NAMIBIA MEDICINES REGULATORY COUNCIL

THERAPEUTICS INFORMATION AND PHARMACOVIGILANCE CENTRE

STATISTICS OF ADVERSE DRUG REACTIONS

(APR 2020 – MAR 2021)

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INTRODUCTION

The World Health Organization (WHO) defines pharmacovigilance as the "science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem" (World Health Organization, 2015). Pharmacovigilance focuses on investigating and monitoring adverse drug reactions (ADRs) after medicinal products are licensed.

Post-marketing pharmacovigilance is crucial to monitor the rare events as well as long-term safety of drugs, particularly in specific populations and situations that are not usually included in pre-marketing studies. Underlying this is the significance of appropriately collecting and reporting safety data to provide information for clinical and regulatory decision-making. The pharmacovigilance of ADRs is essential to ensuring that medicines continue to be safe for use.

The ADR reports received by the Therapeutic Information and Pharmacovigilance Centre (TIPC) are entered into the WHO's global database for ADRs (VigiBase) and analysed periodically to identify any safety signals. Namibia has entered a total of **2 618** ADR reports into the database since 2009.

The TIPC wishes to share statistics on the ADR reports received during the previous financial year (2020/21).

STATISTICS

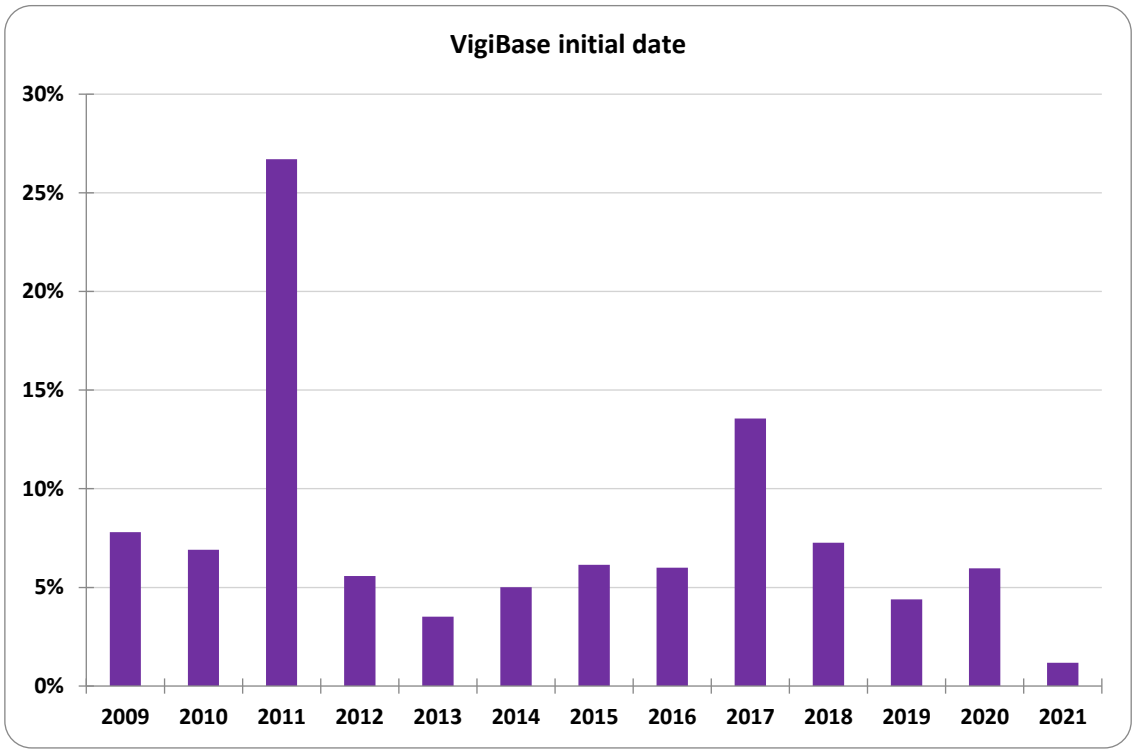

Figure 1: Percentage of ADR reports in the Namibian database (Vigibase) since 2009

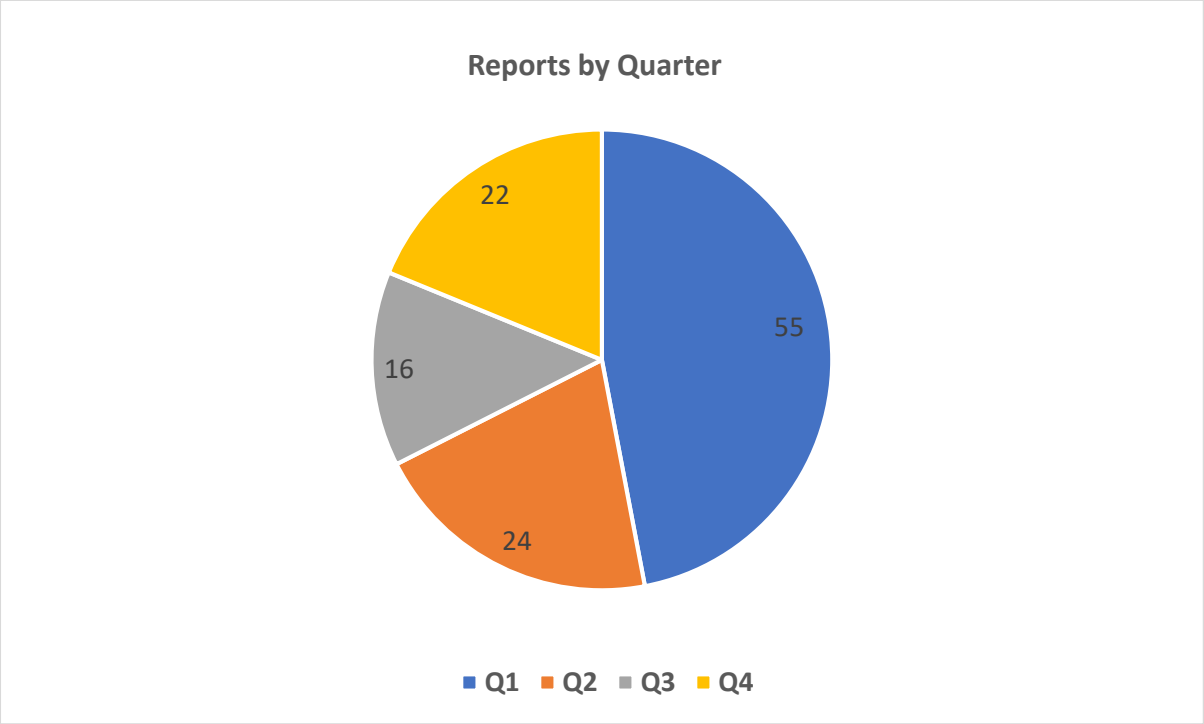

Figure 2: A total of 117 ADR reported from quarter 1 (April 2020) to quarter 4 (March 2021).

