Application for Inclusion of Tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) Tablets on the WHO Model List of Essential Medicines (EML)

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General Information

1. Summary statement of the proposal for inclusion, change or deletion.

This document proposes the inclusion of tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) 300mg/300mg/50mg as a fixed dose combination product for treatment of HIV-1 infection among adults and adolescents living with HIV/AIDS in the WHO Model List of Essential Medicines (EML). We further propose TLD be added to the core list of the EML.

The principal reasons for requesting this inclusion are as follows:

• Dolutegravir (DTG), as a representative of the integrase inhibitor class of antiretroviral drugs (ARVs), has demonstrated superior effectiveness in multiple patient populations, a favorable safety profile, a high barrier to emergence of resistance, and an acceptable level of drug-drug interactions, making it an excellent candidate for use in a public health approach to HIV treatment.

• The dual nucleoside/nucleotide backbone of tenofovir DF plus lamivudine has been widely used globally in combination with efavirenz as first line treatment.

• According to the July 2018 WHO HIV Treatment Interim Guidance (Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV), a DTG-based regimen may be recommended as a preferred first-line regimen for adults and adolescents living with HIV initiating ART.1

• TLD achieves the WHO ideal of a complete ARV first line regimen in a once daily, single tablet at a cost comparable to current standard of care.

2. Relevant WHO technical department and focal point (if applicable).

Marco Vitoria, WHO/HTM/HIV/ATC

3. Name of organization(s) consulted and/or supporting the application.

Clinton Health Access Initiative, Inc.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Dolutegravir, lamivudine, tenofovir disoproxil fumarate

ATC: Dolutegravir J05AX12, lamivudine and tenofovir disoproxil J05AR12. There is not an ATC specific to TLD at this time.

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

Each tablet contains tenofovir DF/lamivudine/dolutegravir 300mg/300mg/50mg as a fixed dose combination providing a complete HIV treatment regimen.
TLD tablets are available internationally from the following manufacturers:

FDA tentatively-approved manufacturers:

- **Aurobindo Pharma**
  - Water Mark Building, Plot No. 11, Survey no.9, Kondapur, Hitech City, Hyderabad – 500 084 Telangana, India

- **Mylan Laboratories Limited**
  - Robert J. Coury Global Center
  - 1000 Mylan Blvd.
  - Canonsburg, PA 15317

- **Hetero Labs Limited**
  - 7-2-A2, Hetero Corporate
  - Industrial Estates, Sanath Nagar
  - Hyderabad – 500 018. Telangana, INDIA

Global Fund ERP approved manufacturers:

- **Cipla**
  - Cipla House,
  - Peninsula Business Park,
  - Ganpatrao Kadam Marg,
  - Lower Parel, Mumbai-400013

- **Macleods Pharmaceuticals Limited**
  - Atlanta Arcade,
  - Marol Church Road,
  - Andheri (East),
  - Mumbai - 400059, INDIA.

- **Sun Pharmaceutical Industries**
  - SUN HOUSE,
  - CTS No. 201 B/1,
  - Western Express Highway,
  - Goregaon (E),
  - Mumbai 400063
6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We request inclusion of TLD as a fixed dose combination (FDC) ARV product. This FDC represents two pharmacologic classes of ARVs and provides a complete HIV treatment regimen as a single tablet. There are other single tablet FDCs for the treatment of HIV, including combinations of tenofovir DF/emtricitabine/dolutegravir and abacavir/lamivudine/dolutegravir, but none of these are true therapeutic equivalents. Many HIV experts consider lamivudine and emtricitabine clinically equivalent.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

The recommended dose of TLD in integrase inhibitor treatment naïve adults and adolescents weighing greater than 30kg is one tablet (TLD 300mg/300mg/50mg) once daily. HIV infection in adults can be diagnosed with relatively simple, rapid testing kits or in clinic or hospital laboratories. The WHO recommends treatment in all patients diagnosed with HIV infection regardless of clinical stage or laboratory parameters. While receiving TLD, patients should be monitored for treatment failure according to national guidelines. However, specialized testing is not required for patient diagnosis and management. HIV requires life-long treatment.

