PUBLIC SUMMARY DOCUMENT

Product: First-line anti-retroviral therapy (ART)
Sponsor: Australasian Society for HIV Medicine (ASHM), National Association of People with HIV Australia, Australian Federation of AIDS Organisations
Date of PBAC Consideration: November 2013

1. Purpose of Application

To request the removal of the CD4+ cell count restriction for initiation of first line anti-retroviral therapy (ART) in asymptomatic, ART naïve HIV positive patients.

Anti-retroviral therapy for HIV infection is currently available on the PBS via the Section 100 (Highly Specialised Drugs Program). Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This submission had not previously been considered by the PBAC.

The current restrictions for the initiation of antiretrovirals requires patients to have a CD4+ count of less than 500 cells/mm^3 or symptomatic HIV disease.

3. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private Hospital Authority required
Public Hospital Authority required (STREAMLINED)

Initial treatment of HIV infection in combination with other antiretroviral agents, in a patient who is antiretroviral treatment naïve following diagnosed HIV infection.

Continuing treatment of HIV infection in combination with other antiretroviral agents where the patient has previously received PBS-subsidised therapy for HIV infection.

The PBAC noted that the requested restriction would allow the initiation of ART at a CD4+ count >500 cells/mm^3 for patients with HIV, irrespective of the presence of symptomatic disease.

First line HIV treatment is considered to be ARTs currently listed under Authority streamline codes 3588 and 3589 for the initial and continuing treatment of HIV infection. The pharmaceutical items that would be affected by this change are listed in the table below.

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
ATAZANAVIR capsule 100 mg, 60 capsule 150 mg, 60 capsule 200 mg, 60 capsule 300 mg, 60	 2 2 2 2	 5 5 5 5	 Reyataz	 Bristol Myers Squibb
FOSAMPRENAVIR oral liquid 50 mg/mL, 225 mL tablet 700 mg, 60	 8 2	 5 5	 Telzir	 Viiv Healthcare
INDINAVIR capsule 400 mg, 180	 2	 5	 Crixivan 400 mg	 Merck Sharp & Dohme
RITONAVIR tablet 100 mg, 30 oral liquid 600 mg/7.5 mL, 90 mL	 24 10	 5 5	 Norvir	 AbbVie
SAQUINAVIR tablet 500 mg, 120	 2	 5	 Invirase	 Roche
ABACAVIR oral liquid 20 mg/mL, 240 mL tablet 300 mg, 60	 8 2	 5 5	 Ziagen	 Viiv Healthcare
DIDANOSINE capsule 125 mg, enteric coated, 30 capsule 200 mg, enteric coated, 30 capsule 250 mg, enteric coated, 30 capsule 400 mg, enteric coated, 30	 2 2 2 2	 5 5 5 5	 Videx EC	 Bristol Myers Squibb
EMTRICITABINE capsule 200 mg, 30	 2	 5	 Emtriva	 Gilead Sciences
LAMIVUDINE oral liquid 10 mg/mL, 240 mL tablet 150 mg, 60 tablet 300 mg, 30	 8 2 2	 5 5 5	 3TC 3TC Lamivudine Alphapharm Lamivudine RBX 3TC Lamivudine Alphapharm Lamivudine RBX	 Viiv Healthcare Viiv Healthcare Alphapharm Ranbaxy Viiv Healthcare Alphapharm Ranbaxy
STAVUDINE capsule 20 mg, 60 capsule 30 mg, 60 capsule 40 mg, 60	 2 2 2	 5 5 5	 Zerit	 Bristol Myers Squibb
TENOFIVIR tablet 300 mg, 30	 2	 5	 Viread	 Gilead Sciences
ZIDOVUDINE capsule 100 mg, 100 capsule 250 mg, 40 oral liquid 50 mg/5 mL, 200 mL	 4 6 15	 5 5 5	 Retrovir	 Viiv Healthcare
EFAVIRENZ tablet 200 mg, 90 oral liquid 30 mg/mL, 180 mL tablet 600mg, 30	 2 7 2	 5 5 5	 Stocrin	 Merck Sharp & Dohme
NEVIRAPINE Oral liquid 10 mg/mL, 240 mL tablet 200 mg, 60	 10 2	 5 5	 Viramune Viramune Nevirapine Alphapharm Nevirapine RBX	 Boehringer Ingelheim Boehringer Ingelheim Alphapharm Ranbaxy

