WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

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WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

1. **Summary statement of the proposal for inclusion, change or deletion:**
   This document proposes the inclusion of the tablet formulation of Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz (TDF+3TC+EFV) 300mg/300mg/600mg for treatment of HIV-1 infection among adults living with HIV/AIDS in both the WHO Essential Medicines List and the WHO Essential Medicines List for Adults.

   The principal reasons for requesting this inclusion are as follows:
   - Modern anti-retroviral therapy (ART) mandates the use of three or more drugs and this can require a large number of tablets to be swallowed each day and used lifelong.
   - According to the WHO 2010 Treatment Guidelines TDF+3TC+EFV is one of the preferred first-line regimens for adults in resource-limited settings and is currently widely in use.
   - As a fixed-dose combination with once-daily dosing, this formulation versus single drug formulations, may:
     - Increase patient adherence to treatment;
     - Delay the development of resistance;
     - Lower the total cost, including production, storage, transport, dispensing and other health system costs;
     - Reduce the risk of medication errors by prescribers, dispensers or patients themselves; and
     - Simplify and increase security of supply systems

2. **Name of the focal point in WHO submitting or supporting the application:**
   Marco Vitoria, WHO/HTM/HIV/ATC

3. **Name of the organization(s) consulted and/or supporting the application:**
   Clinton Health Access Initiative, Inc.

4. **International Nonproprietary Name (INN, generic name) of the medicine:**
   Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz (TDF+3TC+EFV)

5. **Dosage form or strength proposed for inclusion:**
   Each film-coated tablet contains 300mg tenofovir disoproxil fumarate (equivalent to 245mg of tenofovir disoproxil or 136mg of tenofovir), 300mg lamivudine, and 600mg efavirenz (WHO supported).

6. **International availability - sources, if possible manufacturers:**
   Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz tablets are manufactured at:

   Matrix Laboratories Limited
   F-4, F-12, Malegaon M.I.D.C
   Sinnar, Nashik 422113
   Maharashtra
   India
7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group:**

Since EFV is a non-nucleoside reverse transcriptase inhibitor, and TDF and 3TC are nucleoside reverse transcriptase inhibitors, inclusion within ‘FIXED-DOSE COMBINATIONS’ (under section 6.4.2) is requested.

8. **Information supporting the public health relevance**

8.1. **Epidemiological information on disease burden:**

UNAIDS reported in 2010 that 97% of the world’s 33.3 million people living with HIV/AIDS (PLHIV) were in low- and middle-income countries. In 2010 there were 2.7 million new HIV-1 infections and 1.8 million AIDS-related deaths. The 2011 WHO Progress Report for HIV/AIDS indicated that at the end of 2010 there were approximately 6.65 million people in low and middle income countries on antiretroviral therapy (47% of those eligible for therapy) but only 456,000 children on ART, a near 13.5 fold difference when compared to adults on treatment.

Lamivudine/Tenofovir/Efavirenz is indicated for the first-line treatment of HIV-1 infected adults and adolescents over 12 years of age.

8.2. **Assessment of current use:**

According to the WHO TUAPR, in 2010 nearly 530,000 adults (~11%) on first-line HIV-1 therapy were treated with TDF+3TC+EFV across 45 low- and middle-income countries (excludes the Region of the Americas).

8.3. **Target population:**

HIV-1 infected adults and adolescents over 12 years of age who have CD4 counts ≤ 350 cells/mm3 and for those with WHO clinical stage 3 or 4 if CD4 testing is not available.

Tenofovir/Lamivudine/Efavirenz is not approved for adolescents under 12 years of age or weighing less than 40kg.

9. **Treatment details**

9.1. **Reference to existing WHO and other clinical guidelines:**

The 2010 WHO adult antiretroviral therapy guidelines make the following recommendations for first-line regimens:

<table>
<thead>
<tr>
<th>When to start</th>
<th>All adolescents and adults including pregnant women with HIV infection and CD4 counts of ≤350 cells/mm3, should start ART, regardless of the presence or absence of clinical symptoms. Those with severe or advanced clinical disease (WHO clinical stage 3 or 4) should start ART irrespective of their CD4 cell count.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What to use in first-line therapy</td>
<td>First-line therapy should consist of an NNRTI + two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF). Countries should take steps to progressively reduce the use of stavudine (d4T) in first-line regimens because of its well-recognized toxicities.</td>
</tr>
</tbody>
</table>
## WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

