Safe Drugs Save Lives

PHARMACOVIGILANCE BULLETIN

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CASE REPORT: ADVERSE EVENT FOLLOWING IMMUNIZATION

Ulceration at Bacillus Calmette – Guerin Inoculation site

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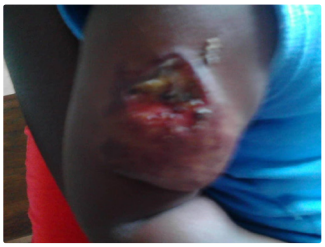

Background

K.R is a 13 weeks old male infant who presented to a health facility in Uganda with a fever of 7 days' duration and swelling of the Right Upper Arm. Medical History revealed that he had been injected with a Bacillus Calmette – Guerin (BCG) vaccination a week before symptoms presented. A physical examination revealed erythematous rash and blistered swelling at the BCG inoculation site. He received the diagnosis of an adverse event following immunization and was treated with paracetamol and Ampicillin/ Cloxacillin syrup. After 2 days, the blister burst exposing an ulcerative lesion at injection site that kept on spreading around the arm. After several treatment attempts with broad-spectrum antibiotics, the child was diagnosed with BCG ulceration and later started on anti TB medication. The patient recovered and the ulcer at the BCG inoculation site healed during the course of treatment. The patient was screened to rule out immunodeficiency disease and there was no family history of Tuberculosis or Immunodeficiency.

BCG Vaccine

The BCG vaccine is a live attenuated strain of Mycobacterium bovis administered intradermal to reduce the risk of pulmonary and extra pulmonary TB by approximately 50%1. Almost all vaccine recipients experience an injection site reaction characterized by a papule, which may be red, tender and indurated[2]

Documented Adverse Drug Reactions to BCG Vaccine

Commonly described local adverse reactions following BCG inoculation include regional lymphadenitis, injection site abscess, persistent injection site reactions and ulcerations[1]. Such local reactions occur despite correct intradermal administration and the extent of the reaction will depend on a number of factors including the strain used in the vaccine, number of viable bacilli in the batch, and variation in injection technique[2]. Usually, no treatment is required for mild injection site reactions with or without mild regional lymphadenopathy[2].

Conclusion

The causality assessment carried out by the National AEFI Committee classified the reaction as the following: A1. Vaccine product-related reaction[3] because the product is a live attenuated Vaccine, the AEFI is a known severe adverse event and that the swelling and abscess progressed into ulceration after 3-4 weeks[3]. It was also important to consider the A3 classification (Immunization error-related reaction) due to poor documentation for both the vaccine and injection materials control book and the temperature monitoring log.

Recommendations to Healthcare providers

- Conduct continuous training to promote better handling of vaccines in healthcare.
- Conduct a comprehensive Clinical assessment of the patient before any vaccination procedure
- Report AEFIs to NDA. This way, there is information that can be used to guide all other HCPs on what they might expect during a vaccination exercise.

Note:

This report was supported by the National AEFI committee.

References

1 Venkataraman, A., Yusuff, M., Liebeschuetz, S., Riddell, A. and Prendergast, A.J., 2015. Management and outcome of Bacille Calmette-Guérin vaccine adverse reactions. Vaccine, 33(41), pp.5470-5474.4

2 WHO Information Sheet, Observed Rate of Vaccine Reactions Bacille Calmette-Guérin (BCG) Vaccine, April 2012

3 WHO, Global Vaccine safety, Immunization, Vaccines and Biologicals

CASE REPORT: ADVERSE DRUG REACTION

Suicidal ideation with Tenofovir / Lamivudine / Dolutegravir

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Introduction

NF, a 46-year-old female was diagnosed with HIV on August 12 2013 at Lukaya HCC Uganda Cares. Her CD4 was 619 cells/mm^3. On that date, she was diagnosed with Taenia corporis, Community Acquired Pneumonia, Pelvic Inflammatory Disease, Vaginal candidiasis and Gastroenteritis. She was treated with oral Ketoconazole, Clotrimazole cream for Taenia; Cetrizine 10mg PO nocte for 5 days; Metronidazole 400 mg PO TID for 5 days; Ciprofloxacin 500 mg PO BID for 5 days; Doxycycline 100 my PO BID for 5 days; Albendazole 400mg PO stat and Multivitamins one-tab PO OD for 7 days and improved. She was maintained on daily Co-trimoxazole 960 mg PO OD. Her repeat CD4 increased increased to 728 cells over the next year.

