Reviewer No.1 check list for application for addition: Tenofovir Disoproxil Fumarate (TDF)

(1) Have all important studies that you are aware of been included?

Yes ☐ No ✓

If "No", add missing references with brief summary of key findings.

Although the submission begins with a description of a systematic search strategy, the inclusion criteria set seem to have applied in a rather restrictive manner, in that only regimens in which TDF is compared with stavudine (d4T) or TDF plus emtricitabine (FTC) with co-formulated zidovudine (ZDV)/lamivudine (3TC) were included in the application, in relation to “comparative effectiveness”. A large proportion of the references cited in the original application are from conference presentations, rather than peer-reviewed articles from the medical literature. A more extensive literature, relating to other regimens and to potential problems with some of these possible choices, is available and was not adequately covered. Some additional materials were provided in the supplement dated October 2006, often in the form of conference materials, but without explanation or analysis.

Trials in which TDF has formed part of the background regimen, and in which alternative protease inhibitor (PI) dosing or choices are tested, can also provide evidence of efficacy, as well as some data relating to adverse effects associated with the use of TDF. Three such studies are summarised below.¹,²³

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Outcome (efficacy)</th>
<th>Outcome (other)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Johnson MA, et al. J Acquir Immune Defic Syndr. 2006</td>
<td>Randomised, open-label, multicentre</td>
<td>ARV-naïve; 45 centres in 7 countries in North America, Europe, Asia, Australia</td>
<td>70% (QD) and 64% (BD) achieved HIV-1 RNA &lt;50 copies/ml (p=0.43)</td>
<td>No participants developed TDF resistance, but 3 (1 in OD, 2 in BD groups) developed FTC resistance</td>
<td>The efficacy of a TDF/FTV NtRTI/NRTI backbone shown here is comparable to that shown for other combinations (e.g. d4T/3TC), when dosed with LPV/r</td>
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<td>TDF 300mg QD + FTC 200mg QD + either ritonavir-boosted lopinavir (LPV/r) 800/200mg QD (n=115) or LPV/r 400/100mg BD (n=75) over 48 weeks</td>
<td>ITT, non-completer = failure</td>
<td>Mean increase in CD4 cell count from baseline 185 (QD) and 196 (BD) cells/ml (p=0.67)</td>
<td>Both groups showed small but statistically significant increases in serum creatinine, decreases in creatinine clearance (per</td>
<td>This was a phase 2b study, with only 60% power to determine noninferiority</td>
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<td>Johnson M, et al. AIDS. 2006</td>
<td>Randomised, open-label, multicentre</td>
<td>All patients had failed two or more prior HAART regimens</td>
<td>Mean reductions in HIV RNA from baseline were -2.29 (ATV/RTV QD) and -2.08 (LPV/r BD) log10 copies/ml; time-averaged difference 0.14 log10 copies/ml (95% CI -0.13 to 0.41)</td>
<td>5 participants had adverse renal events (all in LPV/r group, and all receiving ddI as the second NRTI) – 1 renal insufficiency, 1 renal tubular acidosis, 1 Fanconi syndrome, 2 grade 3 elevation in serum creatinine</td>
<td>Adequately powered for the primary outcome</td>
</tr>
<tr>
<td>Piketty C, et al. Antivir Ther. 2006</td>
<td>Prospective, randomized, open-label study of TDF 300mg QD + ATV/RTV 300/100mg QD + optimized NRTI or current regimen for 2 weeks, then on salvage regimen over 26 weeks</td>
<td>Median decrease of only 0.2 log10 copies/ml in viral load at 26 weeks</td>
<td>Regimen was well tolerated</td>
<td>Poor virological response, despite RTV boosting, but all patients had been very heavily treated. Median number of mutations was 7 to NRTIs, 1 to NNRTIs and 8 to PIs.</td>
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Other studies are referred to in relation to efficacy in different settings, adverse effects and drug-drug interactions. In addition to the data from studies GS 903, GS 934, GS 907 and GS 902, which have been reported in the peer-reviewed literature, data on the triple nucleoside/nucleotide cohort from the DART study has been published. While not a favoured regimen, this may represent an important non-nucleoside reverse transcriptase inhibitor (NNRTI)- and PI-sparing option in resource-constrained settings. The data below coincide with the two conference presentations cited in the application.

