Application for changes to the Pharmaceutical Schedule

A guide to help people, clinicians, clinical groups and consumer groups prepare funding applications to PHARMAC

Foreword

PHARMAC is the government agency that decides, on behalf of District Health Boards, which pharmaceuticals should be publicly funded in New Zealand. For more information on the process PHARMAC uses to make its funding decisions and how we determine if a proposal to fund a treatment would help us achieve our Statutory Objective, please visit the PHARMAC website.

PHARMAC's objective is "to secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided".

Each year, PHARMAC receives a large number of applications that contain proposals either to fund new pharmaceuticals or to widen access to pharmaceuticals that we already fund. As PHARMAC must work within a fixed budget, we need to make difficult choices about which applications we should progress to a funding decision at any given time. This involves assessing large amounts of often complex information, to identify those proposals that would provide the best health outcomes.

We have written this funding application form for people, clinicians, clinical groups and consumer groups to use. We recognise that some individuals and groups won't have the same resource as pharmaceutical suppliers to prepare applications. This form is to help you provide the right information in order to progress the application.

This form is a guide – you don't have to follow it in detail, or at all, but it will make processing your application much easier and may reduce the time involved. If you don't know some information, please feel free to leave those sections blank; however the form does outline the general information that we need to assess a funding application. Having your application address these points may reduce follow-up questions to you, and could speed up how quickly we consider it.

The *Guidelines for Funding Applications to PHARMAC*, updated in 2015, set out the full information that we need to progress any funding application. We expect pharmaceutical suppliers to follow the full *Guidelines for Funding Applications to PHARMAC* when submitting a funding application. However, as an applicant, please feel free to view them should you wish to have more detailed information on submitting an application.

Send your applications to us at:

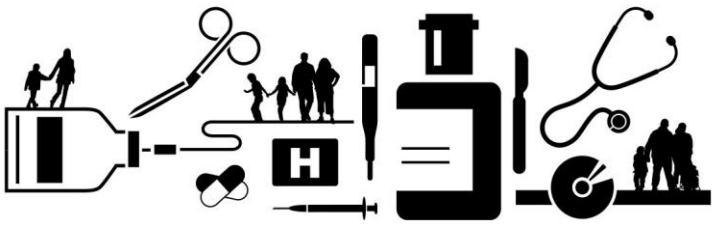
Email: **applications@pharmac.govt.nz**

Post: **PO Box 10254**
The Terrace
Wellington 6143

You may also find it beneficial to talk to the relevant Therapeutic Group Manager at PHARMAC before you make a formal funding application. Please email us as above, and we will contact you.We will keep you informed of progress. We publish and regularly update a record of all current funding applications via the Application Tracker on our website (**www.pharmac.govt.nz**), which details the current status of applications and relevant PTAC and subcommittee minutes.

Please note:

- We need you to supply copies of referenced articles that support the application, wherever possible. Have them referenced in the relevant section of the application form, and clearly say which (if any) cited publications you cannot provide.
- We prefer funding applications related to medicines that have been registered by Medsafe. While we can consider funding applications for unregistered medicines or unregistered indications, this is determined on a case–by-case basis.
- We may decide to defer our assessment of your application until we receive a full funding application from the supplier, which they would need to prepare in accordance with the full *Guidelines*.



PHARMAC
Pharmaceutical Management Agency

New Zealand Government

Changes to the Pharmaceutical Schedule

Application

Applicant

Name

Brooke Hollingshead

Department & DHB, practice or organisation

New Zealand AIDS Foundation

Email address

Brooke.hollingshead@nzaf.org.nz

Phone or pager

09) 306 3424

Are you making this application on behalf of a wider group (department, society, special interest group)? If so, who?

New Zealand National HIV Forum

Is there anyone else that we should contact if we have questions about specific parts of this application?

Joe Rich (NZAF) joe.rich@nzaf.org.nz
Jason Myers (NZAF) jason.myers@nzaf.org.nz
Mark Fisher (Body Positive) mark@bodypositive.org.nz
Massimo Giola (Bay of Plenty/Lakes DHB) Massimo.Giola@bopdhb.govt.nz
Jane Bruning (Positive Women) jane@positivewomen.nz

Proposed pharmaceutical

Chemical

Tenofovir Alafenamide (TAF)

Presentations and strengths

Emtricitabine 200 mg/Tenofovir Alafenamide 25 mg, and
Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg.

Brand name(s)

Descovy

Suppliers (eg pharmaceutical companies, wholesalers)

Gilead Sciences Pty Ltd

Price

To be negotiated with supplier at a later date

Is it registered by Medsafe?

Yes, Emtricitabine/Tenofovir Alafenamide, also known as Descovy, is registered by Medsafe, in combination with other antiretroviral agents:
https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=18339
https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=18340

Describe the indication(s) that funding is being sought for.

For the treatment of human immunodeficiency virus (HIV-1) infection in adults and adolescents aged 12 years and older with body weight at least 35 kg, in combination with other antiretroviral agents, where there is an unmet clinical need and to optimise treatment outcomes.

If this pharmaceutical has been registered by Medsafe, is it licenced for these indications? If not, is it licenced for these indications overseas? Please provide details.

Yes, in New Zealand, Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of DESCOVY.

How many people in New Zealand do you expect would receive the pharmaceutical?

Currently there are estimated to be 3500 of people living with HIV in New Zealand [1]. Sexual Health and Infectious Disease clinicians estimate that **5-10% of people living with HIV (or between 175 and 530 people)** are suffering from suboptimal clinical outcomes with an unmet clinical need and should transition off Tenofovir Disoproxil Fumarate (TDF) and on to TAF in order to optimise treatment outcomes. Clinicians have also advised that **5% of people newly diagnosed with HIV (or 5 to 10 people)** in New Zealand each year would have an unmet need for TAF and would require access according to the clinical criteria [2]. Demand has been demonstrated through the 'Exceptional circumstances' 'Named Patient Pharmaceutical Assessment' compassionate access scheme that is already used to access TAF within New Zealand.

Evidence in support of these approximations include:

- Research has highlighted that renal issues (such as proximal renal tubule toxicity, Fanconi-like syndrome) occur in 0.5-1.5% of people receiving TDF, and a similar estimate could be used in New Zealand [3].
- In a study of 35,192 persons contributing 200,119 person years of follow-up, 135 (0.4%) developed advanced chronic kidney disease (CKD). TDF was particularly frequently discontinued as estimated glomerular filtration rate (eGFR) declined. After adjustment, those previously exposed but currently off TDF had similar advanced CKD/ESRD rate ratios compared with those unexposed [1.00 (95% CI, 0.66–1.51)], while those currently on TDF had reduced rates [0.23 (95% CI, 0.13–0.41) [4].
- Another study found the incidence of CKD among HIV-positive adults is approximately 1.9% in those new to care (presumed treatment naïve) and 3.3% in previously treated participants [5].
- For patients suffering from suboptimal clinical outcomes due to bone density issues, research has found that a fracture rate of 13.5 per 10,000 PY in males and 42.2 per 10,000 PY in females. The mean age for male patients with osteoporosis-related fracture was 43.2 years, whereas it was 65.7 years in female patients. The cumulative probability of osteoporosis-related fracture increased after 5 years of TDF exposure. The rate of hip fracture (95% confidence interval) was 7.2 (3.1–14.2) per 10,000 PY. Among HIV-infected patients in Japan, treatment with TDF for 5 years increases the risk of bone fractures in younger men, in addition to that seen in older post-menopausal women [6].
- Among newly diagnosed ART-naïve, HIV-positive adults from 11 countries during 2011–2013, osteoporosis was rare at 1.9% [7]. In pooled results from two large US cohort studies (SUN and HOPS-DIDC), including predominantly male participants (median age 43) with follow-up data mostly (97%) exceeding 4 years (N=1,006), 3.7% had osteoporosis [8].

In NZ in 2018, 178 people were first known to be infected with HIV and 2643 adults were receiving subsidised antiretroviral therapy (ART) at the end of June 2018 [9]. Using the values above, it is estimated that there would have been approximately 9 incident patients and 185 prevalent patients with CKD or osteoporosis.

