

Note: inconsistent ICER reported for sensitivity analysis of inhibition factor, increasing inhibition factor to 1.1 should improve (reduce ICER).
Source: Table D.2.2, Table D.2.3, p. 96-97 of the resubmission

6.37 Additional sensitivity analyses conducted during the evaluation are summarised in Table 17.

6.38 The results from these additional analyses show that the model is sensitive to assumptions regarding whether or not subjects use PrEP continuously, the assumed force of infection, and the manner in which the inhibition factor is applied. In particular, the latter has not been defined in the resubmission in a way that links

behaviour to risk, making the interpretation of that factor and its resulting impact on the ICER difficult.

Table 17: Results of univariate sensitivity analyses prepared during the evaluation

Parameter	Incremental Costs	QALY	ICER (Cost per QALY gained)
Base case as presented in the resubmission (Seed 1)	$ [redacted]	8,697	$ [redacted]
Base case during the evaluation (Seed 6)	$ [redacted]	8,661	$ [redacted]
Removal of exogenous prevalent HIV	$ [redacted]	8,442	$ [redacted]
Double exogenous prevalent HIV	$ [redacted]	9,813	$ [redacted]
Introduction of continuation criteria, 1%	$ [redacted]	7,880	$ [redacted]
All treated achieve viral suppression	$ [redacted]	6,611	$ [redacted]
Inhibition factor reduced, 0.9	$ [redacted]	9,313	$ [redacted]
Inhibition factor increased, 1.1	$ [redacted]	8,696	$ [redacted]
Discontinuation rate reduced, 0.05	$ [redacted]	9,373	$ [redacted]
Discontinuation rate increased, 0.2	$ [redacted]	8,309	$ [redacted]
Net growth, 1	$ [redacted]	9,203	$ [redacted]
Initiation risk threshold increase, 0.03	$ [redacted]	5,894	$ [redacted]
Infection in PrEP affected by compliance	$ [redacted]	8,403	$ [redacted]
Cost of PrEP if generic[a]	-$ [redacted]	8,661	-$ [redacted]
Cost of PrEP corrected for renal monitoring	$ [redacted]	8,661	$ [redacted]
Individual risk multiplier, gamma dist. mean =1; SD decreased 0.25 (base 0.5)	$ [redacted]	9,114	$ [redacted]
Individual risk multiplier, gamma dist. mean =1; SD increased 1 (base 0.5)	$ [redacted]	7,817	$ [redacted]
Individual risk variation, uniform distribution, broader	$ [redacted]	8,926	$ [redacted]
Individual risk threshold, gamma dist. mean =1; SD reduced 0.05 (base 0.1)	$ [redacted]	8,482	$ [redacted]
Individual risk threshold, gamma dist. mean =1; SD increased 0.2 (base 0.1)	$ [redacted]	8,774	$ [redacted]
Male subjects only	$ [redacted]	8,725	$ [redacted]
Inhibition factor impact individual risk, 0.9	$ [redacted]	7,652	$ [redacted]
Inhibition factor impact individual risk, 1.1	$ [redacted]	10,730	$ [redacted]
Force of infection same for primary and chronic applying July 2016 submission value	$ [redacted]	14,638	$ [redacted]

[a]: Article from Pharma In Focus 10 April 2017 via Green Cross Pharmacy for $148 90 generic PrEP pills and twice yearly renal monitoring
Note: The model results could not be reproduced during the evaluation for simulations with seed 1, 2, 4 and 7. During the evaluation, the median ICER was Seed 7 of $[redacted] per QALY gained compared to the submission median ICER from Seed 1 of $[redacted] per QALY gained. Sensitivity analyses conducted during the evaluation were done using Seed 6 as this could be reproduced and it was closer to being the median result (rank 6 in the resubmission and rank 4 in the evaluation).
Abbreviations: SD, standard deviation
Source: constructed during the evaluation

6.39 The PBAC noted that many of the scenarios in the sensitivity analyses resulted in an ICER that was lower than the base case, and hence that the model was conservative potentially overestimating the ICER. The PBAC noted that the price of TDF/FTC was a key driver of the cost-effectiveness of PrEP.

6.40 The ESC and PBAC noted the estimated cost/QALY gained in the resubmission (More than $200,000/QALY) was very different to that presented in the July 2016 submission (TDF/FTC being dominant). The PBAC recalled that the model included in the July 2016 submission lacked face validity and the submission's base case claim of dominance over SOC was not accepted. Both Committees further noted the predicted number of HIV infections in the SOC arm increased substantially (from

5,842 to 19,614, Table 14) indicating a fundamentally different approach to modelling HIV over time.