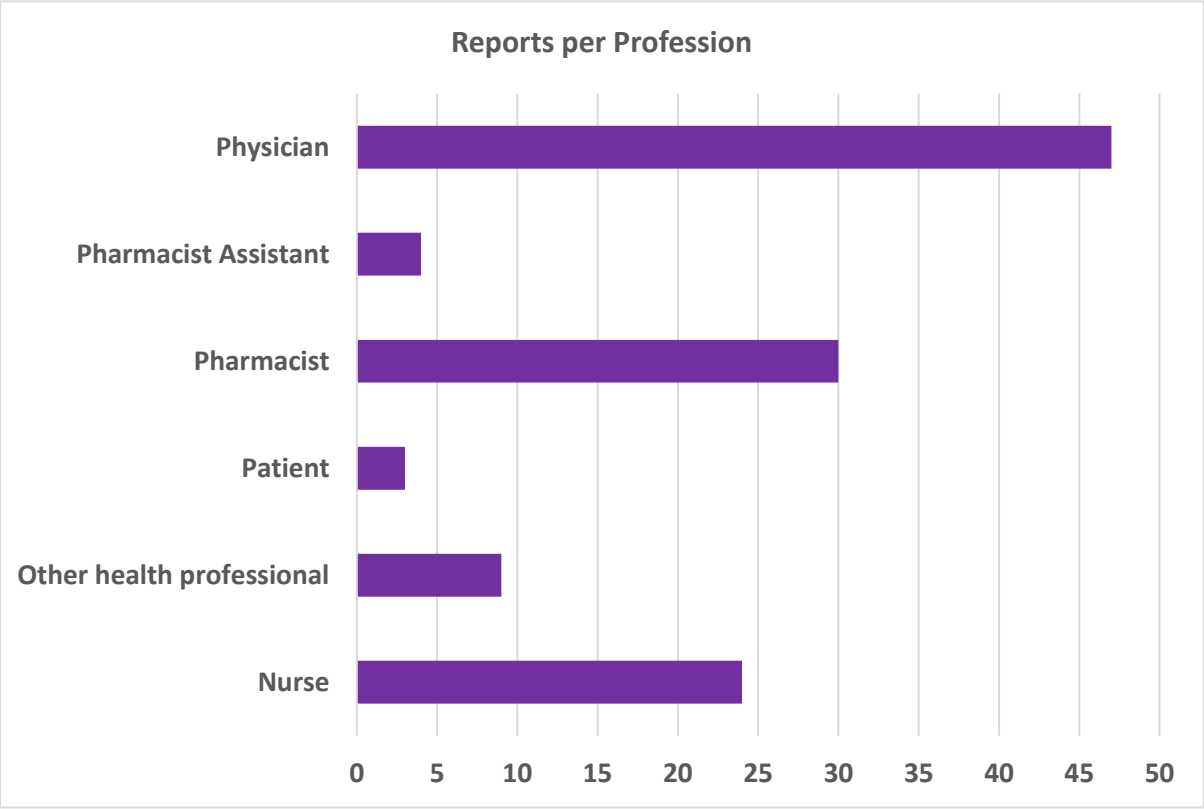

Figure 3: Number of ADR reports received by profession

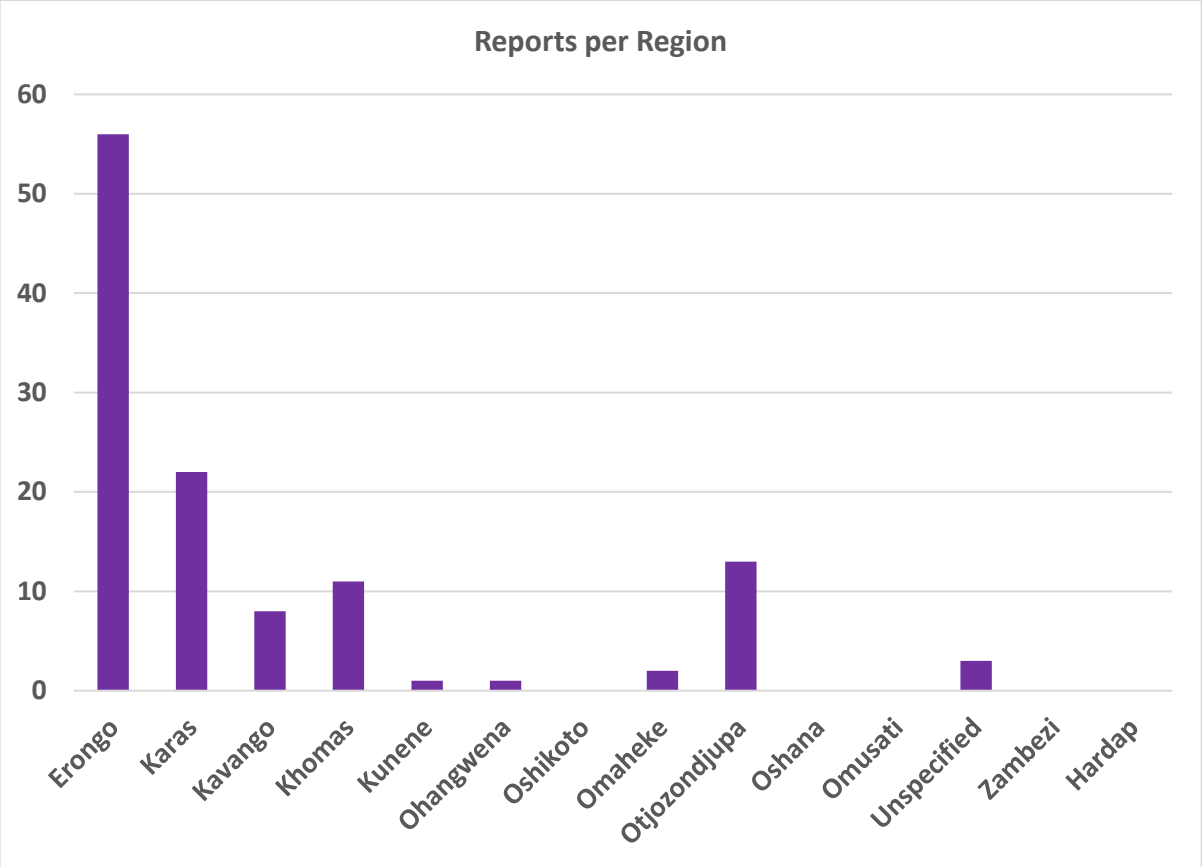