NEVIRAPINE tablet 400 mg, modified release, 30	2	5	Viramune XR	Boehringer Ingelheim
RILPIVIRINE tablet 25 mg, 30	2	5	Edurant	Janssen-Cilag
ABACAVIR + LAMIVUDINE tablet abacavir 600 mg + lamivudine 300 mg, 30	2	5	Kivexa	Viiv Healthcare
ABACAVIR + LAMIVUDINE + ZIDOVUDINE tablet abacavir 600 mg + lamivudine 300 mg + zidovudine 300 mg, 60	2	5	Trizivir	Viiv Healthcare
EMTRICITABINE + RILPIVIRINE + TENOFOVIR tablet emtricitabine 200 mg + relpivirine 25 mg, tenofovir disoproxil fumarate 300 mg, 30	2	5	Eviplera	Gilead Sciences
TENOFOVIR + EMTRICITABINE + EFAVIRENZ tablet tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + efavirenz 600 mg, 30	2	5	Atripla	Gilead Sciences
LAMIVUDINE + ZIDOVUDINE tablet lamivudine 150 mg + zidovudine 300 mg, 60	2	5	Combivir Lamivudine 150 mg + Zidovudine 300 mg Alphapharm	Viiv Healthcare Alphapharm
LOPINAVIR + RITONAVIR tablet lopinavir 100 mg + ritonavir 25 mg, 60 tablet lopinavir 200 mg + ritonavir 50 mg, 120 oral solution lopinavir 400 mg/5 mL + ritonavir 100 mg/5 mL, 60mL	2 2 10	5	Kaletra	AbbVie
TENOFOVIR + EMTRICITABINE tablet tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg, 30	2	5	Truvada	Gilead Sciences
RALTEGRAVIR tablet 400 mg, 60	2	5	Isentress	Merck Sharp & Dohme
COBICISTAT + ELVITEGRAVIR + EMTRICITABINE + TENOFOVIR cobicistat 150 mg + elvitegravir 150 mg + emtricitabine 200 mg + tenofovir 300 mg, tablet, 30	2	5	Stribild	Gilead Sciences

4. Clinical Place for the Proposed Therapy

Infection with the human immunodeficiency virus (HIV) causes progressive failure of the immune system. As the disease progresses, HIV infection leads to severe immune deficiency and/or the development of the opportunistic infections and cancers that define the acquired immune deficiency syndrome (AIDS).

Since the introduction of combination high active ART (HAART) regimens in 1996, the decision about when to initiate ART in treatment naïve patients in relation to the CD4+ count

has changed significantly. Although there has been some shift towards earlier intervention (as shown by agreement across European, UK and US guidelines regarding the initiation of ART in patients with a CD4+ count of less than 350 cells/mm3) there is a lack of consensus in treatment recommendations for the HIV positive patient with CD4+ cell counts of greater than 350 cells/mm^3..

The current PBS restriction for the initiation of ART requires patients to have a CD4+ count of less than 500cells/mm^3 or the presence of symptomatic HIV disease. Patients who have a CD4+ count greater than 500cells/mm^3 at diagnosis with HIV infection are not currently eligible for PBS funded ART and must defer starting ART until their CD4+ count has dropped below 500cells/mm^3 or they have evidence of symptomatic HIV disease. The requested change to listing would allow the initiation of anti-retroviral therapy at a CD4+ count greater than 500 cells/mm^3 for patients with HIV, irrespective of the presence of symptomatic disease.

5. Comparator

The submission nominated no treatment (which in practice is deferred therapy) as the main comparator. The PBAC considered that this was appropriate.

6. Clinical Trials

There were no head-to-head trials available directly comparing the initiation of treatment in ART naïve HIV positive patients with a CD4+ count of >500 cells/mm3 to deferred therapy.

