Republic of Namibia

Ministry of Health and Social Services
Directorate: Tertiary Health Care and Clinical Support Services
Division: Pharmaceutical Services

Therapeutics Information and Pharmacovigilance Centre's Analysis of Spontaneous Adverse Events due to Antiretroviral and Other Medicines

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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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Key Words

therapeutics information, pharmacovigilance, adverse event (AE)

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CONTENTS

Acronyms iv
Introduction 1
Background 1
Objective of the Analysis of Namibia TIPC Data 1
Methods 2
Design 2
Size or Number of AE Reports 2
Data Management 2
Data Analysis 3
Results 4
Data Analysis by PT and Treatment Category 5
Discussion 19
Conclusions 22
Annex 1. Codes for Non-ARV Agents used in Analysis 23
Annex 2. Breakdown of Analysis Tables 25

ACRONYMS

3TC	lamivudine
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
D4T	stavudine
EFV	efavirenz
EMB	ethambutol
HIV	human immunodeficiency virus
INH	isoniazid
MSH	Management Sciences for Health
NVP	nevirapine
PT	preferred term
PZA	pyrazinamide
RMP	rifampicin
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SJS	Stevens-Johnson Syndrome
SOC	system organ class
TB	tuberculosis
TIPC	Therapeutics Information and Pharmacovigilance Centre
UMC	Uppsala Monitoring Center
USAID	United States Agency for International Development
WHO	World Health Organization

INTRODUCTION

Background

The use of antiretrovirals (ARVs) in combination for treating patients with HIV has greatly ameliorated morbidity and mortality by reducing viral load to undetectable levels and boosting the body's immunity. However serious adverse reactions causing long- or short-term effects have been associated with ARV treatment. These reactions have caused major concerns internationally, potentially threatening patient adherence to long-term treatment.

The duration of treatment of patients infected with HIV; co-morbid conditions, such as tuberculosis (TB) and malaria; and the complications due to HIV infection or AIDS make it difficult to determine the exact cause of the adverse events (AEs) experienced by patients taking ARV medicines. The prevalence of co-morbid conditions differs across socioeconomic groups and geographical regions, which may contribute to differences in ARV toxicity profiles . Hence, it is recommended that national HIV treatment programs establish population-level ARV toxicity profiles for their countries. Therefore, with increased survival of patients and the long-term duration of antiretroviral treatment (ART), it is important for national pharmacovigilance centers to monitor the immediate and long-term effects of these ARVs on the population.

A simple, practical, and cost-effective method for evaluating the safety of drugs approved for human use is the spontaneous reporting of AEs to a pharmacovigilance center. This method is helpful for identifying serious and rare medicine-associated AEs. The evaluation of these AEs informs regulatory decisions on improving the safety of medicines in the country and globally.

Objective of the Analysis of Namibia TIPC Data

To identify drug safety concerns associated with the use of antiretroviral medicines in Namibia's HIV treatment program, by analyzing pharmacovigilance data generated from spontaneous reports of suspected adverse events (AEs).

METHODS

Design

This was a case-series analysis of individual case reports of AEs submitted to the Therapeutics Information and Pharmacovigilance Center (TIPC) in Namibia. TIPC is the national coordinating center for pharmacovigilance activities in Nambia. All reported AEs for the years 2011 to 2013 were extracted from the TIPC database and tabulated using WHO's system organ classes (SOCs) and prefered terms (PTs). The tables were one-way line lists of the AE cases, ranked from the most to the least frequent. Where necessary, two-way tables (cross-tables) were created to explore relationships between suspected drugs and AEs. Four treatment categories of specific interest. The treatment categories include ARVs, antimicrobial agents (excluding anti-TB), anti-TB agents, and all other agents, such as antihypertensives, antipsychotics, etc. Drugs used for each treatment category were coded and entered in the tables. The data from SOC and PT tables for each year were further sunmmarized to show total counts and percentages by PT. Patients were counted only once. A final set of tables was developed to summarize the AEs associated with each treatment group.

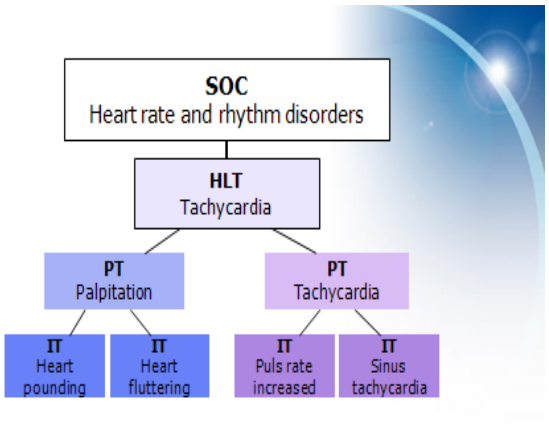
Size or Number of AE Reports

This analysis was conducted on 842 spontaneous AE reports (case-series) submitted to the TIPC by health care workers (physicians, pharmacists, etc.) involved in treating HIV in public health care institutions in Namibia.