In March 2014, she was diagnosed with stage 2 Hypertension. She was started on Captopril 25 mg PO OD and Nifedipine 20 mg PO BID and her blood pressure improved. She was maintained on anti-hypertensive treatment with routine close BP monitoring at every clinic visit. Her blood pressure over time was generally below 140/90 mmHg. On September 24, 2014, NF requested to start ARV treatment citing recurrent fungal skin infestations which were distressing her. At the time, her repeat CD4 had reduced to 519 cells/mm^3. She was started on single tablet regimen (STR): Efavirenz/Lamivudine/Tenofovir. Her anti-hypertensive medication was: Bendroflumethiazide 5 mg PO OD and Captopril 25 mg PO BID. She was stable on this regimen for the next five years.

Regimen switch and Adverse Drug Reactions

On September 4 2019, as required by the current policy for transitioning stable clients from TLE to TLD, NF was transitioned to Dolutegravir / Lamivudine / Tenofovir after a thorough assessment on her eligibility including effective family planning use. She came back on 16/10/19, 6 weeks later before her next appointment. The examination detected suicidal ideation, withdrawal symptoms from her children and apathy. She was diagnosed with minor depression and started on Amitriptyline 50 mg nocte for 2 weeks. However, 2 days later she was returned with aggressive behavior, uncoordinated speech, failure to sleep and visual hallucinations. Clinically she was unkempt, incoherent and her mental state examination was abnormal. She was diagnosed with probable drug (DTG) induced organic psychosis.

Laboratory findings and management

Blood smear: Negative for malaria parasites; CBC: white blood count= 4.8x10^3 cells/L; hemoglobin= 13.7g/dL & other hematologic parameters were normal; CD4= 1062 cells/mm^3; Random blood sugar was 6.3 mmol/litre; Chemistry: ALT and AST were essentially normal: 34.3 & 30.5 U/L respectively; both ALP & GGT were slightly elevated: 137 & 43.3 U/L respectively; Creatinine was 0.78 mg/dL with a computed clearance of 99.59ml/min and Urea was 21.6mg/dL; both renal function parameters were normal. She was started on Chlorpromazine 200mg PO nocte, maintained on Amitriptyline 75mg PO nocte and Benzhexol 5mg PO nocte for 2 weeks. The ARVs were temporarily halted. NF has progressed well clinically and psychotic symptoms and suicidal ideations have ceased following assessment on phone on 24/10/19.

Discussion

Psychiatric symptoms have been observed to be more common in PLHIV than in the general population1 and the cause is multifactorial in the former[2]. Prior to adjustment of her regimen, NF did not have nor demonstrated psychiatric illness. She had been stable for five years on TLE clinically, immunologically and virologically. The temporality of emergency of her psychiatric symptoms certainly coincided with the period of introduction of TLD raising concern of a potential association. Recent literature alludes to occurrence of psychiatric symptoms in people treated with Dolutegravir[3]. Moreover, it was also observed that neuropsychiatric events were higher in the DTG treatment group than in the Raltegravir group and marginally led to treatment discontinuation[4].

Recommendation:

Close clinical monitoring for neurotoxic side-effects is recommended for patients on DTG.

References

1. Dubé, B., Benton, T., Cruess, D.G. and Evans, D.L., 2005. Neuropsychiatric manifestations of HIV infection and AIDS. Journal of Psychiatry and Neuroscience, 30(4), p.237.

2. Gunnell, D., Harbord, R., Singleton, N., Jenkins, R. and Lewis, G., 2004. Factors influencing the development and amelioration of suicidal thoughts in the general population: Cohort study. The British Journal of Psychiatry, 185(5), pp.385-393.Fettiplace, A., Stainsby, C., Winston, A., Givens, N., Puccini, S., Vannappagari, V., Hsu, R., Fusco, J., Quercia, R., Aboud, M. and Curtis, L., 2017. Psychiatric symptoms in patients receiving dolutegravir. Journal of acquired immune deficiency syndromes (1999), 74(4), p.423.

3. Elzi, L., Erb, S., Furrer, H., Cavassini, M., Calmy, A., Vernazza, P., Günthard, H., Bernasconi, E. and Battegay, M., 2017. Adverse events of raltegravir and dolutegravir. AIDS (London, England), 31(13), p.1853.

