NATIONAL DRUG AUTHORITY

Safe Drugs Save Lives

PHARMACOVIGILANCE BULLETIN

INSIDE THIS ISSUE

TERATOGENIC MEDICINES AND AGENTS Pg3
CASE REPORT Pg8
SAFETY UPDATES Pg11
QUARTERLY REPORT Pg12

ISSUE 3 / FEBRUARY 2018

EDITORIAL

Dear readers,
The Hippocrates principle of 'first do no harm' is remembered by most of us but not put in practice as evidenced by the degree of under reporting of adverse events. It is each and everyone's obligation as a health worker to report adverse events as a way to prevent and protect our patients from harm.

Pharmacovigilance in principle involves continuous surveillance of medicines over their entire value chain and it extends beyond the scope of unexpected reactions. There is room to extend pharmacovigilance activities to the assessment and appropriate management of well recognised medicine related safety concerns.

Adverse drug reactions may be comprehensively discussed in pharmacology text books, and taught in detail in school but there is still a gap in the reporting of ADRs by health workers. Reporting of ADRs can contribute to the optimisation of therapy and risk minimisation as it may make it easier to identify risk factors which predispose some patients to harm.

I therefore take this opportunity to thank all health workers who still consider Pharmacovigilance as part of pharmacotherapy and consider the "first do no harm principle" as they prevent, assess, manage and report drug related problems.

You will notice that this time round in our bulletin we have put a particular emphasis on teratogenic drugs. Some medications are safe to take during pregnancy but others are not, or their effects on the baby may not be known. In this issue we document the different teratogens which pregnant women should avoid and their effect on the unborn child.

> *As asserted by Philip Routledge* ***'eternal pharmacovigilance may well be the price of freedom, at least from potentially major adverse drug reaction disasters in years to come'.***

Thank you.

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TERATOGENIC AGENTS: MEDICINE THAT CAN HARM AN UNBORN BABY

During pregnancy, women may require medication just like any other person to prevent disease, treat an underlying chronic condition or to treat a new condition all together. It should also be noted that during pregnancy some underlying conditions may be exacerbated like kidney disorders or heart defects. Therefore, withholding medication from pregnant women is impossible and can have detrimental effects on their health and that of the unborn baby.

A risk versus benefit assessment on a case - by-case basis can be done by a health worker to determine which medicine can be safely used by a pregnant woman. Some medicines can cause harm to the unborn child either by causing birth defects, or slowing down growth of the baby inside the uterus or terminating the pregnancy all together. Medicine which causes birth defects if taken during pregnancy is called a 'teratogen'. A teratogen is a substance that interferes with the normal development of a foetus and may include prescription and over-the-counter medications, alcohol, herbal remedies, supplements and some illegal/illicit drugs.

Medical science cannot always predict how exposure to a teratogenic drug will affect a foetus. The potential for harm depends on a range of factors including: the type of drug, the size of the dose, how often it's taken, the stage of foetal development (gestational age) at the time of drug exposure, the individual response of the foetus to the drug and other factors, such as maternal diet or illness.

Birth defects as a result of the medication used by the mother have been documented from as far back as the 1960's when pregnant women who ingested a drug called thalidomide gave birth to children with phocomalia (hands or feet are under developed or absent).

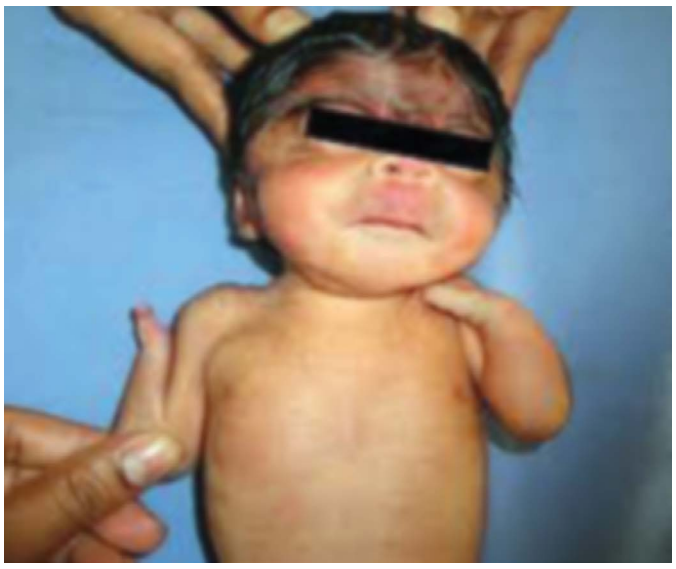

Image of a child with phacomalia (hands or feet are under developed or absent).

