NATIONAL DRUG AUTHORITY

ADVERSE DRUG REACTION REPORTING JULY –SEPTEMBER 2019

Date prepared: 5 /11/2019 Prepared by: Victoria Nambasa Sign:

1.0 Background

This report highlights the descriptive statistics of the Individual Case Safety Reports (ICSR) received at the National Pharmacovigilance centre through spontaneous reporting method for the period July to September 2019.

The report presents frequencies of drug-reaction pairs and highlights some reactions that may need extra attention when administered to patients.

2.0 Adverse Drug Reaction (ADR) Reporting Rates

A total of 542 individual case safety reports were received, with 70% reported to be serious. Kampala district reported highest (71%. n=382) followed by Wakiso (6%; n=34) and Masaka (4%, n=23), as shown in Figure 1 below.

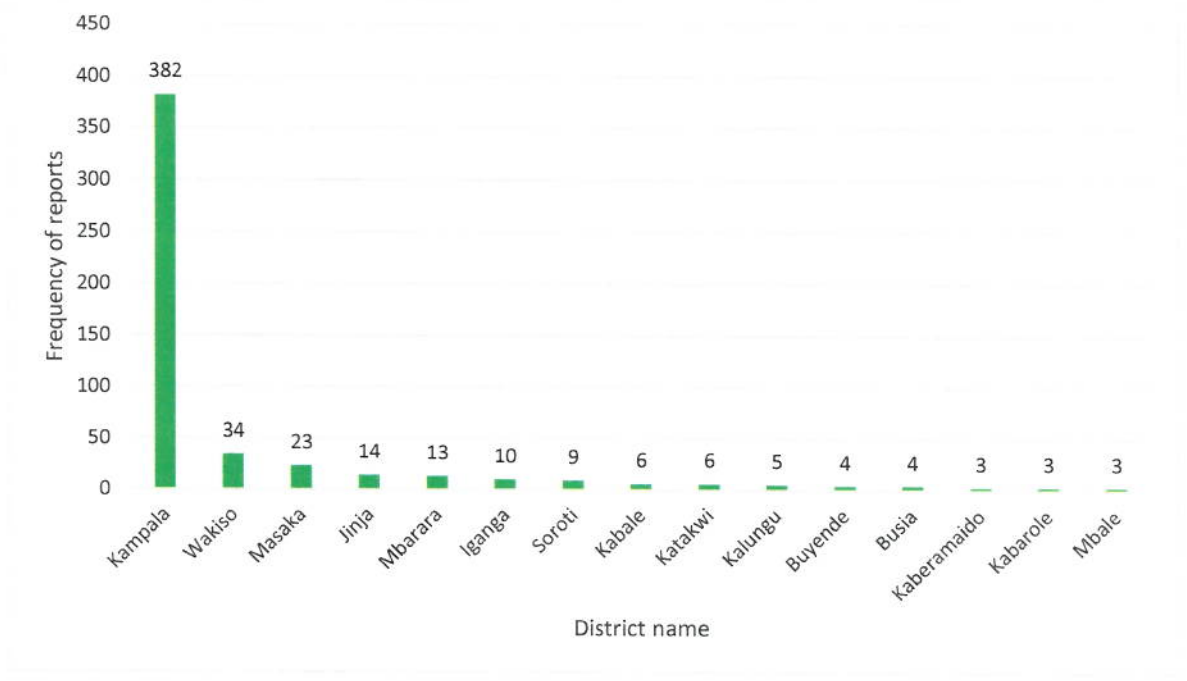

Figure 1: Number of individual case safety reports received from various districts.

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2.1 Institution performance in reporting adverse events

Overall, Infectious Disease Institute Mulago and Baylor Uganda submitted the highest number of reports followed by Mulago National Referral Hospital and Nsambya Home care as demonstrated in Figure 2 below.