[1] NZAF. (2019). *HIV in New Zealand,* https://www.nzaf.org.nz/hiv-aids-stis/hiv-aids/hiv-in-new-zealand/
[2] As advised by Massimo Giola, Clinical Lead of Sexual Health Services, Bay of Plenty DHB
[3] Alfred Health. (2018). *HIV Service Guidelines for the Screening and Management of HIV related Co-Morbidities,* https://ashm.blob.core.windows.net/ashmpublic/HIV-comorbidity-algorithm%20Version%202%20May%202018.pdf
[4] Ryom, L., Mocroft, A., Kirk, O., Ross, M., Reiss, P., Fux, C.A., Morlat, P., Moranne, O., Smith, C., El-Sadr, W., Law, M., Lundgren, J.D., (2014) "Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons," *AIDS,* 28(2), 187-99. [pdf provided].
[5] Schloffelen, A. F., Smit, C., van Lelyveld, et al. (2015). Diminished Impact of Ethnicity as a Risk Factor for Chronic Kidney Disease in the Current HIV Treatment Era. The Journal of Infectious Diseases, 212:264-74. Available at: https://academic.oup.com/jid/article/212/2/264/890531
[6] Komatsu, A., Ikeda, A., Kikuchi, A., Minami, C., Tan, M., Matsushita, S., (2018). "Osteoporosis-Related Fractures in HIV-Infected Patients Receiving Long-Term Tenofovir Disoproxil Fumarate: An Observational Cohort Study", *Drug Safety,* 41(9). pp 843-848 [pdf provided]
[7] Carr, A., Grund, B., Schwarts, A., et al. (2015). Prevalence of and risk factors for low bone mineral density in untreated HIV infection: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) Trial. HIV Medicine, 16(Suppl 1): 137-146. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341957/pdf/nihms-648189.pdf
[8] Battalora, L., Buchacz, K., Armon, C., Overton, E. T., Hammer, J., Patel, P., & et al. (2016). Low bone mineral density and risk of incident fracture in HIV-infected adults. Antiviral Therapy, 21:45-54. [pdf provided]
[9] AIDS Epidemiology Group. (2019). *HIV diagnoses in 2018.* https://www.otago.ac.nz/aidsepigroup/pdf/78-AIDS-NZ-May-2019.pdf;

What is the expected dosing?

In adults and adolescent patients aged 12 years and older and weighing ≥ 35 kg DESCOVY is taken orally once daily with or without food. The recommended dose of DESCOVY is 200/25 mg. The third agent in the treatment regimen could be dolutegravir, efavirenz, nevirapine, or raltegravir. If DESCOVY is used in combination with an HIV-1 protease inhibitor (PI) that is administered with ritonavir, the recommended dose of DESCOVY is 200/10 mg. The third agent in the treatment regimen could be atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, or lopinavir with ritonavir [1].

[1] Medsafe, Descovy Datasheet, Available at: https://medsafe.govt.nz/profs/Datasheet/d/descovytab.pdf

What is the likely duration of treatment, if patients respond to treatment?

Antiretroviral therapy is currently lifelong. There are no limitations in duration of particular treatments when they are effective and well tolerated.

Describe the setting that this pharmaceutical would be used in. Is the need for this this treatment limited to a hospital setting, or is it also required in the community? If in hospital, is it theatre only, on medical wards, or in outpatient clinics?

The pharmaceutical would be used in the community setting, prescribed by named HIV specialists and available from a pharmacist.

If this is a new pharmaceutical, are there likely to be other uses for it?

TAF is also used to treat infections caused by chronic hepatitis B infection, however the use of TAF for this indication is outside the remit of this funding application.

Descovy is in a Phase III, randomised, controlled double-blind clinical trial (the Discover trials) for use as HIV prevention, or pre-exposure prophylaxis (PrEP), among men who have sex with men and transgender women and is currently under consideration by the FDA for approval. 5,387 study participants were randomized in a 1:1 ratio and received either Descovy or Truvada for PrEP. Among the 2,694 participants (4,370 patient-years) who were at risk of HIV-1 infection and received once-daily Descovy, seven HIV infections (HIV incidence 0.16/100 person-years (PY)) were reported. Among the 2,693 participants (4,386 patient-years) who were at risk of HIV-1 infection and received Truvada, 15 HIV infections (0.34/100 PY) were reported. Descovy met the pre-established criteria for non-inferiority to Truvada using a stringent rate ratio statistical comparison, as demonstrated by the upper bound of the 95 percent confidence interval for HIV-1 infection rate ratio being less than the predefined non-inferiority margin of 1.62/100 PY. Additionally, statistically significant advantages with respect to bone and renal laboratory parameters were observed for participants receiving Descovy as compared with those receiving Truvada, which were pre-specified secondary endpoints [1].

The use of Descovy for the prevention of HIV through PrEP has not been approved by Medsafe, however it is a possible future pathway for those who currently have contraindications to TDF for PrEP due to renal issues, for example individuals with an eGFR<60mL/min, and who are at high risk of HIV infection. For people that have been on PrEP and are discontinued due to medical reasons, there may be an increased risk of HIV as their prevention strategies and behaviours may have changed while being on PrEP, which may result in decreased condom use and continued high levels of HIV risk exposure [2]. With 1600 people actively taking funded PrEP the number with renal contraindications to TDF is expected to be very low, possibly at less than 1.5% of PrEP users [3].

[1] Gilead. (2019), *Gilead Announces Data Demonstrating Non-Inferiority of Once-Daily Descovy vs. Once-Daily Truvada for Prevention of HIV Infection*, https://www.gilead.com/news-and-press/press-room/press-releases/2019/3/gilead-announces-data-demonstrating-noninferiority-of-oncedaily-descovy-vs-oncedaily-truvada-for-prevention-of-hiv-infection
[2] Jonas, K., and Yaemim, N., (2018), "HIV Prevention After Discontinuing Pre-Exposure Prophylaxis: Conclusions From a Case Study," Front Public Health, 6, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954039/
[3] Drak, D., Barrat, H., Templeton, D.J., O'Connor, C.C., and Gracey, D.M., (2019), "Renal function and risk factors for renal disease for patients receiving HIV pre-exposure prophylaxis at an inner metropolitan health service", PLoS One, 14(1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336260/

Treatment initiation

Is treatment with the pharmaceutical started empirically? If so, please describe the symptoms, signs or other features necessary to initiate therapy.

Treatment for people living with HIV is based on well-defined therapeutic guidelines that currently recommend early implementation of therapy on the basis of diagnosis.

To initiate treatment on Descovy, we are proposing that PHARMAC introduce a two-tiered system for medications for the treatment of HIV for people failing or unable to take first-line therapy. First-line therapy would be funded for all on the current medications and choices, but we are proposing that there should also be a second tier funded for individuals who are treatment experienced and suffering from sub-optimal clinical outcomes, or for individuals who are treatment-naive with renal or bone issues and for medical reasons cannot access first-line therapy. Where there have been toxicity issues, virological failure or intolerance to first-line antiretrovirals, a special authority application could be made from a named HIV specialist to request a medication from the second-tier. Access to Descovy would therefore be restricted, and tests would be undertaken to confirm toxicity issues, virological failure or intolerance. The symptoms and signs necessary to initiate the therapy are outlined in the next section, which suggest possible tests to check suitability for access to the second-tier medication. These second-tier treatments would not be accessed for first-line treatment, but would be to optimise treatment options to meet the currently unmet clinical need. We understand that precedent has been set for such a two-tier system with access to moxifloxacin for the treatment of tuberculosis.

Are there any specific tests needed to confirm diagnosis? If so, please name these tests, and say whether these are currently performed routinely, where they take place, and whether they are funded.

Tests to confirm suitability for Descovy should be based on an assessment of risk for nephrotoxicity and/or acceleration of bone loss with individuals currently on first-line treatment for HIV or for individuals with renal and bone issues. Tests can be undertaken on a case-by-case approach, and all are currently routinely performed and funded. Criteria for access to Descovy could test for:

- CKD with proteinuria, as defined using a creatinine-based estimate of **eGFR below a certain threshold, most often 60 mL/min**. The NHS criteria/risk matrix is often used for those at risk of renal disease to establish CKD with proteinuria, or the D:A:D risk score can be used to predict CKD risk in people living with HIV.

- **Risk factors such as hypertension, diabetes, or cardiovascular disease** (CVD) (where abacavir is contraindicated and not suitable for simplification to 3TC/DTG)

- Bone mass density (BMD) or bone metabolism through serum bone turnover markers (BTMs). Using established osteoporosis, or **FRAX scoring to assess those at a greater than 10% ten-year risk of fracture**.