6.41 The ESC noted the incidence of HIV in each cycle is calculated as the number of subjects with a primary HIV infection multiplied by the primary force of infection plus the number of subjects with a chronic HIV infection multiplied by the chronic force of infection. The forces of infection remain constant over time and are based on the estimated number of incident cases and the estimated prevalent HIV population in 2014. The ESC considered the estimated forces of infection to be highly uncertain and noted that the ICER was sensitive to these estimates (Table 16). The ESC further noted the reduced force of infection in the resubmission compared with the July 2016 submission partly accounted for the increased ICER in the resubmission (the ICER reduced from $[redacted] to $[redacted] per QALY gained with use of the force of infection from the July 2016 submission, Table 15).

6.42 The ESC noted that the estimation of separate forces of infection for primary and chronic HIV favours PrEP because as incidence decreases the numbers of primary HIV infection cases drop and so new cases of HIV infection drops further because primary HIV infection is assumed to account for 80% of new cases.

6.43 The ESC noted incident cases of HIV are distributed across the susceptible population using average and individual infection risks and that the resubmission used an arbitrary gamma distribution to represent the individual risk threshold for suitability and inform the behavioural multiplier. The ESC noted the ICER was sensitive to the assumed individual risk distribution and use of the distribution from the July 2016 submission reduced the ICER from more than $200,000/QALY to more than $200,000/QALY per QALY gained (Table 15).

6.44 The Australian Federation of AIDS Organisation (AFAO) commissioned the Kirby Institute and the Centre for Social Research in Health to model the cost-effectiveness of PrEP. A copy of the report for this analysis was provided with the resubmission. As part of the PBAC evaluation process, PBAC members and evaluators met with the developers of the Kirby model to examine the model, consistent with the usual examination of sponsor developed models.

6.45 The ESC noted the Commentary (Section D.3) compared the model presented in the resubmission with the economic model developed by the Kirby Institute assessing the cost-effectiveness of PrEP in MSM. The structure and a number of the inputs for the two models differed substantially. The Kirby model partitioned the Australian population into 11 sub-populations: Female sex workers; Clients of female sex workers; Sexually active gay men at low-risk of infection; Sexually active gay men at medium-risk of infection; Sexually active gay men at high-risk of infection including those who inject drugs; Males who inject drugs; Females who inject drugs; Other males 16-69 years old; Other females 16-69 years old; Males older than 69 years and

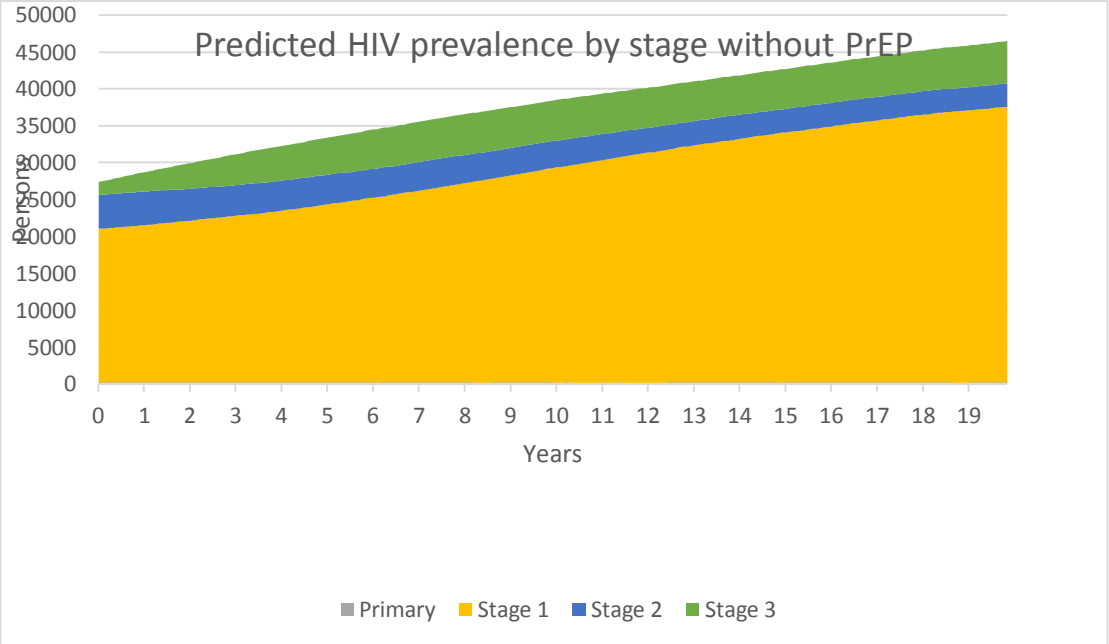
Females older than 69 years. This compared with a simpler differentiation between primary and chronic HIV and the use of arbitrary risk multipliers in the resubmission.

