Comments on EML application: tenofovir alfenamide for HBV infection

The WHO HIV Department does not support the addition of the formulation tenofovir alfenamide (TAF) in the 2017 WHO Model List of Essential Medicines for treatment of chronic HBV infection for the following reasons:

- **No current plans for updating of 2015 HBV treatment guidelines:** Tenofovir alfenamide (TAF) is not yet included as an option in the 2015 WHO guidelines on prevention, care and treatment of persons with chronic hepatitis B infection. There are no current plans to update these guidelines in 2017, but this may be considered in 2018.

- **Not yet included as part of recommended regimen in WHO HIV ARV guidelines:** The inclusion of TAF as part of recommended ARV regimen in HIV-infected persons would be considered as an important initial or concomitant step for inclusion as treatment for HBV infection for reasons of simplification and procurement at regional and national level.

- **Existing effective treatment (Tenofovir) already available as low cost generic worldwide:** Despite the widespread availability of low cost tenofovir worldwide, treatment scale-up remains low especially in HBV mono-infected persons. There are multiple impediments to scale-up of HBV treatment, including costly and complex diagnostics, lack of testing and treatment infrastructure and services and simplified service delivery models. These constitute the most critical barriers that need to be addressed, rather than availability of drug.

- **Uncertainty regarding the extent of reduced renal and bone toxicity:** There remains uncertainty regarding the long-term clinical benefits of TAF compared to Tenofovir in terms of consequences of renal toxicity and bone mineral density in different HBV infected populations, including those at higher risk, such as adolescents and children, or post-menopausal women, especially beyond 72 weeks. Despite overall less 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 in HIV infected populations.

- **Uncertainty on cost:** The proposed no profit price of $10 per month ($120 per year) is still higher than the $50 annual cost for generic tenofovir. It is anticipated as a result of the substantially lower dosage of TAF compared to Tenofovir, it will be available at a lower cost.

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compared to Tenofovir, which would provide significant advantage for low and middle income countries.

- Other data concerns:
  
  o **Lack of data on use in TB coinfected persons:** 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-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 dose adjustment are awaited.

  o **Lack of data on safety in pregnant women:** There are no data available on the safety of TAF in pregnant women. Although preclinical toxicity studies in pregnancy did not identify concerns, preliminary PK data in humans showed a 5-fold higher intracellular tenofovir concentration with TAF when compared with TDF. Although TAF may lower the risk of mother-to-child transmission of HIV, it may also increase the risk of birth abnormalities. There is need to evaluate the safety issues of using TAF in pregnant/breastfeed women.

In conclusion, the inclusion of TAF containing regimens for treatment of chronic HBV infection in low- and middle-income countries is viewed by WHO as premature and requires more data to supports its use in HIV-infected persons as well as in HBV infection. In particular, there remain uncertainties regarding the key potential advantages of TAF in terms of reduced renal and bone toxicity, and lower costs. In particular the benefit/cost (ie long-term data on adverse events and potential lower costs). In addition, there is a need for more data on use of TAF in tuberculosis, and pregnancy.