Research to support these tests:

CKD is defined as CrCl <60mL/min. The Infectious Disease Society of America recommends that for patients on TDF with a baseline eGFR <90 mL/min, who are on other nephrotoxic medications, or who have hypertension or diabetes, physicians should check for a baseline blood pressure, serum creatinine, and urine protein, and monitor kidney function with biannual serum creatinine, serum phosphorous, and urinalysis for proteinuria and glycosuria. Tests could check if there has been a clinically significant decline in eGFR (i.e., GFR decline by >25 % from baseline and to a level ≤60 mL/min) that fails to resolve after potential nephrotoxic drugs are removed, or there is albuminuria in excess of 300mg per day, hematuria is combined with either albuminuria/proteinuria or increasing blood pressure, or for CKD.

It is currently recommended that Descovy be initiated if GFR >30mL/min and <60 mL/min [1]. Estimated creatinine clearance, urine glucose, and urine protein should be measured prior to starting DESCOVY, and should be monitored routinely during treatment. Currently, while serum creatinine is routinely monitored in most settings, cohort data suggest that monitoring of proteinuria is still relatively infrequent despite general consensus in guidelines to include this as a marker of kidney impairment [2]. More frequent monitoring may be required in those with established CKD (eGFR < 50 mL/min/1.73 m2) or risk factors for kidney disease. The most common risk factors are comorbid hypertension, diabetes, HIV-associated kidney disease, hepatitis B or C co-infection, and TDF in combination with a ritonavir-boosted protease inhibitor. If there is a rapid decline in kidney function (eGFR drops by more than 25% and decreases to <50 mL/min/1.73 m2 from baseline function), or there is new onset or worsening of proteinuria or albuminuria, clinicians should review ART and other potentially nephrotoxic medications and comorbidity and conduct further testing if indicated. If kidney function does not improve after addressing reversible causes of renal failure, then referral to a nephrologist is appropriate. In the case of severe CKD, timeous referral for planning for renal replacement therapy is recommended [3].

Bone metabolism can be assessed by measuring BTMs, comprising proteins synthesized during bone formation, bone matrix proteins, and bone collagen degradation products released during bone resorption. High levels of BTMs have been found to predict fractures independently of BMD in post-menopausal women and elderly men. Furthermore, as BTMs can provide a more dynamic estimate of bone metabolism in shorter timescales than BMD, these markers have been suggested as additional tools for more rapid assessment of bone disease [4].

DESCOVY should not be initiated in patients with estimated creatinine clearance below 30 mL per minute as there are no data available regarding the use of DESCOVY in this population. No data are available to make dose recommendations in paediatric patients with renal impairment [5].

[1] Lucas G.M., Ross, M.J., Stock, P.G., Shlipak, M.G.,Wyatt, C.M., Gupta, S.K., (2014) Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America Clin Infect Dis. 59(9):e96-138. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4271038/
[2] Achhra, A.C., Nugent, M., Mocroft, A., Ryom, L., Wyatt, C.M., (2016) “Chronic Kidney Disease and Antiretroviral Therapy in HIV-Positive Individuals: Recent Developments,” *Curr HIV/AIDS Rep*, 13: 149. https://doi.org/10.1007/s11904-016-0315-y
[3] Venter, W.D.F., Fabian, J., Feldman, C., (2018) “An overview of tenofovir and renal disease for the HIV-treating clinician,” *South Afr J HIV Med,* 19(1): 817 https://www.ncbi.nlm.nih.gov/pubmed/30167339
[4] Haskelberg, H., Hoy, J.F., Amin, J., Ebeling, P.R., Emery, S., et al., (2012) “Changes in Bone Turnover and Bone Loss in HIV-Infected Patients Changing Treatment to Tenofovir-Emtricitabine or Abacavir-Lamivudine” *PLoS ONE,* 7(6): e38377. doi:10.1371/journal.pone.0038377 [pdf provided]
[5] Medsafe, Descovy Product Detail, https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=18339

Should other therapies have been used prior to starting treatment with this pharmaceutical? If so, which?

Yes. Any other currently funded first-line antiretroviral treatment for HIV infection should have been taken prior to starting treatment with Descovy, unless the clinical criteria suggest first-line therapy is not suitable.

Treatment continuation

How would treatment success be defined or measured?

Treatment success would be measured by the patient achieving and maintaining viral suppression with an undetectable viral load (<200 copies/ml) with markers for renal and bone safety improving (eGFR > 60), the unmet clinical need being met, and treatment outcomes optimised with ongoing adherence.

What is the average length of treatment required before determining treatment response?

It is recommended that all patients adhere strongly to antiretroviral treatment medication. Ongoing viral load and CD4 monitoring tracks effective treatment, however clinicians have advised that one year of monitoring the treatment response would give sufficient understanding.

What other interventions would be needed in the event of treatment-related adverse events?

Established treatments for CKD and osteoporosis.

Prescribing and dispensing

Should initiation of this therapy be limited to certain prescriber types? If so, please explain why.

Yes. Initiation of therapy should be limited to named HIV specialists.

Prescribing antiretroviral therapy to treat HIV infection is a specialist area that requires appropriate training, experience, and ongoing clinical practice. Accordingly, the Ministry of Health maintains a list of clinicians approved for prescribing antiretroviral therapy in New Zealand. This is consistent with best practice guidelines published by the Department of Health and Human Services in the

United States of America (see the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV on the AIDSinfo website: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0)

If starting this therapy was limited to certain prescriber types, would it be appropriate for ongoing prescribing to be managed by a wider group of prescribers? If so, who?

No. Ongoing prescribing should be managed by named HIV specialists also, as part of their ongoing care and regular check-ups of patients.

Are there any other issues that PHARMAC should be aware of in relation to the administration of this pharmaceutical, such as infusion time, compounding requirements or safety issues?

There are no known issues concerning the administration of TAF.

The PTAC Minutes (9 &10 August 2018) noted "potential adverse lipid changes in the TAF arm" of study '1089'. The clinical data regarding lipids are presented below and in Appendix 1.

Health need

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

What is the health need of people with the indication(s) for which funding is sought? Please include details of whether reduced life expectancy could be expected or details of potential loss of quality of life including the cause of this loss.

Currently TDF is available as a single drug product, as part of a dual formulation with emtricitabine (Truvada or Teva), and in three FDCs: Atripla (efavirenz, emtricitabine, TDF) Eviplera (rilpivirine, emtricitabine, TDF) and Stribild (cobicistat, elvitegravir, emtricitabine, TDF). These are generally well tolerated by people living with HIV, with the most reported adverse events being some dizziness and gastro-intestinal discomfort (i.e., low-grade diarrhoea and nausea), which are rarely significant enough to cause discontinuation. However, for a small population of people living with HIV, the reported adverse effects are more severe.

In people living with HIV and comorbid renal disease, their life expectancy is reduced [1]. Furthermore, the cohort of people with HIV is ageing and as renal dysfunction and decreased BMD are both associated with ageing, there is a need for this population to have suitable treatment options.

The key potential toxicity of TDF remains renal tubular dysfunction. This can vary from low-grade plasma creatinine increases (with a consequent drop in the eGFR) to significant renal tubular dysfunction and Fanconi syndrome. Large meta-analyses have demonstrated a significantly greater loss of renal function in those on TDF (as compared to non-TDF-containing regimens), but only rare severe renal dysfunction [2]. TDF has also been implicated in causing osteoporosis. In the randomized ASSERT study, patients on TDF had a significantly greater decline in hip BMD compared to those in the abacavir arm (−3.5% versus −2.2% at week 96). Furthermore, BTMs like P1NP, osteocalcin, and alkaline phosphatase were increased in those receiving TDF compared to those on abacavir at week 48 and week 96 [3].

There is a health need among people living with HIV who are suffering from adverse side effects such as renal and bone issues from their current medication, as they currently do not have access to alternative treatment options. This therefore requires them to tolerate suboptimal clinical outcomes, affecting their ability to work and perform usual activities in both the short and long term. This not only affects their quality of life, but also impacts on their life expectancy. There is an unmet health need for these individuals to have access to a more tolerable treatment option.

Please see Appendix 1 for a review of the clinical evidence on TDF and TAF, provided by Gilead Sciences.