6.46 The ESC noted the resubmission presented the predicted number of HIV infections in the absence of PrEP for the 20 year model time horizon and concluded "While recognising that these analyses represent predictions of an uncertain future, they are considered to be realistic projections of the Australian HIV epidemic in the absence of PrEP, given current trends and policy settings." The ESC considered that this claim was not supported.

6.47 In comparison, the Kirby model's predictions of the number of infections were calibrated using available demographic, epidemiological, behavioural, and clinical data to match the observed HIV epidemic in Australia over 2000-2015, from which future trends up to 2030 were extrapolated.

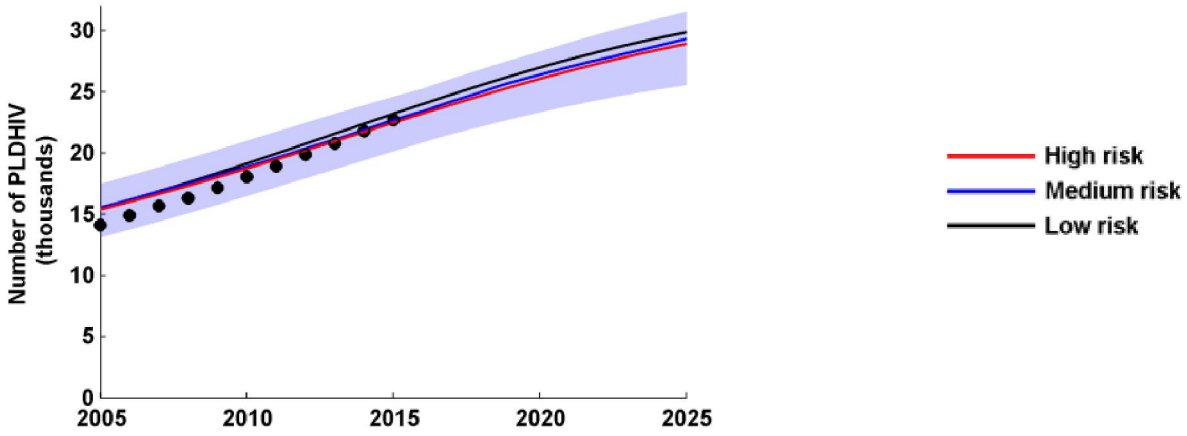
6.48 The predicted HIV prevalence based on the resubmission and Kirby models is presented in Figures 2 and 3, respectively. Over the next 10 years the resubmission's model predicted that the prevalence of HIV would increase from approximately 27,000 to 38,000 individuals. This compared with a prevalence of 21,000 in 2015 increasing to 28,000 in 2025 in the Kirby model.

Figure 2: Resubmission model, predicted HIV prevalence by stage without PrEP



Source: Figure D.8 of the submission, p 86.

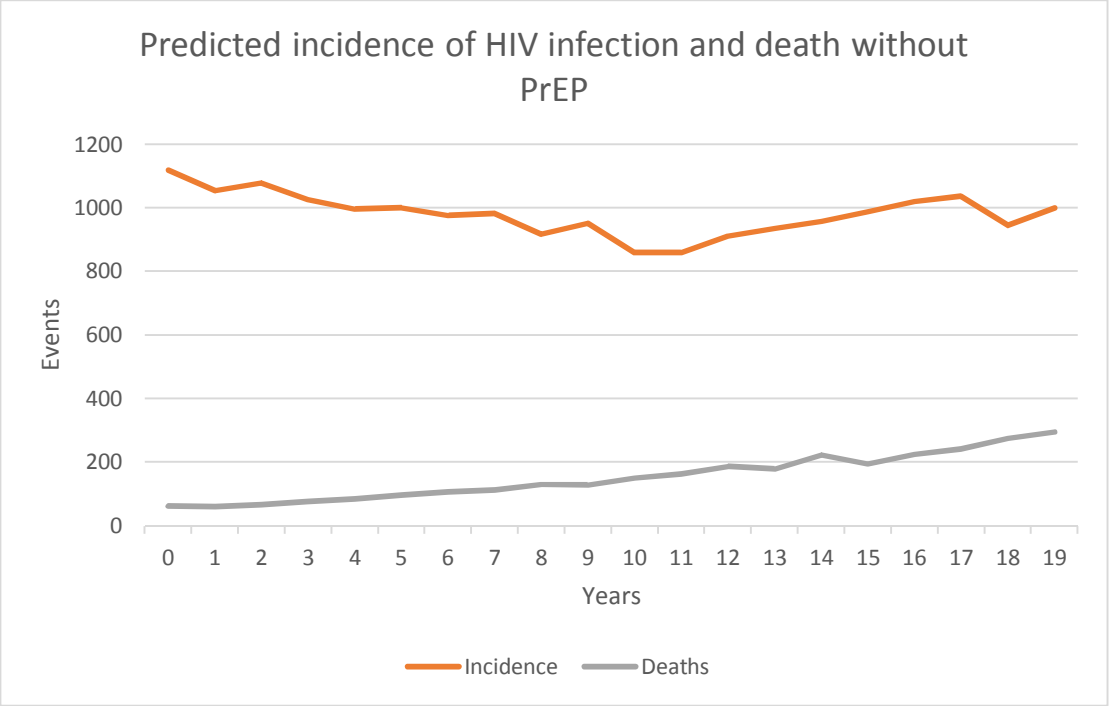
Figure 3: Kirby model, calibration of the model to the number of people living with diagnosed HIV



