Safe Drugs Save Lives

NATIONAL DRUG AUTHORITY

PHARMACOVIGILANCE BULLETIN

Issue 4, June 2019

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Inside this Issue

- Need for continued vigilance for Isoniazid
- Foreign safety updates
- Rolling out aDSM in Uganda
- Quarterly report

Need for Continued Vigilance for Isoniazid: Adverse Drug Reaction Reports from Uganda

Introduction:

Isoniazid Preventive Therapy is the administration of Isoniazid to individuals with a latent infection of Mycobacterium tuberculosis in order to prevent progression to an active TB disease. In PLHIV and HIV negative children under 15 years of age, the risk of developing tuberculosis is reduced by approximately 60% and their chance of survival is also increased. On July 2nd 2019, the Ministry of Health rolled out the 100 day IPT accelerated scale-up plan which aims to enroll 300,000 PLHIV on isoniazid preventive therapy, scale up IPT initiation of children living with HIV and under-5 TB contacts at 1947 ART sites and ensure 100% completion by 30th September 2019.

ADR Reports on Isoniazid between 2017/2019

The National Pharmacovigilance Centre at National Drug Authority is tasked with detecting, assessing, understanding and preventing adverse side effects of drugs. The centre received a total of 61 reports of adverse drug reactions to Isoniazid between July 2017 and May 2019. The patients had been administered Isoniazid either alone or in combination with other drugs reported experiencing adverse drug reactions ranging from nausea, rash, peripheral neuropathy, liver injury and death. Further analysis showed that 30 patients (49.2%) experienced hepatobiliary disorders, 10 (16.4%) experienced nervous system disorders (peripheral neuropathy, whereas 12 (19.7%) experienced skin and sub-coetaneous tissue disorders. Majority of the reactions were serious, with 5 (8%) of the patients dying, 13 (21%) disabled and 10 (17%) requiring prolonged hospitalization. Although the FDA warns that patients older than 35 are more likely to experience liver injury, according to the Ugandan data, children below 21 also got hepatobiliary disorders. A total of 8 (13.11%) children with ages ranging from 3 to 19 years got hepatocellular toxicity.

Figure 1: A graph showing the various adverse drug reactions experienced by patients on Isoniazid