Active Drug Safety Monitoring Roll-out at Regional Referral Hospitals

Beginning 16th September 2019, Active Drug Safety Monitoring for Dolutegravir and Isoniazid was rolled out in all Regional Referral Hospitals. This was a joint activity conducted by the National Drug Authority and the Ministry of Health following a number of reports on Dolutegravir and Isoniazid among patients. The activity was preceded by a successful pilot testing of the tools at China-Uganda Friendship Hospital Naguru, Infectious Diseases Institute-Mulago and Mildmay-Kajjansi. 18 sentinel sites (including the pilot sites) were selected to run this activity: Arua, Lira, Gulu, Mbarara, Masaka, Jinja, Mbale, Kabale, Soroti, Iganga, Moroto, Hoima, Fort Portal, Kayunga and Mubende Regional Referral Hospitals. A total of 625 health care providers were trained and given reporting tools for active drug safety monitoring.

TB and HIV staff at one of the 18 sentinel sites That received training on aDSM

Flow of Activities for Active Drug Safety Monitoring

Under ADSM, patients are to undergo proactive and systematic clinical and laboratory assessment during treatment to detect ADRs and AEs. Clinical and laboratory test records at baseline (treatment initiation) and during regular reviews should be considered as defined in the Monitoring schedules below. All AEs detected should be managed in a timely manner in accordance to the guidelines provided by the program which will be published in December. All identified ADRs have to be reported using the aDSM form and reported to the NDA and regularly assessed for causality.

18 Sentinel sites have been considered priority sites for implementing active drug safety monitoring of patients on INH and DTG. Monitoring of ADRs/AE has been integrated as standard of care to accompany routine patient care especially for patients taking Dolutegravir based regimens and Isoniazid.

Steps for Active Drug Safety Monitoring

Step 1: At triage or clinician's station, use the screening tool to elicit for signs and symptoms of AEs or ADRs. Note any suspected ADRs "Side effects" column in the blue card.

Step 2a: At the clinician's station, take detailed history to further assess for ADRs and request for additional tests to investigate suspected ADRs.

Step 2b: Routine Screening for aDSM: Clinician should request for laboratory tests conducted at baseline (before starting DTG or INH) and periodically. These should be conducted even when the patient has no signs and symptoms of ADRs.

Step 3a: Based on findings of investigations above, manage ADRs appropriately

Step 3b: For baseline tests, defer INH or DTG in case of deranged tests.

Step 4: Complete the aDSM form and forward the filled form to PV Focal person for submission to the NPC at NDA.

Routine Screening for aDSM: (These should be conducted even when the patient has no signs and symptoms.)

Category of Patient	Drugs	Screening to be done
ART naïve client initiating DTG or INH for the first time	DTG	Baseline Random Blood Sugar
	INH	Baseline liver function tests (minimum AST and ALT)
		Hepatitis B test
ART experienced client being switched to DTG or starting INH	Screen	Screen client for symptoms using screening tool below
	DTG	Random Blood Glucose test checked against previous values
	INH	Liver Function Tests checked against previous values
All clients after switching to DTG/INH	DTG	RBS every 3 months in the first one year and every 6 months thereafter
	INH	Liver function tests at 3 months after initiating INH

Investigating ADRs:

These tests are conducted for patients with signs or symptoms suggesting ADRs. For each encounter, the health worker at triage needs to screen for any suspected ADRs as per screening form.

Screening tool for Active Pharmacovigilance

To be placed in the recipient of care's file to be used to screen for side effects of TLD/DTG or INH/TPT at the triage point

Recipient of Care's (RoC) names.....
Patient clinic #. .....

Sex Age Medication (Tick) ☐ DTG based regimen ☐ INH/TPT ☐ DTG based regimen and INH/TPT

Date of assessment

Since you began taking the NEW medication (TLD/DTG or INH/TPT), have you noticed any changes in the following? (Ensure to ask a

Actions to take:

- Record any side effects present & refer (RoC) to clinician to manage them.
- For females on/due for DTG, record if pregnant and refer to clinician to manage.