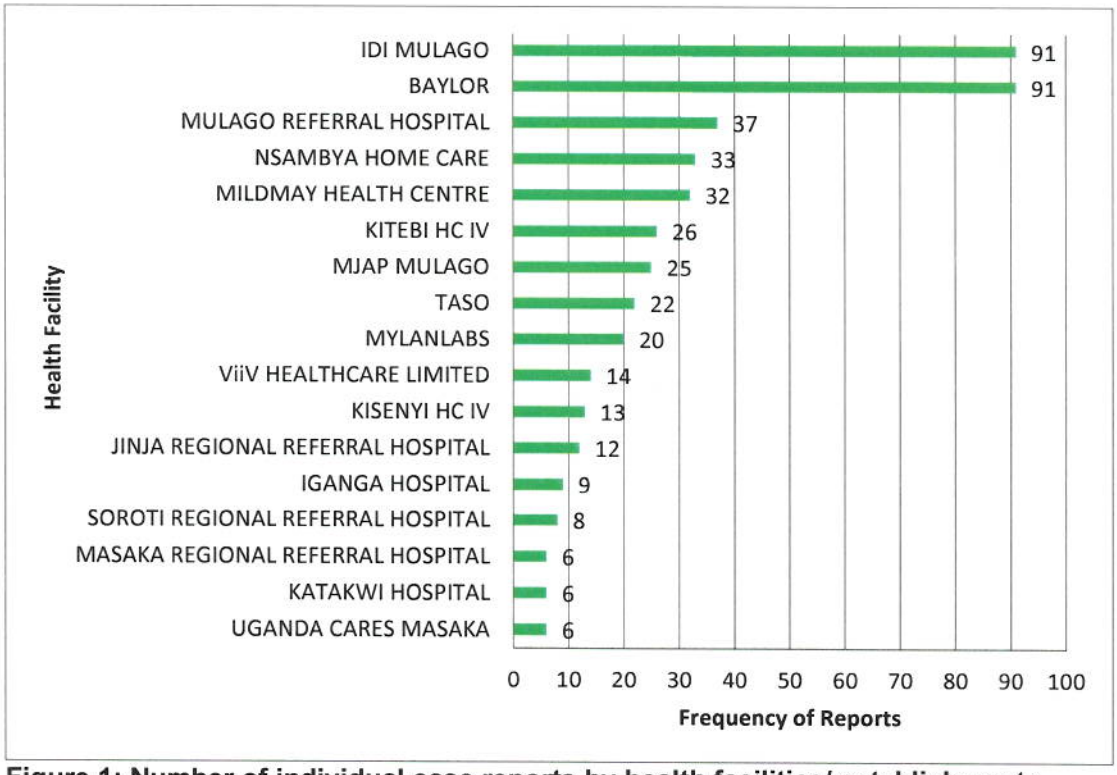

Figure 1: Number of individual case reports by health facilities/ establishments.

2.2 Adverse event reporting by professional cadres

Over all, Medical Officers submitted most reports (n=221, 43%) followed by Pharmacists (n=156, 30%), Clinical medical officers (n=89, 17%), Nurses (n=27, 5%) and Physicians (n=18, 3%) while 8 (2%) were reported by other cadres as illustrated in Figure 3.

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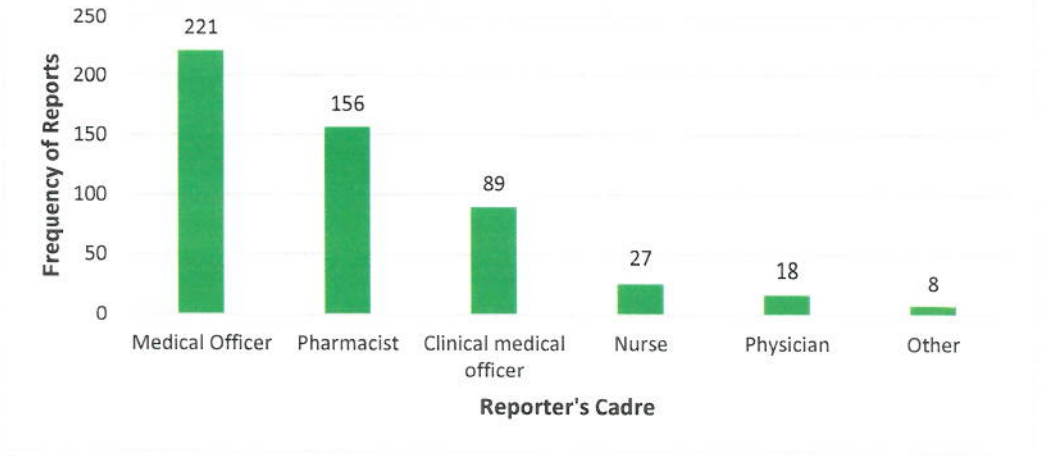

Figure 2: ADR reporting frequency per professional cadre

2.3 Characteristics of ADR reports

Majority of case reports involved known labelled reactions although 70% were serious in nature. Overall medicines used in management of HIV (ARVs) were reported most (69%; n=374), followed by medicines used in management of Tuberculosis (21%; n=116). Only 5% (n=27) of reports involved drugs used in treatment of bacterial infections as demonstrated in figure 4 below:

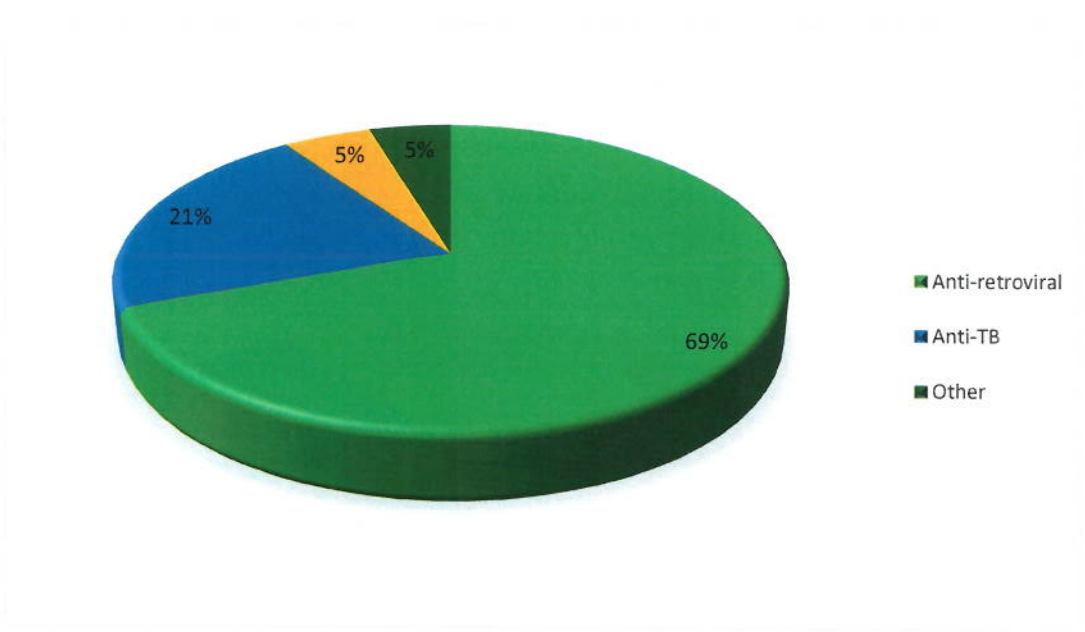

Figure 3: Proportion of ADRs reported for the different classes of Medicines

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The top 10 drug -reaction pairs reported are presented in table 1 below.

Table 1: Top 10 Drug- Reaction/ regimen pairs reported

S/N	Reactions and associated drug(s)	Frequency
1.	**Hyperglyceamia/New onset Diabetes symptoms**	**91**
	Dolutegravir	91
2.	**Liver injury** (characterised by symptoms of jaundice, right upper quadrant pain, nausea and vomiting)	**32**
	Isoniazid Atazanavir Dolutegravir	19 4 4
3.	**Dizziness**	**26**
	Efavirenz Isoniazid	14 3
4.	**Severe Headache**	**21**
	Gentamicin Isoniazid	8 4
5.	**Lipodystrophy**	**14**
	Zidovudine Efavirenz	13 1
6.	**Peripheral neuropathy**	**9**
	Isoniazid Tenofivor/Lamivudine /Dolutegravir Zidovudine	4 4 1
7.	**Itchy skin rash**	**8**
	Carbamazepine Tenofivor/Lamivudine /Dolutegravir Isoniazid Amoxycillin	3 2 2 1
8.	**Gynaecomastia**	**7**
	Efavirenz Dolutegravir	4 3
9.	**Joint Pain**	**6**
	Pyrazinamide Tenofivor/Lamivudine /Efavirenz Tenofivor/Lamivudine /Dolutegravir Isoniazid	3 1 1 1
10.	**Erectile Dysfunction**	**5**
	Tenofovir/Lamivudine/Dolutegravir Isoniazid	4 1

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3.0 Profiles of serious adverse events reported over time at NDA

3.1 Hyperglycaemia/Onset diabetes

Overall, since 2018 to date, the National Pharmacovigilance Centre has received **153** suspected cases of hyperglycaemia/onset diabetes in patients taking Dolutegravir-based regimen of which 52.6% were male and 47.4% female. The average age was 52yrs (range 31year – 81years) while mean weight of patients with diabetic symptoms was 70.16 kg (range 40 and 121 kg). The average time to onset of symptoms was 2.23 months (range 0-11 months). The average duration on ART was 10 years (range 1-16 years). Majority of the patients had previously been on a Nevirapine based regimen. The average random blood sugar at baseline for the reports that had this information was 6.2 mmol/L and at diagnosis, the average random blood sugar was 20.8 mmol/L. Only 19 of the patients were reported to have recovered while the rest were being maintained on oral hypoglycaemics or Insulin and the suspect drug had been withdrawn. Over 60% of the reactions were graded as serious due to being life threatening in nature.