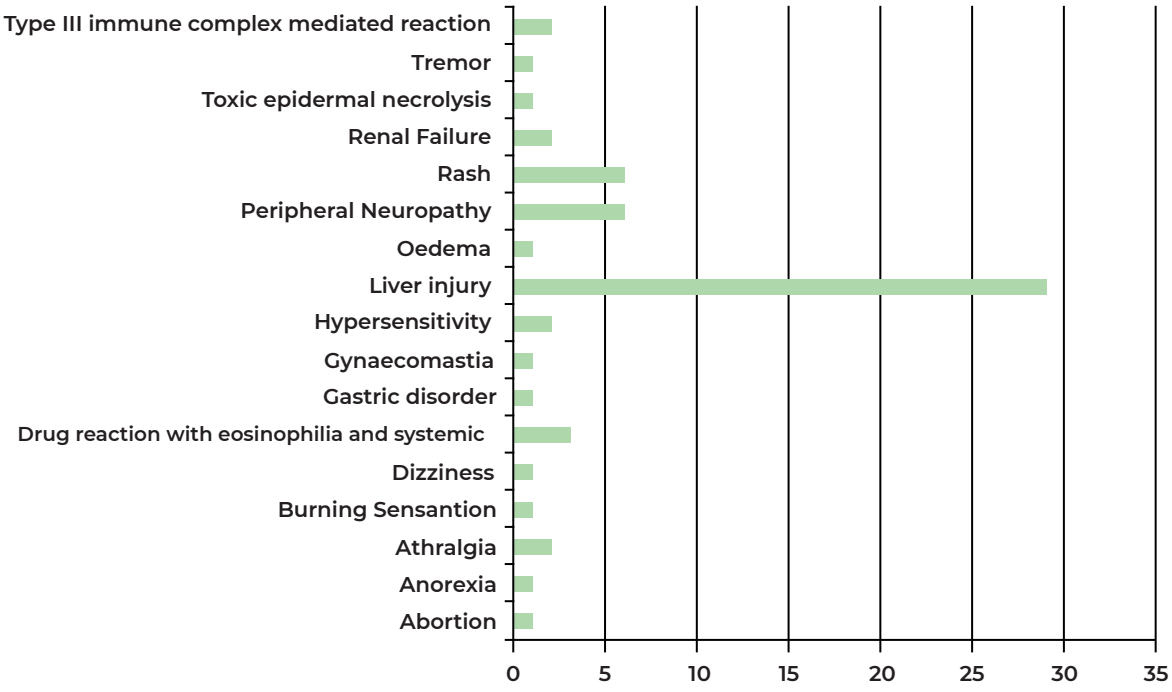
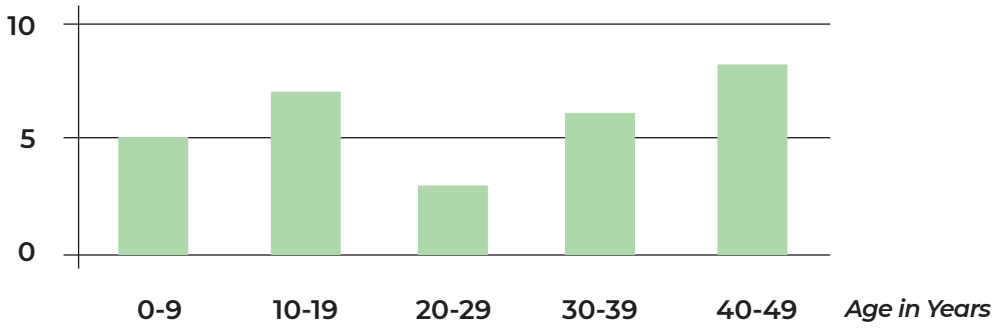


Figure 2:. A graph showing liver injury by age among the reported reactions



Observations and conclusions

Patients with comorbidities were observed to be at a higher risk of developing liver injury. This could be because they are on a combination of several drugs which in itself is taxing to the liver. We recommend that health workers continue to carefully follow the eligibility criteria and observe the contraindications as specified by the MoH IPT guidelines before initiating patients on IPT. The use of INH should be strictly monitored both before, during and after therapy with INH. Whenever possible, liver function tests should be performed for all eligible clients regardless of age and should be continued at regular intervals throughout therapy. In resource limited settings, actively screen patients at each visit by asking about symptoms of liver injury such as jaundice, abdominal pain, nausea and vomiting. When liver injury is identified, the first line of treatment is to stop the drug and monitor the patient for recovery. In most cases patients recover. However, rechallenge of patients with more severe liver injury can result in a rapid onset of symptoms (within hours) and is contraindicated.

Foreign Safety Updates

Magnesium Sulfate: Risk of Skeletal adverse effects in neonates following prolonged or repeated use in pregnancy

Magnesium sulfate is indicated for several conditions including severe acute asthma, Prevention and treatment of seizures in pre-eclampsia and eclampsia respectively, hypomagnesaemia, and others. Maternal administration of magnesium sulfate for longer than 5 – 7 days in pregnancy has been associated with skeletal adverse effects and hypermagnesemia in neonates. If there is prolonged or repeated use Magnesium sulfate, healthcare providers should consider monitoring neonates for abnormal calcium and magnesium levels as well as skeletal adverse effects which may include hypocalcaemia, skeletal demineralization and osteopenia.

Reference: MHRA Drug Safety Update Volume 12 Issue 10 May 2019

Active Drug Safety Monitoring in Uganda

Monitoring product safety has been traditionally done by passive surveillance (voluntary reports) or the collection of spontaneously reported adverse events from healthcare providers and consumers following the administration of a medicinal product.