[1] Driver, T. H., Scherzer, R., Peralta, C. A., Tien, P. C., Estrella, M. M., Parikh, C. R., … Shlipak, M. G. (2013). Comparisons of creatinine and cystatin C for detection of kidney disease and prediction of all-cause mortality in HIV-infected women. AIDS (London, England), 27(14), 2291–2299. doi:10.1097/QAD.0b013e328362e874 Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3919542/

[2] Gupta, S.K., Post, F.A., Arribas, J.R.., Eron, J.J.., Woh,l D.A.., Clarke, AE., Sax, P.E.., Stellbrink, H.J.., Esser, S., Pozniak, A.L.., Podzamczer, D., Waters, L., Orkin, C., Rockstroh, J.K., Mudrikova, T., Negredo, E., Elion, R.A., Guo, S., Zhong, L., Carter, C., Martin, H., Brainard, D., SenGupta, D., Das, M. (2019). Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials, *AIDS*, 15;33(9):1455-1465. doi: 10.1097/QAD.0000000000002223 https://www.ncbi.nlm.nih.gov/pubmed/30932951

[3] Moyle, G.J., Stellbrink, H.J., Compston, J., Orkin, C., Arribas, J.R., Domingo, P., Granier, C., Pearce, H., Sedani, S., Gartland, M., (2013), "96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study." Antivir Ther. 18(7):905-13. https://www.ncbi.nlm.nih.gov/pubmed/23899468 [pdf provided]

Is there an unmet health need in the populations that may potentially receive benefit from this treatment? If so, please explain.

Yes. While antiretroviral medication has made HIV a manageable condition, a small section of the population of people living with HIV suffer from serious side effects from some antiretrovirals that are still greatly affecting the quality of life, resulting in an unmet clinical need. For PLHIV in New Zealand who are experiencing sub-optimal clinical outcomes from their current regimen (such as renal and bone issues), they currently do not have any alternative treatment options and must endure the side-effects of their medication. There is an unmet need for these individuals who require access to second-line treatment options in order to optimise treatment outcomes.

In particular, patients with pre-existing or iatrogenic TDF-related renal issues currently have very limited options for treatment and in some circumstances may need to resort to potentially dangerous or poorly tolerated older treatments (such as ZDV-based regimens). In cases where significant drug resistance is implicated, there may be no fully effective antiretroviral treatments available. Other therapies, such as dual therapies like DTG+3TC, are currently in trials and they may be recommended in special populations, however, at present, they are not considered first-line treatments.

Are there sub-populations within these populations that have a higher health need?

Yes. There are two sub-populations for whom TDF may not be suitable, namely HIV-positive individuals with CKD or significant bone density loss. Definitions of unsuitability from International guidelines are summarised below.

In the UK, the National Health Service (NHS) defined the renal and bone contraindications as follows [1].

1. Patients with definite contra-indications to TDF
    - Patient with confirmed osteoporosis on DEXA or a high risk of major fracture as determined by FRAX who have a definite contra-indication to TDF; or
    - Patients with renal disease based on NICE definitions (CKD stage G3, or CKD stage G1/2 plus stage A3 proteinuria or nearing this threshold) or renal toxicity or other intolerance secondary to TDF (TAF does not have a licensed indication for CKD stage 4 or 5) who have a definite contra-indication to TDF; or
    - Abacavir should be considered as an alternative to TDF unless there are specific contra-indications (HLA-B5701 positive status, cardiovascular disease or high estimated risk of cardiovascular disease in accordance with BHIVA guidelines, need for tenofovir-containing ART in HBV co-infected individuals).

2. Patients with relative contra-indications to TDF
    - Patients approaching the thresholds of osteoporosis outlined above where abacavir is not a suitable alternative;
    - Patients with renal markers approaching the thresholds where TAF is thought to be more appropriate and abacavir not a suitable alternative.

The US Guidelines were last prepared in 2014 (Lucas et al., [2]) and discuss the potential problem of tenofovir (prior to the availability of TAF). Relevant recommendations are as follows:

- In patients infected with HIV who have a GFR <60 mL/minute/1.73 m^2, we recommend avoiding tenofovir and other potential nephrotoxic drugs when feasible.
- In tenofovir-treated patients who experience a confirmed GFR decline by >25% from baseline and to a level <60 mL/minute/1.73 m^2, we recommend substituting alternative antiretroviral drug(s) for tenofovir, particularly in those with evidence of proximal tubular dysfunction.

The European AIDS Clinical Society (EACS) guidelines (2018), recommend replacement of TDF by non-tenofovir drug or TAF if [3]:

- eGFR ≤ 60 mL/min
- urine protein/creatinine (UP/C) > 50 mg/mmol
- nephrotoxic comedication
- previous TDF toxicity (proximal renal tubulopathy).

The population of people living with HIV is gradually ageing. There may be a higher health need for Descovy among older patients, or patients who are treatment experienced and are dealing with the long-term effects of using antiretrovirals. As patients live longer and with prolonged exposure to antiretroviral medications, the burden of medication toxicity is likely to continue to grow, and there will be more challenges around managing comorbidities of HIV and ageing, such as diabetes and hypertension. The use of TDF for elderly populations (who are also more likely to have renal or bone density concerns) has not been well studied. The Medsafe datasheet for TDF (Tenofovir disoproxil tablets, Truvada, Version 1.1) indicates that *"No data are available on which to make a dose recommendation for patients over the age of 65 years"*, likewise for Teva [4]. There is a well-established and strong link between advanced age and CKD [5] and BMD deficits [6]. This is further exacerbated in ageing women, who are at elevated risk of developing osteoporosis, which constitutes a contraindication to TDF [7]. TAF is associated with smaller decreases in BMD and resulting osteomalacia [7]. Therefore, the ageing populations and, in particular, ageing women may particularly benefit from treatment with TAF.

A study that followed 4,350 patients with baseline eGFR of 60ml/mn/1.73 m2 for a median of 5.8 years found an average incidence rate of CKD to be 0.95% person years of follow-up. Incidence of CKD was higher among women, older patients, those with diabetes or high blood pressure, hyperlipidemia, low baseline eGFR and exposure to TDF [8]. This is supported by two longitudinal studies have suggested an additive effect of HIV infection and diabetes in promoting CKD progression in the US veteran population. Diabetes and hypertension have also been identified as independent risk factors for CKD among HIV-infected individuals in Europe. Recent murine studies indicate that an upregulation of local inflammation induced by HIV may aggravate diabetic nephropathy [9].

[1] NHS England. (2017). Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents, https://www.england.nhs.uk/wp-content/uploads/2017/03/f03-taf-policy.pdf

[2] US DHHS, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start

[3] EACS. (2018). Guidelines Version 9.1 - October 2018. Available at http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

[4] Medsafe, New Zealand Data Sheet Truvada, https://medsafe.govt.nz/profs/Datasheet/t/truvadatab.pdf

[5] Sandeep, K. Mallipattu, F.S, Wyatt, C. (2014). The changing epidemiology of HIV-related chronic kidney disease in the era of antiretroviral therapy, Kidney International, 86(2), 259-265, ISSN 0085-2538, https://doi.org/10.1038/ki.2014.44.

[6] Morlat, P., Vivot, A., Vandenhende, M-A., Dauchy, F-A., Asselineau, J., Deti, E., Gerard, Y., Lazaro, E., Duffau, P., Neau, D., Bonnet, F., Chene, G. (2013) Role of Traditional Risk Factors and Antiretroviral Drugs in the Incidence of Chronic Kidney Disease, ANRS CO3 Aquitaine Cohort, France, 2004–2012. PLoS ONE 8(6): e66223. doi:10.1371/journal.pone.0066223 [pdf provided]

[7] US DHHS, "What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient," https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start

[8] Prakash, S., & O'Hare, AM. (2009). "Interaction of Aging and CKD," *Semin Nephrol*, 29(5): 497–503. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771919/

[9] Wright, N.C., Looker, A.C., Saag, K.G., Curtis, J.R., Delzell, E.S., Randall, S., & Dawson-Hughes, B. (2014). The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 29(11), 2520–2526. doi:10.1002/jbmr.2269 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757905/

What are the treatments that patients with these indications currently receive, if any? Please describe the dose, duration of treatment, along with the risks and benefits associated with this treatment.