The 2016 WHO Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommended TDF plus 3TC as a preferred nucleoside/tide backbone in first-line therapy and DTG 50 mg in combination with TDF and 3TC as an alternative first-line regimen. In addition, these guidelines reiterate WHO’s conclusion that FDCs and once-daily regimens are most preferred. At that time, TLD was not available as an FDC. In the most recent WHO treatment guidelines update (July 2018), a DTG-based regimen is recommended as a preferred first-line regimen for adults and adolescents living with HIV who are initiating antiretroviral therapy.

8. Information supporting the public health relevance.

In 2017, UNAIDS reported there were 36.9 million people living with HIV/AIDS globally, 1.8 million new HIV-1 infections, and 940,000 thousand HIV-related deaths. Over 95% of infected people live in low and middle income countries (LMIC) with inadequate resources to effectively combat the epidemic. While some countries have achieved declines in new HIV infections among adults of 50% or more, global data show that many others have not made measurable progress and others have experienced worrying increases in new HIV infections. Overall, approximately 21.7 million people were receiving antiretroviral therapy (ART) in 2017, but this is estimated to represent only 59% of HIV infected people.

Early and effective ART not only significantly improves the health of those living with HIV, but also reduces transmission of the disease as shown in the recently reported START study. For this reason, the WHO
released guidelines in 2015 calling for treatment for all people with HIV. Easy to administer, highly effective, safe treatment options remain desperately needed in many areas of the world to meet the UNAIDS 90-90-90 targets, which call for 90 percent of people living with HIV to know their status, 90 percent of those with known infection to be on ART, and 90 percent of those on ART to be virally suppressed (i.e., on successful therapy) by the year 2020.\(^5\)

Currently, FDCs containing TDF, 3TC or emtricitabine (FTC), and efavirenz (EFV) are the most widely used first-line treatment for adults and adolescents living with HIV in LMIC with greater than 70% of patients using this product. This FDC was recommended as a preferred regimen by the WHO in 2010 and has been successfully used in millions of patients in all types of patient care settings. However, EFV has both short- and long-term adverse events (AEs) in a significant number of HIV-infected patients. These AEs may lead to treatment interruptions that result in viral breakthrough, development of NNRTI resistance, progression of disease, and transmission of HIV.

Recent surveys of HIV resistance in patients initiating ARVs suggest that the prevalence of pre-treatment drug resistance to EFV and nevirapine (both non-nucleoside reverse transcriptase inhibitors, NNRTIs) has significantly increased since 2001, as ART coverage has expanded in LMIC. In WHO’s national survey of pre-treatment resistance conducted in 2014–2016, NNRTI resistance among adults initiating first-line therapy with no prior ARV exposure was 8.3% but it was significantly higher among individuals initiating first-line therapy after some prior ARV drug exposure (21.6%). Six of 11 countries in the WHO survey reported >10% prevalence of pre-treatment resistance to NNRTIs but prevalence of NNRTI resistance among patients receiving treatment may be significantly higher (47-89% of those without viral suppression).\(^6\) These increasing rates of resistance to the previously recommended first-line ARV have prompted WHO to recommend more rapid transition to DTG-based treatment.

DTG represents a best-in-class HIV integrase strand transfer inhibitor (INSTI). DTG is dosed at 50 mg once daily in combination with a standard nucleoside backbone, such as TDF and 3TC or FTC in treatment-naïve adult patients. Numerous clinical trials conducted around the world demonstrate that DTG is superior to EFV, raltegravir, and darunavir/ritonavir.\(^7,8,9\) These trials were gender balanced and included a broad range of ethnicities to account for most pharmacogenetic interactions. DTG was also shown to be safe and well tolerated, so much so that it can be easily administered in settings where laboratory monitoring is performed infrequently because of access or cost. DTG-containing regimens rapidly suppress viral load thereby reducing the risk of HIV transmission.

