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Short Communication

Safety Profile of Dolutegravir in Indian Population

Shatrunajay Shukla* and Vivekanandan Kalaiselvan

Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, Ghaziabad, Uttar Pradesh, India

***Corresponding Author**: Shatrunajay Shukla, Assistant Scientist, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Government of India, Ghaziabad, Uttar Pradesh, India.

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After the first report of Human Immunodeficiency Virus (HIV) infection in 1986 in Chennai, India has made impressive progress in terms of HIV prevention, treatment and palliative care for patients living with or at risk of infection. Prevalence of HIV continued a significant decline from a peak of 0.38% in 2001-2003 through 0.34% in 2007, 0.28% in 2012 and 0.26% in 2015 to 0.22% in 2017 [1]. Despite such a sizeable progress, 87.58 thousands new cases of HIV infection are diagnosed in 2017 alone in India. As per available records, women accounted for 40% of new HIV infection in 2017 in which 22.67 thousands HIV positive women were of child bearing age [1]. Earlier, women of child bearing age were advised to avoid conception because of higher probability of HIV transmission from mother to child. Now, Highly Active Antiretroviral Therapy (HAART) including dolutegravir (DTG) has dramatically improved the management, clinical outcomes and HIV-associated morbidity and mortality in HIV patients and reduced the risk of transmitting the virus from mothers to children.

DTG, an HIV integrase strand transfer inhibitor, has been approved as the preferred first-line and second-line treatment for mass including women of childbearing age. DTG has several advantages over existing HIV integrase inhibitors which covers good tolerability and being highly active against wild-type and drug resistant viruses, such as integrase resistant strains [2]. The WHO guidelines (2016) recommend initiation of DTG in all pregnant and breastfeeding women living with HIV but also recommend that therapy must be continued for life due to the favorable benefits versus risks [3]. This notification followed more than a year of unpredictability and scientific discussion on risks and benefits of using DTG in women including those of childbearing potential.

Initial findings in a birth outcome surveillance study conducted by the Botswana Harvard AIDS Institute Partnership noted a possible link between DTG and neural-tube defects (0.94% prevalence vs. 0.12% in women not on DTG; 4 out of 426) in infants of women exposed to DTG prior to conception [4]. The periconceptually exposed infants suffered with encephalocele, myelomeningocele and iniencephaly. However, they observed a decrease in the incidence rate to 0.3% of deliveries (5 out of 1,683 exposures) in extended studies [5]. In 2018, the World Health Organization also issued a safety signal on possible neural tube defects in the developing foetuses of women who use DTG as HAART at the time of conception or early in the first trimester of pregnancy. The emerging clinical data albeit from a small sample population raised the concern for the safety of DTG during pregnancy and consequently highlighted an urgent need for strengthening the post-market surveillance of DTG therapy including monitoring of birth outcomes.

Post-market surveillance of medicinal products used in India is performed separately by Pharmacovigilance Programme of India (PvPI) under the nodal Ministry of Health and Family Welfare, Government of India and is effective since 2011. PvPI provides an integrated system to collate the adverse drugs reaction (ADR) data through ADR monitoring centres, public health programmes including National AIDS Control Organization (NACO) and pharmaceutical industries and use the inferences derived to recommend regulatory

interventions, besides communicating risks to healthcare settings and public health programme officials. Earlier, PvPI has issued a signal related to use of Lamivudine (3-TC) and hearing loss in patients on HAART in India. The purpose of this correspondence is to offer an update on the safety of DTG in Indian population. In November 2016, DTG is approved in Indian market as DTG Tablet 50 mg and bulk in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults weighing more than 40kg. NACO has also issued national technical guidelines on anti-retroviral treatment in October 2018, which encourages use of 50 mg DTG once daily in all infected population. A possible association between DTG and neural tube defects triggered the PvPI to promptly check the Indian database. We searched VigiBase®, a WHO global database of Individual Case Safety Reports (ICSRs), maintained by Uppsala Monitoring Centre, Sweden and extracted India specific ICSRs (4,13,589 as on December 31, 2019). We observed only 3 cases (1 in 2018 and 2 in 2019; 2 serious and 1 non-serious; 1 male, 1 female and 1 of undisclosed identity) of adverse events followed by DTG therapy. Adverse events reported were hyperbilirubinaemia, increase in serum triglyceride level and foetal death. Hyperbilirubinaemia and increase in serum triglyceride level were noted in patients who were diabetic and on anti-diabetic therapy simultaneously. However, a possible causal relationship on WHO causality scale is established between adverse events noted and DTG therapy. Adverse events noted in database (hyperbilirubinaemia and increase in serum triglyceride level) have also been reported in recent studies [6,7].

The PvPI acknowledge, however, that data for the extent and severity of possible adverse events are limited and no case of neural tube defect with DTG use is reported. We are taking this potential safety alert of neural tube defect is very seriously and issued an advisory to all ADR monitoring centres, public programme officials, marketing authorisation holders and study investigators to inquire and solicit spontaneous ADR reporting. PvPI will update information on use of DTG in Indian population as and when PvPI receive, review and arrive on a meaningful conclusion.

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Conflict of Interest

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