Source: Kirby Institute and the Centre for Social Research in Health. Discussion paper: Estimates of the number of people eligible for PrEP in Australia, and related cost-effectiveness, Figure A.2 p 21.

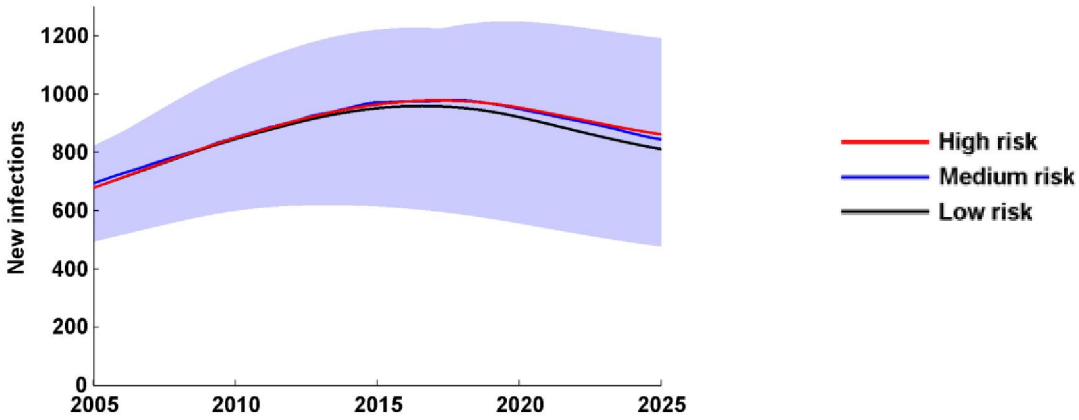
6.49 The predicted HIV incidence based on the resubmission and Kirby models is presented in Figures 4 and 5, respectively. Both models predicted a decline in incidence over the next 10 years; however the resubmission's model predicted a subsequent increase from year 11 onwards. Although the incidence is predicted to decline, the prevalence is predicted to increase (as noted above) due to the long survival for HIV patients treated with ART.

Figure 4: Resubmission model, predicted HIV incidence and death without PrEP



Source: Figure D.7 of the submission, p 86.

Figure 5: Kirby model, predicted HIV incidence without PrEP



Source: Kirby Institute and the Centre for Social Research in Health. Discussion paper: Estimates of the number of people eligible for PrEP in Australia, and related cost-effectiveness, Figure A.6 p 23.

6.50 The ESC considered the Kirby model was more likely to accurately predict HIV incidence and prevalence in the future given the calibration approach used, and it was further noted that the time horizon for the Kirby model was 14 years in

comparison to 20 years for the resubmission's model and hence was associated with less uncertainty regarding the predicted incidence and prevalence of HIV.

6.51 The results for the Kirby model are presented for a number of scenarios based on different uptake in individuals at high, medium or low risk of infection. The uptake scenarios ranged from 30-0-0 (30% uptake in high risk, 0% in medium risk, 0% in low risk; 8.4% overall uptake) to 90-90-90 (90% overall uptake). The results are summarised in Table 18. The Kirby model used a monthly cost for TDF/FTC of $[redacted] compared with $[redacted] in this resubmission.

Table 18: Results of Kirby economic model

Scenario (uptake in high, medium and low risk)	Overall uptake All[a]/high-med risk[b]	Infections averted	QALYs gained (discounted)	Incremental costs (discounted)	Cost per QALY gained
30-0-0	9%/26%	4110	1870	$224,256,430	$127,550
60-0-0	17%/53%	7060	3410	$503,263,520	$157,960
90-0-0	25%/79%	8910	4480	$807,794,350	$191,660
90-20-0	26%/81%	8940	4510	$850,809,840	$200,910
90-60-0	28%/86%	9010	4550	$940,933,410	$218,440
90-20-10	33%/81%	9210	4680	$1,266,376,800	$275,600
90-60-30	48%/86%	9710	5000	$2,128,668,660	$423,490
90-90-90	90%/90%	10660	5770	$4,451,195,750	$759,120

a Based on high risk = 28.2%, medium risk = 4% and low risk = 67.8% of all gay men.
b Based on high risk = 88% (28.2/(28.2+4)) and medium risk = 12% (4/(28.2+4) of medium-high risk gay men.

