Bulletin Volume 12: Issue 4:2020

UGANDA
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PHARMACOVIGILANCE

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DRUGS

All medicine can cause side effects, particularly if you dont use them as advised.

HERE IS HOW TO STOP AND OR MINIMISE THESE SIDE EFFECTS.

STEP 1

Carefully read the Patient Information Leaflet(PIL) supplied with your medicine.

STEP 2

Ask your healthcare provider about the expected side effects and how to reduce the risks of their occurence.

STEP 3

Report to National Drug Authority

Remarks from the
Pharmacovigilance Center

Dr. Helen Byomire Ndagije
Director Product Safety
National Drug Authority

As the country and our health system continues to battle the challenge of COVID-19, health workers have kept at the front line to hold the forte against this and other health challenges. Therefore, every report received this year 2020 has been a sign of this selfless commitment, which continues to inspire us all at the national pharmacovigilance center.

The safety reports in this period broadly related to known and labelled reactions, but some peculiarities were also noted. Mental health in HIV is not uncommon, and the rising drug interaction between carbamazepine and dolutegravir noted in this reporting period threatens treatment outcomes in HIV care.

Additionally, drugs concomitantly administered and known to cause similar reactions make it difficult for any care giver to identify the offending drug to inform therapy decisions. Such incidents were noted and are presented herein. These and other safety issues discussed in this bulletin will need extra scrutiny by health workers and the center moving forward.

We encourage you to continue reporting drug reactions through the channels indicated at the end of this bulletin.

I thank you.

EDITORIAL TEAM >>

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5. Ian Mugisa
6. Douglas Mwesigwa
7. Joanitah Atuhaire
8. Francis Odipiyo
9. Noah Mutebi

Local safety Experience

Adverse Drug Reaction Reports

A total of 445 ADR reports received this second quarter (relative to 561 reports in Q1), with just less than half (38.2%) from facilities in Kampala, followed by Wakiso (8.8%). The traditional paper-form remained the dominant method of reporting, contributing 54% of reports, followed by whatsapp at 26%. Most were related to ARVs (73%), followed by anti-TB drugs (16%), with more than half (62%) reported as serious, majority being life threatening and or incapacitating. Summary trends are presented at the end of the bulletin.

Overall, most cases were related to known and labeled events. The ongoing safety concerns of DTG mediated hyperglycaemia, isoniazid related pellagra and hepatotoxicity continued to register cases and further characterisation is being done by the center to better inform risk mitigation. Notwithstanding, some arising safety concerns were noted and specific discussions are presented below. All health care providers are encouraged to look out for these issues and report them to enable the center better understand them.

Emerging safety issues

Potential Co-occurrence of TDF mediated proximal tubulopathy and DTG mediated hyperglycaemia in TLD patients

Hyperglycaemia among TLD patients is now a known safety concern for which close monitoring has been recommended in the current guidance on HIV care and treatment. We have noted that most of the received cases of Hyperglycaemia among TLD patients reported with at least; polyuria, polydipsia. Some of the cases co-reported with skeleton-muscular events related to limb, back pain and paraesthesia. From the urinalysis results, several of the cases manifested glucosuria, and proteinuria.

From these presentations, we think there might be a co-occurrence of two different events with cross-cutting symptoms, i.e; TDF mediated proximal tubulopathy and DTG mediated hyperglycaemia.

On the one hand; Tenofovir is principally eliminated via the kidney. Renal impairment, with elevated creatinine, and glucosuria, proteinuria, hypokalemia, hypophosphatemia, and hyperchloremic metabolic acidosis related to proximal tubulopathy may

occur in ≥1/1,000 to <1/100 of patients on TDF leading to osteomalacia, rhabdomyolysis, muscular weakness. Additionally, the nephropathy may lead to Fanconi syndrome, which manifests clinically with polyuria, polydipsia, bouts of dehydration (sometimes associated with fever), bone deformities, and impaired growth in children.

On the other hand; DTG mediated hyperglycemia will also present with polyuria and polydipsia, which symptoms also occur in the Fanconi syndrome. However, this event is not known to affect renal function as is the case with TDF.

Concluding remarks;

1. In order to dissociate the two events, the team may have to investigate renal function in future cases with similar symptomatic profiles through performing RFTs or urinalysis (proteinuria, other markers) and blood work for creatinine, hypokalemia, and hypophosphatemia. Patients with normal renal function but with DM symptoms may be cases of exclusively DTG mediated hyperglycaemia.

2. Cases with both hyperglycaemia and renal tubulopathy may not benefit from just the withdrawal of DTG, as TDF may still be the offending drug. The team may have to explore a regimen devoid of TDF and DTG.

3.Patients switching from non TDF based regimens to TDF based regimens will require baseline assessment of their renal function before a decision is made to initiate them as these are at risk of developing the TDF mediated tubulopathy, and associated osteomalacia, muscular events, and fanconi syndrome.

“

We encourage all health workers to continue looking out for and **reporting any cases of ADRs they may encounter during their care.**

Symptoms of confusion among patients on DOLUTEGRAVIR or ATAZANAVIR based regimens taking carbamazepine

The center received a case of a 52 year old female epileptic patient on Cabamazepine, who presented with symptoms of confusion and general malaise immediately after transitioning to tenofovir + lamivudine + dolutegravir regimen in June 2019. These symptoms resolved after the patient was switched to tenofovir + lamivudine + nevirapine in September 2019. These symptoms re-occurred when the patient was transitioned to tenofovir + lamivudine + Atazanavir in September 2020, but have since resolved after switching her back to the nevirapine based regimen.

