19th Expert Committee on The Selection and Use of Essential Medicines

Expert peer review on application for addition of fixed dose combination formulations of antiretroviral medications in the EML (Adults)

- Abacavir + lamivudine (ABC+ 3TC) – Tablet (dispersible): 600mg + 300 mg
- Atazanavir + ritonavir (ATV + r) – Tablet: 300 mg + 100 mg
- Tenofovir disoproxil fumarate + lamivudine (TDF+3TC) – Tablet: 300 mg + 300 mg
- Tenofovir disoproxil fumarate + lamivudine + efavirenz – Tablet: 300 mg + 300 mg + 600 mg

Reason for these applications:
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.

Summary of applications:
The applications are for the addition of formulations of fixed dose combinations (FDC) of medicines already included in the EML (individually and/or combined). Therefore, the section on efficacy is not included in the applications and in this peer review, as efficacy has already been assessed by previous expert committees. All other sections of the peer review form are included.

Advantages to dispersible tablet formulations:
- More convenient for active pharmaceutical ingredients with insufficient stability in water;
- More easily transportable and they generate less handling and transportation costs for the same amount of active ingredient (less volume, less weight);
- Easier to produce and the production costs are less, which makes them more affordable than standard liquid formulations;
- Can be used in very young children (0 – 6 months) and can be dispersed in breast milk;
- Are easy to dispense and they require minimal manipulation by health professionals and parents prior to use which minimizes the risk of errors; and
- Dispersible with only a small amount of water for administration.

Advantages to fixed-dose combination (FDC) formulations:
- Once-daily dosing
- 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. Assessment of safety
a. Have all relevant studies on safety been included
   Yes X No (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
All applications cover the safety issues related to these medications, including adverse effects /reactions and laboratory abnormalities. Safety is also reviewed in regards to interactions with drugs, overdosing, and use in special populations (pregnant women and elderly). Table 1 summarizes the assessments of safety for these FDC.
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Table 1 – Summary of assessment of safety on FDC formulations for HIV medicines:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse effects</th>
<th>Laboratory abnormalities</th>
<th>Special Precautions</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC + 3TC</td>
<td>Adults: nausea, malaise and/or fatigue, vomiting, diarrhoea, anorexia, insomnia and other sleep disorders, fever and/or chills, headache, severe sensitivity reactions</td>
<td>Anaemia, neutropaenia; elevated liver function tests, and CPK elevations; elevations of blood glucose; elevated triglyceride elevations</td>
<td>No studies in pregnant women. Insufficient evidence in use in elderly patients. Patients with creatinine clearance &lt;50 mL/min should not receive ABC + 3TC. Contraindicated in patients with hepatic impairment.</td>
<td>-No significant changes to pharmacokinetic parameters for ABC + 3TC when administered together. -Use in combination with zalcitabine not recommended. -An increased methadone dose may be required</td>
</tr>
<tr>
<td>ATV + r</td>
<td>Abdominal pain, diarrhoea, nausea, jaundice, scleral icterus, myalgia, lipodystrophy, rash, headache, asthenia, malaise, anorexia, dyspepsia, paresthesia, dizziness, taste perversion</td>
<td>Total bilirubin elevation, unconjugated bilirubin elevation, neutropenia, thrombocytopenia, ALT/AST elevation</td>
<td>Contraindicated in patients with liver disease. Patients with chronic hepatitis B or C (increased risk for severe and potentially fatal hepatic adverse reactions). Patients with second degree or higher atrioventricular or complex bundle-branch block Patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances). Little data from the use of ATV in pregnant women. No data is available on which to make a dose recommendation for patients over the age of 65 years.</td>
<td>Caution when prescribing ATV in association with medicinal products which have the potential to increase the QT interval. Co-administration of ATV+r and medicinal products that induce CYP3A4 not recommended</td>
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<td>TDF+3TC</td>
<td>Diarrhoea, nausea, vomiting, fatigue, sinusitis, upper respiratory tract infections, nasopharyngitis, somnolence, headache, dizziness, depression, insomnia, abnormal dreams and rash.</td>
<td>Elevated bilirubin, AST, ALT, GGT, amylase, glucose, CPK, fasting cholesterol, creatine kinase, serum amylase, fasting triglyceride (&gt;750 mg/dL); anaemia, neutropenia and hematuria.</td>
<td>Decreases in bone mineral density. Not indicated for the treatment of chronic HBV infection. 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. Only animal studies on pregnancy.</td>
<td>TDF administered with ddI the Cmax and AUC of ddI increased significantly. ATV without ritonavir should not be coadministered with lamivudine and tenofovir DF fixed dose combination tablets. FDC 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. 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.</td>
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<tr>
<td>TDF+3TC + EFV</td>
<td>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.</td>
<td>Elevated bilirubin, AST, ALT, GGT, amylase, glucose, CPK, fasting cholesterol, creatine kinase, serum amylase, fasting triglyceride (&gt;750 mg/dL); anemia, neutropenia and hematuria.</td>
<td>Some cases of decreased bone mineral density and osteonecrosis have been reported. Central nervous system and psychiatric side effects – use precaution in patients with previous conditions. Not indicated for the treatment of chronic HBV infection. 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. Caution in patients with mild-to-moderate liver disease. Only animal studies on the effect on pregnancy.</td>
<td>In addition to the ones listed in the row above: Co administration of EFV with other medications: Indinavir: doses must be increased from 800 mg to 1000 mg every 8 hours. Methadone: with EFV resulted in decreased plasma levels of methadone and signs of withdrawal. Rifabutin: daily dose must be increased by 50%. Drugs that should not be coadministered with EFV: astemizole, terfenadine, midazolam, triazolam, cisapride, ergot derivatives Other potentially significant drug interactions with EFV: 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 EFV is used concomitantly with alcohol or psychoactive drugs.</td>
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3. Assessment of cost and availability
a. Have all relevant data on cost and availability been provided
   Yes X No (if no, please provide reference and information)