Currently recommended treatments require the use of a dual NRTI backbone. In New Zealand, these are limited to three funded combinations. They may not offer sufficient options to special populations of patients who have conditions that constitute contraindications to the use of specific agents. ABC/3TC, is contraindicated in patients with HLA-B*5701 allele and should be

avoided in patients with significant cardiovascular risk. TDF/FTC is contraindicated in patients with CKD or osteoporosis.The last funded backbone (ZDV/3TC) contains zidovudine, which has significant toxicities, including bone marrow suppression, and is no longer recommended for therapy by ASHM, US DHHS and most other international guidelines [1].

The most commonly used NRTI backbone in New Zealand is TDF/FTC. The second most commonly used backbone is ABC/3TC. The most commonly used “third drugs” are DTG and EFV.

[1] US DHSS, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, Available at:

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start

Are there any issues regarding the availability or suitability of existing treatments for this indication?

Yes. In a small number of patients TDF is linked to serious adverse effects that can be divided into two groups:

Renal issues

Several studies have linked specific regimens to the **increased risk of CKD or CKD progression**. In a large European cohort study, CKD (defined as a confirmed creatinine clearance p60 ml/ min per 1.73 m2 or a 25% decline from a baseline 60 ml/min per 1.73 m2) was associated with increasing cumulative exposure to indinavir and TDF, both of which have established nephrotoxic potential. Most recently, analysis of data from another large European cohort demonstrated an association between confirmed eGFR<70 ml/min per 1.73 m2 and cumulative exposure to TDF, atazanavir, or boosted lopinavir; this level of eGFR was also a strong predictor of TDF discontinuation [1].

TDF in particular is of concern, with research showing links to renal issues (such as Fanconi-like syndrome), acute kidney injury (AKI) or CKD. TDF is associated with unfavourable changes in renal laboratory markers and renal adverse events including proximal renal tubulopathy, which occurs in less than 1% of individuals [2] but can cause permanent renal function decline [3]. TDF has a small but definite negative impact on kidney function (up to a 10% decrease in eGFR). This occurs because of altered tubular function in those exposed to TDF for treatment [4]. In a study by Patil et al. tenofovir was the leading cause of renal failure causing AKI as well as contributing to nephrotoxicity in CKD cases. Their study showed that drug-induced nephrotoxicity mainly due to TDF is a very important cause of morbidity in HIV, showing a strong correlation between advanced immunosuppression and renal failure [5]. This is often reversible if TDF is ceased in the early stages.

TDF is a popular choice because of its potency, convenient once daily dosing, and relatively minimal adverse reactions. Since 2006, it has been the most widely prescribed antiretroviral agent in the USA and New Zealand, and it is increasingly used in low-middle income countries. However, subsequent observational studies have reported a **significant decline in the eGFR** with cumulative use of TDF [6]. A meta-analysis of randomized control trials and observational studies comparing individuals on TDF with those on alternative agents demonstrated a greater decrease in eGFR over a median 48 weeks of follow-up; compared to individuals taking non-TDF regimens, eGFR declined by 3.92 mL/min more in those on TDF [7]. Recent analyses from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) study showed that in participants with normal baseline eGFR followed for a median of over 7 years, TDF use was associated with about 14 % more risk of CKD per year of use after adjusting for key confounders, with the relative risk nearly doubling in 5 years. Because TDF is likely to have been stopped in those with declining eGFR, the actual relative risk could be even higher [6]. ASHM guidelines advise TDF should be ceased if CKD is identified (eGFR <60mL), or a patient is at high risk of CKD, and that TDF should be exchanged for a suitable alternative, such as TAF [8].

Bone issues

While reductions in BMD occur at ART initiation irrespective of regimen, the magnitude of reductions are greater with TDF-containing regimens, suggesting that TDF has an effect on bone that is independent of host, viral and immunologic factors [9]. Whether this negative effect on bone is direct (drug effect on osteoclasts and/or osteoblasts) and/or indirect (drug effect on the proximal renal tubule and/or vitamin D metabolism) is not entirely clear. The TDF Medsafe datasheet indicates that bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Research has also highlighted l**inks between TDF and decreases in BMD**. In the pooled analysis of Studies 0104 and 0111, BMD from baseline to Week 96 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of TAF to that of TDF. In patients who had both baseline and Week 96 hip or spine measurements (N=722 in the FTC+TAF group and N=714 in the FTC+TDF group) there were smaller decreases in BMD in patients receiving FTC+TAF as compared with FTC+TDF, both given with EVG+COBI as a fixed-dose combination tablet [10].

In the STEAL study, virologically suppressed patients randomised to simplify dual NRTI therapy to coformulated TDF/FTC had greater bone loss over 96 weeks than those randomised to co-formulated ABC-3TC. This analysis aimed to explore STEAL bone outcomes in more detail and to determine predictors of BMD change. Some patients might be at greater risk of TDF-related BMD loss over 96 weeks and that this greater loss might be predicted by either baseline or on-study BTM levels. After a median of 38 months on TDF, osteopenia at spine and hip was observed in 49 and 48%, and osteoporosis in 9 and 2%, respectively. There was a lineal correlation between BMD at femoral neck and time on TDF. One or more tubular abnormalities were observed in 80% of cases (hyperphosphaturia, 50%). A lower BMD correlated with phosphaturia, even with phosphataemia within normal limits. In fact, patients with previous improvement in phosphaturia had better BMD at inclusion. A second dual X-ray absorptiometry, after a median of 40.8 months (33.8–45.1; 627.7 patients-year on TDF), showed additional BMD reduction at hip in 50% of cases (36% with bone loss >3%), a decline associated with phosphaturia (b, _0.31; P¼0.01) or number of tubular abnormalities (b, _0.41; P¼0.01), but also with use of boosted protease inhibitors (b, _0.47; P¼0.03) and BMD at inclusion (b, _0.33; P¼0.03). Chronic abnormal phosphaturia explains, at least in part, progressive bone loss during TDF therapy. These data suggest that tubular dysfunction leads to an altered equilibrium between phosphataemia, phosphaturia, and bone as mechanism of progressive BMD decline [11].

Please see Appendix 1 for a review of the clinical evidence comparing TDF and TAF, provided by Gilead Sciences.

[1] Sandeep, K. Mallipattu, F.S, Wyatt, C. (2014). The changing epidemiology of HIV-related chronic kidney disease in the era of antiretroviral therapy, Kidney International, 86(2), 259-265, ISSN 0085-2538, https://doi.org/10.1038/ki.2014.44.
[2] Nelson, M.R., Katlama, C., Montaner, J.S., Cooper, D., Gazzard, B., Clotet, B., Lazzarin, A., Schewe, K., Lange, J., Wyatt, C., Curtis, S., Chen, S.S., Smith, S., Bischofberger, N., Rooney, J.F. (2007). The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS, 21,1273–1281. Available at: https://journals.lww.com/aidsonline/fulltext/2007/06190/The_safety_of_tenofovir_disoproxil_fumarate_for.6.aspx#pdf-link
[3] Waheed, S., Attia, D., Estrella, M.M., Zafar, Y., Atta, M., Lucas, G.M., Fine, D.M. (2015). Proximal tubular dysfunction and kidney injury associated with tenofovir in HIV patients. Clinical Kidney Journal 8(4):420–425. https://doi.org/10.1093/ckj/sfv041
[4] Venter, W.D.F., Fabian, J., Feldman, C. (2018) "An overview of tenofovir and renal disease for the HIV-treating clinician," *South Afr J HIV Med,* 19(1): 817 https://www.ncbi.nlm.nih.gov/pubmed/30167339 [pdf provided].
[5] Patil, P.V., Bansode, J.B., Kore, M.C., Hajare, K. (2018). Acute kidney injury and chronic kidney disease in HIV patients in the era of anti- retroviral therapy. J. Evolution Med. Dent. Sci. 7(9):1082-1086, DOI: 10.14260/jemds/2018/246 Available at: https://jemds.com/data_pdf/jyoti%20bansode-feb-26-.pdf
[6] Achhra, A.C., Nugent, M., Mocroft, A., Ryom, L., Wyatt, C.M., (2016) "Chronic Kidney Disease and Antiretroviral Therapy in HIV-Positive Individuals: Recent Developments," *Curr HIV/AIDS Rep*, 13: 149. https://doi.org/10.1007/s11904-016-0315-y
[7] Cooper R.D., Wiebe, N., Smith, N., Keiser, P., Naicker, S., Tonelli, M. (2010). Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 51(5):496–505. doi:10.1086/655681. [pdf provided]
[8] Alfred Health, *HIV Service Guidelines for the Screening and Management of HIV related Co-Morbidities,*https://ashm.blob.core.windows.net/ashmpublic/HIV-comorbidity-algorithm%20Version%202%20May%202018.pdf
[9] Grant, P.M. and Cotter, A.G. (2016). Tenofovir and Bone Health. Curr Opin HIV AIDS. 11(3): 326–332. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4844450/pdf/nihms777581.pdf
[10] Medsafe, NZ Data Sheet: Descovy, Available at: https://medsafe.govt.nz/profs/Datasheet/d/descovytab.pdf
[11] Casado, J.L., Santiuste, C., Vazquez, M., Banon, S., Rosillo, M., Gomez, A., Perez-Elias, M.J., Caballero, C., Rey, J.M., Moreno, S. (2016). Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS. 30:1423-1431. DOI: 10.1097/QAD.0000000000001067 [pdf provided].