In 2016 the World Health Organisation issued interim policy on the use of two new drugs, bedaquiline and delamanid in 2013 and 2014 respectively, and active TB drug-safety monitoring and management is one of the conditions set for the implementation of the new drugs. Health programmes that systematically monitor patient safety are in a better position to prevent and manage adverse drug reactions (ADRs), relieve patient suffering and improve treatment outcomes.

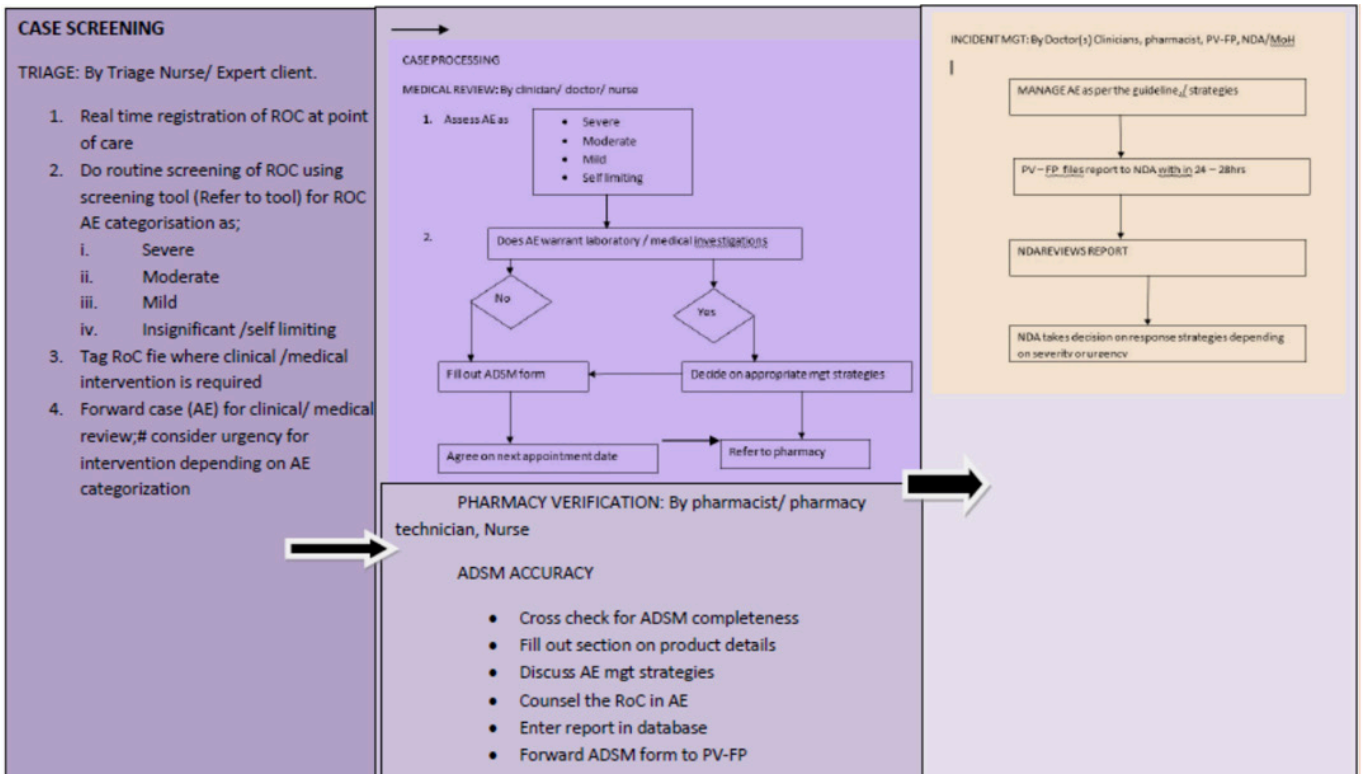
The term 'active drug-safety monitoring and management' (aDSM) defines active and systematic clinical and laboratory assessment of patients while on treatment. aDSM applies to patients on treatment with: (i) new anti-TB or HIV drugs; (ii) novel MDR-TB regimens; or (iii) extensively drug-resistant TB (XDR-TB) regimens, in order to detect, manage and report suspected or confirmed drug toxicities (WHO, 2015).