The submission was based on:

- Three randomised controlled trials - two measuring individual patient endpoints and one measuring transmission as a community endpoint;
- Four observational studies;
- Two ecological studies; and
- Thirteen biological studies that evaluate the use of ART irrespective of CD4+ count.

Details of the trials presented in the submission are in the table below.

Randomised trials, non-randomised studies and associated reports presented in the submission.

Trial/Study ID	Protocol title/ Publication title	Publication citation
Randomised controlled trials: Individual endpoint		
Hogan 2012	Hogan CM, Degruttola V, Sun X, Fiscus SA, Del Rio C, Hare CB, Markowitz M, Connick E, Macatangay B, Tashima KT, Kallungal B, Camp R, Morton T, Daar ES, Little S; A5217 Study Team. The Setpoint Study (ACTG A5217): Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1-Infected Individuals.	*Journal of Infectious Diseases.* 2012; 205(1):87-96
SPARTAC 2013	SPARTAC Trial Investigators, Fidler S, Porter K, Ewings F, Frater J, Ramjee G, Cooper D, Rees H, Fisher M, Schechter M, Kaleebu P, Tambussi G,	*The New England Journal of Medicine.* 2013; 368(3):207-217

Trial/Study ID	Protocol title/ Publication title	Publication citation
	Kinloch S, Miro JM, Kelleher A, McClure M, Kaye S, Gabriel M, Phillips R, Weber J, Babiker A. Short-Course Antiretroviral Therapy in Primary HIV Infection.	
Randomised controlled trials: Community endpoint		
Cohen 2011	Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR; HPTN 052 Study Team. Prevention of HIV-1 Infection with Early Antiretroviral Therapy.	*The New England Journal of Medicine*. 2011; 365(6):493-505
Observational studies		
Kitahata 2009	Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, Hogg RS, Deeks SG, Eron JJ, Brooks JT, Rourke SB, Gill MJ, Bosch RJ, Martin JN, Klein MB, Jacobson LP, Rodriguez B, Sterling TR, Kirk GD, Napravnik S, Rachlis AR, Calzavara LM, Horberg MA, Silverberg MJ, Gebo KA, Goedert JJ, Benson CA, Collier AC, Van Rompaey SE, Crane HM, McKaig RG, Lau B, Freeman AM, Moore RD; NA-ACCORD Investigators. Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival	*The New England Journal of Medicine.* 2009; 360(18):1815-26
CASCADE 2011	Writing Committee for the CASCADE Collaboration. Timing of HAART Initiation and Clinical Outcomes in Human Immunodeficiency Virus Type 1 Seroconverters.	*Archives of Internal Medicine.* 2011; 171(17):1560-1569
Sterne 2009	When To Start Consortium, Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, Harris R, Funk MJ, Geskus RB, Gill J, Dabis F, Miró JM, Justice AC, Ledergerber B, Fätkenheuer G, Hogg RS, Monforte AD, Saag M, Smith C, Staszewski S, Egger M, Cole SR. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies.	*The Lancet.* 2009; 373(9672):1352-1363
Le 2013	Le T, Wright EJ, Smith DM, He W, Catano G, Okulicz JF, Young JA, Clark RA, Richman DD, Little SJ, Ahuja SK. Enhanced CD4+ T-Cell Recovery with Earlier HIV-1 Antiretroviral Therapy.	*The New England Journal of Medicine.* 2013; 368(3):218-230
Ecological studies		
Geng 2012	Geng EH, Hare CB, Kahn JO, Jain V, Van Nunnery T, Christopoulos KA, Deeks SG, Gandhi M, Havlir DV. The Effect of a "Universal Antiretroviral Therapy" Recommendation on HIV RNA Levels Among HIV-Infected Patients Entering Care With a CD4 Count Greater Than 500/μL in a Public Health Setting.	*Clinical Infectious Diseases.* 2012; 55(12):1690-1697
Das 2010	Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, Colfax GN. Decreases in Community Viral Load Are Accompanied by Reductions in New HIV Infections in San Francisco.	*PLoS One.* 2010; 5(6):e11068. doi: 10.1371/journal.pone.0011068.
Biological/Physiological studies		
Zeng(a) 2012	Zeng M, Southern PJ, Reilly CS, Beilman GJ,	*PLoS Pathogens.* 2012; 8(1):