Source: Kirby Institute and the Centre for Social Research in Health (February 2017). Discussion paper: Estimates of the number of people eligible for PrEP in Australia, and related cost-effectiveness. Appendix, Table 7.

Committee-In-Confidence information

[redacted]

End Committee-In-Confidence information

6.52 Uptake of 90% for the three risk categories was considered to be the theoretical maximum across the entire population. Uptake of 90%, 60% and 30% across the three risk strata was considered to reflect the maximum realistic coverage. Both of these scenarios include use in low risk individuals whereas the resubmission has proposed a PBS listing for use in individuals at a high or medium risk of infection only.

6.53 The resubmission's model assumed uptake of 60%. The ESC noted none of the scenarios presented for the Kirby model used an uptake rate similar to the one used in the resubmission. The evaluation suggested the Scenario 90-60-30 is the closest to the resubmission with an overall 48.1% uptake rate. For this scenario the ICER is more than $200,000 per QALY gained. However, this includes use in low risk individuals for which PrEP use is less cost-effective. For the Scenario 60-0-0 (overall uptake 17%, high-medium uptake 53%) the ICER is $105,000/QALY - $200,000/QALY.

6.54 The PBAC noted that with the Kirby model the ICER increased as the uptake of PrEP increased, reflecting diminishing returns as the number of individuals using PrEP increased, particularly when uptake extended to medium and low risk individuals.

6.55 The ESC and PBAC noted both models assumed high efficacy and adherence. The resubmission assumed 100% efficacy and 90% adherence i.e. 100% efficacy in 90% of individuals and 0% efficacy in the remaining 10%. It was not possible to test varying levels of adherence in the resubmission's model. The Kirby model assumed 99% efficacy for 7 doses per week, 96% for 4 doses per week and 76% for 2 doses per week. The base case analysis assumed 90% adherence. The ESC noted a reduction in adherence leads to improved cost-effectiveness of PrEP as a result of the relatively high efficacy with only 2-4 doses per week.

6.56 Both models assumed patients would be treated with PrEP for the model duration (14 years for the Kirby model and 20 years with 10% discontinuing each year for the resubmission model). The ESC and PBAC noted it is proposed that patients are reassessed for eligibility for PrEP every 3 months and considered it likely patients will cease PrEP (and possibly restart at a separate time) as their circumstances change, however neither model assessed the impact of intermittent PrEP.

6.57 The ESC and PBAC noted neither model included the potential for changes in risk behaviour associated with condomless sex to increase the incidence of STIs. The ESC noted this would be anticipated to increase the costs of treatment associated with a PrEP + SOC regime, and to reduce the associated QALYs, but that the magnitude of the impact of TDF/FTC on STI incidence is currently unknown. The PBAC noted the increase in the reported cases of STIs in the clinical studies and considered in clinical practice the requirement of a medical practitioner visit every 3 months to obtain a

prescription for TDF/FTC is likely to increase monitoring for STIs and result in earlier diagnosis.

6.58 The ESC noted that the Kirby model assessed the impact of a reduction in condom use on the impact of HIV transmission. For Scenario 90-0-0 and a 50% decrease in use of condoms in men taking PrEP the base case ICER increased from $105,000/QALY - $200,000/QALY to more than $200,000 per QALY gained.

Committee-In-Confidence information

[redacted]

End Committee-In-Confidence information

6.59 The PBAC considered that the Kirby model was likely to be more robust and reliable than the model included in the resubmission for a number of reasons, including:

- Uptake was modelled separately for high, medium and low risk MSM populations;
- The rate of infection was dependent on the type and number of risk events, and differed with different modes of transmission (as opposed to the single 'risk multiplier' in the submission model);
- The model was calibrated against existing HIV epidemiology in Australia (2000 – 2015), which was likely to be a better predictor of HIV incidence and prevalence into the future; and
- The shorter time horizon (14 years in the Kirby model vs. 20 years in the submission model) provided more certainty in the model extrapolation.

Drug cost/patient/year: $[redacted]

6.60 The cost per pack of TDF/FTC (30 days treatment) was $[redacted]. The cost per pack in the July 2016 submission was $[redacted]. The higher cost per pack is due to the increased mark-ups associated with a Section 85 listing.

6.61 Based on 90% adherence, the resubmission assumed 10.95 ((365/30)*0.9) packs per patient per year at a cost of $[redacted].

