NATIONAL DRUG AUTHORITY

ADVERSE DRUG REACTION REPORTING OCTOBER – DECEMBER 2019

Date prepared: 17th /01/2020 Prepared by: Victoria Nambasa Sign:

1.0 Background

This report provides a summary of individual case safety reports received by the National Pharmacovigilance Centre, as reported by health workers from various health facilities in the country. The report presents profiles and description of drug and adverse drug reactions and highlights some reactions that may need extra attention when certain drugs are administered to patients. The report covers reports received from October to December 2019. During the period, a total of 603 Individual case safety reports (ICSR) were received.

Over a period of eight (8) years, the number and proportion of ADR reports has steadily increased from 136 in 2012 to 1,145 in 2019 as shown in figure 1.

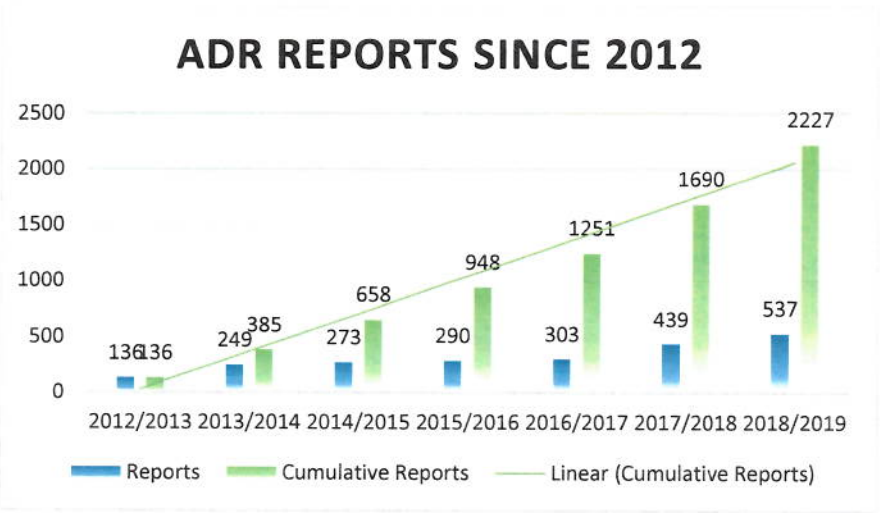

Figure 1: Cumulative ADR Reports received by National Drug Authority

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2.0 Adverse Drug Reaction (ADR) Reporting Rates in the reporting period

For the period of three months, 603 ADR reports were submitted to the NPC as shown in figure 2. This was a sudden increase compared to the earlier months of reporting.

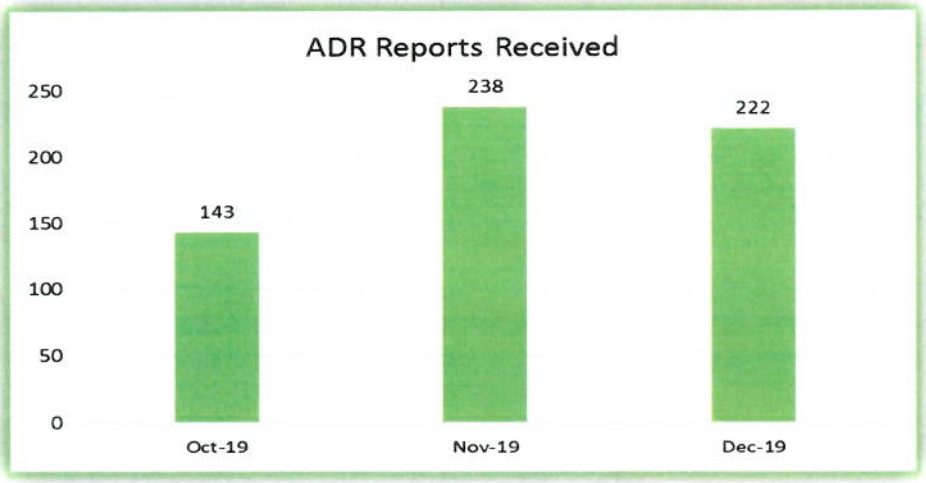

Figure 2: Reports received over the period from 1st October 2019 to 31st December 2019

The reports were received from the health facilities distributed all over the country. Other ADR reports though few were reported by pharmaceutical companies and from sites involved in active drug safety monitoring (ADSM). Figure 3 and 4 describe the reporting rates by District and health facility respectively. Most reports came from Kampala district and there are districts that were reporting for the first time like Iganga and Bugiri districts.