Emerging trends show that certain adverse events such as liver toxicities with some anti-TB and antiretroviral drugs would be prevented if there was active monitoring of liver enzymes in target patient categories.

As such, the Ministry of Health, National Drug Authority and supporting partners are rolling out an active drug safety monitoring tool to be used specifically in the TB and HIV clinics where patients have been initiated on new drugs. The traditional passive surveillance tool will continue to be used alongside the aDSM tool for both TB and HIV and all other conditions.
Beginning June 2019, implementing partners pilot tested the aDSM tool in three select facilities of Naguru, IDI and Mildmay.

Figure 2: Health Care Providers at Mildmay receiving training on piloting the aDSM tool.

Active Pharmacovigiliance SOP (process flow)

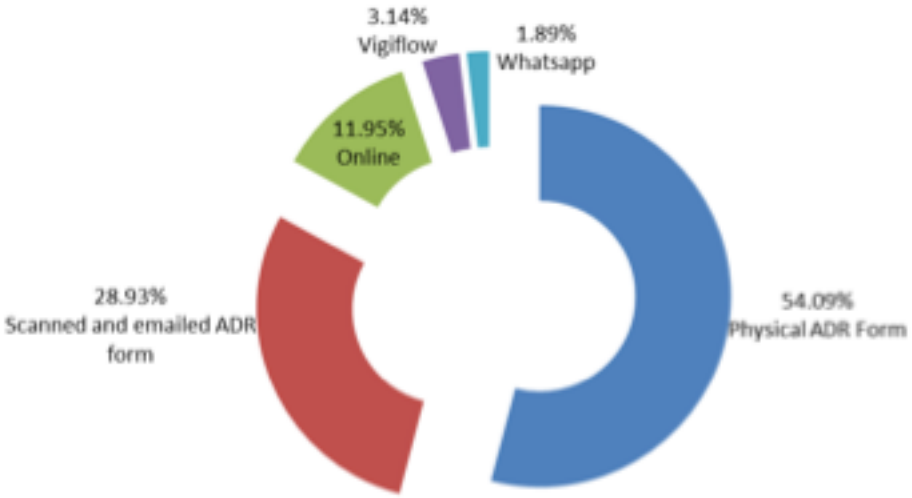


Health workers are encouraged to embrace the aDSM when it is rolled out and to continue passive surveillance at their facilities.

Report for the Pharmacovigilance bulletin for the last quarter of 2018/2019 financial year

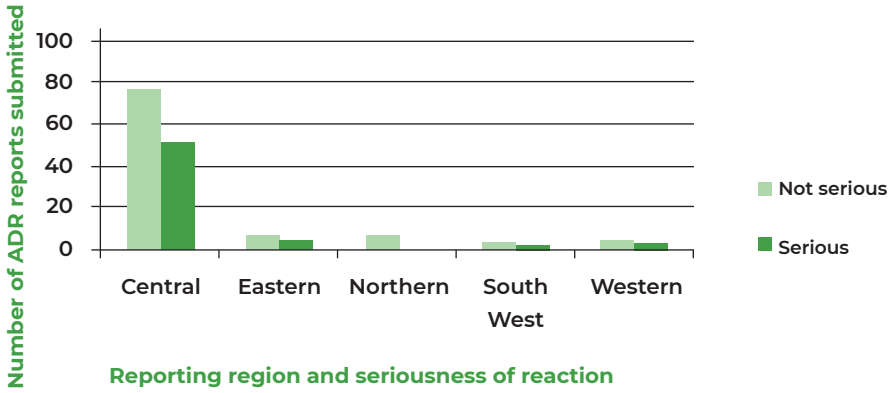
A total of 160 reports were received at the National Pharmacovigilance Centre in the period from 1st April 2019 to 30th June 2019. Over half of them were submitted through hard copy forms.