Data Management

The reports were reviewed and entered by TIPC staff into the WHO global individual case safety report database (Vigibase), which is centrally hosted at the Uppsala Monitoring Center (UMC). The UMC is responsible for implementing the WHO program for international drug monitoring of which Namibia is a member. The individual AEs were further classified and coded according to WHO ART adverse reaction terminology:

- SOC
- High-level terms (HLT)
- PTs
- Synonyms for PTs



Example of the WHO-ART hierarchy

Data Analysis

For the purpose of this analysis:

- AEs were classified under the different SOCs. The number of cases under each SOC was summarized by year of occurrence, as shown in table 1.

- The PTs associated with each reported case were further summarized by the SOC groups. Medicines were grouped into ARV, antimicrobial, anti-TB, and others (antihypertensive, antipsychotics, etc.).

- The number of AEs listed for each PT was charted against each suspected ARV or treatment regimen as reported. The same was performed for non-ARV treatment. However, the latter total consisted of the treatment group and not individual regimens as calculated for the ARVs. This table was useful in calculating the frequency of reports for each PT and treatment.

- Additional analyses of AEs were performed for age, sex, seriousness, and life-threatening events (tables 2 and 3).

RESULTS

The following tables and charts show the distribution of AEs reported from 2011 to 2013 by SOC and PT.

Table 1. WHO-SOC distribution of AEs for 2011-2013

	Frequency/% calculation of total events		
SOC	**2011**	**2012**	**2013**
Skin and appendages disorders	205/64.7%	58/18.3%	54/17%
Red blood cell disorders	113/76.4%	22/14.5%	13/8.7%
Liver and biliary system disorders	69/75%	5/5.4%	18/20%
Central and peripheral nervous system disorders	33/71.7%	7/15.2%	6/13%
Body as a whole/general disorders	24/60%	8/20%	8/20%
Endocrine disorders	16/43.2%	9/24.3%	12/32.4%
Respiratory system disorders	9/36%	7/28%	9/36%
Gastrointestinal system disorders	17/63%	4/14.8%	6/22.2%
Metabolic and nutritional disorders	16/76%	2/9.5%	3/14.2%
Urinary system disorders	7/36.8%	5/26.3%	7/36.8%
Psychiatric disorders	8/53.3%	-	7/46.7%
Musculo-skeletal system disorders	5/50%	-	5/50%
Reproductive disorders, female	6/66.7%	3/33.3%	-
Heart rate and rhythm disorders	2/25%	3/37.7%	3/37.7%
Hearing and vestibular disorders	6/100%	-	-
Vision disorders	4/80%	-	1/10%
Platelet, bleeding, and clotting disorders	4/100%	-	-
Cardiovascular disorders, general	2/66.6%	-	1/33.3%
White cell and respiratory disorders	2/100%	-	-
Fetal disorders	-	2/100%	-
Myo, endo, pericardial, and valve disorders	-	-	1/100%
Resistance mechanism disorders	-	-	1/100%
Neonatal and infancy disorders	-	-	1/100%
Neoplasm	1/100%	-	-
Total	549/65.4%	135/16.1%	156/19%

Table 2. Frequency distribution for non-serious, serious and life-threatening events

	2011	**2012**	**2013**
# of events with no seriousness criteria	6	36	13
# of non-serious events	150	34	65
# of serious events (% of total annual reported events)	357 (70%)	55 (44%)	62 (44.3%)
# of life-threatening events (% of total annual reported events)	104 (20% of total	15* (12%)	10 (7%)

*Two fetal deaths that occurred in 2012 were categorized as life-threatening and associated with levogesterol use.

Table 3. Reported deaths caused by AEs for 2011

# of events	**Reaction**	**Age**	**Sex**	**Suspected drug**
2	Stevens Johnson syndrome (SJS)	39	F	Nevirapine
		39	F	Nevirapine
1	Hepatotoxicity	43	F	Nevirapine
1	Baby died	50 days	F	Pentavalent vaccine

Data Analysis by PT and Treatment Category

The tables below show the AEs by PT with each suspected ART/regimen.

Table 4. SOC 1 − Skin and appendage disorders (317 events, 266 associated with ARVs)

PT	EFV	NVP	3TC	AZT	AZT/3TC	D4T	D4T/NVP/3TC
Acne	✓						
Angioedema	✓						
Dermatitis		✓					
Exfoliative dermatitis	✓	✓					
Epidermal necrolysis	✓	✓					
Pruritus		✓					
Rash	✓	✓	✓	✓	✓	✓	
Rash erythematous		✓					
Rash maculo-papular		✓					✓
Skin discoloration		✓					
SJS	✓	✓*			✓	✓	
Urticaria		✓					

*Highest frequency of AEs was reported for SJS with 94 reports out of 218 AE reports associated with NVP alone (excluding NVP-based regimen) (218/266 [82%])