Abacavir + Lamivudine: According to the WHO TUAPR, 1.1% of adult second-line patients use this NRTI backbone in combination with NVP and a PI; in addition, a smaller population may be using this backbone for TB co-infection treatment. Lastly, a significant portion of the paediatric population uses this NRTI backbone, for which an adult formulation may be important as they progress into adolescence and adulthood.

Atazanavir + ritonavir: ATV/r is currently used as an alternate to lopinavir combined with ritonavir (LPV/r) which is currently the dominant PI used in low and middle income countries. Currently 2.9% of patients in LMIC (excluding the Americas) are on a second line regimen and the majority of them are using LPV/r. (WHO, 2010- TUPR) However, given that the switching rate from first to second line regimens is expected to increase, the use of ATV/r is expected to increase with its wider availability in low and middle income countries after the introduction of a heat-stable generic fixed-dose combination tablet.

Tenofvir Disoproxil Fumarate + Lamivudine: According to the WHO TUAPR in 2010, in combination with NNRTIs (first-line) or PIs (second-line) nearly 700,000 adults (~14%) were treated with TDF+3TC across 45 low- and middle-income countries (excluding the Americas).

Tenofvir Disoproxil Fumarate + Lamivudine + Efavirenz: According to 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 (excluding the Americas).

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Abacavir + lamivudine: The application reports an average price per patient per year (PPPY) for the dispersible tablet of ABC + 3TC (600mg + 300 mg) of $356; a 24% reduction over the PPPY combined cost of the individual formulations. However, this is not consistent with the data presented in the table. As per the table, the individual formulations have a PPPY of $287. Therefore the FDC represents an increase of 24% in the PPPY over the individual formulations.

Atazanavir + ritonavir: The application reports an average PPPY for the tablet of ATV + r (300 mg + 100 mg) of $281, based on the price from CHAI (in spite stating that it is from various sources). The cost of individual formulations is reported as $1,071. The FDC offers a significant advantage of 74% reduction in price.

Tenofvir Disoproxil Fumarate + Lamivudine: The application reports an average PPPY for the tablet of TDF + 3TC (300 mg + 300mg) of USD $113. This is significantly lower than the combined cost of the individual formulations, with a PPPY estimated at $152 (25% less).

Tenofvir Disoproxil Fumarate + Lamivudine + Efavirenz: The application reports an average PPPY for the TDF + 3TC + EFV (300 mg + 300mg +600 mg) tablet of USD $154. This is significantly lower than the combined cost of the individual formulations, with a PPPY estimated at $256 (40% less).

In addition to the cost benefits indicated above for each one of the proposed formulations, there is also potential freight savings associated with procuring fewer packs for FDC formulations. Consolidation around a single product facilitates simpler management of country supply chains.
c. Please provide any additional relevant information with reference
Several of the suggested formulations are manufactured by a single company. The List of ARV Pharmaceutical Products from the Global Fund 2013 does not identify other manufacturers.1

d. Is the product available in several low and middle income countries?
Yes

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)
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) and 456,000 children on ART.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
See table 2 – The applications for (ABC + 3TC) and (ATV + r) mention but do not identify the WHO Guidelines.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences
None additional than those required for other formulations of the same medications.