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<td>DART Virology Group and Trial Team. AIDS. 2006</td>
<td>Cohort analysis within DART study (randomised, controlled trial of two ART management strategies – clinical versus clinical and laboratory monitoring)</td>
<td>ARV-naïve, Uganda and Zimbabwe</td>
<td>24 weeks – 59% achieved HIV RNA &lt;50 copies/ml and 79% &lt; 400 copies/ml</td>
<td>Of 20 genotypes at 24 weeks (all with HIV RNA &gt; 1000 copies/ml), only 3 showed K65R mutation; 14 showed M184V mutation</td>
<td>Good virological efficacy in an African setting, where all participants had advanced disease (all CD4 &lt;200)</td>
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<tr>
<td>Lamarca A, et al. J Acquir Immune Defic Syndr. 2006</td>
<td>Randomized, open-label, multicentre</td>
<td>Prior virological failure on HAART, with not more than 3 NRTI-associated mutations; 57 centres in Europe and North</td>
<td>50% of those on the FDC and 47% of those on the single entities achieved HIV RNA &lt;50 copies/ml</td>
<td>Tolerability was similar in both groups</td>
<td>Good outcome in a setting of high resistance, but important to note that a PI or NNRTI was also part of the regimens</td>
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</table>
Lastly, though mention is made in the application of the low rate of resistance to TDF, and the role of the K65R mutation, these data have been more formally published than is indicated.6,7,8,9,10 The last of these shows an impressive <3% emergence of resistance to TDF over 144 weeks, when dosed together with 3TC and EFV in treatment-naïve patients (Study GS 903).

One additional, rare mutation (K65N) has been described, which confers resistance to TDF, 3TC and ddI.11

Tenofovir has twice been reviewed in “Drugs”, once by Gilead staff,12 and once by the publisher’s own staff.13

**Is there adequate evidence of efficacy for the proposed use?**

Yes ☑ No ☐

If "No", suggest what is needed.

Although the efficacy of TDF has been demonstrated in the pivotal studies cited, and also shown in the extension phases to those studies, there are some remaining concerns that must be considered by the Committee. The original application only references the Viread® package insert in relation to important drug-drug interactions that may affect regimen choices. Some additional references were made available in the October 2006 Supplement.

**a. Interactions with PIs**

In addition to the three studies mentioned above (Johnson MA, et al. J Acquir Immune Defic Syndr. 2006 and Johnson M, et al. AIDS. 2006, Piketty C, et al. Antivir Ther. 2006), which involved co-administration of TDF with ATV or LPV/r, three other studies have specifically addressed these interactions. In a 36-day multiple-dose study in 24 healthy volunteers, co-administration of TDF and LPV/r resulted in a 32% increase in the AUC (over the dosing interval) of TDF, a 15% increase in the maximum concentration and a 51% increase in the concentration at the end of the dosing interval.14 The authors concluded, however, that these increases were not clinically relevant and noted no alteration in adverse effects (including renal effects). The application advises caution with this combination, but provides no supporting data. As part of a clinical trial, 11 HIV-infected patients receiving ATV/RTV 300mg/100mg were given TDF as part of a HAART regimen.15 Co-administration with TDF resulted in significant (25%) decreases in the AUC_{0-24} of ATV, despite ritonavir boosting. The application suggests that ritonavir boosting will be sufficient to overcome the effect of TDF, and that administration of unboosted ATV should not be attempted, but provides no additional supporting data.
b. Interactions with NNRTIs

Importantly, as many settings may wish to use TDF as part of an NNRTI-based HAART regimen, data from routine therapeutic drug monitoring samples in HIV-infected patients have shown no effect on TDF on nevirapine (NVP) or efavirenz (EFV).16

c. Interactions with other nucleoside reverse transcriptase inhibitors (NRTIs)