Would the pharmaceutical replace or complement these existing treatments? Please explain.

The pharmaceutical would partly replace existing treatments only for those who are suffering from suboptimal health outcomes, as evident through the required tests and when clinically indicated.

Does this indication disproportionately affect any populations that may already be experiencing a health disparity?

In New Zealand, HIV infection disproportionately affects gay, bisexual and other men who have sex with men (GBM). In 2018, 62.4% of persons diagnosed with HIV were GBM. Introduction of well-tolerated treatment options would aid to remedy the consequences of this disparity and improve the health outcomes of this population in need.

Is there an unmet health need in other people due to the indication, such as in people who care for or live with those with the indication, or from spread of disease?

HIV is increasingly recognised as an illness that affects couples and families, and not just the individual. This is not only because the virus can be passed on from one person to another, but also because for every person living with HIV, there is a family and community that are also affected. As with other chronic illnesses, partners and families often provide most of the physical and emotional care. This can place a great strain on them and can lead to individual stress and tension between members of the family. Stigma and discrimination may mean the diagnosis is kept hidden. It can prevent wider support from extended family or the community. The stress of living with HIV causes some people to suffer from mental health problems such as anxiety and depression. With HIV, more than one person in a family may be unwell which can add to the burden of care and cause additional emotional and financial problems.

The unmet need for people living with HIV, in which they must tolerate suboptimal treatment outcomes, therefore has an impact on those caring for them. NZ society will benefit if new infections can be reduced and existing patients with HIV are well supported and their condition managed without adverse events from ART.

Health benefits and risks in the indication(s) for which funding is sought

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

Discuss the potential benefits from treatment with the pharmaceutical compared with current treatment options (if any).

Renal adverse events

TDF has been linked to unfavourable changes in renal laboratory markers and renal adverse events, and this may be due to the high circulating plasma levels of tenofovir, which is excreted renally but can accumulate in the proximal tubule resulting in renal toxicity. In contrast, the chemical structure of TAF provides stability against intestinal and plasma enzymatic cleavage with a 200-fold increase in plasma stability relative to TDF and is metabolised within cells to the pharmacologically active metabolite tenofovir diphosphate. A much smaller dose of TAF can be used (10 to 25mg per day) compared to TDF, due to the greater accumulation of tenofovir arising from TAF in cells of the immune system. The mechanism of TDF toxicity seems to be related to the plasma concentration of tenofovir in the blood and some kidney cells, which could cause kidney injuries in some cases. Higher tenofovir plasma concentration can lead to increased intracellular concentrations that cause depletion of mitochondrial DNA and dysfunction of the oxidative respiratory chain in proximal tubular epithelial cells. This leads to a depletion of intracellular ATP, which limits the proximal tubule's ability to reabsorb electrolytes and low molecular weight proteins. TAF achieves higher intracellular concentrations of the active metabolite tenofovir-diphosphate in immune cells at a much lower dose and nearly 90% lower plasma concentration as compared to TDF. Also, TAF does not appear to enter renal tubular cells, as it is not a substrate for the membrane transporters that facilitate tenofovir entry into these cells. Owing to these properties, TAF holds promise as a safer alternative to TDF in terms of both kidney and bone toxicities [1].

The key clinical evidence comparing TAF with TDF is Study 1089 (NCT02121795, [2]), in which virologically suppressed HIV-positive patients were randomised to either switch to TAF+FTC or remain on TDF+FTC, while continuing their third agent (boosted protease inhibitor or unboosted third agent) [2]. At 96 weeks follow-up, renal parameters improved in patients who switched to TAF+FTC, with an increase in eGFR and a reduction in proteinuria, especially in the excretion of β2-microglobulin and retinol-binding protein, which are considered specific markers of proximal tubulopathy [2].

Additional clinical evidence is available in the pooled data of Trials 104 and 111 (NCT01780506 and NCT01797445) that compared initiation of HIV therapy with TAF versus TDF in those also receiving elvitegravir (EVG, E), cobicistat (C), and emtricitabine (FTC) in single-tablet formulations. In the 144-week follow-up, there were no cases of proximal renal tubulopathy (PRT) or renal discontinuations compared with four cases of PRT and 12 renal discontinuations in the EVG/COBI/FTC/TDF group [3]. Additional data are also available in study 112 (NCT01818596, Post et al. 2017,[4]) enrolling HIV-infected adults with renal impairment (creatinine clearance 30–69 mL/min) and study 109 (NCT01815736, DeJesus et al. 2018,[5]).

In order to determine whether the favourable biomarker profile of TAF translates into improved renal clinical outcomes, considering the rarity of PRT and resulting low rates of renal events in individual trials, Gupta et al. (2019) conducted a large integrated analysis of people living with HIV to better understand the renal clinical outcomes in TAF vs. TDF-containing HIV regimens [6]. The analysis included pooled data from 26 TAF clinical trials, with cumulative exposures of 12,519 person-years to TAF and 5,947 person-years to TDF, thereby providing increased statistical power to evaluate the comparative impact on renal adverse events and renal function over time. In the primary analyses of incidence of proximal renal tubulopathy events, there were no cases of PRT or Fanconi syndrome reported in the TAF group, compared with 10 cases of PRT, including Fanconi syndrome, for the TDF group (0.34% of participants, P<0.001 vs. TAF). A significant difference between TAF and TDF was also observed for renal adverse events leading to study drug discontinuation and changes in renal laboratory parameters and biomarkers in both treatment naïve and treatment-experienced patients. The authors of this recent and comprehensive study conclude that the favourable renal biomarker profile observed with TAF vs. TDF in the individual trials translates into a lower rate of clinically significant renal events. These data support a comparative renal safety advantage of TAF over TDF in a broad range of people living with HIV.

Arribas et al. (2017) found that TAF may even be superior to TDF in virologic efficacy. In 2 double-blind phase 3 trials, 1733 antiretroviral naïve adults were randomized to TAF or TDF, each coformulated with elvitegravir/ cobicistat/ emtricitabine (E/C/F). At 144 weeks, TAF was superior to TDF in virologic efficacy, with 84.2% vs 80.0% having HIV-1 RNA ,50 copies/mL (difference 4.2%; 95% confidence interval: 0.6% to 7.8%). No participants on TAF had renal-related discontinuations vs 12 on TDF (P, 0.001), with no

cases of proximal tubulopathy for TAF vs 4 for TDF. There were greater increases in lipids with TAF vs TDF, with no difference in the total cholesterol to high-density lipoprotein ratio. For initial HIV therapy, E/C/F/TAF is superior to E/C/F/TDF in efficacy and bone and renal safety [3].

Bone mineral density (BMD)

A secondary objective of Study 1089 was to evaluate the bone safety of two regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) at week 48. From baseline to week 96, BMD increased in the FTC+TAF group but not in the FTC+TDF group [median change: hip 1.78% vs. 20.17% (P < 0.001) and spine 1.85% vs. 20.33% (P<0.001)]. In the FTC+TAF group, BMD continued to increase in the second year and results were similar regardless of third agent. More participants in the FTC+TAF group had increase in BMD of at least 3% [spine 40% vs. 18% (P < 0.001) and hip 29% vs. 11% (P<0.001)]. There were 4 fractures (1 on FTC+TAF and 3 on FTC+TDF), all related to mechanical trauma and considered by the investigator to be unrelated to study drug [2].

