Comments on EML application: emtricitabine + tenofovir alfenamide

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

- Tenofovir alfenamide (TAF) is not included as an option in 2016 WHO consolidated guidelines on use of antiretrovirals for treating and preventing of HIV infection.

- There are important concerns with the use of TAF in PLHIV with TB co-infection. There are no published data available on the pharmacokinetics and real-world efficacy of TAF in TB-infected 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 dose adjustment are awaited.

- There are no data available on the safety of TAF in pregnant women. Despite preclinical toxicity studies 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 TAF in humans. Until results from pK and large database of TAF-treated pregnant women have been analysed, it is not possible to evaluate the real safety risk of using TAF 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An unpublished meta-analysis of 10 clinical trials compared TDF- and TAF-based regimens, which together comprised almost 7000 participants and more than 8000 patient-years of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 metaanalysis did not reveal statistically significant differences in virological outcomes, adverse events, lab abnormalities, or deaths, and only showed differences when specific bone and renal laboratory parameters were compared.

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2 Descovy [package insert]. Food and Drug Administration. 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s000lbl.pdf
6 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
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 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 inclusion of TAF containing regimens for treatment of HIV infection in low- and middle-income countries is viewed by WHO as premature and requires more data for tuberculosis, pregnancy, children and PLHIV with severe immunosuppression.

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