Estimated PBS usage & financial implications

6.62 This resubmission was considered by DUSC.

6.63 The financial impact analysis presented in the resubmission takes an epidemiological, prevalence-based approach but the subject and treatment flows are

derived from the underlying dynamic transmission model described above. Therefore, the financial forecasts are subject to the assumptions of that model. The same approach was used in the July 2016 submission.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	8,763	22,076	26,857	28,717	29,397	29,614
Number of scripts dispensed[a]	95,951	241,729	294,081	314,447	321,893	324,272
Estimated financial implications of TDF/FTC						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to MBS	$5,214,663	$13,137,229	$15,982,452	$17,089,239	$17,493,907	$17,623,242
Overall impact on government health budgets	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a]Assuming 10.95 per year as estimated by the submission.
Source Table E.3, p.102Table E.4; Table E.5, p.103 of the resubmission

6.64 The submission estimated that the cost to the PBS/RPBS of listing TNF/FTC for PrEP at the proposed price would be substantially more than $100 million over 6 years. However, the DUSC considered the estimates presented in the submission to be underestimated in the first listing year and high over the remaining forward estimates period. The main issues are:

- The reliability of projecting the treated population based on the dynamic transmission model is uncertain. The estimate of the susceptible population at risk of acquiring HIV could not be verified. The model is highly sensitive to the way the force of infection is applied between the acute and chronic infection states.
- The forecasted treated population for Year 1 was likely to be an underestimate. Individuals receiving PrEP through existing demonstration projects would be expected to transition to PBS subsidised PrEP. It was estimated that around 8,000 individuals were enrolled in demonstration projects.
- The projected treated population from Year 2 is likely to be overestimated. The eligible population for males who have sex with males (MSM) is considered to be between 20,000 and 26,000. While the heterosexual population will also have access to PrEP, this population is relatively small (representing around 19% of infections) compared to the MSM population. The assumption of a treatment

uptake of 90% in the outer years appears high in the context of only 75% of individuals with HIV being treated with antiretroviral therapy (ART).[3]

- The treatment duration for PrEP is uncertain and there is no rule for stopping therapy in the proposed restriction.
- How PrEP will be used in practice is uncertain. The financial estimates assume PrEP will be administered as a once daily dosing consistent with the approved Product Information. However intermittent and episodic dosing is being trialled, and if adopted in practice, the number of prescriptions and cost to the PBS could be substantially lower than predicted. Reducing adherence to moderate levels has a minor impact on the epidemiological impact of PrEP intervention.
- The success of PrEP relies on medication adherence, notwithstanding the promotion of safer sexual practices remains critically important. Strategies to promote adherence to these practices were not reported in the submission.
- Individuals who are currently diagnosed and treated with antiretroviral therapy (ART) will have a lower viral load and thus will be less likely to infect the person taking PrEP. In 2015, around 75% of people living with diagnosed HIV received ART out of a target of 90%.[4] This suggests there are potential systems issues in delivering ART which may also affect the implementation of PrEP.

6.65 The PBAC considered the utilisation and financial estimates were highly uncertain, and in particular the uptake of PrEP is uncertain. Overall the PBAC agreed with the DUSC and considered the utilisation estimates were likely to be underestimated in the first year and likely to be overestimated in years 2-6.

Quality Use of Medicines

6.66 The resubmission did not address the specific quality use of medicines principles that apply to TDF/FTC as PrEP, including those previously raised by DUSC in relation to the July 2016 submission.

6.67 The ESC noted the resubmission proposed that management of the PrEP program be administered by ASHM. However, it does not contain any further information about the administration or nature of the program, other than the following: "The proposed PrEP Prescriber Program is modelled on that which currently applies to PBS prescribing of mifepristone and misoprostol and would consist of a brief online registration and training requirement aimed at assisting prescribers to identify those subjects at medium to high risk of HIV infection and maximising quality use of medicines principles in relation to Truvada (PrEP)." (March 2017 Resubmission, p 25). The ESC noted that the costs of the Prescriber Program may not have been adequately captured in the economic model, although the marginal costs may be

[3] The Kirby Institute. National Blood-borne Viruses and Sexually Transmissible Infections Surveillance and Monitoring Report, 2016. The Kirby Institute, UNSW Sydney, Sydney, NSW. Table 5 p69.
[4] *Seventh National HIV Strategy 2014–2017.*

minimal if the Program is managed through existing clinics and utilises the systems already in place.

6.68 The resubmission did not specifically address what measures might be used to address concerns over an increase in risky (condomless) sex associated with PrEP use. This has important public health implications which were not considered in the economic model or financial estimates.

6.69 The ESC considered that adherence was a key issue which has a substantial effect on the efficacy of PrEP, but would be difficult to measure and ensure. DUSC considered that there is a high risk of non-adherence as the target population may be mainly young and otherwise healthy individuals with no regular medication taking behaviours established. DUSC considered that provision of adherence support, such as through PrEP services, had not been adequately addressed in the previous submission.

6.70 The DUSC noted the following issues raised by the Advisory Committee on Prescription Medicines (ACPM) in making its recommendations:

- The long term safety of PrEP is unknown.
- There is a need for active surveillance for bone and renal toxicity.
- There is a lack of data on bone safety, in particular for women. Consideration should be given about warnings to women for use longer than one to two years.