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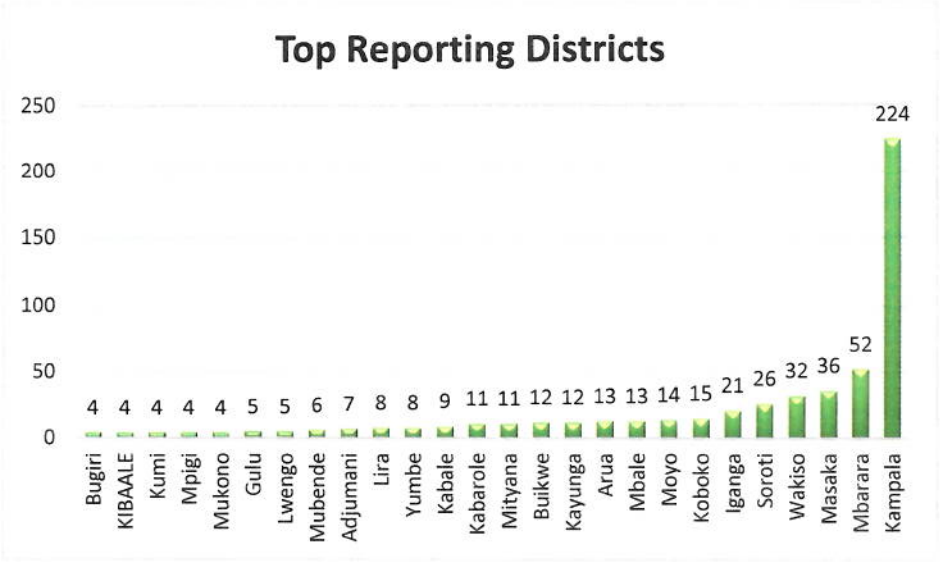