Until recently, DTG was not available as a fixed dose combination. Thus, prior usage of DTG-based regimens was limited to a relatively small number of early adopting countries. In addition, some countries previously reserved DTG-based treatment for those patients needing third-line treatment. The availability of TLD has greatly expanded the number of patients who will be able to receive a first line DTG-based regimen.


- **Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

• Summary of available data (appraisal of quality, outcome measures, summary of results)

DTG has been shown to be effective in diverse patient populations enrolled in multiple clinical trials conducted internationally. As TLD will be recommended for first-line treatment, only results of studies in patients first initiating ARVs will be described below.

DTG efficacy has been demonstrated in ART-naïve subjects in three randomized, controlled, multinational, phase III studies. The SPRING-2 study demonstrated that DTG is non-inferior to raltegravir (RAL) over a 96-week period regardless of baseline viral load and irrespective of the NRTI backbone.8 The SINGLE study showed that when DTG was dosed with abacavir (ABC)/3TC, it was statistically superior to TDF/FTC/EFV over a 144-week period.7 Importantly, patients on the DTG regimen achieved virologic suppression faster and no DTG resistance developed over the time period studied. Table 1 (displayed below) showing results from both studies was reproduced from the Tivicay® (DTG, ViiV Healthcare) U.S. package insert.10 The FLAMINGO study demonstrated that DTG dosed with two NRTIs was statistically superior to darunavir/ritonavir dosed with two NRTIs over 96 weeks. Although the virological non-response was slightly better with DTG, much of the overall difference in success was due to differences in the number of patients with missing data at 96 weeks, i.e. more patients discontinued DRV/r treatment (see Table 2, reproduced from the publication).9
Table 1: Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)\(^9\)

<table>
<thead>
<tr>
<th>VIROLOGIC OUTCOMES</th>
<th>SPRING-2 Week 96</th>
<th>SINGLE Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL</td>
<td>82%</td>
<td>78%</td>
</tr>
<tr>
<td>Treatment difference(^a)</td>
<td>4.9% (95% CI: 0.6%, 10.3%)(^f)</td>
<td>8.3% (95% CI: 2.0%, 14.6%)(^f)</td>
</tr>
<tr>
<td>VIROLOGIC NONRESPONSE</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Data in window not &lt;50 copies/mL</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Discontinued for other reasons while not suppressed</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Change in ART regimen</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>NO VIROLOGIC DATA</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Reasons</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Discontinued study/study drug due to adverse event or death(^b)</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Discontinued study/study drug for other reasons(^c)</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category

<table>
<thead>
<tr>
<th>PLASMA VIRAL LOAD (copies/mL)</th>
<th>SPRING-2 Week 96</th>
<th>SINGLE Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>79%</td>
<td>63%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GENDER</th>
<th>SPRING-2 Week 96</th>
<th>SINGLE Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>84%</td>
<td>79%</td>
</tr>
<tr>
<td>Female</td>
<td>70%</td>
<td>68%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RACE</th>
<th>SPRING-2 Week 96</th>
<th>SINGLE Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>African-American/African Heritage/Other</td>
<td>77%</td>
<td>75%</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for pre-specified stratification factors.
Table 2: FLAMINGO Study: Snapshot outcomes for plasma HIV-1 RNA concentration (<50 copies/mL)$^8$