Figure 4: Number of ADR reports received by region

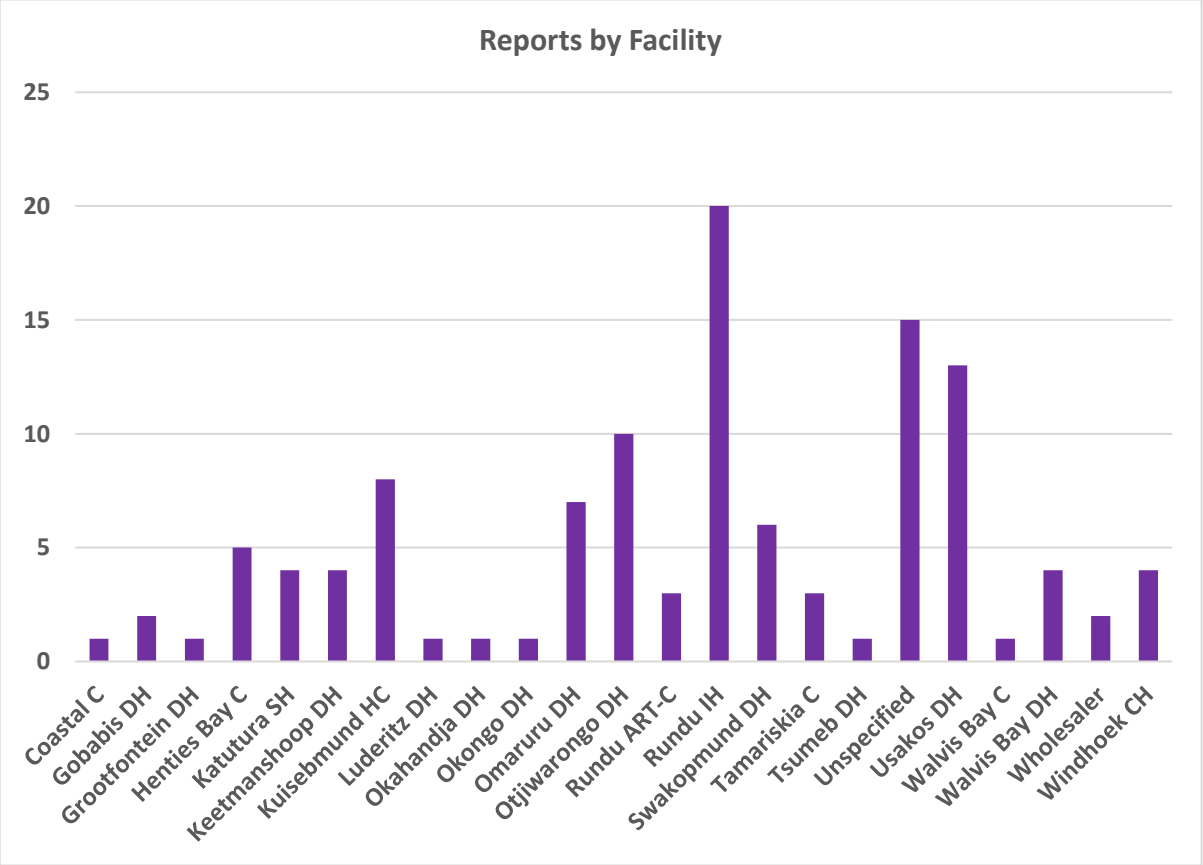

Figure 5: Number of ADR reports received by healthcare facility.