<table>
<thead>
<tr>
<th>What to use in second-line therapy</th>
<th>Second-line ART should consist of a ritonavir-boosted protease inhibitor (PI) plus two NRTIs, one of which should be AZT or TDF, based on what was used in first-line therapy. Ritonavir-boosted atazanavir (ATV/r) or lopinavir/ritonavir (LPV/r) are the preferred PIs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory monitoring</td>
<td>All patients should have access to CD4 cell–count testing to optimize pre-ART care and ART management. HIVRNA (viral-load) testing is recommended to confirm suspected treatment failure. Drug toxicity monitoring should be symptom-directed.</td>
</tr>
<tr>
<td>HIV/TB coinfection</td>
<td>Irrespective of CD4 cell counts, patients coinfected with HIV and TB should be started on ART as soon as possible after starting TB treatment. Irrespective of CD4 cell counts or WHO clinical stage, patients</td>
</tr>
<tr>
<td>HIV/HBV coinfection</td>
<td>Irrespective of CD4 cell counts or WHO clinical stage, patients who require treatment for HBV infection should start ART. First-line and second-line regimens for these individuals should contain TDF and either emtricitabine (FTC) or lamivudine (3TC).</td>
</tr>
</tbody>
</table>

### 9.2. Dosage regimen, duration:

The recommended dose of Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300mg/300mg/600mg tablets is one tablet, taken orally, once daily. It should be taken on an empty stomach (commonly defined as 1 hour before or 2 hours after a meal). Swallow Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300mg/300mg/600mg tablets whole with water.

### 9.3. Need for special diagnostic or treatment facilities and skills:

Not needed.

### 10. Summary of comparative effectiveness in a variety of clinical settings:

#### 10.1. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

In compiling evidence for this application it was recognized that 3TC and EFV have been included as a part of the WHO EML since 2002. In 2004 applications for TDF and a fixed dose combination of TDF/FTC was subsequently submitted by Gilead Sciences Inc which included complete summaries of studies relevant to demonstrating the safety and efficacy of this combination.

Please refer to the WHO [XX]th EML [XX] Application

- [http://archives.who.int/eml/expcom/expcom14/tenofovir/tenofovir_Gilead_application_27oct04.pdf](http://archives.who.int/eml/expcom/expcom14/tenofovir/tenofovir_Gilead_application_27oct04.pdf)
- [http://archives.who.int/eml/expcom/expcom14/lamivudine_tenofovir/lamivudine_tenofovirFDC_Gilead_application_28oct04.pdf](http://archives.who.int/eml/expcom/expcom14/lamivudine_tenofovir/lamivudine_tenofovirFDC_Gilead_application_28oct04.pdf)
- [http://archives.who.int/eml/expcom/expcom14/lamivudine/lamivudine_Gilead_application_28oct04.pdf](http://archives.who.int/eml/expcom/expcom14/lamivudine/lamivudine_Gilead_application_28oct04.pdf)
- [http://archives.who.int/eml/expcom/expcom12/expertnotes.htm](http://archives.who.int/eml/expcom/expcom12/expertnotes.htm)
10.2. Summary of available data (appraisal of quality, outcome measures, summary of results)

Both 3TC and FTC have been proven to be effective when used as part of once-daily three-drug regimens. Although head-to-head comparisons of once daily 3TC to once daily FTC have not been conducted, available evidence suggests that once-daily 3TC and FTC are equivalent with respect to clinical efficacy and safety. Based on the available data, WHO Treatment Guidelines and the U.S. FDA support the use of either 3TC or FTC interchangeably.

Clinical evidence supporting 3TC dosing at 300 mg once-daily

Two clinical trials have demonstrated the efficacy of once-daily dosing of 3TC at a dose of 300mg

- **EPV 2000**
  
  This is the principal study supporting once-daily dosing based on a randomized, double-blind, multi-center, equivalence trial in which 554 patients were given 3TC 300 QD versus 150 mg BID, each in combination with zidovudine (AZT) and EF. Once-daily dosing met FDA criteria for equivalence and the FDA has approved an amendment to the Epivir drug label to permit 300 mg QD dosing.

- **Gilead 903**

  In addition to demonstrating the safety and efficacy of switching d4T to TDF, one of the study’s open-label extension studies provides evidence of the efficacy of dosing 3TC 300 mg once-daily with TDF and EFV. After three years on TDF QD/EFV QD/3TC 150 mg BID, 86 patients in three countries rolled over onto TDF/EFV/3TC 300 mg, all QD, and were then followed for four more years. The study states the following: “In virologically suppressed patients, switching d4T to TDF as part of a once-daily regimen with 3TC and EFV resulted in maintenance of virologic suppression and continued CD4 cell increases through 144 weeks, with significant improvements in metabolic parameters.”