Reporting Cahnnels



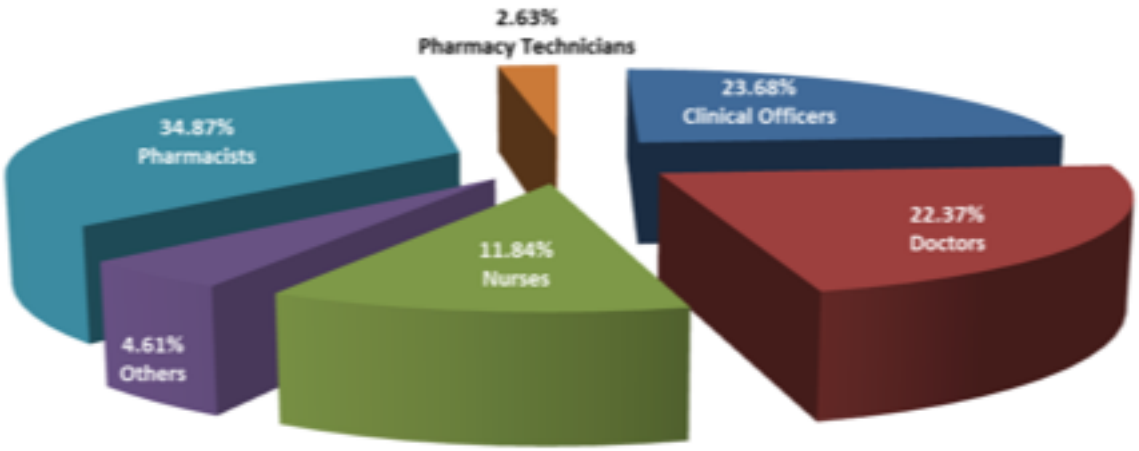
The Central region submitted the highest number of reports at 82%, followed by the Eastern region which submitted 7% of the total reports, 4.46% reports were from Western Uganda 2.5% from Northern and 3.18% from the South West. Of the reported ADRs 40.13% were reported as serious.

