**Comments on EML application: cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide**

The WHO HIV Department **does not support** the addition of the formulation **cobicistat + elvitegravir + emtricitabine + tenofovir alafenamide** in 2017 WHO Model List of Essential Medicines for treatment of HIV infection for the following reasons:

- Cobicistat (COBI), elvitegravir (EVG) and tenofovir alafenamide (TAF) are not included as options in 2016 WHO consolidated guidelines on use of antiretrovirals for treating and preventing HIV infection.

- A recent WHO systematic review comparing the use of integrase inhibitors in 1st line showed that dolutegravir and raltegravir were superior to elvitegravir/cobicistat (EVG/COBI) in terms of viral suppression, CD4 recovery and risk of treatment discontinuation.

- There are important concerns with the use of TAF and EVG/COBI in TB co-infection. EGV/COBI has important and well documented drug interactions with rifampicin and must not be co-administered, as will result in loss of its antiviral effect. Regarding TAF, there are no published data available on the pharmacokinetics and real-world efficacy of TAF in TB-coinfected patients. While the current available tenofovir prodrug (tenofovir disoproxil fumarate or TDF) does not require dose-adjustment if co-administered with rifampicin, TAF is currently contraindicated by the originator in patients being treated with rifampicin, as significant drug interaction is predicted based on pK modelling. Data on the potential for TAF dose adjustment are awaited.

- There are very limited data available on the safety of EVG/COBI and TAF during pregnancy. Preliminary pK studies in pregnant women showed that EVG and COBI exposure are substantially lower during pregnancy compared to postpartum and standard doses may not be adequate for sustained viral suppression. Despite preclinical toxicity studies with TAF in pregnancy didn’t reveal concerns, preliminary pK data in humans showed a 5-fold higher intracellular tenofovir concentration with TAF when compared with TDF. It might lower the risk of mother-to-child transmission of HIV, but it can also increase the risk of birth abnormalities. There is no data are available on placental or breast milk passage of EVG/COBI or TAF in pregnancy.

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3. Lee JSF, Calmy A, Andrieux C, Meyer I, Ford N. Review of the safety, efficacy, and pharmacokinetics of elvitegravir with cobicistat (COBI), elvitegravir (EVG) and  tenofovir alafenamide  (TAF) are not included as options in 2016 WHO consolidated guidelines on use of antiretrovirals for treating and preventing HIV infection.
humans. Until results from pK and large database of TAF- and EVG/COBI treated pregnant women have been analysed, it is not possible to evaluate the real safety risk of using these drugs in pregnant/breastfeed women.

- Despite lesser detrimental effects on bone and renal lab markers with TAF use, there is no difference in adverse event rates in major TAF and TDF comparative studies. An unpublished meta-analysis of 10 clinical trials compared TDF- and TAF-based regimens, which together comprised almost 7000 participants and more than 8000 patient-years of follow-up. This metanalysis did not reveal statistically significant differences in virological outcomes, adverse events, lab abnormalities, or deaths, and only showed differences when specific bone and renal laboratorial parameters were compared.

- Data on the effectiveness of TAF in severely immunocompromised HIV patients is also missing: none of the available studies had mean/median baseline CD4 cell counts below 350 cells/mm3. Important to emphasize that the median CD4 cell count at ART initiation among PLHIV in all regions of the globe, including high income countries, are still below this threshold.

- Data on EVG/COBI and TAF use in adolescents (12-18 years old) are available only for a comparatively small sample (50 participants in total), and only for 48 weeks of study follow-up. Clinical studies in children younger than 12 years old are still ongoing.

In conclusion, the recommendation to use therapeutic regimens containing COBI, EVG and TAF as a standard options for low- and middle-income countries is viewed by WHO as premature and requires more data for tuberculosis, pregnancy, children and PLHIV with severe immunosuppression.

11 Sax P, Wohl D, Yin M et al. 2015. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. The Lancet, 385, pp 2606-2615
18 Raffi F. Long-term (96-week) efficacy and safety after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) in HIV-infected, virologically suppressed adults. In: HIV Glasgow. Glasgow; 2016