Trial/Study ID	Protocol title/ Publication title	Publication citation
	Chipman JG, Schacker TW, Haase AT. Lymphoid Tissue Damage in HIV-1 Infection Depletes Naïve T Cells and Limits T Cell Reconstitution after Antiretroviral Therapy.	e1002437. doi: 10.1371/journal.ppat.1002437
Zeng(b) 2012	Zeng M, Paiardini M, Engram JC, Beilman GJ, Chipman JG, Schacker TW, Silvestri G, Haase AT. Critical role of CD4 T cells in maintaining lymphoid tissue structure for immune cell homeostasis and reconstitution.	*Blood*. 2012; 120(9):1856-1867
Chomont 2009	Chomont N, El-Far M, Ancuta P, Trautmann L, Procopio FA,Yassine-Diab B, Boucher G, Boulassel MR, Ghattas G, Brenchley JM, Schacker TW, Hill BJ, Douek DC, Routy JP, Haddad EK, Sekaly RP. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation.	*Nature Medicine.* 2009; 15(8):893-900
Brenchley 2004	Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, Douek DC. CD4 T Cell Depletion during all stages of HIV disease Occurs predominantly in the gastrointestinal tract.	*The Journal of Experimental Medicine.* 2004:200(6)749-759
Hocqueloux 2013	Hocqueloux L, Avettand-Fènoël V, Prazuck T, Mélard A, Legac E, Niang M, Mille C, Buret J, Rouzioux C, 'Coordinated Action on HIV Reservoirs' (AC32) of the ANRS (Agence Nationale de Recherches sur le Sida et les hépatites virales). In chronically HIV-1-infected patients long-term antiretroviral therapy initiated above 500 CD4/mm3 achieves better HIV-1 reservoirs' depletion and T-cell count restoration.	*Seventh International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention.* Abstract WeAB0102, Kuala Lumpur, 2013.
Hunt 2012	Hunt PW. HIV and Inflammation: Mechanisms and consequences.	*Current HIV/AIDS reports.* 2012; 9(2):139-147
*Markowitz 2012**	Markowitz M, Evering T, Figueroa A, Rodriguez K, La Mar M, Garmon D, Sahi V, Mohri H. Very early initiation of combination antiviral therapy results in normal levels of markers of immune activation.	*19th International AIDS Conference.* Abstract no TUPDB0304
Supportive studies		
Masia 2013	Masiá M, Padilla S, Álvarez D, López JC, Santos I, Soriano V, Hernández-Quero J, Santos J, Tural C, del Amo J, Gutiérrez F; CoRIS. Risk, predictors, and mortality associated with non-AIDS events in newly diagnosed HIV-infected patients: role of antiretroviral therapy.	*AIDS.* 2013; 27(2):181-189
Limketkai 2012	Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, Moore RD, Thomas DL, Sulkowski MS. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV.	*The Journal of the American Medical Association.* 2012; 308(4):370-378
Reekie 2011	Reekie J, Gatell JM, Yust I, Bakowska E, Rakhmanova A, Losso M, Krasnov M, Francioli P, Kowalska JD, Mocroft A; EuroSIDA in EuroCoord. Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata.	*AIDS.* 2011; 25(18):2259-2268
Guiguet 2009	Guiguet M, Boué F, Cadranel J, Lang JM, Rosenthal E, Costagliola D; Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort. Effect of	*The Lancet Oncology.* 2009; 10(23):1152-1159

Trial/Study ID	Protocol title/ Publication title	Publication citation
	immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study.	
Tanser 2013	Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa.	*Science.* 2013; 339(6112):966-971.
Jia 2012	Jia Z, Ruan Y, Li Q, Xie P, Li P, Wang X, Chen RY, Shao Y. Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study.	*The Lancet.* 2012; S0140-6736(12)61898-4. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61898-4

7. Results of Trials

With regard to comparative effectiveness, the PBAC noted the following summary of the results of the randomised trials, observational studies and ecological studies presented in the submission.