Thus it is very important to avoid teratogenic drugs in the first trimester when organogenesis is taking place.

CATEGORIES OF MEDICATION USED IN PREGNANCY

These categories include **A, B, C, D** and **X** depending on its ability to cause harm during pregnancy. This categorisation however is being phased out by the FDA and replaced with a more detailed categorisation. But, since some drugs are still labelled with this categorisation, we will describe each category briefly as follows:

A. Drugs that have been taken by a large number of pregnant women without any proven increase risk of birth defect (there is no evidence of risk in later trimesters). E.g folic acid.

B. Drugs that have been taken by only a limited number of pregnant women. There are no adequate and well-controlled studies in pregnant women and are categorised based on available data from animal studies (there does not seem to be any increased risk) e.g metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole

C. Drugs that, due to their effects, may cause harm to the fetus without causing birth defects (there is a risk of harm). These potential benefits may warrant use of the drug in pregnant women despite potential risks e.g tramadol, gabapentin, amlodipine, trazodone

D. Drugs that have caused or may cause birth defects; however, the health benefit may outweigh the risk e.g lisinopril, alprazolam, losartan, clonazepam, lorazepam

X. Drugs that have a high risk of birth defects and should not be used during pregnancy e.g atorvastatin, simvastatin, warfarin, methotrexate, finasteride

The new FDA labelling, the Pregnancy and Lactation Labelling Final Rule (PLLR) went into effect on June 30, 2015 and replaces the pregnancy letter category described above. It has the following categories:

1. Pregnancy (includes Labor and Delivery) under which are details of the Pregnancy Exposure Registry, Risk Summary, Clinical Considerations and Data
2. Lactation (includes Nursing Mothers) under which are details of Risk Summary, Clinical Considerations and Data.
3. Females and Males of Reproductive Potential under which are details of Pregnancy Testing, Contraception and Infertility

EXAMPLES OF TERATOGENIC DRUGS

Below is a list of teratogenic medicines and medicines which are harmful during pregnancy;

TERATOGENIC DRUGS			
NO	MEDICINE CLASS / CHEMICAL	MEDICINE / CHEMICAL	EFFECT
1	Androgenic agents	Ethisterone, testosterone, Norethisterone,	Ambiguous external genitalia, masculinisation of female foetus. Avoid before conception and during pregnancy
2	Alcohol	Alcohol	Mental retardation, intra uterine growth retardation, small head, foetal alcohol; syndrome characterised by maxillary hypoplasia, congenital heart disease. Avoid during pregnancy.
3	Antibiotics	Tetracycline	Yellow staining of teeth and diminished growth of the long bones. Avoid during second and third trimester.
4	Anticonvulsants	Phenytoin, valproic acid, carbamazepine, lamotrigine, phenobarbital	Foetal hydantoin syndrome consisting of intrauterine growth retardation, microcephaly, mental retardation. Avoid during pregnancy
5	Chemotherapeutic agents	Busulfan, Aminopterine	Stunted growth , cleft palate, microanencephally (large part of the brain is missing) etc.avoid during pregnancy.
6	Vitamin A	Retinoic acid eg isotretinoin used to treat pimples	Very teratogenic even at low doses. Cleft palate, neural tube defects, thymic aplasia etc. Avoid during pregnancy.
7	Tranquilisers	Thalidomide	Limb abnormalities including absence of limbs, abnormally shortened limbs, absence of external ears, congenital heart disease etc. Avoid during pregnancy.
8	Radiation	Ionising radiation	Chromosome injury. Avoid during pregnancy.
9	Folic antagonist	Methotrexate	Multiple malformations. Avoid during pregnancy.