<table>
<thead>
<tr>
<th></th>
<th>Doktegravir 50 mg once daily (n=242)</th>
<th>Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 48*</td>
<td>Week 96</td>
</tr>
<tr>
<td>Viriological success</td>
<td>212 (90%)</td>
<td>194 (80%)</td>
</tr>
<tr>
<td>Difference in proportion (95% CI; success)</td>
<td>7.0 (0.9-13.1)</td>
<td>12.4 (4.7-20.4)</td>
</tr>
<tr>
<td>Adjusted difference in proportion (95% CI; success)</td>
<td>7.1 (0.9-13.2)</td>
<td>12.4 (4.7-20.2)</td>
</tr>
<tr>
<td>Viriological non-response</td>
<td>15 (5%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Data in window &lt;50 copies/mL</td>
<td>6 (2%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Discontinued because of lack of efficacy</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50 copies/mL</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Change in antiretroviral therapy</td>
<td>5 (2%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>No virological data</td>
<td>10 (4%)</td>
<td>29 (12%)</td>
</tr>
<tr>
<td>Discontinued because of adverse event or death</td>
<td>3 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Discontinued for other reason</td>
<td>6 (2%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>1 (&lt;1%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Data are number (%); unless otherwise indicated. $^*$Week 48 data have been previously reported. $^5$ (Cochran-Mantel-Haenszel analysis stratified by baseline plasma HIV-1 RNA (≥100,000 copies per mL vs <100,000 copies per mL) and baseline background nucleoside reverse transcriptase inhibitor treatment (combined abacavir and lamivudine vs combined tenofovir and emtricitabine). $^7$Test for superiority p=0.002. $^8$Including protocol deviation, loss to follow-up, and withdrawal of consent.

More recently, clinicians and researchers have begun evaluating DTG-based regimens, particularly TLD, in resource-limited settings where the more effective treatment regimens could have significant public health impact. Safety, tolerability, and efficacy was evaluated in a prospectively-enrolled, open-label cohort of 564 Indian adults receiving DTG in combination with other ARVs (primarily TDF and 3TC) or FTC as either first or second line therapy. Among the treatment-naive patients initiating DTG plus TDF/3TC or TDF/FTC, all had viral suppression at the 6 month follow-up, and overall, viral suppression occurred in 82.9% at 6 months.$^{11}$ In addition, the NAMSAL ANRS study randomized HIV-infected adults in Cameroon to receive either TLD (n=310) or TLE-400 (n=303) for first-line treatment. Preliminary efficacy results at 48 weeks on treatment indicate the proportion of patients with HIV RNA <50 copies/mL was 74.5% in the TLD arm and 69% in the TLE-400 arm. Fewer patients with initial HIV RNA levels >100,000 copies/mL had virologic suppression to <50 copies/mL: 66.2% in the TLD arm and 61.5% in the TLE-400 arm. In this study, viral suppression with TLD was numerically higher but not statistically superior to TLE-400; NNRTI resistance was an important determinant of TLE-400 failure.$^{12}$

- **Summary of available estimates of comparative effectiveness**

In the clinical studies to date, DTG-based regimens were either non-inferior or superior in efficacy to comparator regimens containing other integrase inhibitors, boosted protease inhibitors, and NNRTIs regardless of patient population. In patients initiating first line treatment, successful virologic suppression occurred in more patients receiving DTG than the comparators. A systematic review and meta-analysis conducted by the WHO in 2016 concluded that among treatment-naive patients,
treatment with an integrase inhibitor (particularly DTG) plus two NRTIs, had superior efficacy and tolerance to the current standard of care regimens of efavirenz plus two NRTIs.13


- **Estimate of total patient exposure to date**

  Since its approval in 2013, DTG has become a widely used anchor for ARV regimens around the world. The WHO estimates that as of 2017, around 300,000 persons living with HIV are receiving a DTG-based regimen in high income countries. Lower income countries such as Botswana, Brazil, and Kenya that were early to adopt DTG-based treatment were estimated to have 80,000, 60,000, and 13,000 patients, respectively, receiving the drug.14 The NRTI backbone of TDF plus 3TC has been part of the preferred first-line treatment regimen recommended by WHO since 2015 and the dual combination has been used by millions of patients. Wider implementation is expected as the single tablet TLD becomes more available globally. As of September 2018, the annual CHAI HIV Market Report indicates that over two dozen high-burden LMICs have already included or are planning to include DTG-based regimens in their national HIV treatment guidelines and at least 15 LMICs have already received first shipments of TLD. CHAI market analysis predicts that over the next 5 years, DTG-based regimens (primarily as TLD) will account for > 60% of the first line ARV market.15