Summary of results from the randomised controlled trial, observational studies and the ecological studies

Trial/Study	Results
Randomised controlled trials: Individual outcomes	
Hogan 2012	- S/T 36 week ART: Statistically significant difference in viral load (HIV RNA), that favoured immediate treatment with S/T 36 week ART when compared to deferred treatment.
SPARTAC 2013	- S/T 48 week ART: Statistically significant difference in the composite measure of CD4+ count <350 or initiation of LART, favouring S/T 48 week ART compared to standard care. - S/T 12 week ART: No difference in the composite measure of CD4+ count <350 or initiation of LART, when comparing S/T 12 week ART to standard care - No significant between group differences in incidence of AIDS or death.
Randomised controlled trials: Transmission outcomes	
Cohen 2011	- Serodiscordant couples: statistically significant reduction in transmission events in those allocated to early LART when compared to the deferred LART group. - Statistically significant difference in clinical events that favoured the use of early therapy.
Observational studies: Individual outcomes	
Kitahata 2009	- Statistically significant increase in the risk of death in the deferred therapy group when compared to the early therapy group.
CASCADE 2011	- No statistically significant difference when comparing immediate treatment versus deferred treatment in the composite measure of AIDS or death in patients with a CD4+ count of 500-799 cells/mm^3*.
Sterne 2009	- No statistically significant difference in the composite measure of AIDS or death when comparing patients with CD4+ count of 451-550 cells/mm^3 versus 351-450 cells/mm^3.
Le 2013	- Statistically significant difference in patients that reached a CD4+ T-cell recovery of ≥900 cells/mm^3, favouring patients with a CD4+ count ≥500 cells/mm3 when compared with patients with a CD4+ count <500 cells/mm^3.
Ecological studies: Community outcomes	
Geng 2012	- There was an increase in the cumulative incidence of virologic suppression in patients with a CD4+ count >500 cells/mm^3. - This coincided with the increased ART coverage for patients with a CD4+ count >500 cells/mm^3.

Trial/Study	Results
Das 2010	- Significant decrease in newly diagnosed HIV cases over the 2004 to 2008 period and a decline in annual measures of total CVL over the same period. - This coincided with a range of public health measures implement in San Francisco, which included increased rates of HIV testing and ARTcoverage.

* The reference group is composed of a subcohort observations during which HAART was not initiated during the index month

Abbreviations: ART = Antiretroviral therapy; CVL = community viral load; HAART = Highly active antiretroviral therapy; LART = Long term antiretroviral therapy; S/T = Short term

The PBAC noted that overall, the clinical claim was not fully supported by the results because of the following factors:

- In the randomised trials, Hogan 2012 and SPARTAC 2013 used short term (12, 36 or 48 weeks) interrupted ART regimens prior to the commencement of long term ART (LART). These treatment strategies are of no direct relevance to current clinical practice, because treatment interruption is not recommended (DHHS Guidelines, 2013).
- The results for risk of death or progression to AIDS from the observational studies were inconsistent.
- The results reported in the ecological studies (Das 2010 and Geng 2012) are based on an assumption of cause and effect, and the analyses are unable to fully account for significant confounders (patient characteristics, differences in treatment regimens and health care practices).

The PBAC considered that based on the available information, it was not possible to quantify the clinical benefit to an individual patient from removing the CD4+ threshold for initiation of ART. They noted, however, that current expert opinion in Australia suggests that there is likely to be a net clinical benefit to patients from removal of the threshold compared to current clinical practice.

With regard to comparative harms, overall, the adverse events in the randomised trials were similar across the patient groups for Cohen 2011 and SPARTAC 2013. There was limited reporting of adverse events in Hogan 2012. Differences in grade 3 or 4 laboratory abnormalities were reported in Cohen 2011: early therapy group (n=242, 27.3%); delayed therapy group (n=161, 18.4%), $p<0.001$. The most frequent abnormalities included neutropenia, abnormal phosphate level and total bilirubin elevations (bilirubin elevations observed primarily in patients administered atazanavir).

The PBAC noted that the risks of treating asymptomatic patients with high CD4+ counts are largely similar to those of treating patients with advanced HIV (if time on treatment is not considered), with the exception of nevirapine, which was associated with an increased risk of toxicity in patients with higher CD4+ counts.