10	Antimanic agents	Lithium	Various malformations . Avoid during pregnancy.
11	Antifungal	Fluconazole	Congenital abnormalities when used in first trimester at high doses e.g malformed bones, face, head, heart. Avoid during pregnancy.
DRUGS THAT CAN CAUSE HARM IN PREGNANCY APART FROM BIRTH DEFECTS			
1	Nicotine	Nicotine	Intrauterine growth restriction. Premature delivery. Nicotine constricts uterine blood vessels and cause decreased uterine blood flow thus reducing oxygen supply and nutrients to the growing baby affecting mental development
2	NSAIDs	Naproxen, celecoxib, Acetylsalicylic acid (e.g Aspirin), Diclofenac, Ibuprofen	Ibuprofen, naproxen, diclofenac, and celecoxib increase the risk of miscarriage in the first half of pregnancy. NSAIDs in the third trimester of pregnancy cause a blood vessel in the foetus to close prematurely.Avoid during pregnancy especially in 3rd trimester.
3	Opioids	oxycodone, morphine, codeine, hydrocodone, and hydromorphone	birth defects of the brain, spine, or spinal cord Avoid during pregnancy
4	Anti coagulants	Warfarin	Crosses the placenta and causes bleeding in the foetus resulting into spontaneous abortion, stillbirth, neonatal death, and preterm birth. Cause birth defects like mental retardation, blindness etc
5	Lipid Lowering	Statins	Congenital anomalies, including vertebral, anal, cardiac, tracheal, esophageal, renal, and limb deficiency and intrauterine growth retardation (IUGR) especially if used in the first trimester.
6	Antibiotics	Nitrofurantoin	Has hemolytic effects on the new born when used in the last trimester. Avoid at term.

For a comprehensive list of teratogenic drugs in Uganda, visit the NDA website at **www.nda.or.ug.**

WHAT HEALTHCARE WORKERS CAN DO TO PREVENT TERATOGENIC EFFECTS OF DRUGS?

1. Always read the product leaflet found in each medicine pack to ensure that the medicine is safe in pregnancy before prescribing it, dispensing it or administering it to a pregnant woman.
2. Get detailed patient history including the date of last menstruation as some patients may be pregnant and they may not yet be aware.
3. Health facilities should develop an institutional list of medicines available to them which are teratogenic and share the list with all hospital staff.
4. Avoid prescribing, dispensing or administering medication to pregnant women in the first 8 weeks of pregnancy unless there is a strong medical reason. Do not prescribe, dispense or administer known teratogenic medicine to pregnant women.
5. Proper patient counselling to explain that even non- prescription medicine, herbal medicine and nutritional supplements can contain substances which can harm an unborn baby
6. Advise all pregnant women to take folic acid supplement prior to conception and during the first trimester to reduce the risk of neural tube defects in the developing baby. Pregnant women should also consume a balanced diet and foods rich in folate.
7. Report adverse events which occur in pregnant women to NDA

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CASE REPORT; ISONIAZID PREVENTIVE THERAPY: ISONIAZID INDUCED HEPATOTOXITY.

INTRODUCTION

Tuberculosis (TB) continues to affect many people in Uganda. The incidence of TB is at 234/100,000 population for all TB cases and the prevalence of TB is at 253/100,000 population (MOH, 2017a).

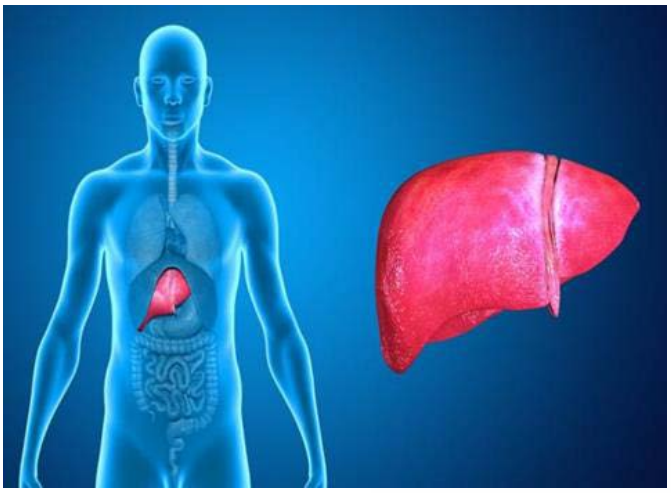

Image of the liver

The standard treatment for TB includes a combination of medicines and is divided into the First-line anti-TB medicines, used for the treatment of susceptible TB and the second line medicines which are used for treatment of drug resistant TB. The first line TB medicines include isoniazid(H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Isoniazid or INH is also used for TB prevention where the patient receives INH for six months and this is called Isoniazid Preventive Therapy (IPT) (MOH, 2017b).

The Ministry of Health in Uganda has adopted several key interventions as part of the TB prevention strategy including IPT. This preventive therapy is recommended for HIV–infected persons and children under five years of age with a history of contact with a TB case.