	Month	1	2	3	4	5	6	7	8	9	10	11	12
1	**Neuropsychiatric side effects.** Does the client have any of the following (Y/N)? (Bad Dreams, Trouble sleeping/ insomnia, headaches, Anxiety or nervousness, change in memory, Change in mood)? Younger children: Ask for irritability (in addition to the above symptoms)												
2	**Hepatotoxicity.** Does the client have any of the following (Y/N)? (Nausea, vomiting, right upper quadrant abdominal pain, yellow urine or eyes).												
3	**Peripheral Neuropathy.** Does the client have any of the following in the hands or feet (Y/N)? (Numbness, tingling, burning sensation). If any is present, record side effect in patients' file and refer to clinician. Younger children: Ask for pain in hands and feet, regression in motor milestones - refusal to crawl, walk or run, reduced playfulness (in addition to the above symptoms)												
4	**Hyperglycemia or diabetes.** Does the client have any of the following (Y/N)? (Increased appetite, increased thirst, and excessive urination). Younger children: Ask for irritability (in addition to the above symptoms)												
5	**Other Abdominal symptoms.** Does the client have any of the following (Y/N)? (Diarrhea, generalized abdominal pain).												
6	**Skin rash.** Does the patient have any new skin rash (Y/N)?												
7	**Musculoskeletal symptoms.** Does the client have any of the following (Y/N)? (Muscle or joint aches, tiredness).												
8	**General SEs.** Does the client have any of the following (Y/N)? (fever, body swelling)												
9	**Other side effect (Please specify):** _____												
	For Females on DTG, review LNMP to rule out pregnancy. **For Males on DTG, inquire about libido and ability to maintain erection.**												

Send a report on any side effect identified to national drug authority (NDA)

The clinician should request for additional tests to investigate suspected ADRs. Information will be collected using aDSM reporting tool.Detailed Standard Operating Procedures (SOPs) and job aides have been developed by MoH to guide on identifying and reporting the reactions.

Identified reactions will be reviewed at site by the facility safety focal person and then relayed to the NDA

either online or through the reporting form. Analysis of data on ADRs will be done regularly by the NDA with co-opted members as agreed upon by the pharmacovigilance technical working group.

The forms are best scanned and sent to the National Drug Authority at druginfo@nda.or.ug or whatsapp 0791415555 or given to the facility Pharmacovigilance Focal Person who will then send them to NDA.
Screen the following for hyperglycemia: (Standard: ***Once hyperglycemia of any grade develops immediately discontinue all drugs***, *and manage the medical event and substitute the offending drug when the patient is stabilized*).

a. Patient presenting with symptoms of hyperglycemia/Diabetes
b. Patient at risk for hyperglycemia/ diabetes
c. ART-experienced patients > 5years with 5% weight change

The diagnostic criteria for Hyperglycemia/DM is as follows:

- Random Plasma Glucose (RPG) >11.0mmol/l
  - This is the most convenient
  - It must always be followed by a fasting blood sugar except in presence of grade III and Grade IV hyperglycemia.
- Fasting plasma Glucose (FBG) >7.0mmol/l
  - Preferred in the absence of the OGTT
- Oral Glucose Tolerance Test (OGTT)
  - This is the gold standard. However, it is not commonly available.
- HBA1c >6.5%
  - This is recommended for follow up of Diabetic patients to assess control while on hypoglycemic agents. Not to be used for screening.

Classification of the hyperglycemia grading

a. Grade I: >117- <160mg/dl (6.5-8.9 mmol/l)
b. Grade II: 160-250mg/dl (8.9-13.9 mmol/l)
c. Grade III: 250-500 mg/dl (13.9-27.8 mmol/l)
d. Grade IV: >500mg/dl (>27.8mmol/l) or Life threatening complications like HHONK, DKA
e. Grade V: death

Management of Hyperglycaemia following DTG Initiation
(*Once hyperglycemia of any grade develops immediately discontinue all drugs*)

Hyperglycemia grading	Management	Comments
Grade I >117- <160mg/dl (6.5-8.9 mmol/l)	Encourage diet modification and exercise control Perform Fasting blood sugar after 1 week	For all patients: • Encourage diet modification and exercise for better glycemic control • Encourage regular monitoring of blood sugar while at home. • Encourage foot care. • Stop smoking and reduce alcohol intake • Counsel on symptoms of hypoglycemia. • Do lipid profile • Serum creatinine, Urea and Electrolytes. • Do regular screening for macro and microvascular complications of DM. • Consider stopping DTG.
Grade II 160-250mg/dl (8.9-13.9 mmol/l)	Encourage diet and exercise control Initiate oral hypoglycemics Start with metformin 500mg daily increase as needed to a maximum of 2000mg daily.	
Grade III 250-500 mg/dl (13.9-27.8 mmol/l)	Refer for specialist management and consider admission if RBS> 20mmol/l Counsel patient on signs and symptoms of hypoglycemia Ensure close monitoring of Fasting Blood Glucose.	
Grade IV >500mg/dl (>27.8mmol/l) or Life threatening complications like HHONK, DKA	Refer for admission If possible, Institute IV fluids(crystalloids–normal saline) immediately while preparing for transfer or give ORS if there is likely to be delay in accessing care.	