According to product labelling, Atazanavir may increase plasma levels of carbamazepine due to CYP3A4 inhibition. Since raised plasma carbamazepine levels may result in adverse reactions including; feeling confused, or behavioral changes, dizziness, drowsiness, ataxia, diplopia, it's reasonable to suspect that ATZ induced the confusion and general malaise seen in this patient. Dolutegravir neither induces nor inhibits CYP isoenzymes and it's still unclear the possible mechanism by which the patient manifested similar symptoms on the DTG regimen.

Additionally, due to carbamazepine inducing effect on the CYP isoenzymes, a reduction in Atazanavir and Dolutegravir exposure cannot be ruled out. The DTG summary of product characteristics recommends doubling the dose of DTG in Cabamazepine co-administration. This potential for sub-therapeutic levels of DTG and ATZ predisposes the patients to poor virologic responses.

The center advises that Carbamazepine should be used with caution in combination with Atazanavir and DTG based regimens, preferably avoided where possible. Close monitoring of the Patient`s virologic response should be exercised where co-administration cannot be avoided.

Hepatitis-B mass vaccination See any adverse effects?

In 2015, the Ministry of Health Uganda started the vaccination of adolescents and adults against Hepatitis B virus disease targeting 17,636,153 people in this category. Mass vaccinations involve administration of vaccine doses to a large population over a short period of time. This increases the chances of adverse events following immunization (AEFIs), including rare previously undetected events.

Safety labeling for the monovalent Hep B vaccine indicates that AEFIs are usually mild and confined to the first few days of the vaccination. The most common reactions are mild soreness, erythema, injection site induration, fatigue, fever, malaise, influenza-like symptoms. Less common systemic reaction include nausea, vomiting, diarrhea, abdominal pain, abnormal liver function tests, arthralgia, myalgia, rash, pruritus, urticaria, liver function.

There are a total of 102 575 AEFIs related to the vaccine predominantly among age groups of 18-44 years (30%) followed by neonates (25%), and 45-64 years (10%) occurring marginally more in females (58%). Although labelled as rare, skin reactions are the third most reported AEFIs with the vaccine (25%), after injection site complications (54%) and nervous disorders (31%).

In Uganda, the center has received only 2 reports of a 34 and a 35 year old females who developed pruritic skin reactions after vaccination. The reporters indicated “Generalized itchy body swelling in the whole body since giving the Hep b jab” and “34 year old female reported complaining of body rash affecting the face, thoracic and pelvic regions following administration of Hepatitis B vaccine”. One of the patients had the reaction on the day of vaccination whilst the other after 6 days.

Receiving only 2 reports in a mass vaccination of this magnitude is reasonably a sign of under reporting. This limits our capacity to appraise the vaccines safety in this new subpopulation and any previously unknown AEFI trends may be missed. The center would like to encourage all health workers to look out for and report any negative effects among vaccinated individuals. You are also encouraged to educate patients on the known adverse effects and urge them to report back in case they experience negative effects.

Adverse Reactions	Frequency
General disorders and administration site conditions	
Local reactions (injection site); transient soreness, Erythema Induration	Common (≥1/100 to, <1/10>
Fatigue, fever , malaise, influenza-like symptoms	Very rare (<1/10,000)
Blood and lymphatic system disorders	
Thrombocytopaenia, Lymphadenopathy	Very rare (<1/10,000)
Immune system disorders	
Serum sickness, Anaphylaxis , Polyarteritis nodosa	Very rare (<1/10,000)
Nervous system disorders	
Paresthesia, Paralysis (including Bell's palsy, facial paralysis) Peripheral neuropathies (polyradiculoneuritis, Guillain Barre Syndrome), Neuritis (including optical neuritis), Myelitis (including transverse Myelitis), Encephalitis, Demyelinating disease of central nervous system. Exacerbation of multiple sclerosis, Seizure, Headache, Dizziness, Syncope	Very rare (<1/10,000)
Eye disorders	
Uveitis	Very rare (<1/10,000)
Vascular disorders	
Hypertension, Vasculitis	Very rare (<1/10,000)
Respiratory , thoracic and mediastinal disorders	
Bronchospasm-like symptoms	Very rare (<1/10,000)
Gastrointestinal disorders	
Vomiting, Nausea, Diarrhoea, Abdominal pain	Very rare (<1/10,000)
Skin and subcutaneous tissue disorders	
Rash, Alopecia, Pruritus, Urticaria, Erythema multiforme, Angioedema, Eczema	Very rare (<1/10,000)
Musculoskeletal, connective tissue and bone disorders	
Arthralgia, Arthritis, Myalgia, Pain in extremity	Very rare (<1/10,000)
Investigations	
Elevation of liver enzymes	Very rare (<1/10,000)

Safety communications from other regulatory bodies

Interaction between efavirenz and Ginkgo biloba extracts (European Medicines Agency (EMA)

Based on two published cases suggestive of an interaction between efavirenz and Ginkgo biloba extracts with a negative impact on efavirenz and/or on viral load and having reviewed the manufacturer`s response the same, the EMA considers that a deleterious pharmacokinetic interaction between efavirenz and Ginkgo biloba extracts is plausible. The Agency has asked the manufacturers` to reflect this risk in the product information of efavirenz-containing medicinal products. Two publications, on this risk were encountered that demonstrated sub-therapeutic efavirenz concentrations with Ginkgo biloba extracts, possibly through induction of CYP3A4 or CYP2B6 enzymes. Although the EMA doesn't advise contraindication, concomitant use of Gingko biloba extracts is not recommended and should be avoided where possible.