Additional BMD information is available in the pooled data of Trials 104 and 111 (Arribas et al. 2017 [3]), study 112 (Post et al. 2017 [4]) and study 109 (DeJesus et al. 2018, [5]). In Trials 104/111 at 144-week follow-up, fractures occurred for 6 participants (0.7%) on TAF and 16 (1.8%) on TDF (P=0.051); all fractures were due to trauma and considered unrelated to study drug. No discontinuations due to BMD decreases occurred with TAF, however between weeks 48 and 144, 6 men discontinued TDF because of a >5% decrease in BMD (ages ranged from 20 to 50 years). Fewer participants on TAF compared with TDF initiated calcium, vitamin D, or other nutritional supplements during the study (16.2% vs 20.7%, P=0.018).

Please see Appendix 1 for a review of the clinical evidence comparing TDF and TAF, provided by Gilead Sciences.

[1] Achhra, A.C., Nugent, M., Mocroft, A., Ryom, L., Wyatt, C.M., (2016) “Chronic Kidney Disease and Antiretroviral Therapy in HIV-Positive Individuals: Recent Developments,” *Curr HIV/AIDS Rep*, 13: 149. https://doi.org/10.1007/s11904-016-0315-y

[2] Raffi, F., Orkin, C., Clarke, A., Slama, L., Gallant, J., Daar, E., Henry, K., Santana-Bagur, J., Stein, D.K., Bellos, N., Scarsella, A., Yan, M., Abram, M.E., Cheng, A., Rhee, M.S. (2017). Long-Term (96-Week) Efficacy and Safety After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in HIV-Infected, Virologically Suppressed Adults. Journal of Acquired Immune Deficiency Syndrome 2017;75:226-231. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5427981/pdf/qai-75-226.pdf

[3] Arribas, J.R., Thompson, M., Sax, P.E., Haas, B., McDonald, C., Wohl, D.A., DeJesus, E., Clarke, A.E., Guo, S., Wang, H., Callebaut, C., Plummer, A., Cheng, A., Das, M., McCallister, S., (2017). Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. *J Acquir Immune Defic Syndr*, 1;75(2):211-218. doi: 10.1097/QAI.0000000000001350. https://www.ncbi.nlm.nih.gov/pubmed/28282300 Available at: https://journals.lww.com/jaids/fulltext/2017/06010/Brief_Report___Randomized,_Double_Blind_Comparison.10.aspx#pdf-link

[4] Post, F.A., Yazdanpanah, Y., Schembri, G., Lazzarin, A., Reynes, J., Maggiolo, F., Yan, M., Abram, M.E., Tran-Muchowski, C., Cheng, A., & Rhee, M.S. (2017) Efficacy and safety of emtricitabine/tenofovir alafenamide (FTC/TAF) vs. emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a backbone for treatment of HIV-1 infection in virologically suppressed adults: subgroup analysis by third agent of a randomized, double-blind, active-controlled phase 3 trial, HIV Clinical Trials, 18:3, 135-140, DOI: 10.1080/15284336.2017.1291867 [pdf provided].

[5] DeJesus, E., Haas, B., Segal-Mauer, S., Ramgopal, M.N., Mills, A., Margot, N., Liu, Y-P., Makadzange, T., & McCallister, S. (2018). Superior Efficacy and Improved Renal and Bone Safety After Switching From a Tenofovir Disoproxil Fumarate (TDF)- to a Tenofovir Alafenamide (TAF)-based Regimen Through 96 Weeks of Treatment. AIDS Res Hum Retroviruses. 34(4). doi: 10.1089/AID.2017.0203 [pdf provided].

[6] Gupta, S.K., Post, F.A., Arribas, J.R.., Eron, J.J.., Woh,l D.A.., Clarke, AE., Sax, P.E.., Stellbrink, H.J.., Esser, S., Pozniak, A.L.., Podzamczer, D., Waters, L., Orkin, C., Rockstroh, J.K., Mudrikova, T., Negredo, E., Elion, R.A., Guo, S., Zhong, L., Carter, C., Martin, H., Brainard, D., SenGupta, D., Das, M. (2019). Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials, *AIDS*, 15;33(9):1455-1465. doi: 10.1097/QAD.0000000000002223 https://www.ncbi.nlm.nih.gov/pubmed/30932951

Discuss the potential risks from treatment with the pharmaceutical compared with current treatment options (if any).

The PTAC Minutes (9 &10 August 2018) “noted potential adverse lipid changes in the TAF arm” of study ‘1089’. Initial trials indicate that the use of TAF could result in loss of the lipid-lowering effect afforded by TDF. It has been consistently noted that TDF exhibits clinically significant (“statin-like”) beneficial effects on lipid profiles when compared to numerous other antiretrovirals [4]. Because of the lower concentrations of tenofovir in plasma with TAF when compared to TDF, this effect may be lost, which possibly leads to higher lipid levels in patients treated with TAF [2, 3]. It is therefore postulated that worsening of the lipid profiles following the switch from TDF to TAF is not an adverse effect of TAF, but rather a result of the loss of protective effect of TDF [2, 3]. The long-term clinical consequences of this are still unclear, but observational studies suggest this effect may be clinically significant in real-world settings and patients treated with TAF may require adjustments to lipid-lowering medication dosing when switching from TDF [5, 6].

However, as summarised in the study publication by Raffi et al. 2017 [1]: no differences in total cholesterol to HDL ratio or initiation of lipid-modifying medications were noted between groups at week 96 (FTC/TAF 7.2%, FTC/TDF 6.4%, P=0.76) [7]. Likewise in studies 104/111 with 144 week follow-up [2], there were no differences between TAF and TDF in use of lipid-modifying agents: 48 (5.5%) vs 50 (5.8%) (P=0.92), cardiovascular / cerebrovascular events: 24 participants (2.8%) vs 33 (3.8%) (P=0.28) or serious cardiovascular / cerebrovascular events: 5 (0.6%) vs 6 (0.7%) (P = 1.00). As TDF has previously been shown to lower lipid levels (Tungsiripat et al., 2010, [8]; Santos et al., 2015, [9]), it is likely that lower tenofovir exposures through switching TDF to TAF has driven the difference between treatment groups. The availability of outcomes data for cardiovascular events and the uncommon and similar use of lipid-modifying agents suggest the differences in surrogate outcomes (lipid levels) are probably of minimal clinical relevance.

Current guidelines [4,7] recommend avoiding ABC - the currently recommended and available alternative to TAF when there are renal or bone-related contraindications to TDF – in patients with high cardiovascular risk. Clinicians should carefully consider the risks and benefits of selecting the specific agents in selecting ARV therapy in patients with dyslipidaemia or cardiovascular risk factors. In patients with dyslipidaemia and lack of renal or bone concerns, TDF may be a preferred agent to both TAF and ABC [7].

Please see Appendix 1 for a review of the clinical evidence comparing TDF and TAF, provided by Gilead Sciences.

[1] Raffi, F., Orkin, C., Clarke, A., Slama, L., Gallant, J., Daar, E., Henry, K., Santana-Bagur, J., Stein, D.K., Bellos, N., Scarsella, A., Yan, M., Abram, M.E., Cheng, A., Rhee, M.S. (2017). Long-Term (96-Week) Efficacy and Safety After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in HIV-Infected, Virologically Suppressed Adults. Journal of Acquired Immune Deficiency Syndrome 2017;75:226-231. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5427981/pdf/qai-75-226.pdf

[2] Arribas, J.R., Thompson, M., Sax, P.E., Haas, B., McDonald, C., Wohl, D.A., DeJesus, E., Clarke, A.E., Guo, S., Wang, H., Callebaut, C., Plummer, A., Cheng, A., Das, M., McCallister, S., (2017). Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. *J Acquir Immune Defic Syndr*, 1;75(2):211-218. doi:

10.1097/QAI.0000000000001350. https://www.ncbi.nlm.nih.gov/pubmed/28282300 Available at: https://journals.lww.com/jaids/fulltext/2017/06010/Brief_Report___Randomized,_Double_Blind_Comparison.10.aspx#pdf-link

[3] Maggi, P., Di Biagio, A., Rusconi, S., Cicalini, S., D'Abbraccio, M., d'Ettorre, G., … Squillace, N. (2017). Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC infectious diseases, 17(1), 551. doi:10.1186/s12879-017-2626-z https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5550957/

