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ASIA EDITION

BioIVT examines link between HIV Integrase inhibitor drugs and NTD during pregnancy

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The research investigates the risk of drug-induced folate deficiency with HIV integrase inhibitors and published in Drug Metabolism and Disposition (DMD)

BioIVT, a leading provider of research models and services for drug and diagnostic development, on 15 August 2019, announced that researchers in its Transporter Sciences Group have co-authored a peer-reviewed *DMD* paper, which investigates the inhibitory effects of a class of HIV drugs known as integrase inhibitors on folate transporter pathways. Previously published studies had appeared to show a correlation between exposure to dolutegravir, and other HIV integrase inhibitor drugs, at conception and an increased risk of neural-tube defects (NTDs). NTDs are birth defects of the brain and spinal cord that cause conditions such as spina bifida in infants. NTDs can be caused by several factors, including inhibition of folate transporters in the gut, brain, and placenta.

This new research, which results from a collaboration between BioIVT and GlaxoSmithKline (GSK) and is based on studies conducted in BioIVT's laboratory in Santa Clara, CA, set out to investigate whether HIV integrase inhibitor drugs also inhibit folate transporters, leading to drug-induced folate deficiency and an increased likelihood of NTDs.

"We were pleased to collaborate with our colleagues at GSK on this important research, using BioIVT's technology platform and our combined scientific knowledge and thinking. Through timely and effective communication, we were able to develop new assays quickly and generate high-quality data," said Dr Xuexiang Zhang, BioIVT's lead investigator on the study. "We hope that our investigation into the pharmacology of dolutegravir will help physicians to develop optimal recommendations for their patients."

Their study assessed the impact of dolutegravir and four other integrase inhibitor drugs, together with positive controls (methotrexate and pemetrexed) and a negative control (valproic acid), *in vitro* on the three major folate transport pathways: reduced folate carrier (RFC), proton-coupled folate transporter (PCFT), and folate receptor ? (FR?) endocytosis.

Their research set out to determine what effects if any, dolutegravir and the other HIV integrase inhibitors had on folate transporter activity. Particular attention was paid to FR? since concerns about dolutegravir's interaction with that pathway had been expressed recently in the scientific literature.

BioIVT used its proprietary OPTI-EXPRESSION™ technology to express human folate transporters in mammalian cells (MDCK-II cells). Then the potential of dolutegravir to inhibit folate transporters was measured using well-described, validated methods.

The study demonstrated that dolutegravir is not a clinical inhibitor of folate transport pathways and is not predicted to elicit clinical decreases in maternal and fetal folate levels.

Reaching a related conclusion, the World Health Organization (WHO) recommended on July 22, 2019, that dolutegravir be used as the preferred first-line and second-line treatment for all populations with HIV, including pregnant women and those of childbearing potential. It based its decision in part on two large clinical trials comparing the efficacy and safety of dolutegravir and efavirenz in Africa.

BioIVT's approach can also be used to predict the risk of folate transporter inhibition by drugs in other classes. It is employed during the drug discovery process to select and develop drugs with optimal pharmacological properties, i.e. high efficacy and minimized risk to patients.