Ondansetron (Potential risk of oral cleft defects)

New Zealand. Medsafe has announced that the data sheets of ondansetron-containing medicines are being updated with information on the increased risk of oral cleft defects associated with first trimester use.

Ondansetron is a selective serotonin receptor antagonist and is used to manage and prevent nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron is also used off-label during early pregnancy. In New Zealand, first trimester use of ondansetron is increasing. Two recent epidemiological studies investigated the risk of orofacial cleft defects and other congenital malformations in infants who were exposed to ondansetron in utero, using data in the United States. The result of one study showed statistically significant increase in oral cleft with the use of ondansetron, whereas the result from the other study was not statistically significant.

The Medicines Adverse Reactions Committee (MARC) noted that although the effect sizes in the studies were small and there is some uncertainty in the data, the current evidence suggests a small increase in the risk of oral cleft defects associated with the use of ondansetron in the first trimester.

References

: **Prescriber Update, Medsafe, June 2020** *(www.medsafe.govt.nz/)*
(See also WHO Pharmaceuticals Newsletter No.2, 2020: Risk of oral clefts in UK; No.6, 2016: Assessing potential harm to the foetus: insufficient information in Canada)

Fluoroquinolone
Risk of aortic aneurysm and dissection

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for fluoroquinolone antibiotics has been updated to include the risk of aortic aneurysm and dissection.

Fluoroquinolones are broad-spectrum antibiotics that are active against both Gram-negative and Gram-positive bacteria. Fluoroquinolone antibiotics marketed in Australia include ciprofloxacin, norfloxacin and moxifloxacin.

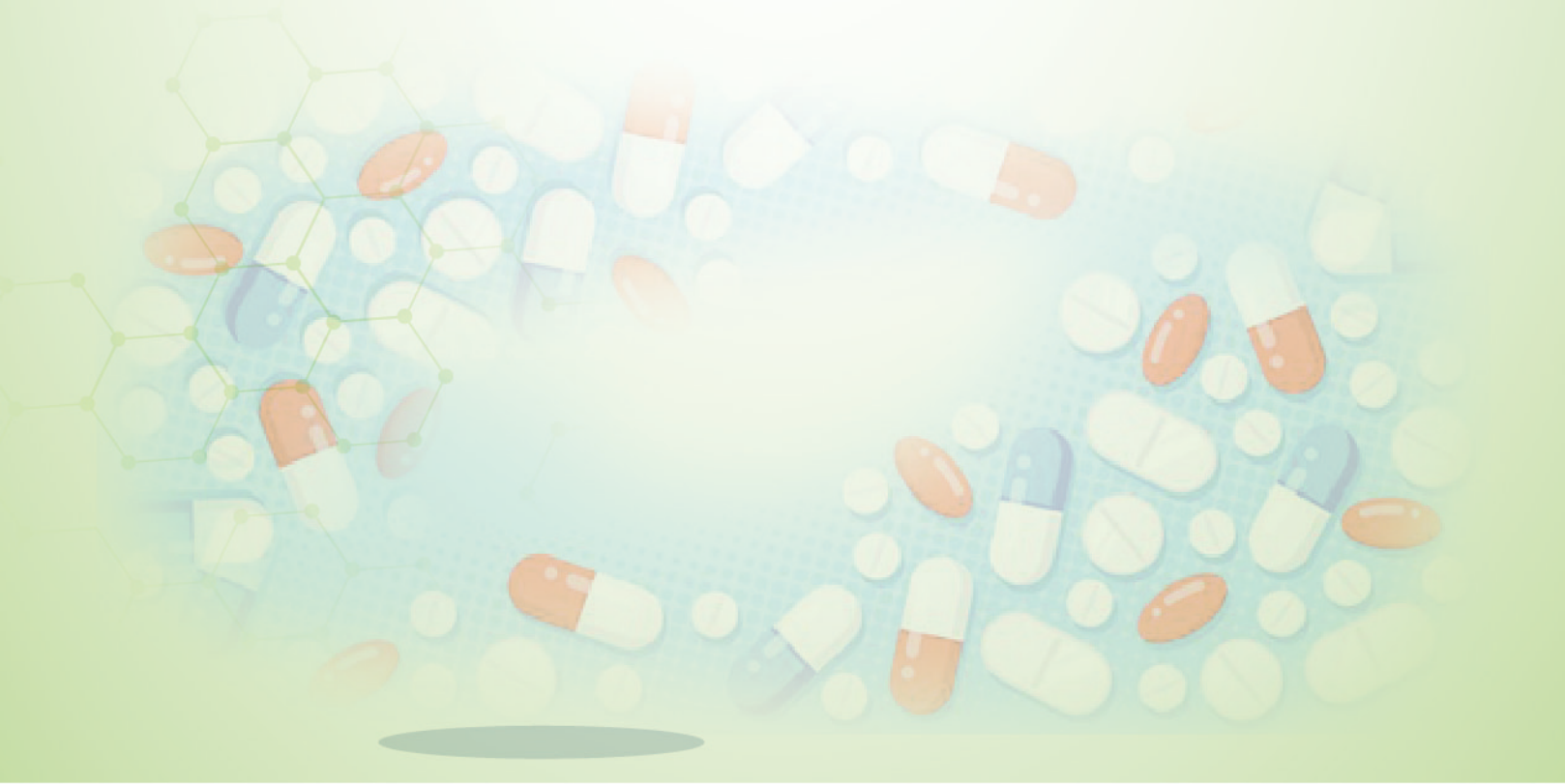
The TGA investigated a safety signal relating to the rare but serious potential adverse event of aortic aneurysm and dissection associated with fluoroquinolones.