- **Description of the adverse effects/reactions and estimates of their frequency**

  The overall safety profile of DTG in adults compared favorably to other ARVs included in the clinical trials reported above. In treatment-naïve adults, patients receiving DTG had an acceptable, low rate of treatment discontinuation due to adverse reactions (2%), compared to those receiving either RAL (2%) or efavirenz (10%). The most common adverse drug reactions noted in the Tivicay® (ViiV Healthcare) product label of at least moderate intensity were insomnia, headache, and fatigue (see Table 3). More adverse reactions were mild and had little impact on treatment outcomes. In the original clinical trials, patients on DTG experienced significantly fewer incidences of nervous system disorders and psychiatric disorders than those receiving EFV.
Table 3: Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)\textsuperscript{10}

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>SPRING-2</th>
<th>SINGLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)</td>
<td>Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Depression</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Headache</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Rash\textsuperscript{a}</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>General Disorders</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ear and Labyrinth</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

As noted above, while the FLAMINGO study demonstrated a slightly lower rate of virological non-response among patients receiving DTG, there was a substantially larger proportion of patients receiving DRV/r who discontinued treatment due to adverse events, loss to follow-up, and withdrawal of consent. In this study, more patients receiving DRV/r had diarrhea (31% vs 18% with DTG) and nausea (20% vs 17%) while more patients receiving DTG had headache (17% vs 11 with DRV/r).\textsuperscript{9}

There have been multiple reports of neuropsychiatric events among patients receiving DTG-based treatment since its approval. Although DTG appears to result in fewer of these events compared to EFV in comparative clinical trials (such as the SINGLE study described above), some patients receiving DTG experience episodes of insomnia or depression. Causality for these events has been difficult to determine as many patients are reported to have a previous history of psychiatric symptoms.

In the South Indian cohort of first-line and second-line patients, DTG regimens were well tolerated. Mean ALT and AST decreased slightly in the cohort during the 6-month evaluation period, mean hemoglobin increased slightly, and kidney function remained stable. In this cohort, sleep disturbances and neuropsychiatric symptoms were not reported. The frequency of opportunistic infections decreased from 7.4% prior to starting DTG to 3.3% after 6 months follow up. None of the patients
in this cohort discontinued DTG during the evaluation period but 4 of the 564 patients died (2 sepsis and 2 CMV encephalitis considered unrelated to ARVs).11

In spite of significant worldwide usage, global public health officials noted a relative lack of data in pregnant and lactating women. A nationwide birth outcomes surveillance program conducted in Botswana began collecting data in women initiating dolutegravir in 2014. An initial report of pregnant women who began taking either a DTG- (n=1729) or EFV-based (n=4593) treatment regimen identified no difference in risk for adverse birth outcomes, even among those beginning treatment during the first trimester (i.e., post-conception ART).19 However, an interim analysis of a second surveillance study of women becoming pregnant while already receiving ART (i.e., pre-conception ART) identified an excess number of neural tube defects among infants of women receiving a dolutegravir-based regimen. Neural tube defects were observed in 4 of 426 (0.94%) infants born to women receiving dolutegravir compared to 14 of 11,300 (0.12%) infants born to women receiving any other ART regimen and 61 of 66,057 (0.09%) infants born to HIV-uninfected women. Although none of the affected women were receiving folate supplements, no other risk factors for neural tube defects have been identified.17 This study is ongoing and expects to have a final analysis in 2019. While awaiting the final study results and data from other sources, the WHO recommends counseling for women of child bearing potential and access to effective contraception in those receiving DTG. However, they also suggest that an EFV-based regimen remains a safe and effective regimen in women who plan to become pregnant.1

The NRTI backbone of TDF/3TC has an extensive history of use in ART globally and has accumulated a favorable safety and tolerability profile. Initial concerns regarding potentially serious renal and bone toxicity due to the TDF component have not been borne out over years of clinical experience although it requires dose adjustment in patients with significant renal impairment and so is not generally used in this subgroup.