8. Clinical Claim

The PBAC noted that the applicant had clarified the clinical claim in the Pre-Sub-Committee Response. The submission's claim was that there was sufficient evidence on pathophysiological, clinical, immunological, virological and ecological grounds to be able to

offer ART to HIV+ individuals with a CD4+ count greater than 500 cells/mm^3. The PBAC considered this claim to be reasonable and consistent with current Australian expert opinion.

The submission claimed that the early initiation of ART and increased viral suppression results in a reduction in the risk of transmission between partners. The PBAC noted that this claim was supported by evidence from Cohen 2011. The PBAC agreed with the Economic Sub-Committee (ESC)that the claim of reduced transmission was reasonable but that the size of any benefit remained unknown, given:

- differences between the population in Cohen 2011 and the relevant Australian population including: 98% of couples enrolled in the trial were heterosexual; some HIV-related events in the trial were tuberculosis-related; and the criteria for initiating treatment in the trial was a CD4+ count of ≤250, not >500.
- the likely presence of significant confounding in the ecological studies (Das 2010, Geng 2012), as described above.

9. Economic Analysis

The submission presented a modelled economic analysis using an epidemiological approach, based on a comparison between current clinical practice and the clinical situation under the proposed changes to the restriction.

The incremental cost effectiveness ratios were calculated in the submission as between $15,000-45,000 per quality adjusted life year (QALY) for Scenario 1, where ART initiation for people living with HIV (PLHIV) with CD4>500 would occur but at a lower rate than PLHIV with lower CD4 levels; and higher, though in the same range for Scenario 2, where ART initiation for PLHIV with CD4>500 would occur at the same rate as PLHIV with lower CD4 levels.

The PBAC considered the economic analysis did not allow for a meaningful linkage between the clinical evidence presented in the submission and the modelled incremental costs and outcomes, including utilities.

The PBAC considered that although the economic model had limitations, it was as accurate a depiction of the cost effectiveness as could be generated with the clinical data available.

10. Estimated PBS Usage and Financial Implications

The submission estimated the number of incident patients (newly diagnosed with HIV) to be less than 10,000 in Year 5 of listing. The PBAC considered that in the current policy context, which encourages increased testing for HIV, the projected incidence of HIV infections could be an underestimate.

The submission estimated the number of ART initiators to be less than 10,000 in the first 5 years of listing, at a total cost to the PBS/RPBS of less than $10 million over the first 5 years. The PBAC agreed with Drug Utilisation Sub-Committee (DUSC) that the utilisation estimates presented in the submission were likely to be underestimated.

The DUSC estimated the eligible patient population to be greater than that estimated in the submission in the first 5 years of listing at a cost to the PBS/RPBS in the first 5 years of listing in the range of $10-30 million. The PBAC considered that the DUSC re-estimates were a more reliable estimate of uptake and expenditure.

The PBAC considered that not all patients diagnosed with HIV infection would automatically start ART. Factors including age, adherence, preparedness and awareness of the lifelong commitment to therapy will all impact on the patient and physician decision to initiate treatment. The PBAC agreed with the statement in the Pre-Sub-Committee Response (PSCR) that the decision to initiate treatment is individualised and that people living with HIV in Australia are managed by a relatively small number of clinicians who are specifically trained to become Section 100 Highly Specialised Drug prescribers of ART. This promotes a relatively standardised approach to initiating and monitoring ART.

11. Recommendation and Reasons

The PBAC recommended the removal of the CD4+ requirement from the PBS restrictions for initiation of first-line ART of the products listed below. The change to the listings was recommended on the basis of acceptable cost-effectiveness over no treatment (deferred therapy).

The PBAC noted the reference in the Pre-Sub-Committee Response (PSCR) that stated 'In July 2013, the Commonwealth Health Minister and all State/Territory Health Ministers endorsed the recommendations contained in the Report on Progress on the Australian Response to HIV and AIDS ('the report') which includes agreement to a national set of prevention and treatment targets for HIV, including achieving a 50% reduction in new HIV infections by 2015 and 90% coverage of ART among people with HIV by 2015 irrespective of CD4 count. The Report notes that achieving these targets necessitates removing barriers to ART uptake, including current PBAC prescribing restriction for ART for asymptomatic HIV patients with a CD4 count >500cells/mm3. In line with this Commonwealth initiative, NSW and Queensland have also developed strategies which include these targets.'