3.1.1 Discussion

Onset diabetes has not been indicated in the labelled information for the drug, but hyper glyceamia was observed in the SPRING-2 and SINGLE Clinical Trials at a frequency of 1 case in less than 1000 patients.The association between Dolutegravir and diabetes mellitus is not well understood but it has been hypothesized that due to chelation of magnesium, Dolutegravir inhibits the release and signaling of insulin (Kamal and Sharma, 2019).

Since identifying this signal, the National Pharmacovigilance Centre has worked with the Ministry of Health to institute baseline and routine monitoring tests for patients to be initiated on Dolutegravir and those already on Dolutegravir.

3.1.2 Recommendation

We recommend active monitoring of patients on Dolutegravir based regimen and NDA will provide a full analysis of the cases in the subsequent publication.

3.2 Lipodystrophy:

From July to September 2019, the centre has received 14 reports of lipodystrophy. However, overall, there are 23 case reports related to Lipodystrophy attributed to the use of Zidovudine (21), Stavudine (1 case) and Dolutegravir (1case) since 2017. Majority of the cases occurred in females (65% n=20), with male 35% n=8.The mean time recorded in months for patients to on treatment to develop Lipodystrophy is 64.31. The figure below provides the age groups presenting lipodystrophy in the cases reported.

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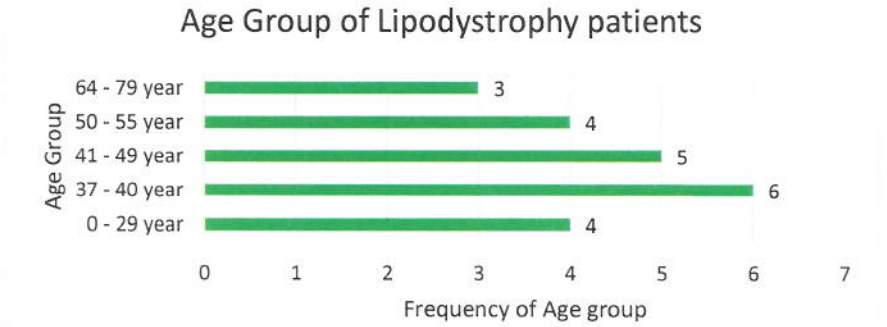

3.2.1 Discussion

Lipodystrophy refers to abnormal changes in the distribution of fat around the body along with resulting metabolic complications like elevated blood triglycerides, elevated cholesterol levels and insulin resistance. It is comprised of lipohypertrophy, which refers to abnormal central fat accumulation manifesting as a dorso-cervical fat pad, circumferential expansion of the neck, breast enlargement and abdominal visceral fat accumulation, and lipoatrophy manifesting as peripheral fat wasting in the face, arms, legs and buttocks.

According to literature most patients are observed to exhibit either one of the forms, however, less commonly; a few may exhibit both forms.

Lipodystrophy is managed by switching regimens, that is, removing Stavudine and Zidovudine from the regimen, dieting, exercising to build muscle and decrease abdominal fat and liposuction in the extreme cases.

3.2.2 Recommendation

Health workers should be aware of this adverse event that may occur in patients taking the above medicines and should counsel patients accordingly

3.3 Erectile dysfunction/ loss of libido/ impotence:

In the period between July 2019 to September 2019, there have been 5 case reports of loss of libido and erectile dysfunction suspected to be related to Dolutegravir based regimen occurring in males. Overall, there have been 16 total cases reported since 2018.

Majority of the cases reported were within the age group of 40 – 47 years as illustrated in the figure below with the mean time to onset in months 6.67.