Figure 3: Top reporting districts

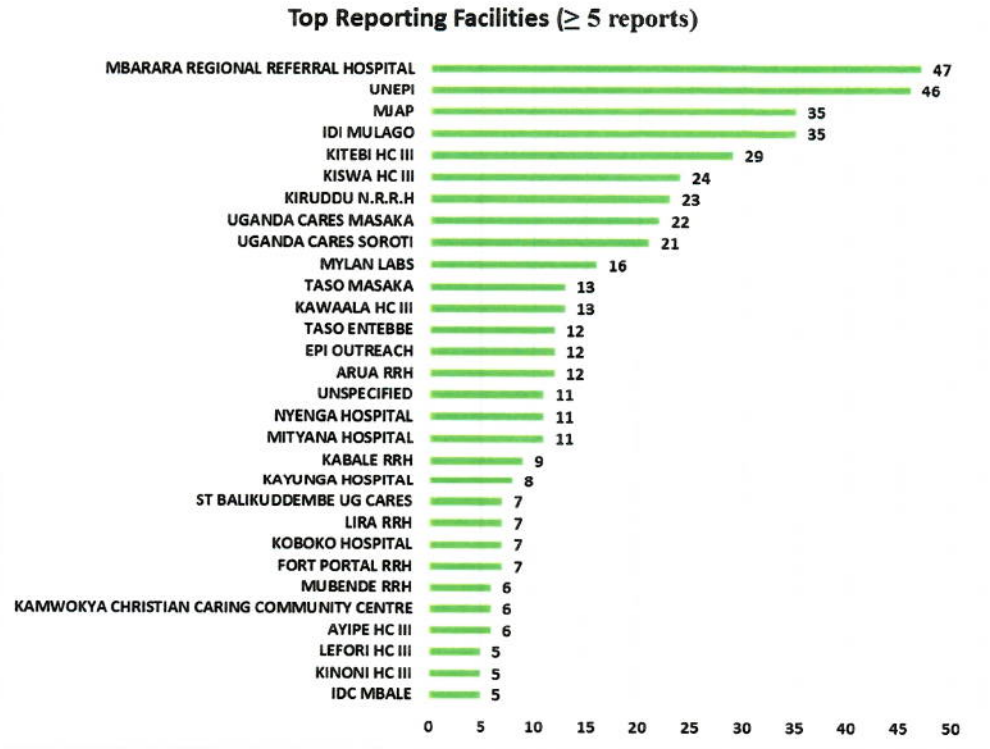

Figure 4: Top reporting facilities

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2.1 Characteristics of individual case reports received

Majority of ADRs (n = 380; 63.02%) were reported from females. In terms of age distribution, most of the adverse drug reaction reports are from young adults and middle aged patients between 18 to 44 years (n =238; 40%) with fewer reports from the elderly (above 65 years) and pediatric population. Reports from those aged 50 years and above were 176 (29%) and children less than 12 years were fewer (14%) as shown in table 1.

Table 1: Characteristics of ADR reports in the Uganda National Drug Authority pharmacovigilance database, distributed over three months (October to December 2019)

Report characteristics	***Oct -Dec (N=603) n (%)***
Patient sex	
Female	380 (63.02%)
Male	217 (35.99%)
Unknown (gender not indicated)	6 (1%)
Seriousness	
Yes	309 (51.24%)
No	294 (48.76%)
Seriousness Criteria	
Death	30 (5%)
Prolonged Hospitalization	67 (11%)
Disabling	68 (11%)
Life threatening	141 (23%)
Congenital anomaly/Birth defect	3 (1%)
Type of reporter	
Patient	2 (0.3%)
Pharmacist	87 (14%)
Doctor	142 (22%)
Clinical Officer	205 (34%)
Nurse	74 (12%)
Patient Age groups	
0-28 days	1 (0.17%)
28 days to 23 months	17 (2.8%)
2 to 11 years	69 (11.44%)
12 to 17 years	31 (5.14%)
18 to 44 years	238 (39.47%)
45-64 years	176 (29.19%)
65 to 75 years	20 (3.32%)
Above 75 years	8 (1.3%)
Unspecified	43 (7.1%)

2.2 Type of Reporter

Overall, most of the ADR reports were submitted by Clinical officers (n=205; 34%) followed by doctors (n = 142; 22%), pharmacists (n = 87; 14%) and nurses (n = 74; 12%). There was an increase in reports from pharmacists from 1.7% before 2012 to 14% presently, even though reports were generally few (n=87). There is still low reporting from the consumers of medicines in Uganda (n=2; 0.3%).

2.3 Seriousness

Regarding severity, a half of the reports were reported as serious (n = 309; 51.24%), where majority of ADRs were considered Life threatening (n=141; 23%); sixty-eight (n=68; 11%) led to hospitalization and 67 (11%) led to prolonged hospitalization. Five prevent of the ADRs reported caused death (n = 30; 5%) and congenital anomalies in the offspring (n = 3; 1%). The majority of cases had patients whose ADRs recovered/resolved (39%), those recovering were 20.3% while those whose outcome was unknown at the time of reporting was 27.6%.

2.4 Distribution of drugs characterization

The distribution of most frequently reported drugs is given in Fig. 5. Isoniazid, Dolutegravir and Efavirenz were the most commonly reported as suspected drug in the ADR reports received, whereas drugs like Lamivudine and Tenofovir were mainly reported as concomitant drugs. Majority of reports for HIV and TB treating drugs could thus not specify the suspect drug for the reported reactions. Table 3 provides the drug-reaction pairs in details.