The precaution advises that fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options.

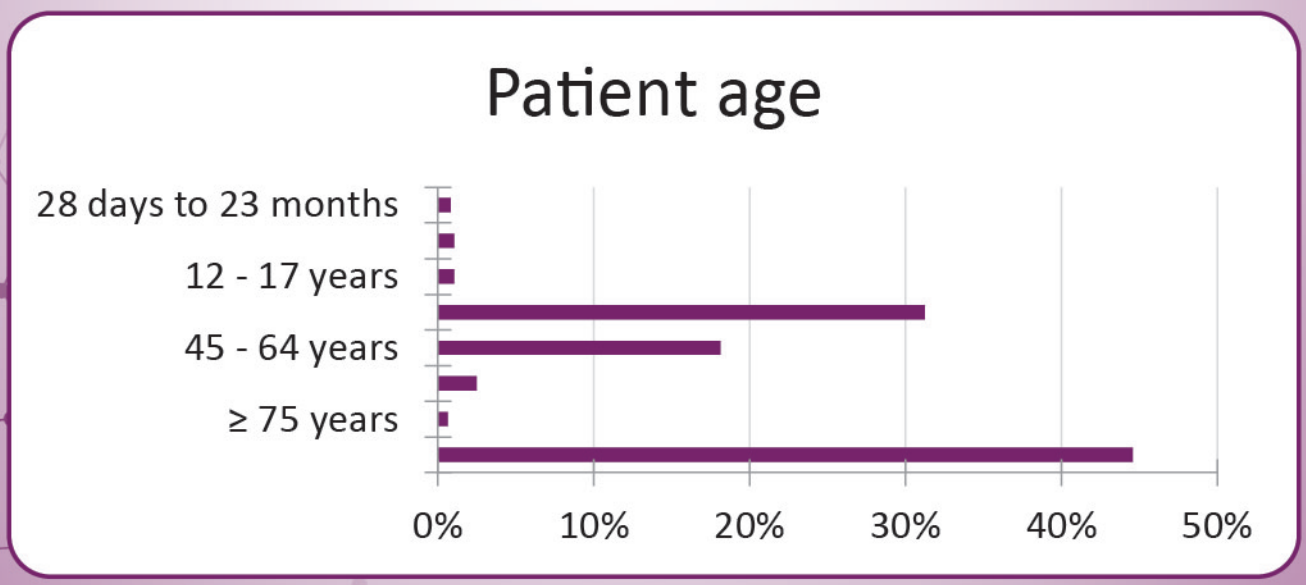
During the TGA's investigation, it was also identified that the product information for fluoroquinolones should be updated to include the potential adverse events of dysglycemia and psychiatric adverse reactions, including toxic psychosis, psychotic reactions progressing to suicidal ideations, hallucinations or paranoia, as precautions.

References

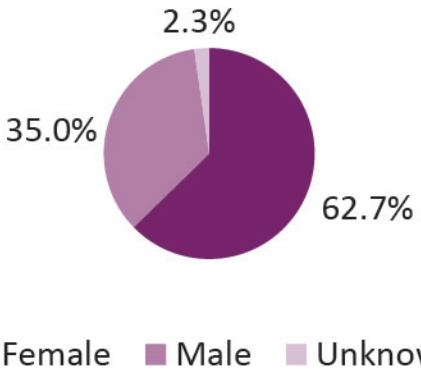
Medicines Safety Update, TGA, 27 February 2020 *(www.tga.gov.au/)*
(See WHO Pharmaceuticals Newsletter No.6, 2019: Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms in Japan; No.3, 2019: Risk of musculoskeletal and nervous systems damage in UK; No.1, 2019