Figure 3 **Frequency of submitted ADR reports by NDA Region**

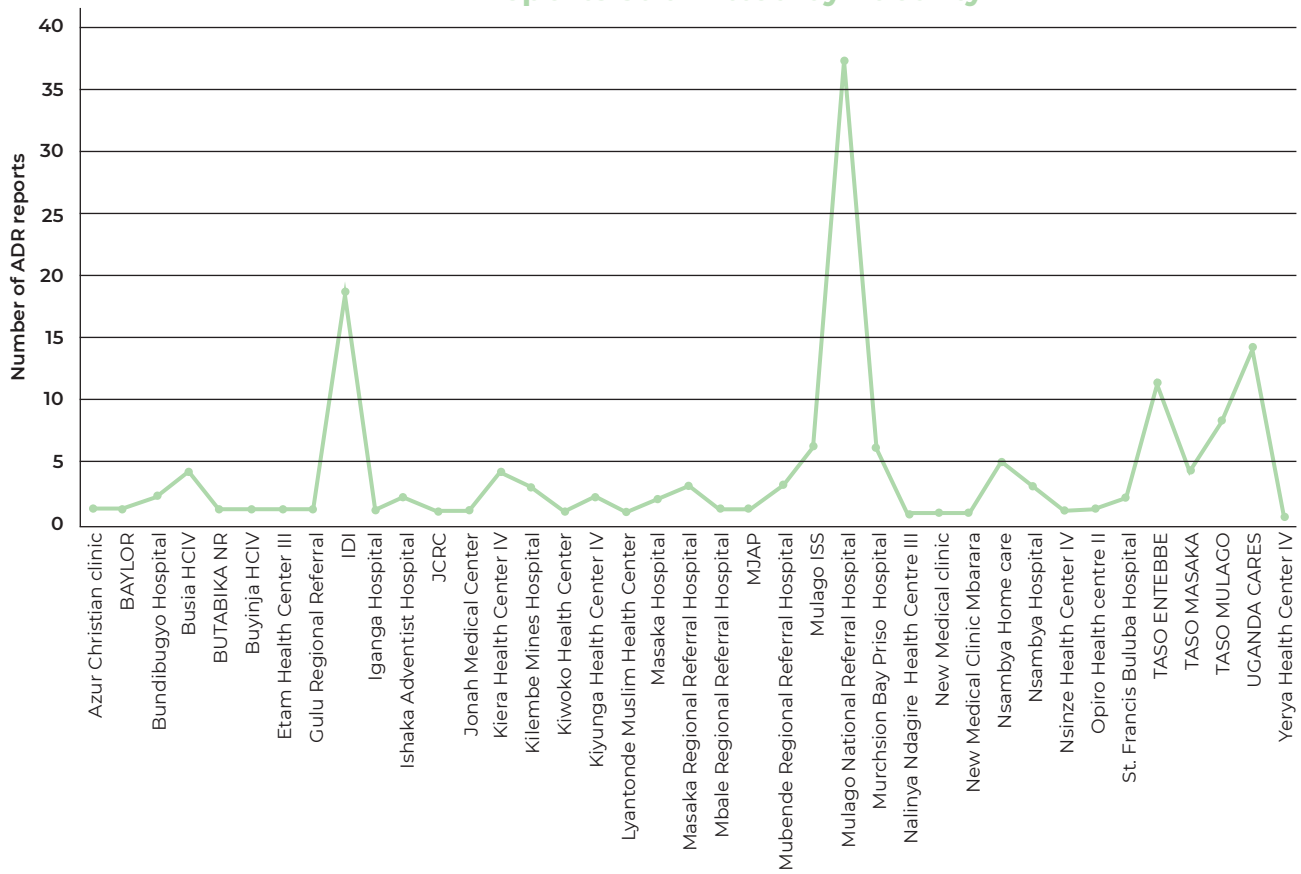


34.87% of the reports were submitted by Pharmacists, 23.68 were submitted by clinical officers, 22.37% were submitted by Doctors, 11.84% by Nurses, 4.61% by others and 2.63% by Pharmacy technicians.

Total Reports Submitted by Professional Cadre

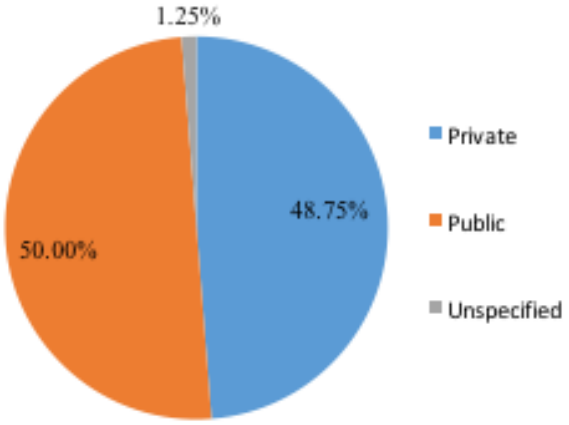


Reports submitted by Faculity



Mulago National Referral Hospital submitted the highest number of ADR reports (37), followed by Infectious Diseases Institute (18), Uganda Cares (14). The TASO clinics of Mulago (8), Entebbe (11) and Masaka (4) had a combined total of 23 reports, the second highest. Health Centre IV facilities in the new districts of Bunyangabu, Luuka, Buyende, Kyankwanzi and Namutumba were diligent in reporting at least one ADR each in the period of April to June 2019. The ADR reported in Kyankwanzi was an adverse event following immunization with BCG vaccine. The reports were almost equally distributed between public and private facilities with public facilities submitting 50% of the reports.