6.71 The PBAC also noted the submission did not address the risk the development of viral resistance to TDF/FTC, and considered the risk was unclear due to the lack of long-term efficacy and safety data for use as PrEP.

Financial Management – Risk Sharing Arrangements

6.72 The resubmission did not state if the sponsor is willing to enter into a risk sharing arrangement regarding the use of TDF/FTC as PrEP. The PBAC recommended consideration be given to a risk sharing arrangement as a component of any listing for TDF/FTC for PrEP to address the substantial uncertainties in the utilisation and financial estimates, noting however that with the 1 August 2017 listing of generic brands of Truvada, the financial risk to Government will likely be mitigated by price reductions resulting from the operations of price disclosure.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on tenofovir with emtricitabine (TDF/FTC) for HIV Pre-exposure Prophylaxis (PrEP) to seek additional results for the cost-effectiveness model developed by the Kirby Institute. Specifically the Committee requested additional analyses considering alternative uptake scenarios

where the extent of uptake is reduced and use is limited to medium and high risk individuals, and varying the TDF/FTC price.

7.2 The PBAC recalled the July 2016 PrEP submission was rejected on the basis of unacceptable and uncertain cost-effectiveness at the proposed price. At that time, the PBAC considered attempts to severely restrict the eligible population based on individual risk calculation in the submission may not have been feasible, appropriate or acceptable to clinicians and consumers, and considered it may be more appropriate for a broader group of individuals to have access to PrEP. Further, the Committee had concerns regarding the applicability of the trial data with the majority of data generated in communities known to have a substantially higher incidence of HIV infection (and therefore higher risk) than the Australian population, and considered it uncertain if other safe sex practices would be utilised to the same extent in the Australian population. The Committee also considered that the economic models presented in the July 2016 submission lacked face validity and were biased towards underestimating future need.

7.3 The PBAC noted the resubmission appropriately proposed listing for a broader population of individuals compared with the July 2016 submission. The PBAC considered it reasonable for the eligible population to include medium and high risk individuals as defined in the ASHM Guidelines, including people who share injecting equipment. The PBAC considered that TDF/FTC for PrEP should be listed as a General Schedule item to ensure widest access, and should include provision for nurse-practitioner prescribing. The PBAC noted the requested price for TDF/FTC was the same as in the July 2016 submission and that TDF/FTC was previously considered not cost-effective at this price.

7.4 The PBAC reaffirmed it accepted standard of care (SOC), a combination of other safe sex practices, as the appropriate comparator for TDF/FTC plus SOC.

7.5 The PBAC recalled the July 2016 submission included the results for six randomised trials comparing TDF/FTC with SOC however, the efficacy estimate used in the economic model (relative risk reduction in HIV infections of 90%) was sourced from the case control analysis of adherent subjects from only two of the randomised trials (iPrEx and Partner's PrEP) trials, which were presented in the original July 2016 submission. This estimate of efficacy was also used in the economic model in the resubmission.

7.6 The PBAC noted the new evidence provided in the resubmission included two randomised trials assessing intermittent dosing regimens of TDF/FTC (IPERGAY and ADAPT) and five non-randomised observational studies. In the IPERGAY trial a reduction in the relative risk of HIV infection of 82-86% was observed. The PBAC noted this reduction with intermittent TDF/FTC was slightly lower than observed with adherent individuals using daily TDF/FTC. The PBAC noted intermittent use of TDF/FTC as per the regimen used in the IPERGAY trial appeared effective, and

considered that there would be a considerable amount of intermittent use in clinical practice. The PBAC noted the economic model and financial forecasts presented in the resubmission were based on daily use of TDF/FTC.

7.7 The PBAC noted, with the exception of VicPrEP, results were not available for the Australian demonstration programs. No additional results were presented for VicPrEP were presented in the resubmission compared with the July 2016 submission and these results were limited due to the short duration of follow-up.

7.8 The PBAC noted the increase in the reported cases of STIs in the IPERGAY trial and observational studies and considered in clinical practice the requirement of a medical practitioner visit every 3 months to obtain a prescription for TDF/FTC is likely to increase monitoring for STIs and result in earlier diagnosis.

7.9 The PBAC accepted, based on the evidence presented, that TDF/FTC as PrEP appeared to be effective in reducing the transmission of HIV.

7.10 The PBAC reaffirmed its previous advice that it considered the claim of non-inferior comparative safety was not strongly supported by the available data, however given the duration of experience with TDF/FTC for the treatment of HIV, the claim of non-inferior comparative safety was probably reasonable. The PBAC noted there was an increase in adverse events over SOC in the IPERGAY trial, including gastrointestinal events and increased serum creatinine levels. The PBAC also considered long-term use of TDF/FTC may be associated with bone loss and reduced renal function.