The recommended dose for IPT in adults is 5mg/kg/day (maximum 300 mg per day) and 10 mg/kg/day (maximum 300 mg per day) in children. Vitamin B6 (pyridoxine) 25 mg per day is given concomitantly with INH for the duration of therapy to prevent the occurrence of peripheral neuropathy (MOH ,2014).

Common side effect of INH include: dizziness, dark urine, loss of appetite, nausea and vomiting, numbness, tingling and burning sensation, unusual fatigue, yellow eyes or skin. Hepatotoxicity is also a common side effect of INH (Nolan et al 1999).

CASE PRESENTATION

KE is a 24-year-old male weighing 50 kg who reported to hospital with no complaint / asymptomatic on 15/9/2017. He is a known HIV patient on Zidovudine, Lamivudine and Efavirenz since 26/8/2007 and cotrimoxazole. KE started taking IPT on 21/7/2017 receiving 300mg once a day. He had Liver Function Tests (LFT) done on 15/9/2017 and the results showed elevated liver enzymes. Below is the patient's LFTs previously and after the hepatic injury:

LFTs (25/07/2017)	LFTs (15/09/2017)
AST 34 (0 - 40) U/L	AST 174 U/L (0 - 40)
ALT 25.7 (0 - 41) U/L	ALT 467.7 U/L (0 - 41)
ALP 72.2 (35 - 129) U/L	GGT 285 U/L (0 - 53)

The INH was discontinued on 3/10/ 2017 but the ARVs were continued and he is recovering.

DISCUSSION

Approximately 10% – 20% of patients receiving INH experience transient elevation of liver enzymes (Mitchell et al, 1976) and are asymptomatic and can only be diagnosed by measuring Liver enzymes. Majority of these patients have their ALT levels return to normal without the discontinuation of their treatment a phenomenon called adaptation (Watkins, 2005). However, a certain number of these patients affected by Drug Induce Liver Injury (DILI), (less than 1% - 3%) progress to severe liver injury and even liver failure (Wang et al ,2016).

DILI is characterized by nausea and vomiting, malaise, fatigue and elevated liver enzymes. Hepatic injury due to INH is idiosyncratic in nature and it has not been documented to have a relationship with the duration of treatment or dose of the drug (Maddrey and Boitnott 1973). Hence it is not surprising that KE developed liver injury after 10 weeks of IPT.

For all patients who develop signs of liver damage while on INH, their liver function should be checked and if the liver enzymes (ALT/AST) are elevated more than three times the normal upper limit, all medications including non-TB medications should be discontinued and the patient monitored until the enzymes normalize. This was not done in KE's case as his ALT/AST were elevated more than three times the normal upper limit but he continued taking his ARVs.

When the liver enzymes normalize, the drugs can be reinitiated following guidance from the Manual for management and control of Tuberculosis and Leprosy in Uganda (M0H, 2017). Re challenging patients who experience severe liver injury with INH is contraindicated (Maddrey and Boitnott 1973).

It is important that patients who are contraindicated to the use of IPT are not given this therapy and these include;

- Patients with symptoms of TB and those with active TB, Patients on TB treatment or PLHIV previously treated for MDR-TB
- Alcoholics, patient with history of psychosis or convulsions, patients with peripheral neuropathy (burning sensations of the limbs)
- Known or suspected hypersensitivity to Isoniazid
- Patients with chronic liver disease or symptoms of active hepatitis (jaundice, right upper quadrant pain, dark urine, pale stools)
- Patients on phenytoin, carbamazepine, warfarin, theophylline, disulfiram, selective serotonin re-uptake inhibitor, antidepressants (e.g. citalopram, fluoxetine, paroxetine, sertraline), oral ketoconazole, or itraconazole.

Many efforts have been made by the ministry of health to scale up access to IPT and this means that many more patients are exposed to Isoniazid than previously registered. This is already visible from the increased number of reports received at NDA detailing cases of hepatic injury in patients receiving IPT than previously reported. Thus, it is imperative that there is a robust system of pharmacovigilance to actively monitor these patients so as to safe guard their wellbeing. The purpose of this case report is to remind health workers to actively monitor their patients receiving IPT for any signs of hepatic injury and to document and report such cases to the National Drug Authority.

CONCLUSION

Isoniazid induced liver injury is a serious medical problem that can lead to death. Health care workers should prevent its occurrence and in case it occurs, they should manage it appropriately and report all such cases to NDA.