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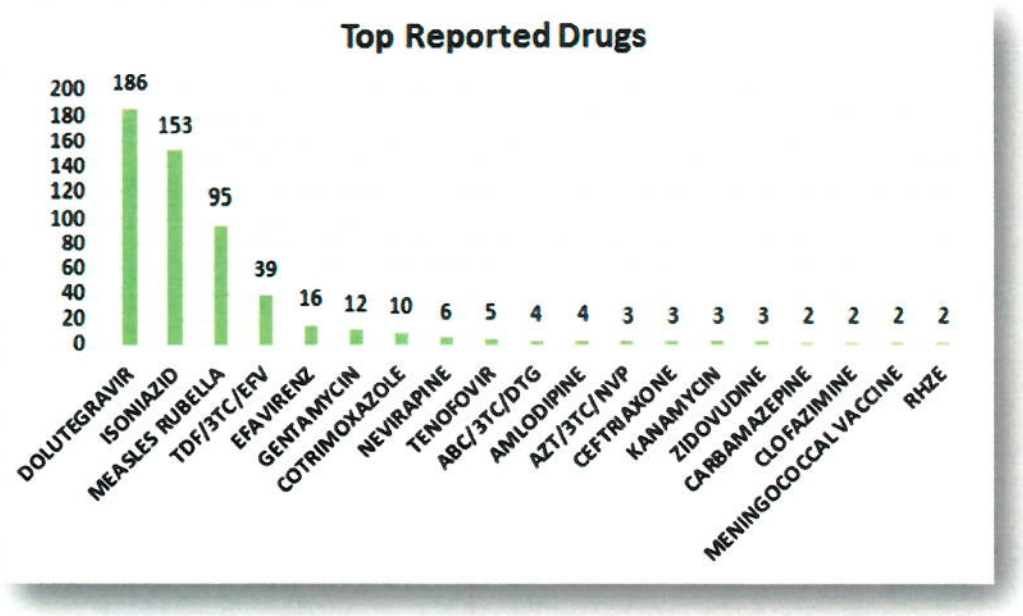

Figure 5: Most commonly suspected drugs

2.5 *The Anatomical Therapeutic Chemical (ATC) classification of medications*

In the reporting period half (51%) of the reports were for drugs suspected to cause the ADR and the rest reported as concomitant. Majority of the reports had at least more than one drug. Most commonly reported drugs belong to the ATC classes antiretroviral (n=264; 43.7%), anti-tuberculous drugs (26.2%), vaccines (16%) and antibiotics (4.5%). ADR reports related to vaccines constituted a modest percentage out of the total ADRs reported. Majority of cases were reported in the period following the mass immunization for Measles and Rubella. Generally, Measles vaccine (24 reports), Diphtheria vaccine; Hep B vaccine (22 reports) and Polio vaccine (20 reports) were among those whose ADRs were reported in the analysis period. There were 21 ADRs due to vaccines that were Serious out of which eight (8) were fatal.

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Table 2: ATC Classification of most reported drugs

ATC Classification	Reports received	Percentage
Anti-retrovirals	264	43.7%
Anti-TB	158	26.2%
Vaccines	106	16%
Antibiotics	27	4.5%
Antihypertensives	4	0.6%
Antipsychotics	2	0.33%

Below are the reactions associated with the top reported drugs.

Table 3: Drug-Reaction pairs commonly reported

Drug as suspect	Total Reports	Commonly reported reactions	Frequency
Isoniazid	**156**	**Liver injury**	**37**
		Hypersensitivity reaction	33
		Peripheral neuropathy	6
		Pellagra	3
		Blurred vision, dizziness	5
Dolutegravir	**152**	**Hyperglycaemia**	**78**
		Erectile dysfunction	4
		Headache, malaise	17
		Liver injury	7
Efavirenz	**96**	**Generalised skin rash**	**6**
		Gynaecomastia	5
		Dizziness, headache	9
		Liver injury	8
		Loss of taste	1
Measles Rubella Vaccine	**95**	**Allergic Reaction**	**28**
		Generalised Itching	12
		Headache, Body Weakness, Dizziness	6
		Fever	3
		Toxic Epidermal Necrolysis	3
Gentamycin	**12**	**Severe headache**	**8**
		Syncope	4
Cotrimoxazole	**10**	**Generalised itching**	**6**
		Swelling of lymph nodes	1
Tenofovir	**5**	**Renal toxicity**	**1**
		Osteoporosis	2
Zidovudine	**5**	**Darkening of fingernails**	**2**
		Lipodystrophy	2
Amlodipine	**4**	**Oedema**	**3**
		Amlodipine poisoning	1
Ceftriaxone	**3**	**Hypotension**	**2**
		Hives	2
Nevirapine	**3**	**Steven Johnson's Syndrome**	**1**
		Pallour, malaise, anaemia	2
Atorvastatin	**1**	Statin-induced necrotizing autoimmune myopathy, muscle weakness	1
Kanamycin	**3**	**Hearing loss**	**2**
		Wheezing	2
		Dizziness	1