6. Is the proposed product registered by a stringent regulatory authority?
Yes    No
See table 2

7. Any other comments
Even if these applications are for the inclusion of new formulations or specifying dispersibility for an existing medication in the EML, they should have included the references to the articles mentioned in the applications. References for prices and cost-effectiveness are not provided.

Several of these formulations are manufactured by only one company. Given the need of these medications and formulations in the adult population, it would be necessary to plan for scaled up manufacture of the recommended formulation to meet the increase in demand if these formulations are added to the EML.

8. What is your recommendation to the committee (please provide the rationale)
See table 2

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Table 2 - Summary of applications for addition of fixed dose combinations (FDC) formulations for HIV medicines in the WHO EML (adults):

<table>
<thead>
<tr>
<th>Medication</th>
<th>Proposed formulation</th>
<th>Strength</th>
<th>Current section and indication in WHO EML</th>
<th>Proposed section WHO EML</th>
<th>WHO Guidelines</th>
<th>Regulatory authority</th>
<th>Expert recommendation</th>
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| **Abacavir + Lamivudine**   | Tablet (dispersible) | 600 mg + 300 mg| **Abacavir:** Nucleoside/Nucleotide reverse transcriptase inhibitors (NNRTI): 6.4.2.1  
Oral liquid: 100 mg (as sulfate)/5 mL  
Tablet: 300 mg (as sulfate).  
**Lamivudine:** Nucleoside/Nucleotide reverse transcriptase inhibitors 6.4.2.1.  
Oral liquid: 50 mg/5 ml.  
Tablet: 150 mg. Lamivudine is also listed in the FDC section in the following combinations: lamivudine + nevirapine + stavudine  
• lamivudine + nevirapine + zidovudine  
• lamivudine + zidovudine | 6.4.2 Fixed dose combinations | WHO Guideline not referenced. Application states that triple nucleoside regimens (AZT + 3TC + ABC) should be used for individuals with intolerance or contraindications to NNRTI regimens or PI based regimens. | Tentative approval by the FDA on Sept 2008 as part of PEPFAR. | Include the tablet formulation of ABC + 3TC 600mg/300mg in the EML and EML (c) for the treatment of 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. |
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<td><strong>Atazanavir + ritonavir</strong> (ATV + r)</td>
<td>Tablet</td>
<td>300 mg + 100 mg</td>
<td><strong>Atazanavir</strong>: Section 6.4.2.3: Solid oral dosage form: 100 mg; 150 mg; 300 mg (as sulfate). a &gt;25 kg.</td>
<td>6.4.2.3 Protease Inhibitors</td>
<td>WHO Guideline is not referenced. Application states that ATV/r is recommended as a preferred PI for use in adult second-line regimens, in combination with an appropriate NRTI backbone.</td>
<td>Tentative approval by the FDA on November 2011 as part of PEPFAR.</td>
<td>Include ATVC + r tablet 300mg + 100mg in the EML for adults and adolescents at least 40kg with HIV-1, who require a protease inhibitor-containing first or second line.</td>
</tr>
<tr>
<td><strong>Tenofovir Disoproxil Fumarate + Lamivudine</strong> (TDF+3TC)</td>
<td>Tablet</td>
<td>300mg + 300mg</td>
<td><strong>TDF</strong>: Section 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors Tablet: 300 mg</td>
<td>6.4.2 Fixed dose combinations</td>
<td>WHO adult antiretroviral therapy guidelines (2010).</td>
<td>Tentative approval by the FDA on September 2008 as part of PEPFAR.</td>
<td>Include TDF + 3TC FDC in the WHO EML for 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.</td>
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| Tenofovir Disoproxil Fumarate + Lamivudine + Efavirenz (TDF+3TC + EFV) | Tablet | 300 mg + 300 mg + 600 mg | **TDF:** Section 6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors. Tablet: 300 mg  
**3TC:** see first row in table.  
**EFV:** 6.4.2.2 Non-nucleoside reverse transcriptase inhibitors. Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg. a >3 years or >10 kg weight. Also included in a FDC: efavirenz + emtricitabine* + tenofovir | 6.4.2 Fixed dose combinations | WHO antiretroviral treatment Guidelines (2010) | Tentative approval by the FDA on September 2009 as part of PEPFAR.  
WHO list of prequalified products on 25 October 2010. | Include the tablet formulation of TDF+3TC+EFV 300mg/300mg/600mg in EML and EML(c) for 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. |