10.3. Summary of available estimates of comparative effectiveness

Antiretroviral therapy generally requires the use of three or more drugs. This often requires taking a large number of tablets/capsules each day. Fixed-dose combinations (FDCs) of ARV drugs may:

- Allow for once- or twice-daily dosing using one or two pills, reducing the pill-burden;
- Increase patient adherence to treatment;
- Delay the development of resistance;
- Lower the total cost, including production, storage, transport, dispensing and other health system costs; and
- Reduce the risk of medication errors by prescribers, dispensers or patients themselves

Please reference the WHO Adaptation Guidelines and Treatment for Adults and Adolescents Guidelines.

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11. Summary of comparative evidence on safety:

11.1. Estimate of total patient exposure to date
TDF, 3TC and EFV have been used extensively as an adult first-line regimen.

11.2. Description of adverse effects/reactions

**Adverse effects:** Arthralgia, diarrhea, nausea, vomiting, fatigue, sinusitis, upper respiratory tract infections, nasopharyngitis, somnolence, headache, dizziness, depression, insomnia, abnormal dreams, anxiety, impaired concentration pain, abdominal pain, back pain, peripheral neuritis, peripheral neuropathy, pruritis, anorexia, pneumonia and rash.

**Laboratory Abnormalities:** (Grade 3 or 4) elevated bilirubin, AST, ALT, GGT, amylase, glucose, CPK, fasting cholesterol, creatine kinase, serum amylase, fasting triglyceride (>750 mg/dL); anemia, neutropenia and hematuria.

**Bone effects:** In a controlled clinical study decreases in bone mineral density of spine and changes in bone biomarkers from baseline were observed in both treatment groups, but were significantly greater in the tenofovir disoproxil fumarate treatment group than in the comparator group treated with stavudine (each in combination with lamivudine and efavirenz) at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

Tenofovir was studied in HIV-1 infected paediatric subjects 12 years of age and older. Under normal circumstances, bone mineral density increases rapidly in this age group. In this study, the mean rate of bone gain was less in the tenofovir-treated group compared to the placebo group. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in tenofovir-treated paediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults, due to the possible effects of tenofovir on bone metabolism.

**Osteonecrosis:** Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

**Central nervous system and psychiatric effects:** Central nervous system and psychiatric side effects are very common after starting efavirenz. These symptoms typically occur within the first week of treatment and usually resolve within 4 weeks of treatment. There is a potential additive effect with alcohol and other psychoactive drugs. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation they should contact their doctor or health care provider immediately to determine whether the benefits outweigh the risks of continued therapy.

11.3. Special Populations

**HIV and HBV co-infection:** It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. Lamivudine and tenofovir DF fixed dose combination tablet is not indicated for the treatment of chronic HBV infection and the safety and efficacy has not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of lamivudine and tenofovir DF. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue lamivudine and tenofovir DF fixed dose combination tablet.
and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

**Renal Impairment:** Lamivudine and tenofovir DF are principally eliminated by the kidney. Tenofovir, Lamivudine Efavirenz fixed dose combination tablet should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

**Hepatic Impairment:**

* Tenofovir DF: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients.

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild-to-moderate liver disease. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals. In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

* Lamivudine: The pharmacokinetics of lamivudine have not been studied in patients with hepatic impairment; however, lamivudine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

**Pregnancy/Breastfeeding:** Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

The incidence of fetal variations and malformations was not increased in embryo fetal toxicity studies performed with lamivudine.

EFV was rated pregnancy category D by the FDA in 2005 based on animal studies and a limited number of case reports of neural tube defects in human infants. However, definitive evidence linking EFV with a higher incidence of birth defects in humans is lacking and more recent reviews suggest that the risk of teratogenicity from EFV is much lower than previously thought.

**Other:** Convulsions have been observed rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medications primarily metabolised by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels. Caution must be taken in any patient with a history of seizures.

### 11.4 Drug Interactions

**Tenofovir DF:** When tenofovir DF was administered with ddI the Cmax and AUC of ddI administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher ddI concentrations could potentiate ddI associated adverse events, including pancreatitis, and neuropathy. In adults weighing >60 kg, the ddI dose should be reduced to
250 mg when it is coadministered with lamivudine and tenofovir DF fixed dose combination tablets. Data are not available to recommend a dose adjustment of ddI for patients weighing <60 kg. When coadministered, lamivudine and tenofovir DF fixed dose combination tablets and Videx EC® may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of ddI buffered tablet formulation with lamivudine and tenofovir DF fixed dose combination tablets should be under fasted conditions. Coadministration of lamivudine and tenofovir DF fixed dose combination tablets and ddI should be undertaken with caution and patients receiving this combination should be monitored closely for ddI-associated adverse events. ddI should be discontinued in patients who develop ddI-associated adverse events.