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2.6 Description of adverse event suspected to be related to isoniazid used in the prevention of tuberculosis in patients living with HIV

Background

Following the MoH guidelines in HIV and TB management in July 2018, the ACP and the NTLP rolled out Dolutegravir in a bid to optimize HIV care and the Isoniazid(INH) for the TB prophylaxis among the PLHIV.

The National Pharmacovigilance Centre has since received reports of adverse reactions to these drugs and top the list for INH being drug induced Liver toxicity among other reactions and death.

A total of 297 individual case safety reports related to INH have been received with majority of reports (n = 123; 81.5%) from females. Stratification by age of patients showed that the highest number of reports were from those aged 19 to 45 years (n =89; 62.57 %) followed by those above 46 -65 years (n=38; 26.57%) while the reports from patients above 65 years were fewer (1%) as shown in table 4 below.
Based on organ classification, Hepatobiliary disorders presenting as liver toxicity were reported most (n=49; 28.32%), followed by skin and subcutaneous disorder (48; 27.75%), Gastrointestinal disorders (n =21; 12.14%3) and nervous system disorders 17(9.83%) as presented in table 4.

Table 4 Characteristics of ADR reports suspected to be caused by Isoniazid used for Tuberculosis preventive therapy distributed over three months (October to December 2019)

Report characteristics	***n (%)***
Patient sex	
Female	123(81.5%)
Male	28 (18.5%)
Patient Age groups	
0-5	0
6_ 12	10(6.9%)
13_ 18	4(2.8%)
19 _45	89(62.2%)
46 _65	38(26.57%)
< 65	1(0.7%)
Seriousness	
Yes	42(14.14%)
No	297 (85,9%)
Time to onset	
1 month	61(55.96%)
2-3 months	36(33.03%)
4-6 months	11(10.09%)
>6 months	1(0.92%)

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Liver enzyme ranges (AST,ALA)	
<36	2(7.14%), 4(13.33%)
37-75	3(10.7), 3(10%)
76-150	3(10.7), 3(10%)
151-300	3(10.7), 7(23.33%)
> 300	57.14, 13(43.3%)
Reactions based on system classification	
Blood and lymph(anemia,	2(1.16%)
Ear and labyrinth(hearing impairment)	2(1.16%)
Gastrointestinal(constipation Dry mouth Nausea, Vomiting)	21(12.14%)
General disorders and admin site (fever, general weakness)	1(.58%)
Hepatobiliary disorders (Hepatitis, Acute hepatic failure, Liver injury, Jaundice)	49(28.32%)
Musculoskeletal(Arthralgia)	9(5.2%)
Nervous system(Neuropathy peripheral)	17(9.83%)
Psychiatric disorders(Mood swings, Psychosis)	6(3.47%)
Reproductive system (Gynecomastia)	2(1.16%)
Respiratory	2(1.16%)
Skin and subcutaneous(itchy skin, itchy skin eruptions, SJS, Skin hyperpigmentation)	48(27.75%)
Miscellaneous(insomnia, , convulsions	14(8.09%)
Duration on ART	
<5 months	38(40%)
>5 months	57(60%)

Case summary of some deaths suspected to be due to isoniazid

Case 1:
55 years old Female referred from an unknown Health facility in Wakiso to Kiruddu Referral Hospital on the 21st/12/2019.
Major Complaints;

1. Yellow discoloration of the eyes x 2/52
2. Progressive abdominal distension x 2/52
3. Altered level of consciousness x 1/7

History – A known ISS on HAART for 10 years (unknown regimen) who got switched to DTG and also enrolled on INH for 3/12. She was also on an unknown concoction of Herbs. She was admitted complaining of abdominal pain, yellowing eyes and was managed for Acute liver injury secondary to INH complicated by Hepatic Encephalopathy grade 3 type A. Patient was very sick and unfortunately died at 5:07pm on the 23rd/12/2019.