While the application does advise a dose adjustment for didanosine (ddl) when co-administered with TDF, this issue deserves more complete exploration. A list of additional references was supplied in the Supplement, but without any indication of how this evidence should be considered. At first glance, TDF + ddl would seem to be an attractive, QD NtRTI/NRTI back-bone regimen. A number of studies have shown less than optimal results when TDF and ddl are co-administered, such as paradoxical CD4 declines or sub-optimal increases17,18,19,20,21,22 pancreatitis23,24,25 and hyperglycaemia,26 in addition to the expected lactic acidosis.27 This combination would seem to be associated with a higher risk of mitochondrial damage.28 Dose adjustment in low weight patients may not be sufficient to avoid significant toxicity.29 Early virological failure has been associated with the use of the combination, but some data do point to better tolerance of the lower dose regimen.30,31,32,33,34,35,36,37 While a review in 2005 by Gilead staff supported the dose reduction on the basis of the presumed drug-drug-food interaction,38 in line with previous suggestions,39 there is evidence that the interaction is not purely pharmacokinetic, so a simple dosing adjustment may not be sufficient.40 The authors of a small retrospective analysis has argued for continued use of this combination.41

Although not specifically covered in the application, the “triple nuke” regimen of TDF + ABC + 3TC deserves close attention. In 2003, a letter to Lancet reported virological failure in 5/8 patients switched to this regimen after having achieved complete virological suppression ion another regimen.42 A pilot study in ARV-naïve patients showed early virological failure.43 Although patients from this small study showed K65R and/or M184V mutations, these did not appear to prevent subsequent successful treatment with other regimens.44 A randomised, open-label, multicentre study (ESS30009) comparing TDF + ABC/3TC and EFV + ABC/3TC underwent an unplanned interim analysis, which also showed poor efficacy of the apparently attractive, QD “triple nuke” option.45 Virological non-response occurred in 50/102 (49%) of the patients in the TDF arm, compared to 5/92 (5%) in the EFV arm, at 12 weeks. Within 12 weeks, 40/41 (98%) non-responders in the TDF arm showed M184V or I/M/V mixtures and 22/41 (54%) showed both K65R and M184V or mixtures. A statement by Dan Kuritzkes in an editorial accompanying this paper is worth repeating: “The results of Gallant et al.’s study highlight the need for formal clinical trials to evaluate novel antiretroviral regimens before they are adopted into routine clinical practice, even when all components of the regimen are approved drugs.”46 Similarly disappointing results were shown in the TONUS (IMEA 021) study.47 Here, 12/36 (33%) of ARV-naïve patients given TDF + 3TC + ABC had virological failure at 24 weeks, and 76% developed K65R or M184V/I mutations by that time point. Finally, a small randomized, open-label, pilot study of a quadruple “nuke” regimen of ABC + 3TC + ZDV + TDF (n= 56) versus a standard ZDV + 3TC + EFV regimen (n=57) in treatment-naïve patients showed similar outcomes at 48 weeks (68 vs 67% achieving HIV RNA < 50 copies/ml), with no unexpected adverse effects.48
d. **Interactions with rifampicin**

Given the need to treat patients co-infected with both HIV and TB, it is important to note that there is some evidence (from a multiple dose study in 24 health volunteers) that no dose adjustments are needed when TDF is co-administered with rifampicin. In this regard, the application does not that TDF is free from interactions related to hepatic CYP 450.

(3) **Is there evidence of efficacy in diverse settings and/or populations?**

Yes ✔ No ☐

If "No", suggest what is needed.

Although TDF has been shown to be effective in both ARV-naïve and ARV-experienced patients, for both initial and intensified treatment, an area that is not given sufficient attention in the application is that of hepatitis B co-infection. Mention is made only of the warning in the Viread® package insert that patients be tested for HBV before commencing ART. It is thus important to establish whether or not TDF can be used safely in HIV/HBV co-infected patients.

In ACTG A5127, TDF was shown to be noninferior to adefovir as an add-on to stable ART in co-infected patients. In a single case, TDF was also shown to be effective as a replacement for adefovir after resistance to that drug developed in a patient who also exhibited 3TC resistance. A French case series of 6 HIV patients showed that 96 weeks of TDF + 3TC + either an NNRTI or PI resulted in complete and sustained antiviral action against HBV. The same effect was seen in a cohort of 31 German patients co-infected with HIV and HBV, who received TDF for 48 weeks. Substudies from the Gilead 903 and 907 studies have also shown that TDF has potent anti-HBV efficacy. A recent review has confirmed the risks of monotherapy with one anti-HBV antiviral (such as 3TC or FTC), and has recommended that a combination of TDF with either of the other two ARVs showing anti-HBV activity be considered when HAART is indicated in an HBV/HIV co-infected patient. The development of novel resistance mutations in co-infected patients cannot, however, be ruled out.