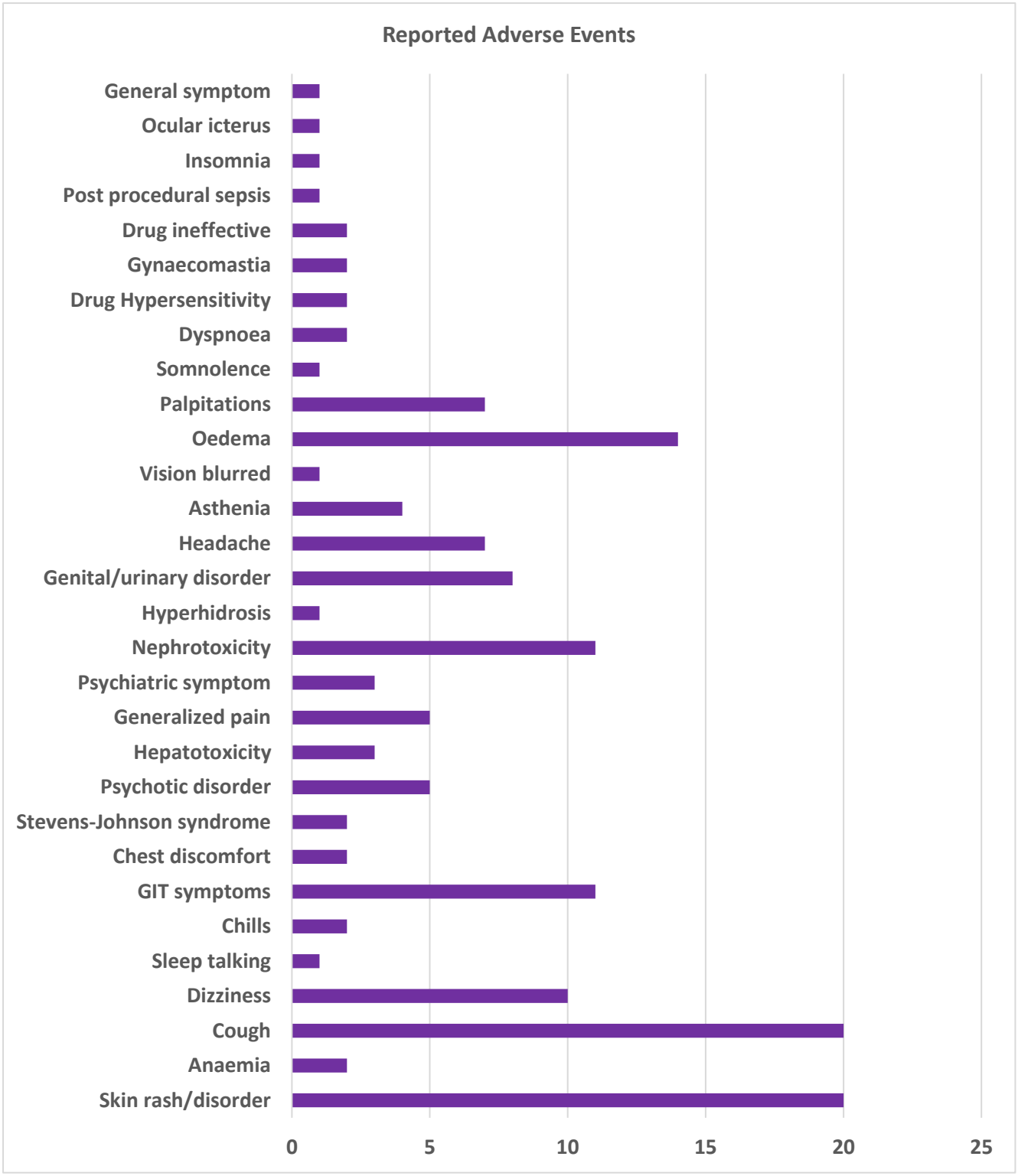

Figure 6: Type of adverse drug reactions reported

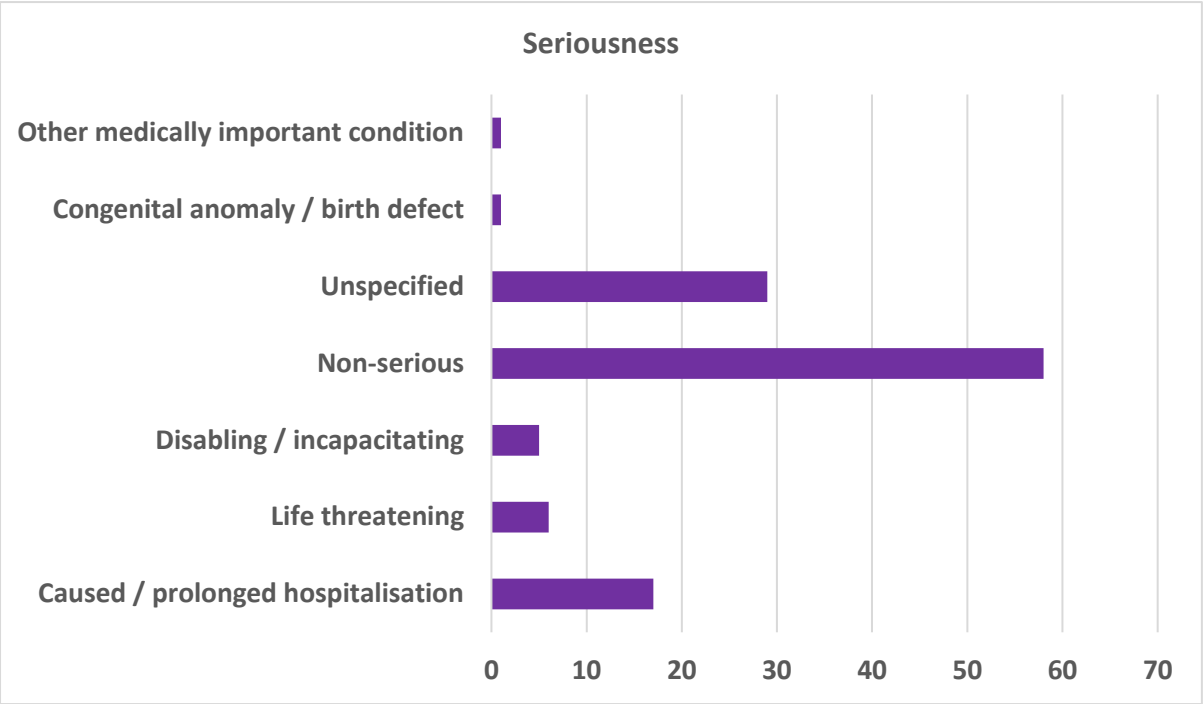

Figure 7: Seriousness of reported adverse drug reactions

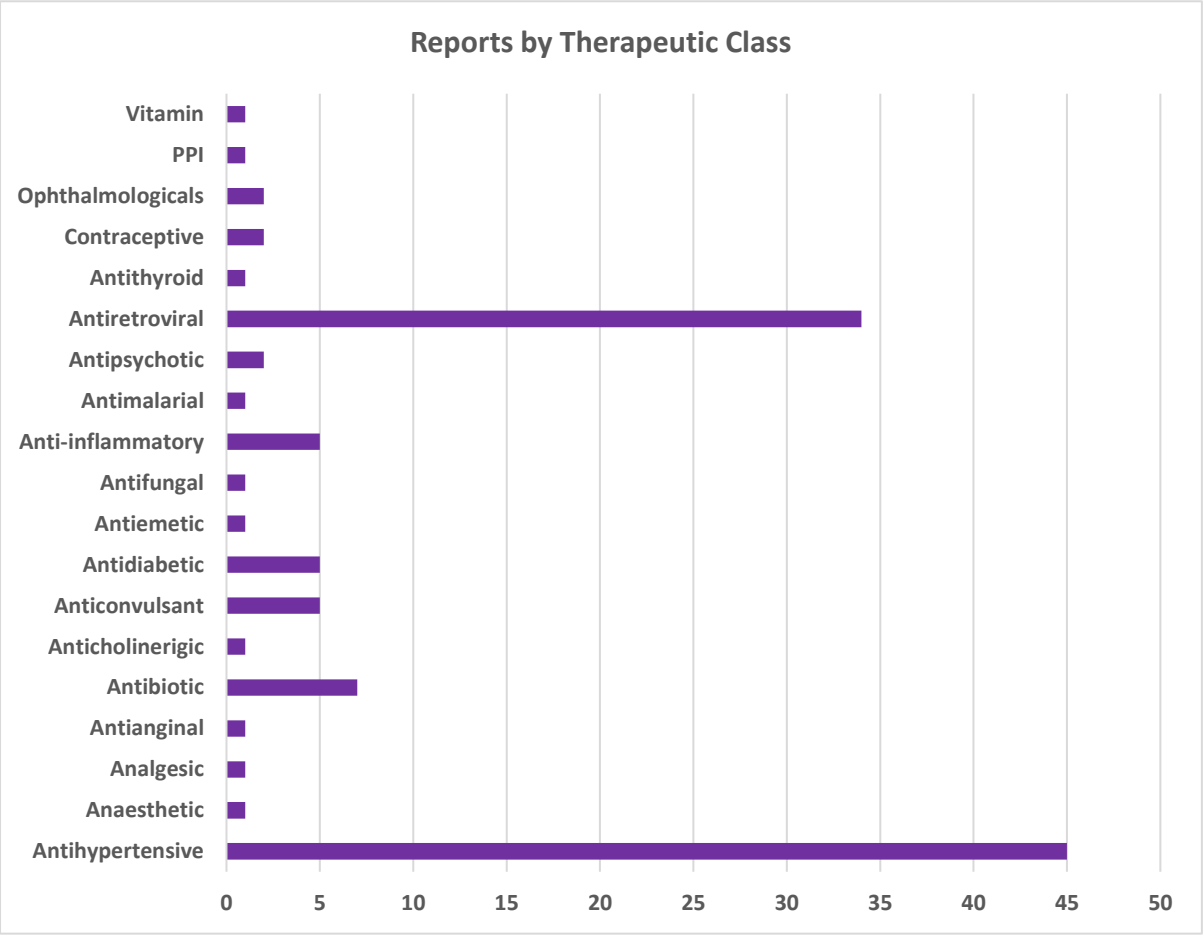