ATV and LPV/r have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving ATV and LPV/r and lamivudine and tenofovir DF fixed dose combination tablets should be monitored for lamivudine and tenofovir DF fixed dose combination tablet-associated adverse events. Lamivudine and tenofovir DF fixed dose combination tablets should be discontinued in patients who develop lamivudine and tenofovir DF fixed dose combination tablet-associated adverse events.

Tenofovir decreases the AUC and Cmin of ATV. When coadministered with lamivudine and tenofovir DF fixed dose combination tablets, it is recommended that ATV 300 mg is given with ritonavir 100 mg. ATV without ritonavir should not be coadministered with lamivudine and tenofovir DF fixed dose combination tablets.

Since lamivudine and tenofovir are primarily eliminated by the kidneys, coadministration of lamivudine and tenofovir DF fixed dose combination tablets with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine, tenofovir, and/or other renally eliminated drugs.

Efavirenz: Efavirenz has been shown in vivo to induce CYP3A4 (cytochrome P450 3A4). Other compounds that are substrates of CYP 3A4 may have decreased plasma concentrations when coadministered with efavirenz. In vitro studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolised by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs that should not be coadministered with efavirenz: astemizole, terfenadine, midazolam, triazolam, cisapride, ergot derivatives.

Drugs which require a dose increase when coadministered with efavirenz: When coadministered with efavirenz, indinavir doses must be increased from 800 mg to 1000 mg every 8 hours. Coadministration of methadone with efavirenz resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. When coadministered with efavirenz, the daily dose of rifabutin must be increased by 50 per cent.

Other potentially clinically significant drug interactions with efavirenz: warfarin, saquinavir, ritonavir, clarithromycin, rifampin, ethinyl estradiol. Concomitant use of efavirenz and St. John's wort (Hypericum perforatum) or St. John's wort-containing products is not recommended. There is a potential for additive CNS system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs.
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

12.1. Range of costs of the proposed medicine

As illustrated in the following table, various sources indicate an average price per patient per year (PPPY) for the TDF /3TC / EFV (300/300mg/600 mg) tablet of USD $154.

<table>
<thead>
<tr>
<th>Source</th>
<th>Median/Avg Unit Price*</th>
<th>PPPY**</th>
<th>Median/Avg Unit Price*</th>
<th>PPPY**</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAI ARV Price Ceiling Price List, 2011</td>
<td>$0.47</td>
<td>$171</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>International Drug Price Indicator Guide</td>
<td>$0.39</td>
<td>$142</td>
<td>$0.85</td>
<td>$311</td>
</tr>
<tr>
<td>WHO Global Price Reporting Mechanism***</td>
<td>$0.55</td>
<td>$199</td>
<td>$0.57</td>
<td>$210</td>
</tr>
<tr>
<td>Medecins Sans Frontieres, 2011</td>
<td>$0.28</td>
<td>$103</td>
<td>$0.67</td>
<td>$246</td>
</tr>
<tr>
<td><strong>Average of reported prices:</strong></td>
<td><strong>$0.42</strong></td>
<td><strong>$154</strong></td>
<td><strong>$0.70</strong></td>
<td><strong>$256</strong></td>
</tr>
</tbody>
</table>

*Median or average used depending on data available from each source.

**Price per patient per year based on WHO 2010 dosing guidelines; 365 days per year.

***Pricing data in low- and middle-income countries from January 2010 through October 2011 (as of March 30, 2012).

12.2. Comparative cost-effectiveness presented as range of cost per routine outcome

As the table in section 12.1 indicates, this formulation offers a significant price advantage over the combined cost of the individual formulations, costing approximately 40% less in PPPY terms. In addition to the cost of the product itself, there is also potential freight savings associated with procuring fewer packs. Moreover, consolidation around a single product facilitates simpler management of country supply chains.

13. Summary of regulatory status of the medicine

The FDA granted Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300mg/300mg/600mg "tentative approval" status on 3 September 2009 for purchase and use only as part of the President's Emergency Plan for AIDS Relief (PEPFAR) in resource-limited countries.

Tenofovir Disoproxil Fumarate/Lamivudine/Efavirenz 300mg/300mg/600mg tablets were added to the World Health Organization’s (WHO) list of prequalified products on 25 October 2010.


International Pharmacopoeia

15. Proposed (new/adapted) text for the WHO Model Formulary

Dosage forms: Tablet, 300mg/300mg/600mg