The original application states that safety and effectiveness in patients less than 18 years has not been established. There is, nonetheless, some data to support paediatric use, at least as salvage therapy, but conflicting evidence about effects on bone mineral density, and at least one reported case of nephrotoxicity. The Supplement provides 11 additional references, some of which are mentioned above. There is no indication, however, of whether paediatric registration is being pursued or not.

An important decision facing many ART programmes in resource-constrained settings is whether to replace d4T as a first-line NRTI choice with an alternative. The two most common alternatives would seem to be ZDV or TDF. It is therefore important that evidence of TDF’s usefulness in ameliorating problems associated with d4T use be carefully considered. The application does make mention of a conference presentation of results from the RAVE study. The results of this phase IV open label study, completed at 10 United Kingdom sites, have now been published. While noting that peripheral lipoatrophy linked to prior thymidine nucleoside analogue use resolves slowly, the authors were able to show that limb fat was increased by 48 weeks in patients received either TDF (mean 329g, n=52) or ABC (mean 483g, n=53). While less impressive, some
improvement in lipid profiles was also noted with TDF but not with ABC. Recently, data from the GS 934 study have been published, showing that median limb fat (based on whole-body DEXA scans) at week 96 was significantly greater in the TDF + FTC + EFV arm (7.7 kg, IQR 5.3-11.3, n=144) than in those receiving ZDV/3TC + EFV (5.5kg, IQR 3.9-7.6, n=136). In this study, participants in the TDF arm had a lower increase in total fasting cholesterol, but similar fasting low-density lipoprotein cholesterol. While the change in triglyceride levels was not significantly different, those in the ZDV arm had a higher increase in high-density lipoprotein cholesterol. There is other evidence for a positive effect of TDF on lipid parameters. The “Recover” study was a prospective, multicentre study performed at 120 Spanish sites. TDF was substituted for d4T in 873 adult patients (based on adverse events), of which 352 were randomly recruited to the lipid sub-study. At 48 weeks, a significant reduction in median total cholesterol (-17.5 mg/dl, p<0.001), low-density lipoprotein cholesterol (-8.1 mg/dl, p<0.001) and triglycerides (-35 mg/dl, p<0.001) was noted. There was no change in high-density lipoprotein cholesterol. Two retrospective chart analyses have also shown positive effects from a switch to TDF. Of relevance both to this section and the previous point about use in paediatric settings, a 48-week prospective evaluation showed that changing a PI to EFV and d4T to TDF in children with stable viral loads had a positive effect on lipid profiles, without any deleterious impact on virological or immunological parameters.

(4) Are there adverse effects of concern?

Yes ☑
No ☐

If "Yes", (list / describe)

Although reference is made to 3 independent reviews of the effect of TDF on renal status, no analysis of those data is presented. In one case, the DART study, only a photograph of the poster is provided. The published paper on this trial contains no data on renal safety. The Supplement cites two published studies. Retrospective data from 4183 HIV patients treated at the Chelsea and Westminster services was used for both a cohort and case-control study. Looking at all ARV-naïve patients who had presented with elevated serum creatinine (defined here as greater than 120µmol/l or 1.36 mg/dl, which is far lower than the 2.0 mg/dl cutoff used in the pivotal studies cited) while on treatment, exposure to TDF was not associated with any additional risk compared to other ARV regimens. When the 84 cases of elevated creatinine while on TDF treatment were matched with 84 controls who had received TDF but not experienced an elevated creatinine, no differences in renal parameters was detected. In 75/84 cases, other causes of renal impairment could be identified. In the Johns Hopkins cohort study, use of TDF was associated with a greater decline in renal function than was any alternative NRTI. The median change in creatinine clearance was -13.3 (IQR -24.0, 0.00) on TDF (n=344) and -7.5 (IQR -20.5, +6.5) on other NRTIs (n=314). Importantly, few patients showed anything more than a modest decline is renal function, and there were no differences in discontinuation rates.