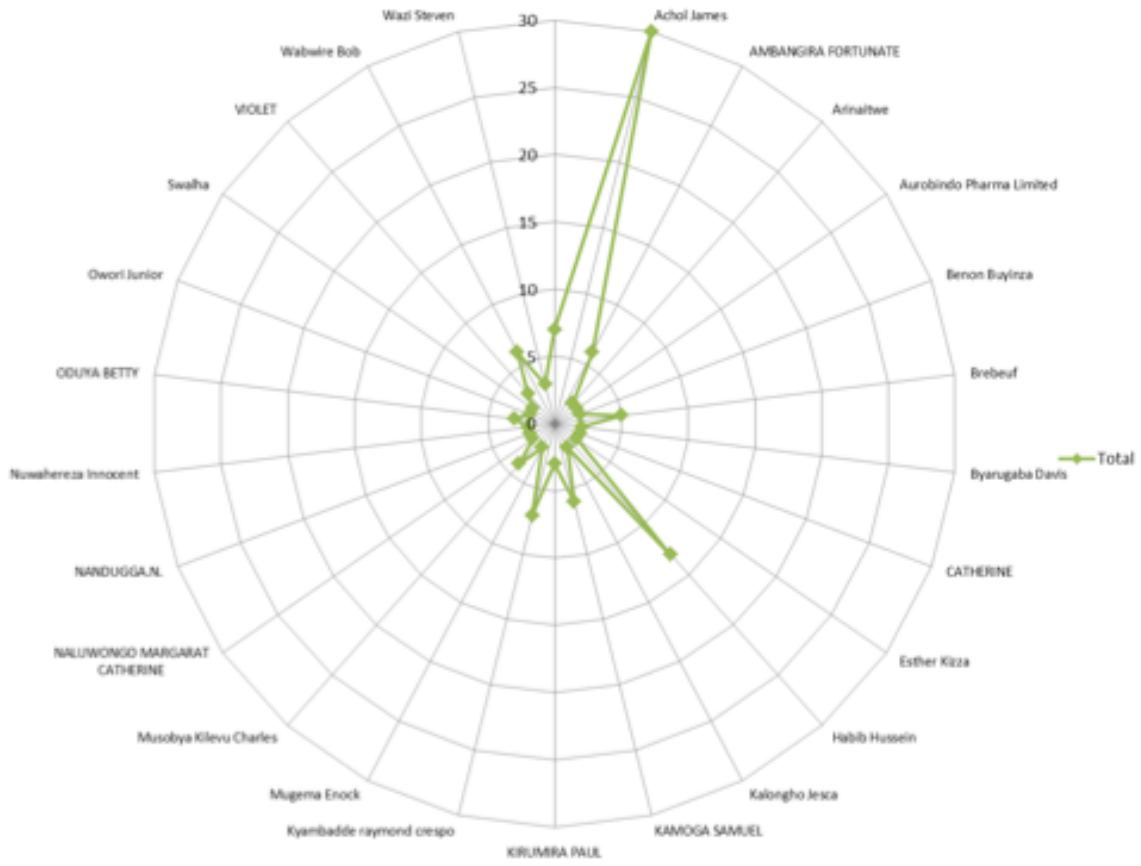
Total Reports by Facility Type



Diligent reporters

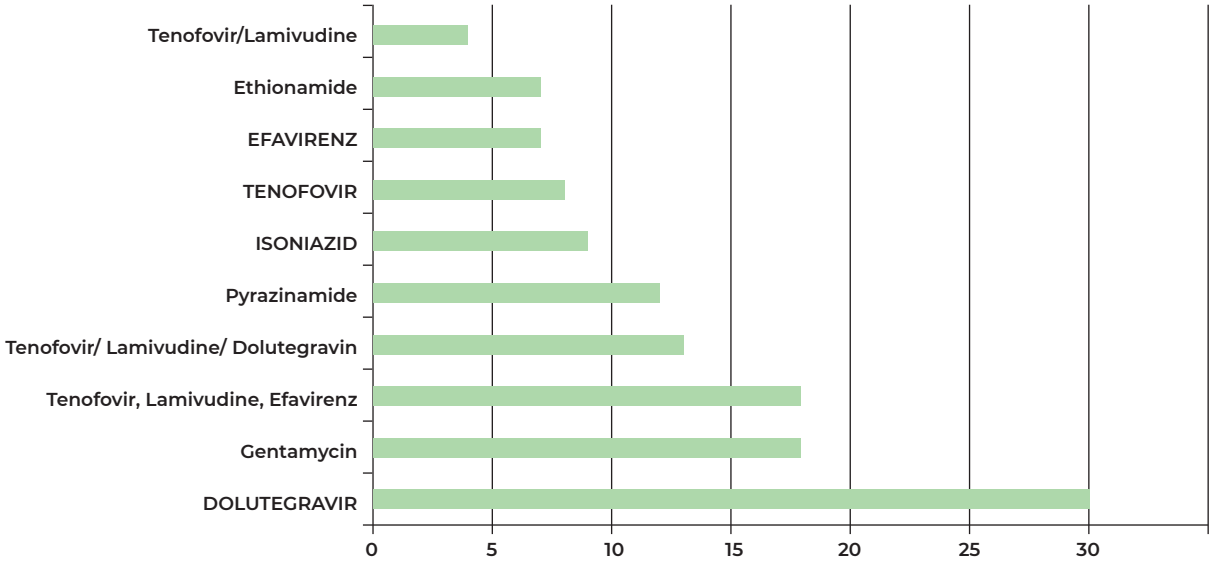
Health Workers with the highest number of submitted reports were Achol James, Habib Hussein, Kyambadde Raymond Crespo, Kamoga Samuel, Wabwire Bob, Ambangira Fortunate, Brebeuf and Musobya Kilevu Charles.

Reports Submitted by Health Workers



The top ten drugs with the commonest reactions were: Dolutegravir 30 reports, Gentamycin 18, Efavirenz 18, Tenofovir/Lamivudine/Dolutegravir combination 13, Pyrazinamide 12, Isoniazid 9, Tenofovir 8, Efavirenz alone 7 reactions, Ethionamide 7 and Tenofovir/Lamivudine 4. At least two reactions indicated by "?" could not be pinned down to a specific drug in patients co-infected with HIV and TB who were on up to 10 different medications at the time.

Commonly Suspected Drugs in ADRs



Drug Reaction Pairs

Suspected Drug Generic Name	Patients reporting	Commonest Reactions	
Dolutegravir	**29**	Diabetes Mellitus	2
		Hyperglycaemia	6
		Headache	2
		Athralgia and Myalgia	3
		Facial puffiness	1
		Skin rash	2
		Loss of Libido	2
		Insomnia	3
		Weakness	4
Gentamycin	**18**	Severe Headache	18
		Palpitations	6
		Shortness of Breath	5
		Sweating	1