Figure 8: Number of reports by therapeutic class

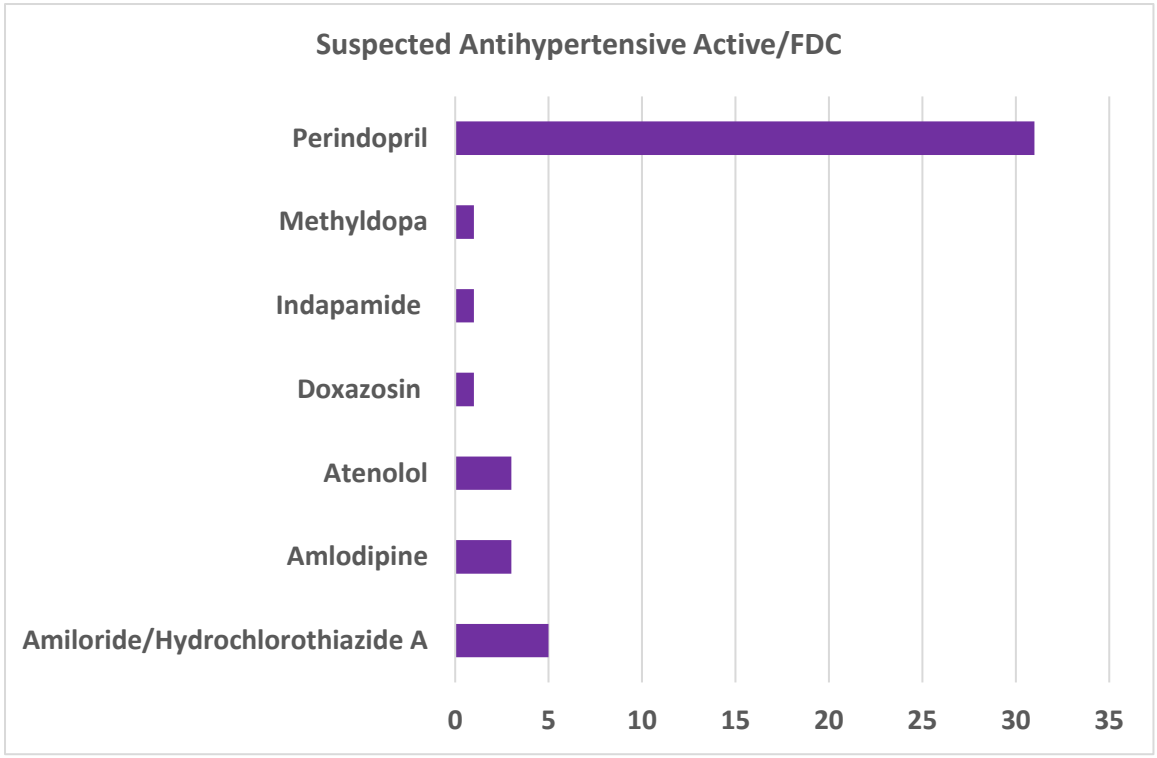

Figure 9: Number of ADR reports received on antihypertensive drugs and Fixed Dose Combinations (FDC)