Workshop on Opportunities and challenges of Patient involvement in the development and safe use of medicines in resource limited settings

Compiled by Ian Mugisa

National Drug Authority (NDA), Community Health And Information Network (CHAIN) and Uganda Alliance of Patient's Organisations (UAPO) in partnership with CIOMS organized a one day dialogue that took place at the National Drug Authority head offices at Lumumba Avenue on August 29, 2019.

This meeting was conceived to facilitate The Council for International Organisations of Medical Sciences (CIOMS), which is developing guidelines for patient involvement in the development and safe use of medicines in resource-limited settings. Ms. Regina Kamoga of CHAIN, Ms. Helen Ndagije, Director Product Safety, NDA and Dr. Frederick Nakwagala, FRECCU developed the meeting concept.

There is growing global recognition for the role and contribution of patients at all levels in the process of drug development. CIOMS currently has four on-going international Working Groups composed of experts from different countries and regions, these include;

- Regulators
- Academia
- Industries
- World Health Organisation (as member/ observer of group)and other interested member organizations in the prevailing topic

CIOMS has made significant contributions on the International Council for the Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), guidelines. CIOMS is an ICH observer having first attained this status in 2016. Ms. Kamoga informed participants that the 72nd World Health Assembly (WHA), which was held from 18th to 20th May, 2018 made a resolution WHA72.6 'Global Action on Patient Safety' and endorsed the establishment of World Patient Safety Day, to be observed annually on 17th September 2019. The theme for 2019 is, "Patient Safety: a global health priority" under the slogan, "Speak up for Patient Safety!"

Dr. Frederick Nakwagala, the chairperson for Forum of Research Ethics Committee Chairpersons of Uganda (FRECCU) guided the participants through the drug discovery and development process. He engaged with the audience while educating them on the phases in the development of Drugs.

Dr. Nakwagala describing the medicines development process

Ms. Katana, a renowned patient advocate and HIV expert led the first breakout session. During this session, the attendees were tasked to discuss opportunities and challenges for patients to participate effectively in the drug development process.

Mr. Robert Sekubugu from Rakai Health Sciences Project moderated the last session of the workshop in which recommendations were developed. The participants were in agreement that Patients have a pivotal role in the drug development process

David Walusimbi explains the various ways that the NDA facilitates patient safety in the Q&A session

Recommendation

1. They specifically wanted to see more representation of patients at the concept development, and earlier phases of drug development.

2. They also recommended that the drug development process should incorporate the direct contributions of patients who have the disease condition for which the indication is being developed.

3. The attendees pushed for more sensitization on the patient role to the communities outside of greater Kampala area.

Sensitization Meetings and Trainings

Compiled by Douglas Mwesigwa

The NDP/A (Pharmacovigilance) regulations 2014 state that a licensed person, a doctor or health professional who is involved in handling drugs intended for human use in public health programs and programs organized and sponsored by NGOs shall have appropriate mechanisms of monitoring the safety of drugs that are handled in their day to day activities.

Following the regulations and having the main objective of the Pharmacovigilance team this year as increasing awareness of PV activities and visibility of the same to the health professionals and the general public, the National Pharmacovigilance Centre has conducted sensitizations in both private for profit hospitals and private not for profit hospitals. So far these include:

1. National Pharmacovigilance Centre

No.	HEALTH FACILITY	NO. ATTENDED	TOTAL
1.	Ntinda Independent hospital	20	
2.	City Medical and Ambulances	11	
3.	AAR Healthcare Clinic Ntinda	9	
4.	Mengo hospital	38	
5.	Lwala Hospital Kaberamaido	16	
6.	Soroti regional referral hospital	Unspecified	
7.	Nsambya Home care	14	
			108

2. West Nile

No.	HEALTH FACILITY	TOTAL NO. ATTENDED
1.	Arua Hospital	
2.	Ediofe HC IV	
3.	Oli HC IV	
4.	Arua Police HC IV	
		115