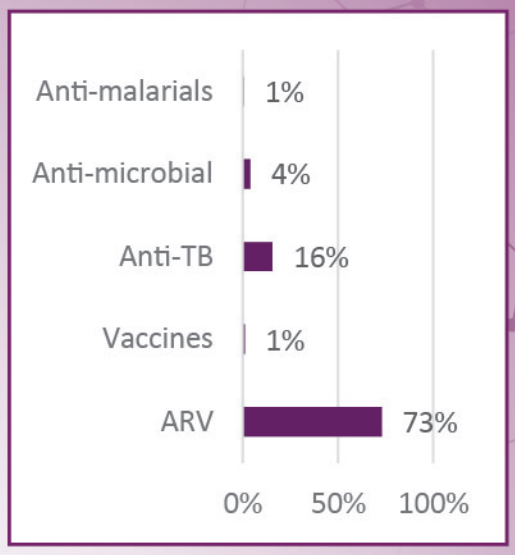


Quarterly summary of ADR reported cases

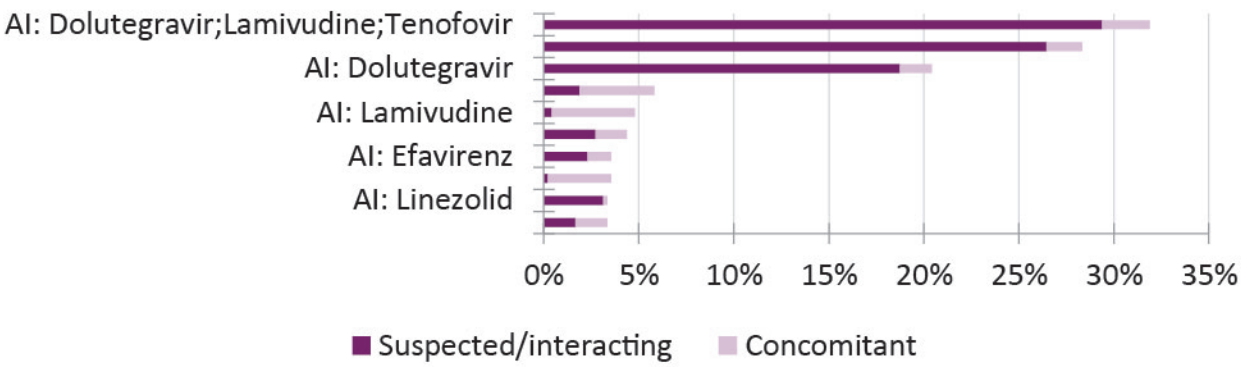


Patient sex

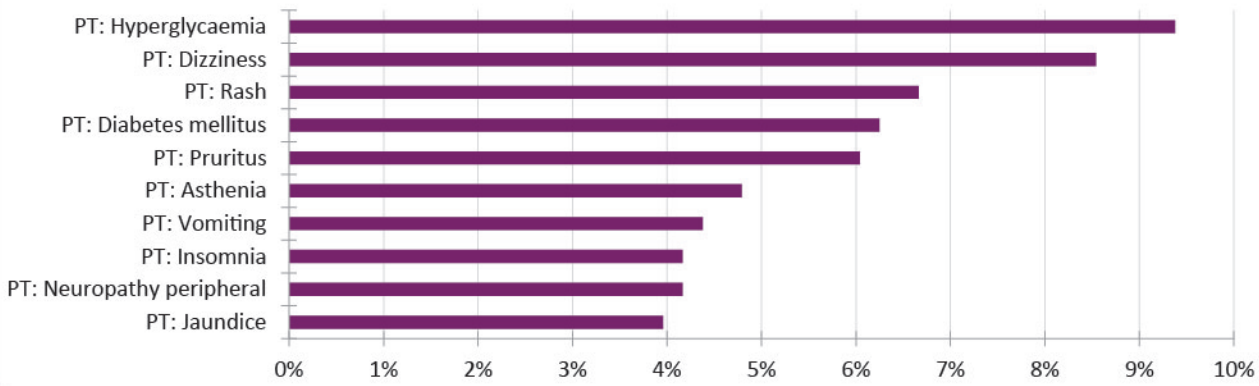


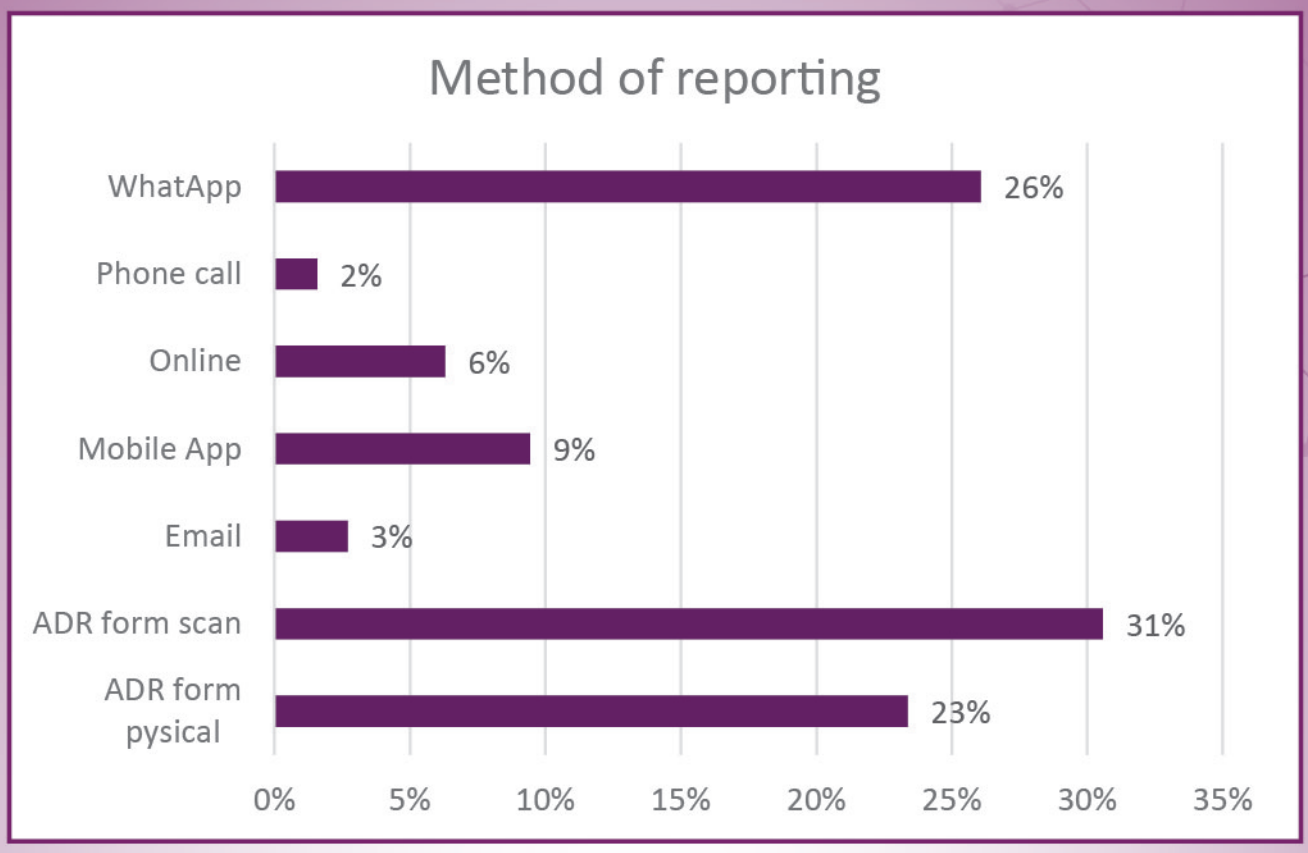


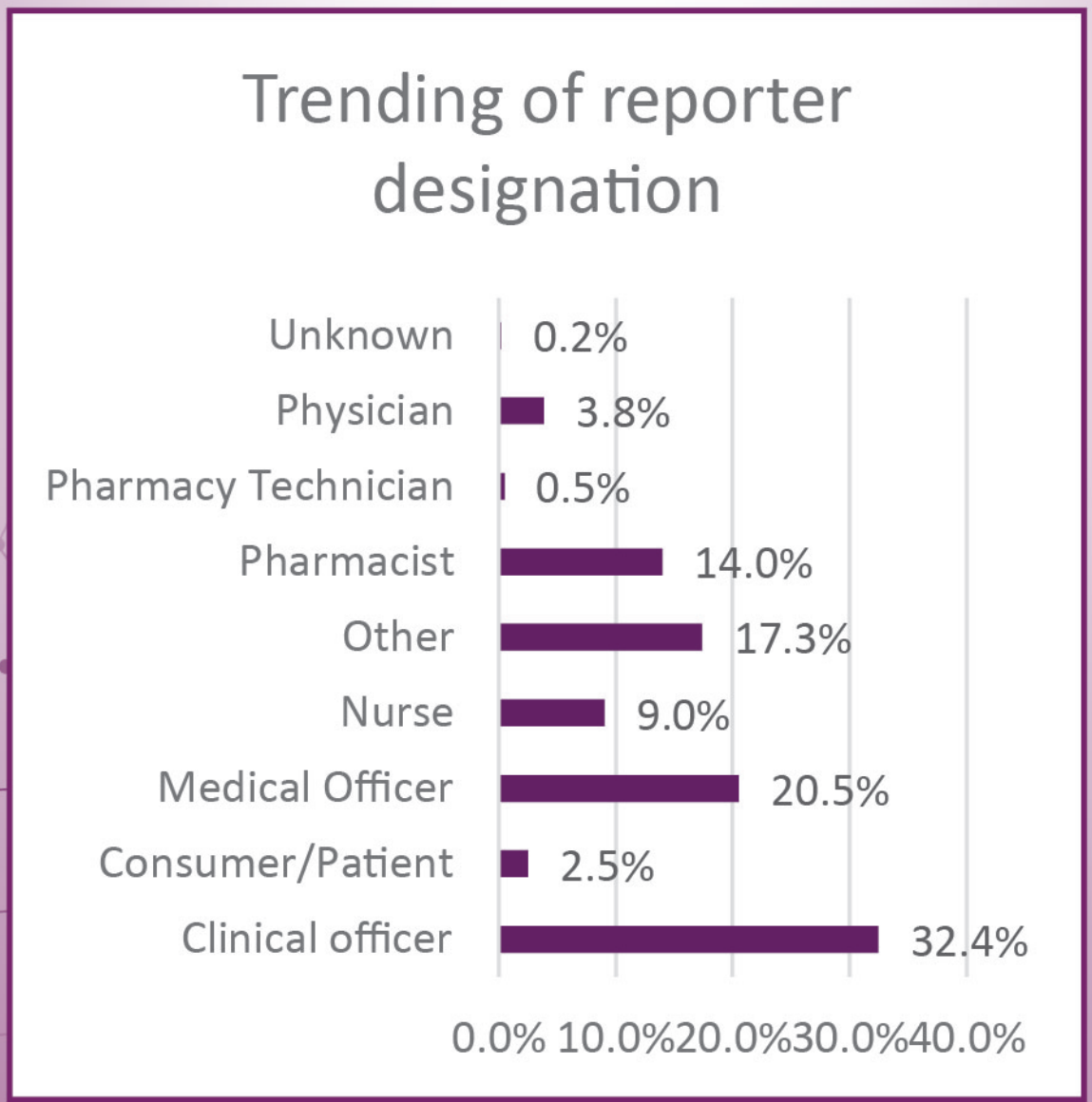
Top Reported active ingredients (WHODrug)



Top Reported preferred terms (MedDRA)




Method of reporting
WhatApp
26%
Phone call
2%
Online
6%
Mobile App
9%
Email
3%
ADR form scan
31%
ADR form pysical
23%
0%
5%
10%
15%
20%
25%
30%
35%


