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Letter

Letter to the editor in re: Mohan et al., 2020 'dolutegravir in pregnant mice is associated with increased rates of fetal defects at therapeutic but not at supratherapeutic levels'

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We would like to share some thoughts on the study design and proposed hypotheses in Mohan et al. [1].

Mice were administered dolutegravir and tenofovir/emtricitabine without inclusion of single agent control groups making it impossible to determine the causative agent. Administered formulations were prepared by crushing pills and suspending in water. Tablets contain large amounts of inactive excipients and the absence of dose concentration analysis and determination of relative exposure to each agent further confounds the ability to ascribe causality to any test agent. The selection of the DTG doses assume linearity of exposure and no impact from the co-administered entities. The projected Cmax concentrations achieved (3000 and 12,000 ng/ml) do not provide adequate separation in exposure (only 4-fold) to achieve such different results between these two doses.

The explanation for the non-dose responsive developmental defects are contrary to preclinical study results (Stanislaus et al. [2], Posobiec et al. [3]) and the established principles of teratology (Wilson [4]) and principles of establishing causality as espoused by Hill [5]. The explanation on non-monotonic responses is not well supported for these types of developmental toxicity. Furthermore, it is hard to reconcile the observed small increase in NTDs in the lower dose group when both total maternal and fetal folate levels remained unchanged, while providing evidence for a small decrease in a minor folate metabolite (methylene tetrahydrofolate).

In summary, based on the lack of dose-response and sub-optimal study design without single agent controls the proposed hypothesis is not well supported.

Contributors

Writing, reviewing, editing, all equal contributions.

Declaration of Competing Interest

Authors are employees of Viiv Healthcare (EHR) and GlaxoSmithKline (LMP, JCB, MJZ, DJS). There are no conflicts of interest.

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