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The Importance of Antiretroviral Pharmacovigilance

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Dear Editor,

Eswatini, formerly Swaziland, is one of Africa's geographically smallest countries. The country has one of the highest incidence rates of human immunodeficiency virus (HIV) in the world. The Swaziland HIV Incidence Measurement Survey, a household-level population survey, found that 27% of the adult population of the country, or approximately 210,100 adults, were living with HIV, reaching to 35.1% of all women compared to 19.3% of men (1). However, there has been a 44% reduction in the HIV incidence rate since 2011 and a decline in AIDS-related mortality from 3800 in 2010 to 2400 in 2018 (1, 2).

The main contributors to the decline in HIV incidence and AIDS-related mortality include an increase in antiretroviral therapy (ART) coverage and universal testing to increase HIV case-identification. Highly active antiretroviral therapy (HAART) eligibility criteria were revised from CD4 < 200 to CD4 < 350 in 2011 and from CD4 < 350 to CD4 < 500 and life-long treatment for HIV positive pregnant women regardless of CD4 count in 2015 to life-long treatment for all people living with HIV regardless of CD4 count in 2016. In addition to adopting the World Health Organization (WHO) recommendation of test-and-start, Eswatini also adopted the use of dolutegravir (transitioning patients from tenofovir to dolutegravir) as the first line antiretroviral (ARV) from 2018.

However, there are known side effects and toxicities associated with ARVs, especially when they are used for long periods (3). The earliest suspected toxicity associated with dolutegravir is neural tube defect leading to birth deformities in the fetuses of pregnant women taking this medication (4). Subsequently, a retrospective national cohort study from Brazil on 1427 women did not identify any association between dolutegravir and neural tube defects (5). Given the high number of people living with HIV on ARVs and the predominance of affected women in Eswatini, this potential side effect and other complications, which are yet to be discovered, are among the main concerns of using dolutegravir. This underscores the need for consistently and systematically monitoring the safety of ARVs used for treating HIV patients and determining their risk-benefit profiles.

An adverse drug reaction (ADR) is any "noxious and unintended" response from a medicine, which happens when the medicine is used at the usual dose "used in man for the prevention, diagnosis, or treatment of a disease, or for modifying physiological function"(6). This requires that the linkage or causality of a specific drug used at the routine dose to be established. However, HIV programs in developing countries generally underreport and underestimate the ADRs related to ARVs. The inadequate monitoring and management of the ADRs associated with ARVs increase the health burden of managing HIV patients due to the direct costs of managing the reactions and indirect costs associated with ADRs.

Adverse drug reactions are associated with morbidity and mortality. A study reported the ADRs of ARVs or the medications used to treat opportunistic infections in 2.5 to 18% of HIV patients (7). Another study from South Africa identified that 16% of AIDS-related deaths in four hospitals were related to ADRs, of which 43% were preventable (8), highlighting the need for proactively monitoring and managing ADRs.

Adverse drug reactions also lead to non-adherence to treatment, which results in poor treatment outcomes (9). Increased treatment coverage and adherence to treatment improved the survival rates of HIV patients and reduced the incidence of opportunistic infections, mother-to-child transmission, as well as transmission to HIV-negative partners (10). In Eswatini, there are 191,000 HIV patients under treatment coverage until September 2019 (2), necessitating the establishment of a robust monitoring system for iden-

tifying a growing population at the risk of ARVs-associated ADRs.

In summary, high HIV prevalence in Eswatini necessitates the treatment of a significant number of people with ARVs. The introduction of dolutegravir as the first line treatment for HIV for such a large number of people highlights the importance of pharmacovigilance as an essential component of drug safety monitoring. Overall, public health decision-makers and health-care workers should have an obligation to assure that the benefits of medicines outweigh the risks associated with using them. For the effective management of HIV, pharmacovigilance is essential to monitor ADRs and ensure access to ARVs.

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