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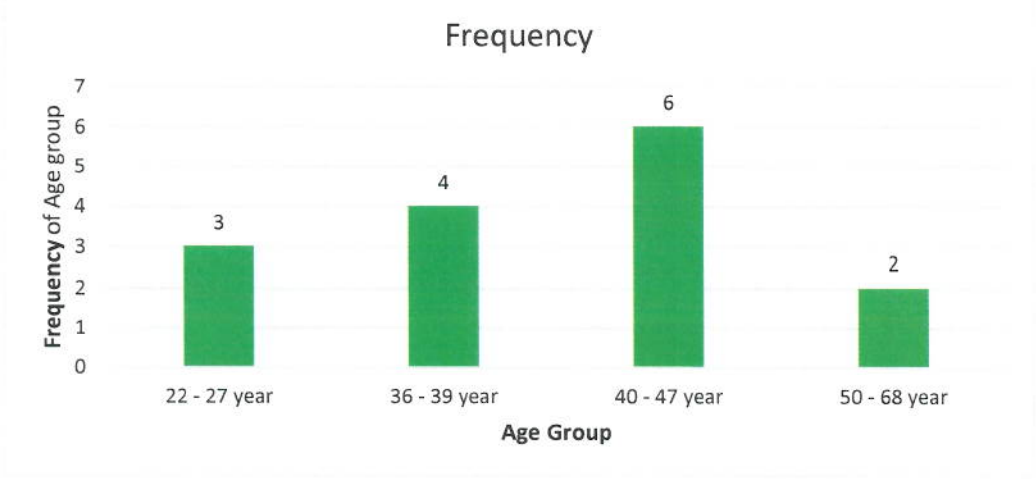

3.3.1 Discussion

Erectile dysfunction is defined as the inability to achieve or maintain an erection that is satisfactory for the completion of sexual intercourse. It is caused by factors which prevent blood flow to the penis which can either be psychological or physiological. The physiological causes have been noted to include older age, diabetes, heart disease, low testosterone levels and some medicines like, ritonavir-boosted protease inhibitors), anti-depressants and opioid painkillers. Although the summary of product characteristic for dolutegravir does not list erectile function as a side effect for the drug, some observation studies have reported erectile dysfunction in patients taking dolutegravir, which resulted in discontinuation of treatment in some patients

3.3.2 Recommendation

Although erectile dysfunction is not a well-characterised event in the Dolutegravir product label, it should be noted that the event not only could lower the quality of life, but can also be an early warning sign of heart disease and also affect patient compliance to treatment.

It is recommended that patients complaining about erectile dysfunction are managed for other possible disease conditions and counselled appropriately

3.4 Gynaecomastia

This quarter, there have been 7 reports of gynaecomastia with various suspected drugs. Overall, NDA has recorded 55 case reports of gynaecomastia in male patients taking various antiretroviral and anti-TB drugs since 2017 as presented in table 1 below.

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Table 1 Drugs suspected to be causing Gynecomastia in patients taking Antiretroviral and Anti Tuberculosis drugs

Drug name	Frequency of reaction
Efavirenz	37
Ethionamide	10
Dolutegravir	4
Tenofovir	1
Nevirapine	1
Isoniazid	1
Zidovudine	1
Grand Total	**55**

3.4.1 Discussion

Gynaecomastia is characterized by benign and generally reversible enlargement of the male breast, which may be caused by glandular proliferation and fat deposition and has been described in HIV-infected men undergoing highly active antiretroviral therapy (HAART). Gynaecomastia is caused by an increased ratio of circulating oestrogens to androgens. It manifests as a rubbery mass extending concentrically under the areola, can affect either one mammary gland or both, and may be associated with discomfort or pain and psychological distress.

There are several drugs commonly implicated with drug-induced gynaecomastia e.g. ARVs (protease inhibitors, reverse transcriptase inhibitors like Stavudine and Zidovudine), diuretics like spironolactone, antiandrogens (bicalutamide, finasteride,dutasteride), calcium-channel blockers (verapamil, nifedipine, and diltiazem), ACE inhibitors (captopril, enalapril), digoxin, β-blockers, amiodarone, methyldopa, nitrates, neuroleptics, diazepam, phenytoin, tricyclic antidepressants, , cimetidine, omeprazole, antituberculosis drugs (isoniazid, thioacetazone, and ethionamide).

Although Nevirapine and Tenofovir were reported among the possible causative drugs, there is limited literature and gynaecomastia is not a labelled reaction for these two drugs. In these individual cases reported to NDA, gynaecomastia completely resolved after a median time of 9 months (range: 5-22 months)

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These cases are presented therefore to inform healthcare providers of these events and to counsel patients appropriately to ensure compliance.

3.4.2 Recommendation

In case of suspected drug-induced gynaecomastia, discontinuation of the causative drug and reducing the dose of the causative drug often reverse the effect. If these approaches are not effective, a therapy based on tamoxifen 20mg daily may be taken into consideration and surgery in extreme cases.

3.5 Conclusion and recommendations

We thank all healthcare providers who have submitted ADR reports to NDA. We will continue to investigate the reported adverse drug reactions that are not currently labelled in the drug information leaflets especially for the new drugs that have been rolled out for use in the country.

The NDA continues to appeal to all health workers to monitor and report suspected adverse events using the national ADR reporting form or online via https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=UG

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