Social History – No history of alcohol use nor smoking reported.

General Examination – Normal Blood Sugar 4.0mmol/L, BP 124/80mmHg
LFTs – AST 848IU/L, ALT 297IU/L, ALP 340IU/L all raised taken on the 21st/12/2019
This was her index admission and had never had any surgical history nor blood transfusion.

Complimentary Examination – The Liver Ultra sound scan had shown Mild Hepatomegaly with peri portal fibrosis and Acute Cholecystitis.

Management – She had been managed on Tabs Rifaximin 550mgs x 1/52 from time of admission at Kiruddu plus IV Fluids.

Case 2:
60 years old Male referred from Bukomero HC IV in Kiboga District to Kiruddu Referral Hospital and admitted on the 21st/12/2019.

History – Known HIV patient admitted with six months` history of abdominal distension which progressively worsened with abdominal pain, loss of appetite and altered mentation. He was managed for drug induced hepatitis with complications of hepatic encephalopathy type A grad IV.

The patient had been on HAART (TDF/3TC/EFV) and Cotrimoxazole for 2 years and he has been unwell throughout that time. He had been transitioned to TLD and enrolled on INH for IPT the last six months and he had in fact completed the INH prophylaxis, but with progressive abdominal distension, Anorexia and abdominal pain. A week prior to admission he had developed altered mentation, general body weakness and inability to walk without support.

He was referred from Emergency with the Diagnosis of Drug Induced Hepatitis with hepatic encephalopathy. He had had four admissions for the same illness and had also been using herbs.

Social history – He had been using alcohol for the last 2years but no history of smoking.

General Examination BP of 110/70mmHg
LFTs – ALP 76.8IU/L, ALT 5.7IU/L
RFTs – Creatinine 90.0mmol/L and Urea 4.68mmol/L
The Abdominal Ultra Sound scan revealed Multiple hepatic masses.

Diagnosis – HIV infected patient with Drug Induced Cirrhosis with complications of hepatic encephalopathy type C grade III.

Management – Had been managed on
Tabs Rifaximin 550mgs bd x1/52
Syrup Lactulose 20mls tds x 1/52 and IV Fluids
He died on the 24th/12/2019 at 1330hours

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Case 3:
31 years old female who was admitted on the 23rd/12/2019 in Kiruddu referral hospital and died two days later on the 25th/12/2019 at 10:20 pm.

Major complaints;

1. Altered mentation
2. Abdominal distension
3. Yellowing of the eyes

History – Known HIV patient presenting with yellow discoloration of eyes x 2/52. The HAART regimen she had been on is not clear and time period too is unknown (this is due to altered mentation). She also reports passing out of yellow urine. She had been initiated on Isoniazid 5 months ago.

Social History – takes alcohol, she doesn't smoke and has also been using herbs as well.

General Examination – Previous LFTs results had shown raised transaminases and amino transferases enzymes taken on the 14th/11/2019. Reports having been admitted for Drug Induced Liver Injury in November.

Current LFTs as of 3rd/12/2019; ALT 365IU/L, AST 806IU/L, D. Bilirubin 256.5umol/L, T. Bilirubin 563.6umol/L, GGT 201IU/L

A Diagnosis of Drug Induced Liver Injury had been made by the physician.

Management – On admission, was managed with
Syrup Lactulose 15mls tds x 1/52
Tabs Rifamixin 550mg OD x 1/52
Patient died on the 25th/12/2019.

Case 4:
45 years old female admitted at Kiruddu referral hospital on the 19th/12/2019 at 10:00am. He had been referred from House of Holy Family nursing home in Kalisizo.

History – Known ISS who had been on AZT/3TC/NVP for 20 years, unknown CD4+ cell count. Was started on INH for IPT five months ago. She had reportedly been well until 2/52 ago, developed yellowing of eyes associated with fevers and vomiting, non-projectile, constipation for 1 week, has had reduced appetite too. No abdominal pain or swelling only reported facial puffiness and had been receiving treatment from a private clinic at Kalisizo from where she was referred to Kiruddu referral hospital. Reported no history of hypertension, diabetes mellitus nor asthma.