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SAFETY UPDATES

CODEINE CONTAINING PRODUCTS NOT SAFE IN CHILDREN UNDER 12 YEARS.

Codeine and hydrocodone containing products carry a high risk of addiction and respiratory depression. These products are available in combination with other medicines, such as antihistamines and decongestants to treat coughs, colds and symptoms of allergies.

Codeine and hydrocodone are narcotic medicines called opioids. Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, shortness of breath and headache.

These products should no longer be used in children under 12 years or in children aged 12 – 18 years who have recently undergone surgery to remove their tonsils or adenoids. Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

Codeine containing products have a high risk of misuse, abuse, addiction, overdose, death, slowed and difficulty in breathing.

ADVICE TO HEALTH CARE WORKERS:

1. Proper patient counselling to explain the risk of addiction and over dose.
2. Use alternative medicine which does not contain codeine in children who need cough treatment.
3. Report adverse events or side effects related to the use of codeine containing products to NDA.

REFERENCES

FDA News release. Accessed from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592109.htm

GABAPENTIN (NEURONTIN): RISK OF SEVERE RESPIRATORY DEPRESSION

Gabapentin is associated with a rare (may affect 1 in 1,000) risk of severe respiratory depression even without concomitant opioid medicines. Gabapentin is an anti-epileptic drug indicated for partial seizures and peripheral neuropathic pain. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of central nervous system (CNS) depressants, and elderly people might be at higher risk of experiencing severe respiratory depression. Dose adjustments might be necessary in these patients.

ADVICE TO HEALTH CARE WORKERS:

1. Be aware of the risk of CNS depression, including severe respiratory depression when using gabapentin and the increased risk of respiratory depression with concomitant use of opioids.
2. Advise patients to look out for signs of CNS depression, such as somnolence, sedation, and respiratory depression and they report to a health worker if these occur.
3. Dose adjustments may be necessary for patients at higher risk of respiratory depression, including the elderly people, patients with compromised respiratory function, respiratory or neurological disease, or renal impairment, and patients taking other CNS depressants.
4. Report any suspected adverse reactions to NDA.

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Drug Safety Update volume 11, issue 3; October 2017: 2.

ADVERSE DRUG REACTION REPORTS RECEIVED BETWEEN OCTOBER TO DECEMBER 2017

INTRODUCTION

The National Pharmacovigilance centre receives Adverse Drug Reaction (ADR) reports through spontaneous reporting from health workers across the country. These Individual Case Safety Reports (ICR) are reviewed and summarized on a quarterly basis. This report is a summary of the reports received from October to December 2017.

A total of 78 reports were received and of these 53 were received in October, 11 in November and 14 in December.
There were 58 (74%) serious reactions and 20 (26%) non serious. Most reports were submitted by the physical ADR form (46%) followed by online reporting (41%) and the rest were sent by ADR form scan (13%).

Most reports were submitted by medical officer (n=24, 30.8%) followed by clinical medical officer (n=21, 26.9%), pharmacists (n=17, 21.8%), nurse (n=12, 15.4%), Physician (n=2, 2.6%) and others (n=2, 2.6%)

REPORTS PER DISTRICT AND HEALTH FACILITY

Mubende district submitted the most reports (n=25, 32.1%) followed by Wakiso (n=19 24.4%), Kampala district (n=15, 19.2%) and Arua (n=10, 12.8%). Other reporting districts include Mbale (n=3, 3.8%), Kabarole (n=2, 2.6%), Bugiri (n=1, 1.3%), Gomba (n=1, 1.3%), Kabale (n=1, 1.3%) and Mbarara (n=1, 1.3%). Mubende RRH (n=21, 26.9%) submitted the most reports, followed by Mild May (n=20, 25.6%). Other reporting health facilities included Arua RRH (n=10, 12.8%), Butabika NRH (n=6, 7.7%), Infectious Diseases Institute (n=4, 5.1%), Kiganda HCIV (N=4, 5.1%), Mbale RRH (n=3, 3.8%) among others as shown in the figure 3 below.

Fig 3: Frequency of reports per health facility

COMMON REPORTED DRUGS

Most reported drugs were ARVs followed by anti TBs as shown in figure 4 below.