3. South Eastern

No.	HEALTH FACILITY	NO. ATTENDED
1.	Taso Unit of Jinja Hospital	**16**

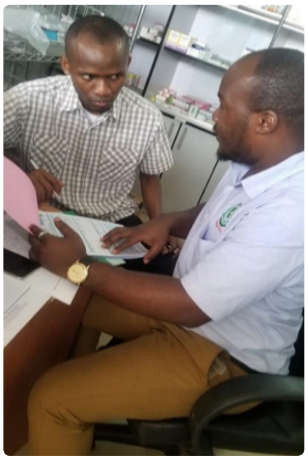
More sensitizations are planned before the end of the year

Milestones

- Over 230 health professionals have been sensitized in the basics of pharmacovigilance, detecting signals, signal assessment and causality assessment; especially for the ART and anti TB drugs including the new drug Dolutegravir and Isoniazid for TB prophylaxis from where new signals have been identified: Hyperglycaemia in patients transitioned to DTG and Hepatotoxicity for the Isoniazid in IPT among other adverse drug reactions.

Health Workers at AAR Ntinda attending the Pharmacovigilance Continuous Medical Education

- ADR booklets for reporting were distributed and professionals taken through proper filling of these forms. Other reporting channels including via the website directly, WhatsApp and a toll free number were shared.
- Pharmacovigilance quarterly bulletins and the PV annual report for the year 2018/2019 given out



"A Pharmacovigilance Officer reviewing steps for filling the Adverse Drug Reaction reports with one of the Health Care Providers"

Conclusion:

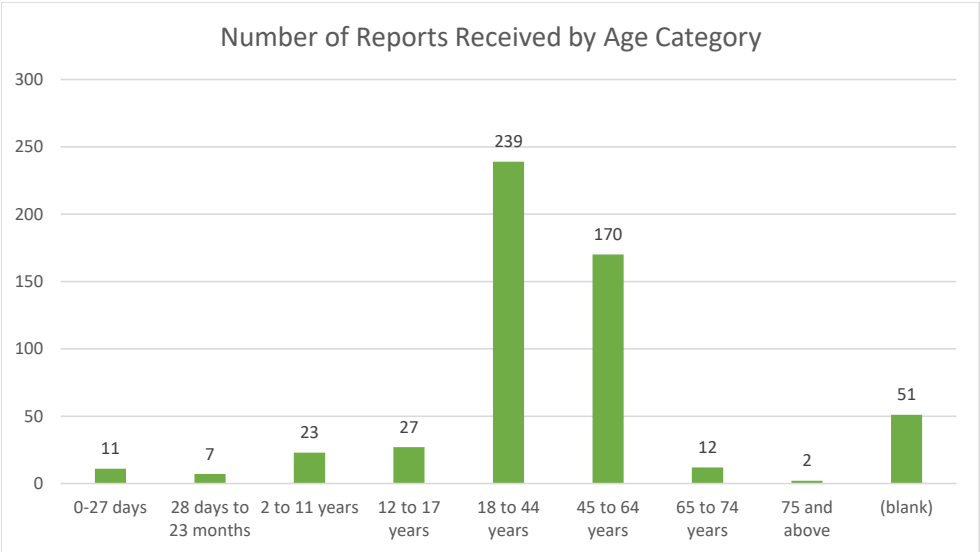
It's the mandate of the NDA to ensure the safety and efficacy of drugs in Uganda but this is only possible with a collective effort from all the stakeholders, starting from the public, HCPs and the National Drug Authority. We take this opportunity to thank all the members actively reporting the adverse reactions and we call upon those that haven't been actively involved to also start as this is the only way we can ensure that only safe drugs remain in supply to the entire population.

Quarterly ADR Summary Report

This quarter (July to September 2019), a total of 542 Adverse Drug Reaction reports were received from various health facilities across the country. This is a 238% increase from the last quarter where 160 reports were received. This points to the increased vigilance among health workers and we thank all who submitted reports.