The PBAC considered that no treatment (which is deferred therapy in clinical practice) was the appropriate comparator.

The PBAC considered that based on the available information, it was not possible to quantify the clinical benefit from removing the CD4+ threshold for initiation of ART to an individual patient. They noted however, that current expert opinion in Australia suggests that there is likely to be a net clinical benefit to patients from removal of the threshold compared to current clinical practice.

The PBAC noted that the potential benefits of removing the CD4+ count restriction include:

- Reduced transmission of HIV infection
- Individualisation of patient therapy
- Empowering patients to be able to choose when to commence therapy

The PBAC considered there to be an advantage to patients associated with being able to have greater choice, together with their prescribers, of when to initiate therapy with ART. The PBAC considered this greater choice to represent good Quality Use of Medicines.

The PBAC agreed with DUSC that the estimates presented in the submission were likely underestimates. The PBAC considered that the DUSC re-estimates were a more reliable estimate of uptake and expenditure following the requested restriction change.

The PBAC requested that DUSC monitor the proportion of newly diagnosed HIV patients commencing ART earlier, and ongoing HIV rates following implementation of this recommendation.

The PBAC noted and welcomed the input received from individuals (1), healthcare professionals (7) and organisations (3) via the Consumer Comments facility on the PBS website, in support of the submission.

The PBAC acknowledged that as this was not a sponsor driven submission, the sponsor companies of medicines affected by the recommendation will need to be consulted and given opportunity to comment, before any change to the listings can proceed. The applicant is requested to provide consent for the Department to initiate this process prior to publication of the outcome on the PBS website.

Outcome:
Recommended.

Following consultation and agreement with sponsor companies, amend the following listings as described.

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
ATAZANAVIR capsule 100 mg, 60 capsule 150 mg, 60 capsule 200 mg, 60 capsule 300 mg, 60	 2 2 2 2	 5 5 5 5	 Reyataz	 Bristol Myers Squibb
FOSAMPRENAVIR oral liquid 50 mg/mL, 225 mL tablet 700 mg, 60	 8 2	 5 5	 Telzir	 Viiv Healthcare
INDINAVIR capsule 400 mg, 180	 2	 5	 Crixivan 400 mg	 Merck Sharp & Dohme
RITONAVIR tablet 100 mg, 30 oral liquid 600 mg/7.5 mL, 90 mL	 24 10	 5 5	 Norvir	 AbbVie
SAQUINAVIR tablet 500 mg, 120	 2	 5	 Invirase	 Roche
ABACAVIR oral liquid 20 mg/mL, 240 mL tablet 300 mg, 60	 8 2	 5 5	 Ziagen	 Viiv Healthcare
DIDANOSINE capsule 125 mg, enteric coated, 30 capsule 200 mg, enteric coated, 30 capsule 250 mg, enteric coated, 30 capsule 400 mg, enteric coated, 30	 2 2 2 2	 5 5 5 5	 Videx EC	 Bristol Myers Squibb
EMTRICITABINE capsule 200 mg, 30	 2	 5	 Emtriva	 Gilead Sciences
LAMIVUDINE oral liquid 10 mg/mL, 240 mL tablet 150 mg, 60 tablet 300 mg, 30	 8 2 2	 5 5 5	 3TC 3TC Lamivudine Alphapharm Lamivudine RBX 3TC Lamivudine Alphapharm Lamivudine RBX	 Viiv Healthcare Viiv Healthcare Alphapharm Ranbaxy Viiv Healthcare Alphapharm Ranbaxy
STAVUDINE capsule 20 mg, 60 capsule 30 mg, 60 capsule 40 mg, 60	 2 2 2	 5 5 5	 Zerit	 Bristol Myers Squibb
TENOFIVIR tablet 300 mg, 30	 2	 5	 Viread	 Gilead Sciences
ZIDOVUDINE capsule 100 mg, 100 capsule 250 mg, 40 oral liquid 50 mg/5 mL, 200 mL	 4 6 15	 5 5 5	 Retrovir	 Viiv Healthcare
EFAVIRENZ tablet 200 mg, 90 oral liquid 30 mg/mL, 180 mL tablet 600mg, 30	 2 7 2	 5 5 5	 Stocrin	 Merck Sharp & Dohme
NEVIRAPINE Oral liquid 10 mg/mL, 240 mL tablet 200 mg, 60	 10 2	 5 5	 Viramune Viramune Nevirapine Alphapharm Nevirapine RBX	 Boehringer Ingelheim Boehringer Ingelheim Alphapharm Ranbaxy