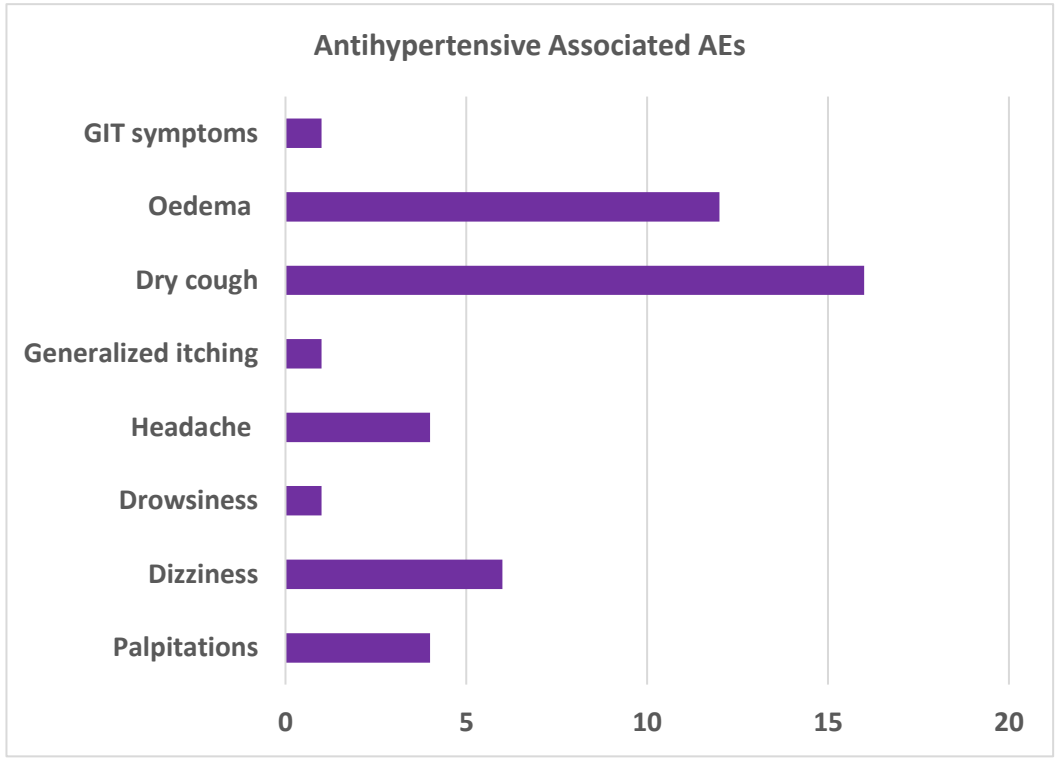

Figure 10: ADRs associated with antihypertensive drugs

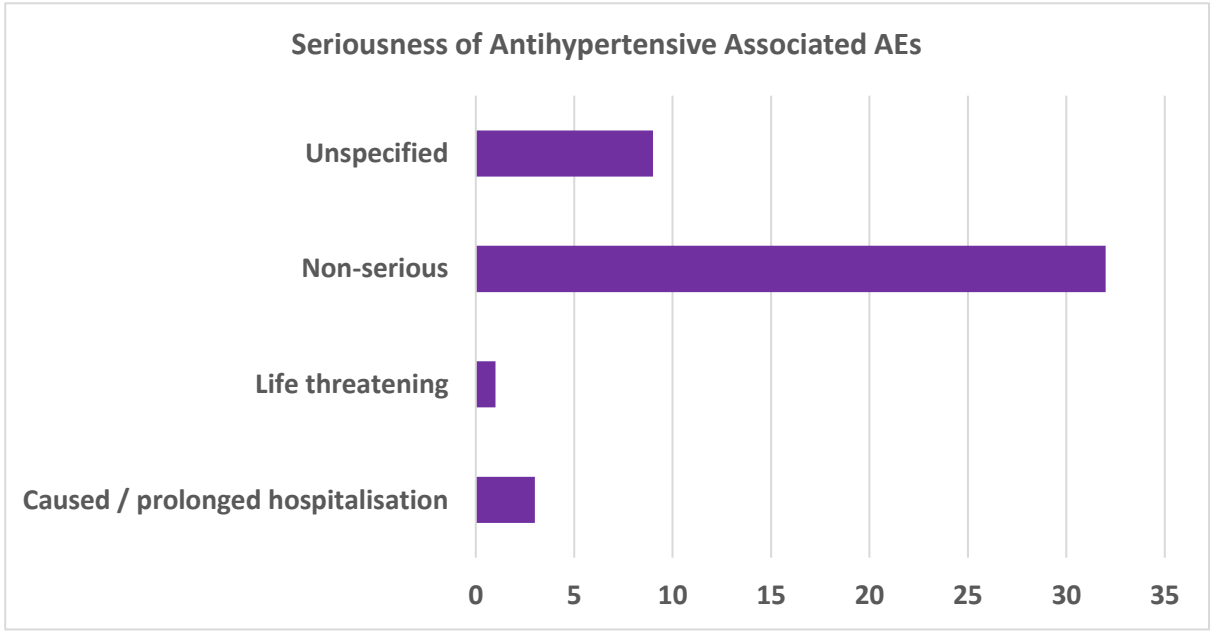

Figure 11: Seriousness of ADRs associated with antihypertensive drugs

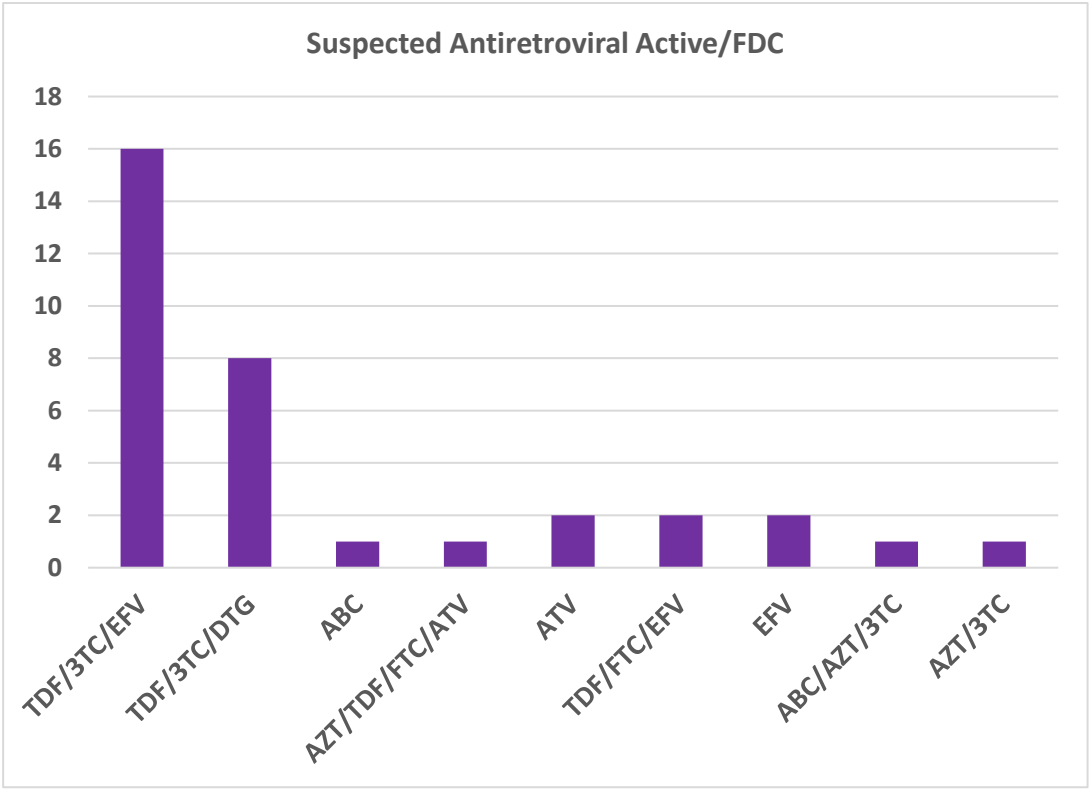

Figure 12: Number of ADR reports received on antiretroviral drugs and Fixed Dose Combinations (FDC)

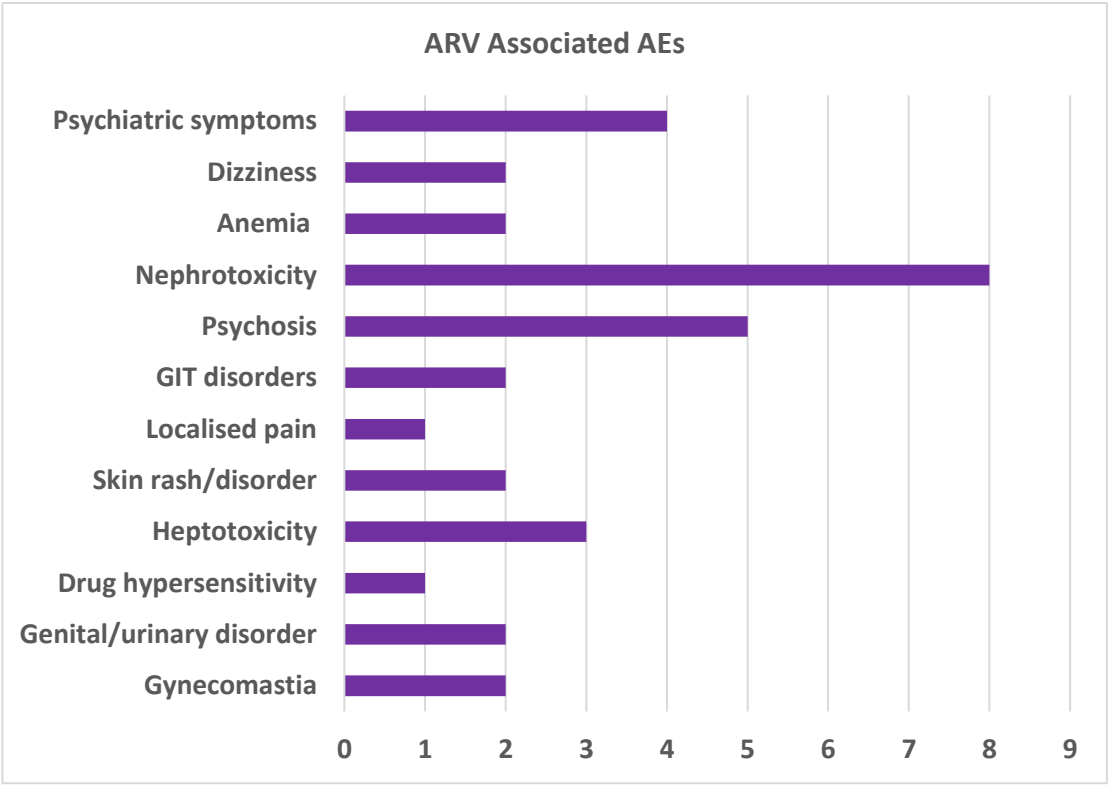

Figure 13: ADRs associated with antiretroviral

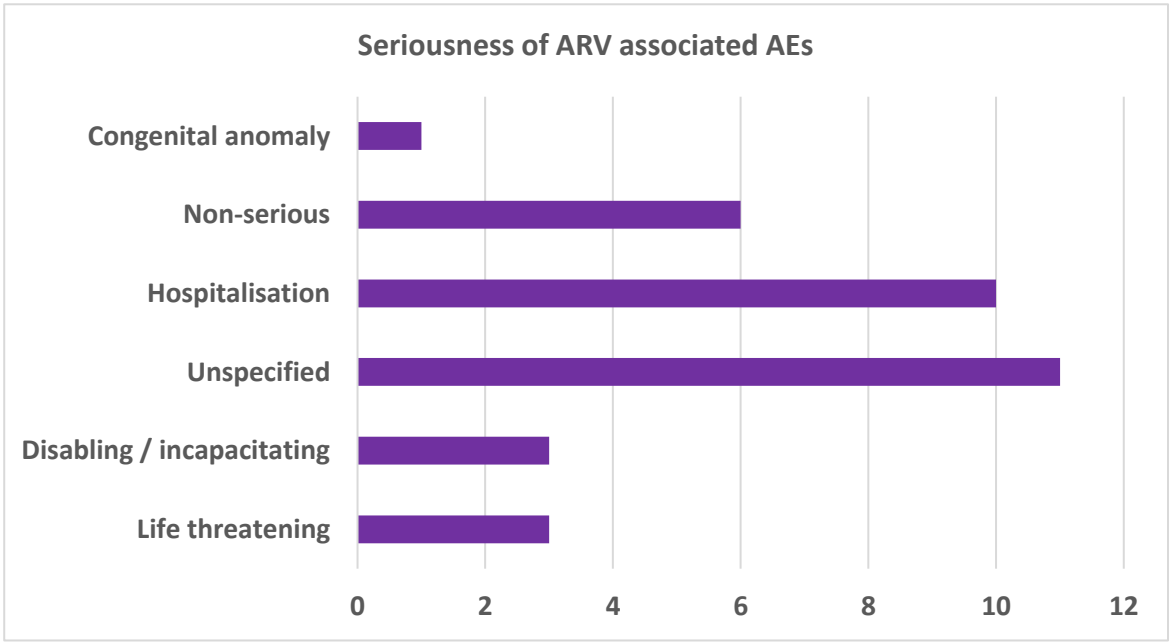

Figure 14: Seriousness of ADRs associated with antiretroviral

SUMMARY OF REPORTS

Reporter information

A total of 117 ADRs were received during the last financial year, with the first quarter of the year receiving the most reports (*Fig. 2*). The majority of the reports were reported by physicians, pharmacists and nurses (*Fig. 3*). A small proportion of reports was received from patients. The patient reports were sent through the e-Reporting tool.