Patient characteristics

Age

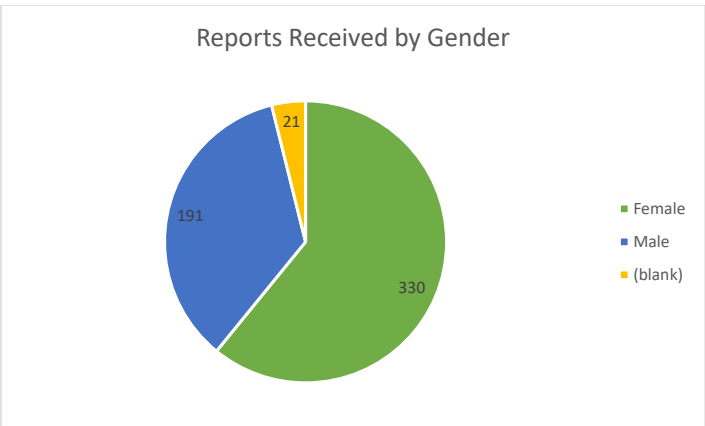


Generally, the 18-44 and 45-64 years' age groups had the highest number of reactions. Majority of the reactions are suspected to be due to HAART and TB medications and HIV and TB prevalence is higher in these age groups. However, ADR risk also increases with age-related changes in pharmacokinetics and pharmacodynamics, increasing burden of comorbidity, polypharmacy, inappropriate prescribing and suboptimal monitoring of drugs1. As shown above 51 reports did not have information on ages of the patients.

Recommendation to Health Workers

Good clinical practice for detecting and predicting ADRs in vulnerable patients includes detailed documentation and regular review of prescribed and over-the-counter medications through standardized medication reconciliation.

Sex



Reports from female patients are nearly twice those of male clients. Research has shown that female patients have a 1.5- to 1.7-fold greater risk of developing an ADR, including adverse skin reactions, compared with male patients2. Women generally have a lower lean body mass, a reduced hepatic clearance, have differences in activity of cytochrome P450 (CYP) enzymes (40% increase in CYP3A4, varied decrease in CYP2D6, CYP2C19 and CYP1A2), and metabolize drugs at different rates compared with men.

Recommendation to Health Workers

The health care team needs to be aware of these differences and look out for reactions in this group of patients.

Top Reaction-Drug Pairs for the period from July to September 2019

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	19
	Atazanavir	4
	DTG	4
3.	**Dizziness**	**26**
	Efavirenz	14
	Isoniazid	3
4.	**Severe Headache**	**21**
	Gentamicin	8
	Isoniazid	4
5.	**Lipodystrophy**	**14**
	Zidovudine	13
	Efavirenz	1
6.	**Peripheral neuropathy**	**9**
	Isoniazid	4
	TDF/3TC/DTG	4
	Zidovudine	1
7.	**Itchy skin rash**	**8**
	Carbamazepine	3
	TDF/3TC/DTG	2
	Isoniazid	2
	Amoxycillin	1
8.	**Gynaecomastia**	**7**
	Efavirenz	4
	Dolutegravir	3
9.	**Joint Pain**	**6**
	Pyrazinamide	3
	TDF/3TC/EFV	1
	TDF/3TC/DTG	1
	Isoniazid	1
10.	**Erectile Dysfunction**	**5**
	Tenofovir/Lamivudine/Dolutegravir	4
	Isoniazid	1

Important Drug-Reaction Profiles

Hyperglycaemia/Onset diabetes

In the period from July to September 2019, there have been 91 reports of hyperglycaemic symptoms with Dolutegravir of which 52.6% were male and 47.4% female. The average age was 52yrs (range 31year – 81years) while mean weight of patients with diabetes 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

Discussion

This reaction has not been indicated in the labelled information for the drug but has been 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 signalling 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.

Recommendation

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

Lipodystrophy:

From July to September 2019, the centre has received 14 reports of lipodystrophy.

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.

Recommendation

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

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.

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

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

Gynaecomastia

This quarter, there have been 7 reports of gynaecomastia with various suspected drugs. 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). These cases are presented therefore to inform healthcare providers of these events and to counsel patients appropriately to ensure compliance.

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.

Quality of Reports

Whereas the National Pharmacovigilance Centre makes every effort to follow up with reporters and fill in missing information in all ADR reports received, it is possible if contact details of the reporter are included on the report. A report that is missing the four Ps: Patient details such as age, sex, weight or patient number, Product (drug) details, Problem (reaction) details and Person reporting details is invalid and can therefore not be assessed for causality. The quality of the report is as important as the submission of the report and we encourage reporters to ensure that all missing information is filled in before submission to avoid loss of important patient safety data.

Although physical forms are necessary and accessible, electronic reports are a quicker and more efficient method and we encourage reporters to scan and email the reports to druginfo@nda.or.ug whenever possible for immediate analysis.

References

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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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