Trending of reporter designation
Unknown
0.2%
Physician
3.8%
Pharmacy Technician
0.5%
Pharmacist
14.0%
Other
17.3%
Nurse
9.0%
Medical Officer
20.5%
Consumer/Patient
2.5%
Clinical officer
32.4%
0.0%
10.0%
20.0%
30.0%
40.0%

Reporting performance of health facilities

HEALTH FACILITY	FREQUENCY
IDI MULAGO	44
MJAP MULAGO	36
TASO MASAKA	34
MILDMAY UGANDA	26
ARUA RRH	24
KISENYI HC IV	18
FORT PORTAL RRH	15
VILLA MARIA HOSPITAL	15
LYANTONDE HOSPITAL	14
KITEBI HC III	12
OLI HC IV	9
ALIVE MEDICAL SERVICES	8
JCRC	8
BAYLOR	7

HEALTH FACILITY	FREQUENCY
MUBENDE RRH	7
UNKNOWN	7
LIRA RRH	6
KALUNGU HC III	5
KAWAALA HC III	5
MENGO HOSPITAL	5
ST BALIKUDDEMBE UG CARES	5
BUKOMERO HC IV	4
CONSUMER	4
HOPE CLINIC	4
KASSANDA HC IV	4
KIGANDA HC IV	4
LWAMATA HC III	4

HEALTH FACILITY	FREQUENCY
MBARARA RRH	4
NURTURE AFRICA	4
SOROTI RRH	4
YERYA HC III	4
BUGIRI HOSPITAL	3
KANYAMWIRIMA HC III	3
KIRUDDU NR HOSPITAL	3
MAGADA HC III	3
MOROTO RRH	3
PFIZER GLOBAL PHARMACEUTICALS	3
AAR BWEYOGERERE	2
AMUCU HC III	2
BUWAMBO HC IV	2
BUYINJA HC IV	2
IGANGA HOSPITAL	2
KAMULI MISSION HOSPITAL	2
KIBOGA HOSPITAL	2
LUWERO HOSPITAL	2
MASINDI HOSPITAL	2
MBALE RRH	2
MITYANA HOSPITAL	2
NAKAWUKA HC III	2
NAMAYUMBA HC IV	2

HEALTH FACILITY	FREQUENCY
DR CHARLES CLINIC	1
HOLY INNOCENTS HOSPITAL	1
KAKUMIRO HC IV	1
KASANGA HC	1
KATOOKE HC III	1
KAWEMPE HOME CARE	1
KIBAALE HC IV	1
KYAKA HC II	1
KYANTUNGO HC IV	1
LIRA UNIVERSITY HOSPITAL	1
MAANYI HC III	1
MASAFU GENERAL HOSPITAL	1
MOROTO PRISONS HC III	1
MPUNGU HC III	1
MUINANIA PRISON	1
MULAGO NATIONAL REFERRAL	1
MUNGULA HC IV	1
MUTUMBA HC III	1
MYENGA HOSPITAL	1
NAKASONGOLA MILITARY	1

Reporting performance by District

District	Count of ADR reports	%age of ADR reports	Rate per 100,000 inhabitants	Population UBOS Estimates
Kampala	170	38.20%	10	1,680,600
Wakiso	39	8.80%	1	2,915,200
Arua	33	7.40%	4	915,200
Masaka	33	7.40%	10	335,700
Kalungu	21	4.70%	11	194,100
Kabarole	15	3.40%	4	337,800
Lyantonde	14	3.10%	13	110,500
Kiboga	11	2.50%	6	171,200
Lira	9	2.00%	2	478,500
Kassanda	8	1.80%	3	312,700
Mubende	8	1.80%	1	554,800
Bugiri	7	1.60%	1	480,400
Mbale	5	1.10%	1	586,300
Mbarara	5	1.10%	1	535,300
Namutumba	5	1.10%	2	306,500

District	Count of ADR reports	%age of ADR reports	Rate per 100,000 inhabitants	Population UBOS Estimates
Bundibugyo	4	0.90%	2	263,800
Bunyangabu	4	0.90%	2	195,100
Masindi	4	0.90%	1	340,500
Mityana	4	0.90%	1	362,500
Moroto	4	0.90%	3	118,500
Namayingo	4	0.90%	2	237,000
Soroti	4	0.90%	1	363,600
Buyende	3	0.70%	1	414,600
Iganga	3	0.70%	1	402,600
Kamuli	3	0.70%	1	558,500
Kyegegwa	3	0.70%	1	441,000
Kabale	2	0.40%	1	248,700
Luwero	2	0.40%	0.4	523,600
Tororo	2	0.40%	0.3	597,500
Amuria	1	0.20%	0.4	225,000
Buikwe	1	0.20%	0.2	474,100
Buliisa	1	0.20%	1	149,300
Busia	1	0.20%	0.3	384,000
Gulu	1	0.20%	0.3	325,600
Hoima	1	0.20%	0.3	374,500
Kamwenge	1	0.20%	0.2	513,500
Kanungu	1	0.20%	0.4	277,300
Kasese	1	0.20%	0.1	793,200
Kibaale	1	0.20%	1	198,200
Koboko	1	0.20%	0.4	258,000
Nakasongola	1	0.20%	0.5	215,200

From the table above, Lyantonde, Kalungu, Kampala and Masaka presented the highest rate of reports of ADR reports per 100,000 inhabitants basing on the Uganda Bureau of Statistics (UBOS Uganda) Population Estimates and the least were Kasese, Buikwe and Kamwenge districts.