7.11 The PBAC noted a number of revisions had been made to the economic model included in the July 2016 submission, and that in general the model assumptions were more conservative. The PBAC noted the results of the economic model were fundamentally different with an incremental cost-effectiveness ratio (ICER) of more than $200,000 per QALY gained (compared with TDF/FTC being dominant), the eligible population being approximately four times larger, the number of infections avoided increasing from 1,969 to 13,550 and the number of deaths avoided increasing from 82 to 458.

7.12 The PBAC noted the issues raised by ESC regarding the economic model including how the incidence of HIV was modelled over time and how the incident cases were distributed across the susceptible population. The PBAC also noted the economic model assumed that individuals essentially remain on PrEP indefinitely and considered that this was not reflective of the way PrEP would be used in practice. Further, the Committee noted that the impact of adherence with TDF/FTC could not be tested in the model.

7.13 The PBAC noted that many of the scenarios tested in the sensitivity analyses resulted in an ICER that was lower than the base case, and hence that the model was likely conservative, potentially overestimating the ICER. The PBAC noted that the price of TDF/FTC was a key driver of the cost-effectiveness of PrEP, and considered despite

the issues noted with the economic model, that TDF/FTC was not cost-effective at the requested price.

7.14 The PBAC noted the resubmission included an economic model developed by the Kirby Institute assessing the cost-effectiveness of PrEP in MSM, and that the ESC considered the Kirby model was more likely to accurately predict HIV incidence and prevalence in the future given the calibration approach used, and as the time horizon for the Kirby model was 14 years in comparison to 20 years for the resubmission's model and was associated with less uncertainty regarding the predicted incidence and prevalence of HIV.

7.15 The PBAC agreed with ESC and considered that the Kirby model was likely to be more robust and reliable than the model included in the resubmission because:

- Uptake was modelled separately for high, medium and low risk MSM populations;
- The rate of infection was dependent on the type and number of risk events, and differed with different modes of transmission (as opposed to the single 'risk multiplier' in the submission model);
- The model was calibrated against existing HIV epidemiology in Australia (2000 – 2015), which was likely to be a better predictor of HIV incidence and prevalence into the future; and
- The shorter time horizon (14 years in the Kirby model vs. 20 years in the submission model) provided more certainty in the model extrapolation.

7.16 The PBAC noted the results for the Kirby model were presented for a number of scenarios based on different uptake in individuals at high, medium or low risk of infection. The uptake scenarios ranged from 30-0-0 (30% uptake in high risk, 0% in medium risk, 0% in low risk; 8.4% overall uptake) to 90-90-90 (90% overall uptake). Although, the PBAC considered that TDF/FTC was not cost effective at the requested price for any of the uptake scenarios modelled in the Kirby model, the PBAC noted that only two of the scenarios presented considered use in individuals at high and medium risk of infection, the population proposed in the resubmission which the PBAC agreed to be appropriate. Further, both of the scenarios assumed 90% uptake in high risk individuals and the PBAC considered that this level of uptake was unlikely to be achieved in clinical practice. The PBAC considered alternative scenarios assuming lower uptake in medium and high risk individuals would be informative.

7.17 The PBAC further requested sensitivity analyses varying the TDF/FTC price to be undertaken for these additional scenarios. The PBAC recalled that the threshold of incremental QALYs gained for treatments with large opportunity costs, such as population preventative interventions including lipid-lowering, anti-hypertensive drugs and vaccines was at the lower end of the ICER range that PBAC has accepted

because these treatments typically have a high opportunity cost. Though not completely analogous to a vaccination program such as against Human Papillomavirus (HPV), the PBAC considered that subsidisation of PrEP, like the HPV vaccine, would provide both direct benefits to the treated individual and wider benefits to society with reductions in the prevalence of HIV infection over time. The PBAC considered that the acceptable ICER/QALY for PrEP should be at the low end of the range previously accepted for these other population preventative interventions with large opportunity costs.

7.18 The PBAC considered the utilisation estimates were highly uncertain and difficult to predict, however agreed with DUSC that utilisation was likely underestimated in year 1 and overestimated in years 2-5. The PBAC noted that the submission estimated annual expenditure exceeding $100 million per year in five of the six years of the estimates and considered the opportunity cost was unacceptably high at the proposed price.

7.19 The PBAC noted that, depending on the further information being sought, there may be considerable uncertainties associated with the cost effective usage of this drug and consideration should be given to how to best manage those uncertainties if a recommendation is made for a PBS listing in future. The PBAC noted that this submission is not eligible for an Independent Review as it was deferred.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Gilead will continue to work with the PBAC to achieve a recommendation for pre-exposure prophylaxis against HIV infection. Gilead is aware that there are now generic companies providing multiple brands of tenofovir with emtricitabine.