This is her index admission.

Social History – She does not smoke nor take alcohol
General Examination – BP 134/65mmHg
LFTs – AST 1163IU/L, ALT 907IU/L, ALP 406IU/L, GGT 891IU/L, T. Bilirubin 187.2umol/L, D. Bilirubin 144.1umol/L

RFTs – Na+ 143.6mmol/L, K+ 4.62mmol/L, Cl- 102.2mmol/L, Serum Urea 2.6mmol, Cr-39umol/L.

Diagnosis – Acute hepatitis drug induced liver failure secondary to INH complicated with hepatic encephalopathy type A grade II, severe malaria, HIV disease, she was also diagnosed with Hypertension and she started on Nifedipine 5mgs.

Management on admission with Amitriptyline, Diazepam and was also treated for Malaria with Duotexin
The patient died on the 26th/12/2019.

Case 5:
9 years old female whose biological mother died of HIV/AIDS when the child was 5 months old. The child tested HIV+ and was started on antiretroviral therapy (AZT/3TC/NVP) on the 12th/11/2010.

In the beginning her CD4 results were all above 2000 and since August 2015 all her Viral Load tests were undetectable. The child did well on AZT/3TC and Nevirapine. She was attached to the HIV clinic in Soroti Regional Referral Hospital.

The child was started on Isoniazid on the 24th/04/2019, given 250mg OD as prophylaxis for TB.On the 1st/07/2019 her adoptive Mother was told that the ART regimen of the child had to be changed the child was then switched to ABC/3TC/LPV/r and given 1-month supply.

After 5 days on this new regimen, the child`s eyes became yellowish, they took her to hospital and they were told that the Lopinavir could cause some Jaundice and that she had to get used to it. 5 days later, the worried mother had liver function tests done and the results were out of range; (ASAT/GOT 1998, ALAT/GPT 935).

On the 12th/07/2019 after taking the new medicine for 10days, they were told to stop the ARVs. 5 days later on the 17th/07/2019 another Liver functional test was done and the results were even higher (ASAT/GOT 2841, ALAT/GPT 1499). Following this, the child was admitted in Soroti Hospital.

2 days later on the 19th/07/2019, the child was in coma and started getting seizures in the evening of that day, the next day (20th/07/2019) she was flown in a medical plane on oxygen to Kampala where she spent 3 days in the ICU in Nakasero Hospital. She was transferred to the ICU in the Women's Hospital in Mulago where she spent 3 and half days and died on the 26th/07/2019.

Case 6:
33 years old NP from Kyotera admitted at Uganda cares Masaka.
History – Known ISS on ART for 8 months, baseline CD4 was 47cells/uL. The baseline ART was TDF/3TC/EFV and Cotrimoxazole.

The patient developed persistent dizziness on EFV and was later substituted to TVD/NVP on the 21st/08/2019, but also initiated on Isoniazid prophylaxis.

On the 19th/09/19, the patient comes back in with worsened epigastric pain, new on set poor appetite, vomiting, GBW, fevers and palpitations, the patient was investigated for a new onset infection and the lab (B/S, CBC, Urinalysis and RBS) results were normal. She was diagnosed with Septicaemia, ruling out INH associated side effects.

Managed by withdrawing the INH but continuing on the ART and antibiotics therapy. This was later on discovered not to have been effected.

On the 8th/10/2019 – the Patient came back in with worsening fevers, new onset jaundice, vomiting but no diarrhoea. It was noted that the patient had not stopped INH and that she had been managed in a clinic on IV Antibiotics and that the client was also on herbal medicines.

Labs done, LFTs: T. Bilirubin 20.28, ALT 842.8U/l, AST 1111.5U/L, ALB 32.8g/dl
An Abdominal Ultrasound scan of the Liver revealed features suggestive of Cholecystitis with no biliary obstruction.