RILPIVIRINE tablet 25 mg, 30	2	5	Edurant	Janssen-Cilag
RALTEGRAVIR tablet 400 mg, 60	2	5	Isentress	Merck Sharp & Dohme
LAMIVUDINE + ZIDOVUDINE tablet lamivudine 150 mg + zidovudine 300 mg, 60	2	5	Combivir Lamivudine 150 mg + Zidovudine 300 mg Alphapharm	Viiv Healthcare Alphapharm
LOPINAVIR + RITONAVIR tablet lopinavir 100 mg + ritonavir 25 mg, 60 tablet lopinavir 200 mg + ritonavir 50 mg, 120 oral solution lopinavir 400 mg/5 mL + ritonavir 100 mg/5 mL, 60mL	2 2 10	5	Kaletra	AbbVie
TENOFOVIR + EMTRICITABINE tablet tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg, 30	2	5	Truvada	Gilead Sciences

Condition:	HIV Infection
Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must be antiretroviral treatment naïve AND Treatment must be in combination with other antiretroviral agents

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND Treatment must be in combination with other antiretroviral agents

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
NEVIRAPINE tablet 400 mg, modified release, 30	2	5	Viramune XR	Boehringer Ingelheim

Condition:	HIV Infection

Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have been stabilised on nevirapine immediate release. AND Treatment must be in combination with other antiretroviral agents

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND Treatment must be in combination with other antiretroviral agents

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
ABACAVIR + LAMIVUDINE tablet abacavir 600 mg + lamivudine 300 mg, 30	2	5	Kivexa	Viiv Healthcare

Condition:	HIV Infection
Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must be antiretroviral treatment naïve. AND Treatment must be in combination with other antiretroviral agents
Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40 kg or more

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required

	Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection AND Treatment must be in combination with other antiretroviral agents
Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40 kg or more

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
ABACAVIR + LAMIVUDINE + ZIDOVUDINE tablet abacavir 600 mg + lamivudine 300 mg + zidovudine 300 mg, 60	2	5	Trizivir	Viiv Healthcare
Condition:	HIV Infection			
Treatment phase:	Initial			
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)			
Clinical criteria:	Patient must be antiretroviral treatment naïve			
Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40 kg or more			

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection
Population criteria:	Patient must be aged 12 years or older AND Patient must weigh 40 kg or more

Name, Restriction, Manner of administration and form	Max Qty	№.of Rpts	Proprietary Name and Manufacturer	
EMTRICITABINE + RILPIVIRINE + TENOFOVIR tablet emtricitabine 200 mg + relpivirine 25 mg, tenofovir disoproxil fumarate 300 mg, 30	2	5	Eviplera	Gilead Sciences
TENOFOVIR + EMTRICITABINE + EFAVIRENZ tablet tenofovir disoproxil fumarate 300 mg + emtricitabine 200 mg + efavirenz 600 mg, 30	2	5	Atripla	Gilead Sciences
COBICISTAT + ELVITEGRAVIR + EMTRICITABINE + TENOFOVIR cobicistat 150 mg + elvitegravir 150 mg + emtricitabine 200 mg + tenofovir 300 mg, tablet, 30	2	5	Stribild	Gilead Sciences

Condition:	HIV Infection
Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must be antiretroviral treatment naïve

Condition:	HIV Infection
Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Private Hospital Authority required Public Hospital Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received PBS-subsidised therapy for HIV infection

12. 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.

13. Sponsor's Comment

The Sponsor would like to thank the PBAC for its consideration and support of the submission.