- **Summary of available data (appraisal of quality, summary of results)**

Overall, the quality and quantity of data supporting the safety of DTG-based regimens is good and includes both randomized clinical trials and observational cohorts in a variety of settings. DTG-based regimens generally, and TLD specifically, have been well tolerated. Additional data and longer-term follow-up are expected to better characterize the neuropsychiatric safety profile and the risk of neural tube defects.

- **Summary of comparative safety against comparators**

As noted, the systematic review and meta-analysis conducted by the WHO concluded that among treatment-naïve patients, treatment with an integrase inhibitor (particularly DTG) plus two NRTIs, had superior efficacy and tolerance to the current standard of care regimens of efavirenz plus two NRTIs and fewer discontinuations.13

In addition, the potential risks and benefits of wide implementation of TLD were evaluated in a 2018 modeling exercise conducted by a group of independent researchers. The group used existing data to estimate HIV transmission and disease progression (taking into account drug resistance, drug potency, differential viral suppression and clinical outcomes) to compare outcomes of different ART regimens in different scenarios. In their model, the greatest number of disability-adjusted life-years was averted in the scenario providing TLD to all adult patients without restrictions over 20 years,
compared to adults based on intent to have children and/or dependent on documentation of viral suppression.  

- **Identification of variation in safety that may relate to health systems and patient factors**

No specific safety issues associated with TLD are expected to pose a differential risk in the international health setting. However, the last remaining question on TLD use is in the population of patients who require concurrent treatment for tuberculosis. This patient population was not included in the registrational trials of DTG. Clinical pharmacology/drug interaction studies suggest that a higher/twice daily dose of DTG may be appropriate in this group. Clinical trials are currently underway in HIV/TB coinfected patients to assess both efficacy and safety in the setting of TB treatment. One such study, the INSPIRING Study enrolled patients receiving rifampicin-based TB treatment to receive either twice daily DTG- (n=69) or EFV(600mg)-based (n=44) ART. The proportion of patients with HIV RNA < 50 copies/mL was 75% among those receiving DTG compared to 82% among those receiving EFV with results driven by non-treatment-related discontinuations (16% vs 7%).

Data from additional clinical trials are expected within the next year and will further clarify optimal ART in this population.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

As illustrated in Table 4, various sources indicate an average price per patient per year (PPPY) for TDF/3TC/DTG (300/300/50 mg) tablets of US$74.00. However, the Global Fund PPM reference price is a *ceiling price*, and LMICs may be able to receive products at lower prices than shown.

**Table 4: Price per Unit and Price per Patient per Year for TDF/3TC/DTG and other First-Line Products**

<table>
<thead>
<tr>
<th>Reference Price Source</th>
<th>TDF/3TC/DTG (300/300/50 mg)</th>
<th>TDF/3TC/EFV (300/300/600 mg)</th>
<th>TDF/3TC/EFV (300/300/400 mg)</th>
<th>AZT/3TC/NVP (300/150/200 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Price/Unit</td>
<td>PPPY*</td>
<td>Price/Unit</td>
<td>PPPY*</td>
</tr>
<tr>
<td>Global Fund PPM, July 2018</td>
<td>$.200</td>
<td>$72</td>
<td>$.200</td>
<td>$72</td>
</tr>
<tr>
<td>GHSC-PSM, August 2018</td>
<td>$.208</td>
<td>$75</td>
<td>$.206</td>
<td>$74.16</td>
</tr>
<tr>
<td>MSF, July 2018</td>
<td>$.207</td>
<td>$75</td>
<td>$.200</td>
<td>$73</td>
</tr>
<tr>
<td>Average</td>
<td>$0.205</td>
<td>$74</td>
<td>$0.202</td>
<td>$73.05</td>
</tr>
</tbody>
</table>

All prices in USD. Please note that the GHSC-PSM prices are not reference prices but represent the latest blended average pricing of actual procurement.