Management – Patient was admitted on ward, put on ART and INH holiday, supportive management including a liver diet, also was started on IV antibiotics. She improved after one week and was discharged with her AST 50U/L, ALT 80U/L wit persistent jaundice. She was advised to stop the use of the herbal medicine too.

On the 29th/10/2019, the patient was re admitted very weak, worsened jaundice, abdominal distention, pruritus, on and off fevers, passage of very deep yellow urine, mild alteration in the levels of conciseness.

An Ultra sound scan and LFTs were done (ALT 397, AST 418, GGT 125ALB 26.6g/d. It was also noted that the patient had resumed to use herbal medicine. She was diagnosed with Acute decompensated hepatitis with mild hepatic encephalopathy.
After 2 days on ward her condition kept worsening and she progressed into unconsciousness and later died in spite of the supportive management that had been instituted.

It was however queried; could have been either INH or NVP induced hepatotoxicity.

Case 7:
Unknown age, female from Mbarara regional Referral Hospital.

History – She was started on ART (TDF/3TC/DTG) on the 8th/04/2019 in clinical stage 1. She was also started later on INH on the 6th/05/2019. She had been stable on ART until 5th/11/2019 when she started developing yellowing of the eyes plus passing of yellow urine with associated general body weakness.

Both the ART and the INH were stopped on the 19th/11/2019.

Patients condition was worsening and she was admitted on the 28th/11/2019. LFTs on admission were ALT 320 and AST 350, the viral load though was suppressed as tested on the 13th/10/2019.

2 days later the patient died and the diagnosis was Liver Encephalopathy.

Case 8:
AM 37 years old female at Mbarara Regional Referral Hospital.

History – She started ART (AZT/3TC/NVP) on the 27th/04/2010. She was optimized to TLE on the 6th/05/2019 and then switched to TLD in the last two weeks.

She had been stable on ART until 30th/10/2019 when she started feeling weak, had fevers and poor appetite. She was treated for salmonellosis. 2 days later on 11th/11/2019 she reported in the clinic with yellowing of the eyes and general body weakness.

LFTs done on the 11th/11/2019 were AST 1077u/l, ALT 418u/L
She died on the 30th/11/2019 and the working made was diagnosis was Hepatic Encephalopathy.

Two More reports on Death with scanty medical history given.
A one AJ 21years old female from Soroti Regional Referral Hospital, on ART (TDF/3TC/LPV/r) since 22nd/02/2012.He was started on Isoniazid on the 24th/04/2019 for IPT. Came in with an enlarged liver and spleen.
Patient died on 3rd/06/2019.

A one KL female of 32 years from Fort portal RRH in Kabarole district who was on an Unknown ART regimen for unspecified time and was also on Isoniazid from the 28th/05/2019 and withdrawn on the 23rd/08/2019.
Died on the 23rd/08/2019.

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3.0 SIGNAL DETECTION:

Signal detection was done in consideration of all Individual case reports (ICSR)s reported in the reporting period as well as cases recorded in the national database. It involved an analysis of the frequencies of occurrence for all reported ADEs in a manner that identifies the spectrum of the most occurring events through to the least occurring events. All newly reported ADRs (un-labelled or previously un-documented at the NPC) were tested using Proportionate Reporting Ratio (PRR) method. Individual ICSRs which suggest a new ADE (or new aspect of a known ADE) with a potential causal association are considered as possible signals and subjected to further signal evaluation. The table below provides a summary of ongoing signals under evaluation at the NPC.

S/N	DRUG RISK	DESCRIPTION NARRATIVE
	ONGOING SIGNALS	
1	Hyper glycaemia/ DM new onset/ diabetic ketoacidosis with dolutegravir	- These safety issues are under investigation. Communication to Ministry of Health along with risk mitigation recommendations.
2	Jaundice, liver injury with isoniazid	
4	Suspect erectile dysfunction with dolutegravir	
5	Hypersensitivity, generalized rash/SJS with measles rubella vaccine	Casualty assessment for the serious events was done by the AEFI committee and recommendations made.
6	Injection site reaction with measles rubella vaccine	
	NEW SIGNALS	
	No new signals were identified from the reports submitted this quarter.	

Acknowledgement

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

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