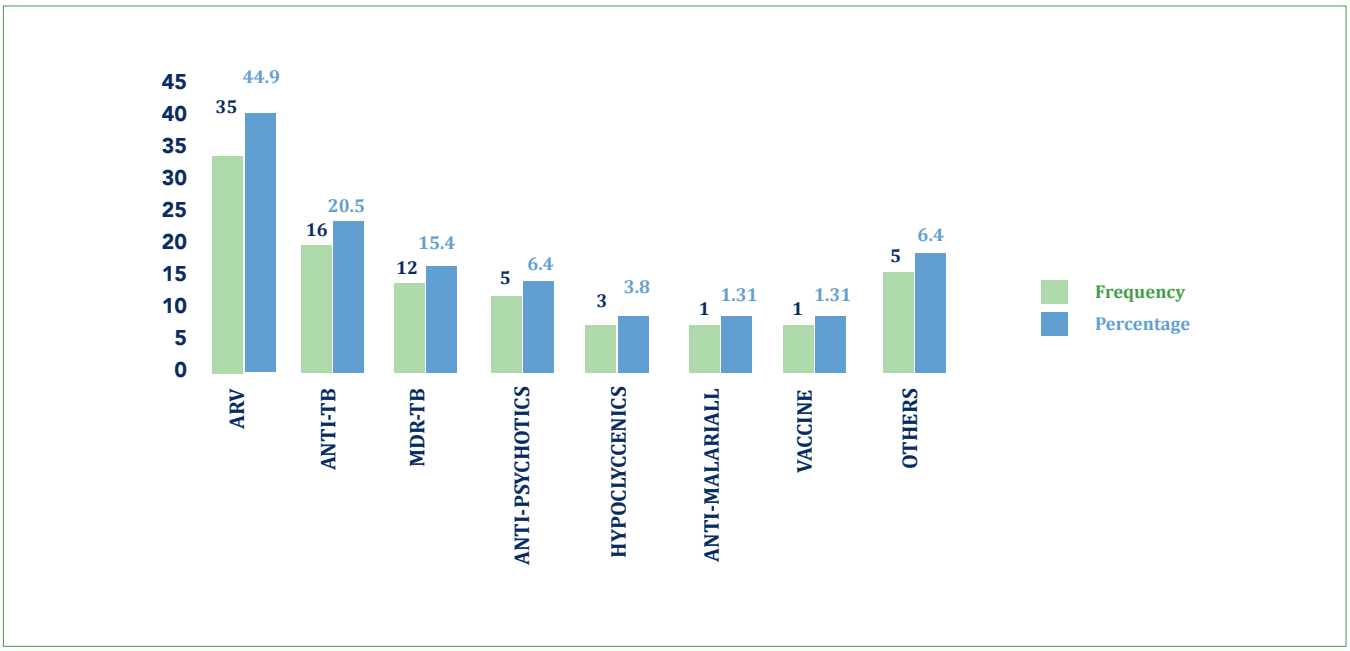

Fig 4: Commonly reported drugs

COMMON INDIVIDUAL DRUGS REPORTED

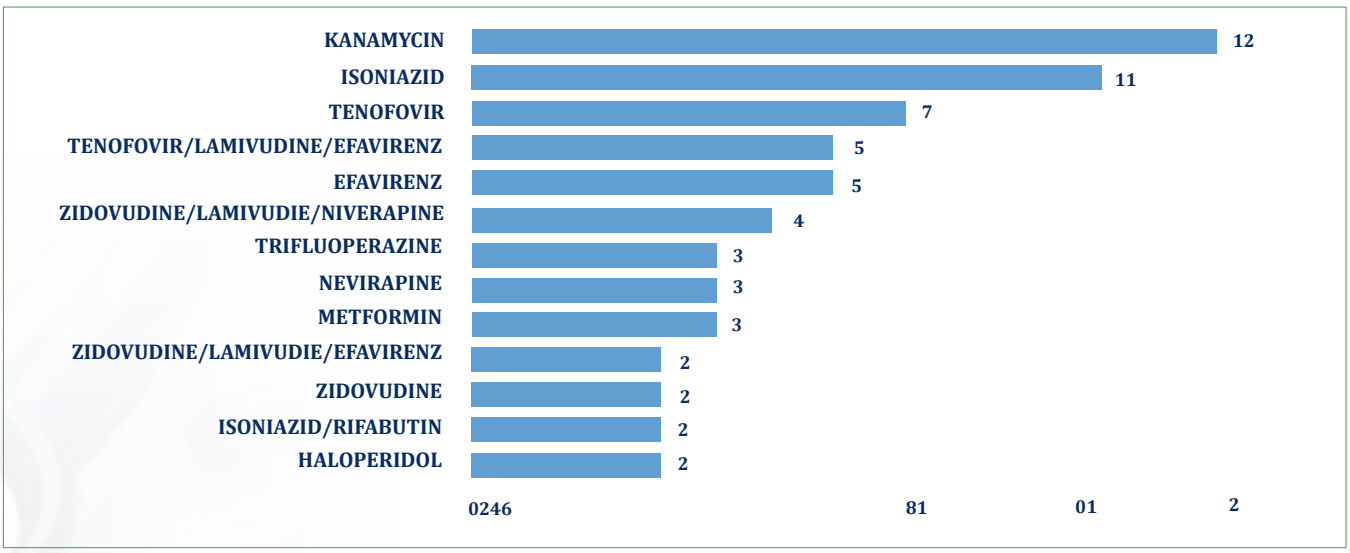

Fig 5: Common drugs reacted to by patients

COMMON REACTIONS

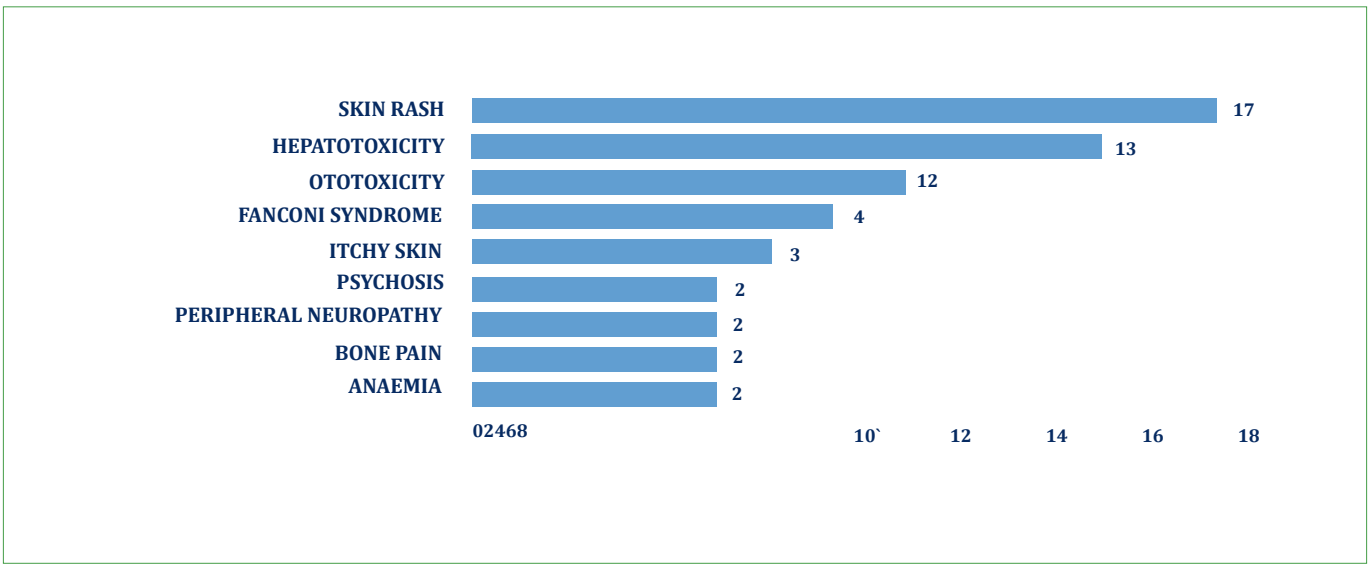

Fig 6: Common reactions reported by patient

CONCLUSION

There has been an increase in the number of reports due to Isoniazid. In the last quarter (July to September) there were only 4 reports due to Isoniazid while the current report has 11 reports due to Isoniazid which is more than 100% increase. This calls for increased efforts to document and report all ADRs especially those due to Isoniazid so that we can have sufficient data which we can use to inform policy, practice and decision making.

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

Further information about adverse reactions may be obtained from;
National Drug Authority, Box 23096 Kampala, Uganda
Tel: +266-414-344052 Fax: +256-414-655.60.80
E-mail: druginfo@nda.or.ug or whatsapp on 0791415555

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?OrganizationID=UG
You can visit us at: www.nda.or.ug

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