The literature does, however, reveal other views and evidence. A case report of an incident of acute renal failure and Fanconi syndrome also reviewed 19 other reported incidents. Of these, 14 had received concomitant LPV/r. Based on cross-sectional data, a number of authors have called for caution when using TDF, but noted that serious events were rare. Similar sentiments have been expressed after a prospective observational study, a retrospective cohort study, and a retrospective case-control...
Data extracted from the GS 902 and 903 studies have also been reported in the literature, emphasising the possible risks of pre-existing renal impairment and concomitant use of RTV. Data from the “Recover” study have also been published, showing that renal toxicity sufficient to cause discontinuation of TDF was rare (0.39 per 100 patient years, based on a cohort of 1286 treatment-experienced patients followed for 48 weeks).78

The problem of how to monitor for TDF-associated renal events remains. Laboratory parameters that have been used, such as urine-beta 2 microglobulin, percentage of tubular reabsorption of phosphate and alkaline phosphatase, may not be practical in all settings or sensitive.81 A case series of 40 cases of hypokalaemia associated with TDF use has also been published recently.82 Of these, 84% were receiving RTV at either boosting or full doses and 38% were receiving ddi. Only 3 were receiving another known nephrotoxic drug. The role of multiple drug interactions was also emphasised in a case series of 5, combined with 22 more cases from the literature.83 Of the 27 cases, 21 received concomitant RTV (with or without LPV), 5 received ATV and 9 received ddi. However, in response, two letters to the journal disputed the role of interactions, arguing that patients without pre-existing renal impairment could safely use TDF.85 In response, the original authors supported the view that monitoring of renal function at routine clinic visits would suffice. A review of HIV-associated renal disease has concluded that “renal tubular dysfunction seems to be an uncommon but important adverse effect of therapy with tenofovir”, but also emphasised the possible link with concomitant use of RTV.87

The other adverse effect mentioned in the 2005 assessment was reduced bone mineral density. The Supplement points to data from the GS 902 and 903 studies. In the former, only 62 patients provided data and no differences were seen over 48 weeks. In the latter, significant differences were seen in the TDF arm compared to the d4T arm. Losses occurred in the first 48 weeks, and stabilised thereafter. Those fractures that were seen (5 in the TDF arm, 11 in the d4T arm), were mostly related to trauma. The conference presentations supplied do not add significantly to these data. A recent review has expressed the opinion that “Available data suggest that while BMD may initially decline modestly after the start of antiretroviral therapy, there is then a gradual recovery in BMD over time. This may reflect the observation that BMD declines as HIV disease progresses and that this decline may be arrested and partially corrected with successful antiretroviral therapy”.88

**Are there special requirements or training needed for safe/effective use?**

Yes ☑️ No ☐

If "Yes", describe.

Although serum creatinine measurements should be available, health workers will need to be able to estimate and interpret creatinine clearance values in order to calculate doses of TDF, as recommended by the manufacturer. Any formulary entry should also include advice on how to calculate ideal or lean body weight, before using a suitable method for creatinine clearance estimation (such as the Cockcroft and Gault equation). An alternative method of dosage adjustment, based on the body weight/serum creatinine ratio, has been explored but is not yet standard practice.89
(6) Is this product needed to meet the majority health needs of the population?

   Yes ☑   No ☐

   If "No", is there a special reason why this should be on the Model List?

(7) Is the proposed dosage form registered by a stringent regulatory authority?

   Yes ☑   No ☐

   If "No", give details.

The delay in obtaining registration in many developing countries is, nonetheless, a cause for concern. It also remains to be seen whether the Aspen-manufactured version will be marketed at a price different from that currently charged by the Gilead Access Program.

(8) What action do you propose for the Committee to take?

That tenofovir disoproxil fumarate (TDF) be added to the core list.

(9) Additional comment, if any.

The formulary entry proposed by the applicant will need to be reviewed in order to more clearly identify TDF-containing regimens for which there is sufficient evidence, and also to identify regimens which are associated with increased risk of virological failure and/or adverse events. Appropriate cautions about concomitant use of ddI, LPV/r, RTV and ATV should be developed, and the triple “nuke” regimen with ABC should be discouraged at this time. Clarity needs to be sought on the appropriate advice to give in relation to paediatric use.
References


73 Scott JD, Wolfe PR, Bolan RK, Guyer B. Serious renal impairment occurs rarely with use of tenofovir DF. HIV Clin Trials. 2006 Mar-Apr;7(2);55-8.