*Price per patient per year based on WHO dosing guidelines, 365 days a year*
In the WHO’s 2018 updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV, TLD is recommended for all adults and adolescents, with special recommendations for women of child-bearing potential who want to become pregnant or have no access to effective contraception. TLD is comparably priced as other common first-line regimens (as seen above), which are not preferred by the WHO.

**Special Pricing Arrangements**

A breakthrough pricing agreement was announced in July 2017 by the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, the UK Department for International Development, PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan.

Under the agreement, Aurobindo and Mylan agreed to offer TLD at ~$75 PPPY, which is the first time that a new, best-in-class treatment regimen has launched at a lower price than the existing standard of care. This lower price is accessible to public sector purchasers in over 92 LMICs worldwide.

**Country Level Cost Effectiveness Analyses**

As a result of the above pricing agreement, numerous analyses have been done to model the financial impact of DTG introduction both at the country and global levels:

- A modelling study found that, in sub-Saharan Africa, a switch to TLD from EFV-containing regimens is predicted to be effective and cost-effective
- A study modelling DTG use in women in South Africa showed that DTG would save more lives, prevent more cases of sexual transmission, and prevent more cases of infant infection than EFV-based regimens
- A study published in the *Journal of the International AIDS Society* that looked at the impact of dolutegravir in India found TLD to cost less than the standard of care in 2 years, and cost-neutral in 5 years
- The Republic of South Africa has estimated that it could save approximately US$900,000,000 over 6 years
- CHAI and other partners have conducted numerous unpublished costing analyses to examine the financial impact of dolutegravir introduction. Given the products relatively low price and strong clinical benefits, many country programs have adopted TLD as preferred for first-line
- Introduction of TLD will also indirectly lower costs as it is expected to reduce rates of first-line treatment failure and non-adherence. As such, country programs will have fewer patients on second-line (compared to the standard of care), which is significantly more expensive than first-line

**Regulatory information**

**12. Summary of regulatory status and market availability of the medicine.**

DTG 50 mg (Tivicay®, Viiv Healthcare), TDF (Viread®, Gilead Sciences), and 3TC (Epivir®, Viiv Healthcare) are approved singly and in multiple FDCs for treatment of HIV in adults and adolescents in both the U.S., the E.U., and many other jurisdictions. License agreements for all of the component ARVs
remaining under patent have been made available by the innovator companies through the Medicines Patent Pool.

Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets (TLD) was granted tentative approval in August 2017, for the treatment of HIV-1 infection alone as a complete regimen in adults and pediatric patients weighing 40 kg and greater. The applications from Aurobindo Pharma and Mylan Pharmas were reviewed under the PEPFAR review program and subsequently cross-listed on the WHO List of Prequalified Medicinal Products. Hetero Drugs Limited has also received FDA tentative approval for TLD but is not cross-listed as pre-qualified yet. Additionally, TLD produced by Cipla, Macleods, Sun Pharma, and Laurus Labs has been reviewed by the Global Fund Expert Review Panel and listed as quality assured.

Therefore, TLD is currently available for procurement from multiple suppliers and production capacity is expected to continue to scale up.


Tenofovir is included in the United States Pharmacopoeia.

Lamivudine is included in the International Pharmacopoeia (Eighth Edition)

Dolutegravir is included in the British Pharmacopoeia.


   http://apps.who.int/iris/bitstream/handle/10665/273632/WHO-CDS-HIV-18.18-eng.pdf?ua=1

   http://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1


   http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf?sequence=1