[4] US DHHS, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start

[5] Cid-Silva, P., Fernández-Bargiela, N., Margusino-Framiñán, L., Balboa-Barreiro, V., Mena-De-Cea, A., Lopez-Calvo, S., Vazquez-Rodriquez, P., Martin-Herranz, I., Miguez-Rey, E., Castro-Iglesias, A. (2019). Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine. Basic Clin Pharmacol Toxicol. 124: 479– 490. https://doi.org/10.1111/bcpt.13161 https://www.ncbi.nlm.nih.gov/pubmed/30388308

[6] Mascolini, M. (2018). Patient Proportion With Above-Target LDL Rises 70% With TDF-to-TAF Switch. HIV Drug Therapy, Glasgow 2018, October 28-31, 2018, Glasgow http://www.natap.org/2018/GLASGOW/GLASGOW_27.htm

[7] ASHM. (2018). What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient http://arv.ashm.org.au/what-to-start-initial-combination-regimens-for-the-antiretroviral-naive-patient/

[8] Tungsiripat, M., Kitch, D., Glesby, M. J., Gupta, S. K., Mellors, J. W., Moran, L., … Aberg, J. A. (2010). A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS (London, England)*, *24*(11), 1781–1784. doi:10.1097/QAD.0b013e32833ad8b4, Available at: http://europepmc.org/abstract/med/20495438

[9] Santos J.R., Saumoy M., Curran A., Bravo, I., Llibre, J.M., Navarro, J., Estany, C.E., Podzamczer, D., Ribera, E., Negredo, E., Clotet, B., Paredes, R. (2015). The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. Clin Infect Dis.61:403–408. Available at: https://academic.oup.com/cid/article/61/3/403/490899

Are there sub-populations that have higher potential benefits or risks? If so, please describe.

Yes. These are the populations for whom treatment is sought.

Furthermore, the HIV-positive population is gradually ageing, and as people get older, some medical concerns become very important, including heart disease, kidney problems and bone problems [1]. As stated above, some HIV drugs have side effects that affect these medical problems, and as it is a lifelong treatment, it is very important to minimise long-term side effects. There is a well-established and strong link between advanced age and CKD [1] and BMD deficits [3]. This is further exacerbated in ageing women, who are at elevated risk of developing osteoporosis, which constitutes a contraindication to TDF [4]. TAF is associated with smaller decreases in BMD and, possibly, resulting osteomalacia [4]. Therefore the ageing populations and, in particular, ageing women may particularly benefit from treatment with TAF.

[1] NHS England. (2017). Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents, https://www.england.nhs.uk/wp-content/uploads/2017/03/f03-taf-policy.pdf
[2] Prakash, S., & O'Hare, AM. (2009). "Interaction of Aging and CKD," *Semin Nephrol*, 29(5): 497–503. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771919/
[3] Wright, N. C., Looker, A. C., Saag, K. G., Curtis, J. R., Delzell, E. S., Randall, S., & Dawson-Hughes, B. (2014). The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 29(11), 2520–2526. doi:10.1002/jbmr.2269 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757905/
[4] US DHHS, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start

Would this treatment provide any health benefits or risks to any people beyond the individual who was receiving treatment? If so, what benefits or risks would result?

The reimbursement of DESCOVY on the Pharmaceutical Schedule will provide a treatment option for patients for whom there is not a suitable option within the current recommended initial ART regimens. The health benefit for family or whānau is expected to be a reduction in emotional stress knowing that the patient is able to take a medicine that does not further compromise their health due to its safety profile. If the patient stays well and is adherent to their medicine, the physical requirements for care from family or whānau are expected to be less. In addition, a patient who is adherent to their medicine increases the probability of achieving an undetectable viral load. The results of Opposites Attract study show that when an undetectable viral load is maintained, the risk of HIV transmission is negligible [1]. This benefits the whole NZ society.

[1] Bavinton, B., Jin, F., Prestage, G., Zablotska, I., Koelsch, K., Phanuphak, N., Grinsztejn, B., Cooper, D.A., Fairley, C., Kelleher, A., Triffit, K., Grulick, A.E. (2014). The Opposites Attract Study of viral load, HIV treatment and HIV transmission in serodiscordant homosexual male couples: design and methods. BMC Public Health, 14:917. Available at: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-14-917

How would funding the pharmaceutical result in other measurable benefits or risks to the health sector, eg changes in number of surgeries, hospitalisations, nursing time, diagnostic tests?

People on ART take a combination of HIV medicines indefinitely, and it is a lifelong treatment. While modern medicines have made HIV a chronic manageable condition, serious side effects from ARVs are still greatly affecting the quality of life for many people living with HIV. Maintaining people with HIV on effective treatment reduces the likelihood of development of AIDS-related complications.

Minimising toxicity and long term side effects is critical in maintaining quality of life. Side effects, both bothersome and serious, can be temporary or have long lasting impacts. These include diarrhoea, lipodystrophy, fatigue, bone pain/disease, nausea, and depression. Drugs approved in 2018 — like Symtuza, Delstrigo and Ibalizumab — as is the case with many other ARVs, are also linked to serious complications such as cardiovascular disease, diabetes, liver, kidney and pancreas disease, and immune reconstitution inflammatory syndrome. As long as HIV medications are required to be taken indefinitely and, from a public health standpoint, to limit new incidents of HIV, special regulatory attention should be given to ensure adverse effects and serious adverse effects are limited — and not impacting adherence in taking them.

Maintaining optimal adherence to antiretroviral medication minimises the risk of resistance developing to the antiretroviral. With limited choice and people living longer due to effective treatment we need to ensure maximum choice in terms of available therapy.

Resistance or lack of adherence due to adverse effects or treatment fatigue (from BID or pill burden for example) can cause viral rebound which leads to comorbidities / AIDS and ongoing transmission. This in turn leads to poor health outcomes resulting in increased testing, Clinic visits, hospitalization and potentially death if treatment options fail. While AIDS diagnoses has dropped we continue to have people diagnosed with AIDS (15 people in 2018) and an increase in deaths.
If TAF offers improved kidney and bone safety, it could potentially reduce monitoring costs and may turn out to be a more cost-effective agent. This could be seen in a reduction in hospital visits, though there would also be an increased cost of testing.

Suitability

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Are there any features of the treatment that may impact on its use (eg method of delivery, size, shape, taste)? If so, please explain.

The combination tablet is administered orally once daily and therefore provides a simple and effective regimen. It must be combined with another treatment to enable a triple therapy regimen.

Costs and savings

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Would the funding of this treatment create any costs or savings to the health system (eg would treatment require increased monitoring, or would it free up clinician time)?

The possible higher cost of TAF as compared with generic TDF could be offset by the savings related to avoidance of significant negative outcomes such as renal failure or osteoporotic fractures. Both CKD and osteoporosis related fractures are a significant health issue and cost burden on the health care system. The use of TAF in place of TDF would reduce monitoring costs and the costs of treatment for the uncommon but serious renal and bone adverse events. The 2015 National Consensus statement from the Ministry of Health notes that at the end of 2012, there were 2,469 CKD patients receiving dialysis. The cost to the health care system of dialysis for an individual ranges from $30,000 to $60,000 per year [1].

A recent study from Australia from Wyld, et al. (2015) found that individuals with CKD incur 85% higher healthcare costs and 50% higher government subsidies than individuals without CKD, and costs increase by CKD stage [2].

A 2007 report commissioned by Osteoporosis New Zealand estimated the cost of treating fractures is estimated to be over $300 million per annum [3]. The total cost is estimated to be over $1.15 billion per annum in health costs, with a heavy burden on hospitals and nursing homes.

Thus, any reduction of risk of CKD and osteoporosis related fractures has the potential to reduce significant associated cost of in-hospital treatment and dialysis. These cost savings may be realised in a number of settings including, in hospital, outpatient and home care.

[1] Ministry of Health. (2015). Managing Chronic Kidney Disease in Primary Care National Consensus Statement, https://www.health.govt.nz/system/files/documents/publications/managing-chronic-kidney-disease-primary-care-mar15-v2.pdf
[2] Wyld, M.L., Lee, C.M., Zhuo, X., Shaw, J.E., Morton, R.L., Colagiuri, S., Chadban, S.J. (2015). Cost to government and society of chronic kid- ney disease stage 1-5: a National Cohort Study. Intern Med J, 45: 741–747. https://www.ncbi.nlm.nih.gov/pubmed/25944415
[3] Osteoporosis New Zealand. 2007. Fractures caused by osteoporosis, https://osteoporosis.org.nz/osteoporosis-fractures/fractires-caused-by-osteoporosis