		Dizziness	4
		Syncope	1
Tenofovir+Lamivudine+Efavirenz	**14**	Dizziness	5
		Nightmares	1
		Nausea and Vomiting	3
		General Body Weakness	3
		Diarrhoea	2
		Jaundice	1
Pyrazinamide	**12**	Athralgia	7
		Peripheral neuropathy	3
		Exertional chest pain	2
Isoniazid	**9**	Hypersensitivity reaction	7
		Blurred vision	2
		General body weakness	1
Tenofovir+Lamivudine+Dolutegravir	**8**	Nausea and vomiting	1
		Jaundice	1
		Hyperglycaemia	2
		Itching	1
Tenofovir	**8**	Renal toxicity	8
Efavirenz	**7**	Dizziness	5
		Drowsiness	5
		Gynaecomastia	2
Ethionamide	**7**	Excessive salivation	2
		Loss of appetite	1
Cycloserine+Ethionamide	**3**	Dizziness	1
		Gynaecomastia	1
		Weight gain	1

If you have any comments or feedback on any of the articles in this bulletin, we would be pleased to receive them at druginfo@nda.or.ug/ dps@nda.or.ug

To report Adverse Drug Reactions complete the Adverse Drug Reaction form and return it to any NDA office near you or send a direct online report at

https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationI D=UG

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E-mail: druginfo@nda.or.ug
Call: 0800 101 999 or whatsapp on 0791 415 555

You can visit us at: **www.nda.or.ug**