Major HIV drug requires vigilance, study says

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A study lead by researchers at the Institute of HIV Research, Medical Faculty of UDE and University Hospital Essen reports a potential toxicity of integrase inhibitors. Integrase inhibitors (INSTI) are a

preferred drug for inclusion in anti-retroviral therapy regimens given its tolerability, efficacy and high resistance barrier. INSTI have been found to improve and prolong lives of millions of people living with HIV who suffer side-effects and resistance to treatment. However, recent laboratory data suggest that INSTI may not be as safe as suggested.

The researchers found that INSTI had a dramatic effect on activity of immune cells, and in particular, reduced the activity and function of CD4 T helper cells. This included a reduced proliferation and multiplication of these cells. As HIV itself attacks and destroys CD4 helper cells, the study raises concerns regarding whether this drug class is the best long-term choice for HIV treatment. Interestingly, other HIV drugs including protease inhibitors (PI) or reverse transcriptase inhibitors ((N)NRTI) or drug combinations did not show these effects.

Furthermore, there was also a difference among the INSTI drug class. While elvitegravir (EVG) and dolutegravir (DTG) had a significant impact on cellular function, raltegravir did not show an effect. To further understand the source of reduced CD4 T cell function and proliferation, the researchers studied the effect of the drugs on mitochondria. Mitochondria are important cell organelles in our body that produce the energy for cellular function. Indeed, INSTI interfered in the electron transportation chain of mitochondria severely impairing their respiratory capacity and thus slowing down cellular activity.

"The impact of DTG and EVG on cellular functions is most likely systemic," senior author Prof. Dr. Hendrik Streeck explains. "However, CD4 T cells are metabolically very active and thus small effects can be easier spotted in these cells compared to others."

In particular, DTG has been suspected for potential severe side effects. In 2018, drug regulators warned of potential harm to babies born to women who took dolutegravir during early pregnancy. Preliminary

findings from the Tsepamo study in Botswana showed a slight increased risk of neural tube defect. The results led to a safety warning and stopped plans to introduce DTG-based treatment in some countries in sub-Saharan Africa. Now, several emerging studies have associated INSTIs with significant weight gain, further raising potential safety concerns of these drugs.

"INSTIs are a great class of drugs and have helped millions of people worldwide. However, our study calls for more pharmacovigilance for potential serious long-term toxicity," Prof Streeck says. "In particular, given the widespread use of INSTIs prospective studies are needed to determine the broader clinical implications of our findings."

More information: Marek Korencak et al. Effect of HIV infection and antiretroviral therapy on immune cellular functions, *JCI Insight* (2019). DOI: 10.1172/jci.insight.126675

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