SENSITISATION ACTIVITIES

1. Engagement of VHTs

The NPC engaged Village health teams in Mpugwe Trading Centre a village in Masaka district as a gate way for future collaboration with the communities on appropriate medicine use and ADR reporting. The team met is involved in treating community ailments much as they have little background to medicine use. The teams was sensitized on monitoring and reporting of side effects as well as ration medicine use,

Pharmacovigilance sensitization of Village health teams (VHTs) in Mpugwe Trading Centre a village in Masaka district.

2. Training and sensitization activities for healthcare providers

The NPC engaged Village health teams in Mpugwe Trading Centre a village in Masaka district as a gate way for future collaboration with the communities on appropriate medicine use and ADR reporting. The team met is involved in treating community ailments much as they have little background to medicine use. The teams was sensitized on monitoring and reporting of side effects as well as ration medicine use,

DISTRICT	HEALTH FACILITIES	NUMBER
Kaabong	General Hospital	1
	HC IIIs	4
	HC IIs	4
Kotido	HC IV	1
	HC IIIs	4
Abim	General Hospital	1
	HC IIIs	2
Napak	General Hospital	1
	HC IIIs	4
Luwero	General Hospital	2
	HC IVs	2
	HC IIIs	2

DISTRICT	HEALTH FACILITIES	NUMBER
Nakaseke	General Hospital	2
	HC IV	1
	HC III	1
	HC II	1
Nakasongola	General Hospital	1
	HC IIIs	3
Arua	Regional referral Hospital	1
	HC IV	1
	HC IIIs	3
Kitgum	General hospitals	2
	HC IIIs	2

DISTRICT	HEALTH FACILITIES	NUMBER
Oyam	General Hospital	1
	HC IV	1
	HC III	1
Otuke	HC IV	1
Lira	Regional Referral Hospital	1
	HC IV	1
	HC IIIs	3
Apac	General Hospital	1
	HC III	1
Agago	HC IIIs	3
Kole	HC III	1
Lamwo	HC IVs	2
	HC III	1
Alebtong	HC IVs	2
	HC III	1
Nwoya	General Hospital	1
	HC IIIs	2
Moroto	Regional referral Hospital	1
	HC IIIs	3
	HC IIs	2
Amudat	General Hospital	1
	HC IV	1
	HC III	1
	HC II	2
	Private Joint clinic	1
Namutumba	HC IVs	2
	HC IIIs	5
	HC IIs	7
Buyende	HC IV	1
	HC IIIs	5
	HC IIs	5
Bugiri	General Hospital	1
	HC IV	1
	HC IIIs	8
	HC IIs	5
Namayingo	HC IV	1
	HC IIIs	8
	HC IIs	5
	Private medical centers	2

DISTRICT	HEALTH FACILITIES	NUMBER
Ntungamo	General Hospital	1
	HC IVs	3
	HC IIIs	6
	HC IIs	5
Rukiga	HC IVs	2
	HC IIIs	7
	HC IIs	5
Rubanda	HC IVs	2
	HC IIIs	8
	HC IIs	15
Kabale	Regional referral hospital	1
	General Hospitals	2
	HC IVs	3
	HC IIIs	9
	HC IIs	7
Kanungu	General Hospital	1
	HC IV	1
	HC IIIs	8
Masindi	General Hospital	1
	HC IVs	2
	HC IIIs	2
	Centre of excellence	1
Kiryandongo	General Hospital	1
	HC III	1
Bulisa	HC IV	1
Kyankwanzi	HC IV	1
	HC III	1
Kiboga	General Hospital	1
	HC IV	1
	HC IIIs	2
Kibaale	HC IV	1
Kakumiro	HC IVs	2
	HC IIIs	1
Mubende	Regional Referral Hospital	1
	HC IIIs	2
	HC II	1
Kassanda	HC IVs	2
	HC III	1
Mityana	General Hospital	1
	HC IVs	3

Strengthening Active Drug Safety Monitoring In HIV/TB Medicines In Ankole Region

The ministry of health recently rolled out Active Drug safety Monitoring (ADSM) in sentinel sites that include regional referral hospitals, two General Hospitals and two centers of excellence to monitor Adverse Drug Reactions(ADRs)/ Adverse Drug Events(ADEs) from Antiretroviral therapy (ART) and anti TB medicines. This has been adopted and integrated as standard to accompany routine patient care especially for patients taking ART and anti T.Bs drugs

Mbarara Regional Referral hospital in partnership with National Drug Authority are scaling up implementation of active drug safety monitoring in HIV/ Anti TB medicines to strengthen adverse event monitoring in Ankole region. Its from the latter that NDA is currently supporting the Mbarara regional referral hospital pharmacovigilance subcommittee to spread the gospel of active drug safety monitoring in facilities in its catchment area. This activity has so far been done in

1) Kinoni Health center IV
2) Makenke Military hospital
3) Rubindi Health center 3
4) Biharwe Health center 3
5) Mbarara Regional referral hospital
6) Mbarara Municipal council health center 4
7) Bwizibwera Health center 4

Mbarara RRH Pharmacovigilance Subcomitteee Training Art Clinic Staffs In Bwizibwera Health Center 4 On ADSM

Have you had a bad reaction after taking any medicine?

NOTIFY THE NATIONAL DRUG AUTHORITY

Med Safety App

Toll Free Line - 0800 101 999

Whatsapp - 0791 415 555

Email: Druinfo@nda.org.ug

Online-Https://primaryreportting.who-umc.org