The reports came from eight (8) out of the thirteen (13) regions with the leading regions being Erongo, Karas and Otjozondjupa (*Fig. 4*). An analysis of the reporting facilities indicated that Rundu intermediate hospital submitted the most reports, followed by Usakos district hospital, Otjiwarongo district hospital, Kuisebmund health centre and Omaruru district hospital (*Fig. 5*).

Adverse event information

Coughs, skin rash/disorders, oedema, gastro-intestinal symptoms and nephrotoxicity overall constituted frequently reported ADRs (*Fig.6*).

The majority of reports received were categorised as non-serious. A small proportion of ADRs resulted in prolonged hospitalisation and a much smaller number were reported to be life threatening (*Fig. 7*).

The antihypertensive and antiretroviral (ARV) medicine were the top therapeutic classes suspected to cause a high frequency of ADRs (*Fig. 8*). Perindopril was most reported, followed by amiloride/hydrochlorothiazide (*Fig. 9*).

The dry cough frequently reported (*Fig. 10*) was mainly suspected with perindopril, confirming what is already known about association with angiotensin-converting enzyme (ACE) inhibitors. The reported oedema was also not a surprise and was commonly suspected with the calcium channel blockers. The majority of the ADRs suspected with antihypertensives were non-serious, a few resulted in hospitalization and one life-threatening (*Fig. 11*) which was linked to perindopril.

The most reported ARVs were Tenofovir disoproxil fumarate/Lamivudine/Efavirenz (TDF/3TC/EFV), followed by Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir (TDF/3TC/DTG) (*Fig. 12).* As this therapeutic class is highly reported, it is no surprise to see more reports associated with the DTG-containing regimen which is now the preferred first-line for children and adult patients infected with HIV in Namibia.

Nephrotoxicity, followed by psychosis and then psychiatric symptoms were commonly reported with the ARVs (*Fig. 13*). The seriousness of most ADRs related to ARV were not specified in the reports. Some resulted in hospitalisation, a few were non-serious with one case of congenital anomaly linked to DTG (*Fig.14*).

ADDITIONAL INFORMATION

Dolutegravir and congenital anomaly

Dolutegravir is considered an important ARV for many patients living with HIV due to its favourable adverse effect profile and few drug-drug interactions, is taken once daily as part of a fixed-dose combination, and grants a low risk of developing resistance compared with other ARV. In 2019, dolutegravir was introduced as the preferred first line regimen in both adult and paediatric patients in Namibia. Dolutegravir, was found to be associated with a lower prevalence of neural tube defects (NTD) in babies born to mothers exposed to the drug. Research suggests that dolutegravir exerts partial antagonism at a folate receptor important for neural tube development. This antagonism can be overcome by administering higher doses of folate. Women living with HIV who are pregnant or wishing to conceive should supplement by taking folic acid once daily.

Tenofovir and nephrotoxicity

Drug-induced nephrotoxicity is an established adverse event associated with TDF, characterized by proximal tubular cell dysfunction and is a significant contributor of kidney disease such as acute kidney injury (AKI) and chronic kidney disease (CKD).

The mechanism of TDF-induced intracellular toxicity is thought to be via mitochondrial depletion, structural changes and leakage of mitochondrial proteins. However, the exact molecular mechanisms of injury is unclear. Withdrawal of the drug usually results in improvement of clinical manifestations of kidney injury, which may also be partial. Upon assessment of the ADR reports, TIPC has also observed the withdrawal and substitution of TDF as an intervention by the healthcare professionals. The earlier TDF related damage is detected and the drug withdrawn, recovery will be more complete.

Understanding the risk factors for nephrotoxicity and consistent monitoring of proximal tubular dysfunction as well as serum creatinine in high-risk patients is important to minimize tenofovir induced-nephrotoxicity.

SHORTCOMINGS

Low reporting

A decline in the number of reports received has been observed in the past financial year compared to the previous year that saw 176 reports. According to WHO recommendations, at least 200 ADR reports per million inhabitants should be entered into the Vigibase (WHO database) by each country. Considering the Namibian population, TIPC is expected to receive at least 400 ADR reports per year. However, the number of reports received was low at a value of 58 reports per million, indicating underreporting.

Another important observation is the lack of reports from the private health sector.

Missing information

A number of ADR reports received are missing critical information such as drug name, date drug started, adverse event and date event started. This poses a great challenge particularly when assessing causality of the case reports.

In addition, there are quite a number of reports in which the region and/or the healthcare facility from where they are reporting from were not

indicated. Hence the unspecified regions and healthcare facilities observed.

Reporter information such as email address and contact number were also missing in some reports, making it difficult for the TIPC team to follow up on reported information when required as well as provide the necessary feedback to the reporters.

All healthcare professionals are therefore encouraged to extensively complete the ADR reports. In addition, healthcare professionals such as pharmacy staff who coordinate pharmacovigilance activities in their facilities should verify completion of the reports before sending them to the TIPC.

ACTIVITY PLANS

The TIPC in collaboration with partners is planning a virtual training for the implementation of active surveillance and active drug safety monitoring for HIV and TB medicines.

REMARKS

The TIPC team wishes to thank all healthcare workers for their continuous dedication to the safety monitoring of medicines on the Namibian market by reporting suspected ADRs and most importantly ensuring that patients are appropriately managed.

Healthcare professionals can reach out to TIPC for technical support on pharmacovigilance.

Email: info.TIPC@mhss.gov.na **Tel**: 061 203 2406 **Fax2mail**: 088 660 6781

e-Reporting: https://primaryreporting.whoumc.org/Reporting/Reporter?OrganizationID=NA