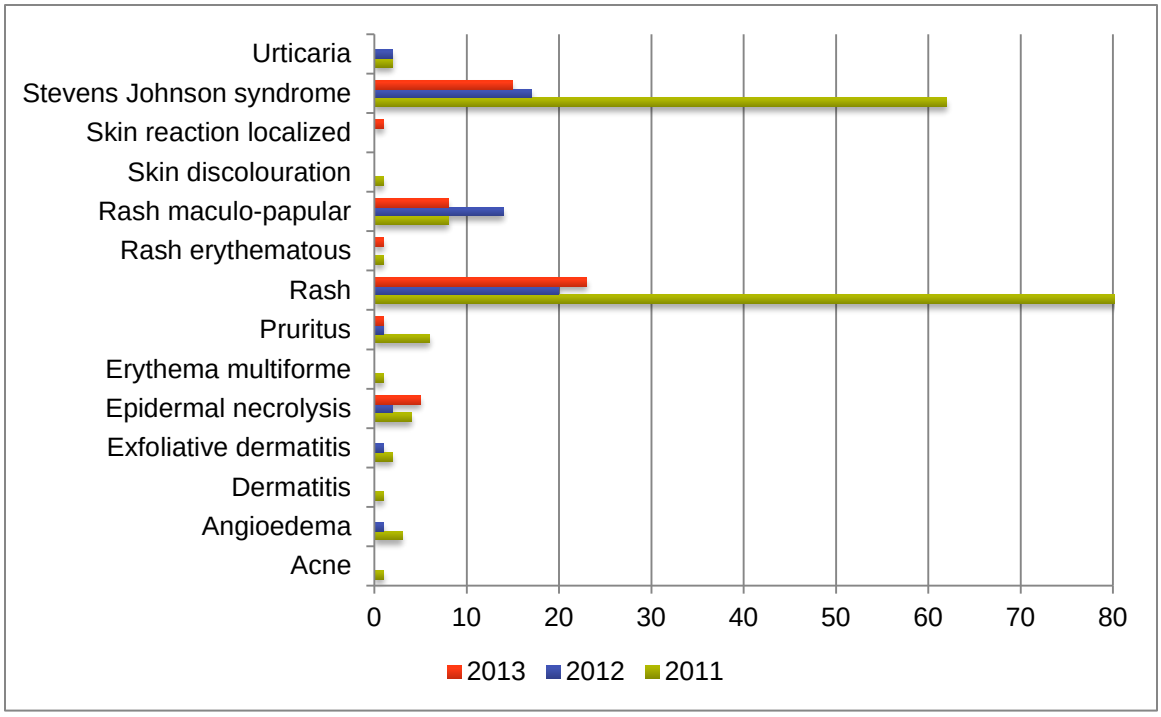


Figure 1. Frequency distribution by PTs for skin and appendage disorders (the scale of the figure was adjusted to better visualize the small-value data points; the value for the green rash bar is off the chart at 113)

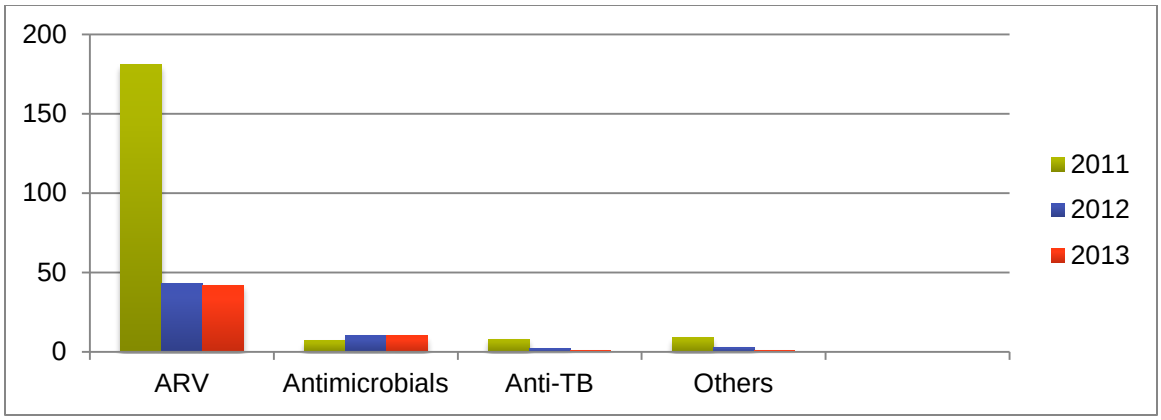


Figure 2. Frequency distribution by treatment category for skin and appendage disorders

Table 5. SOC 2 − Red blood cell disorders (148 events, 100% associated with ARVs)

PT	EFV	NVP	3TC	AZT	AZT/3TC	D4T	AZT/NVP/3TC
Anemia		✓		✓*	✓	✓	✓
Pancytopenia							✓

*Highest frequency of AE was attributed to AZT (97/148 [66%]). Reports for anemia were 96/97 (99%) of total AZT associated events.

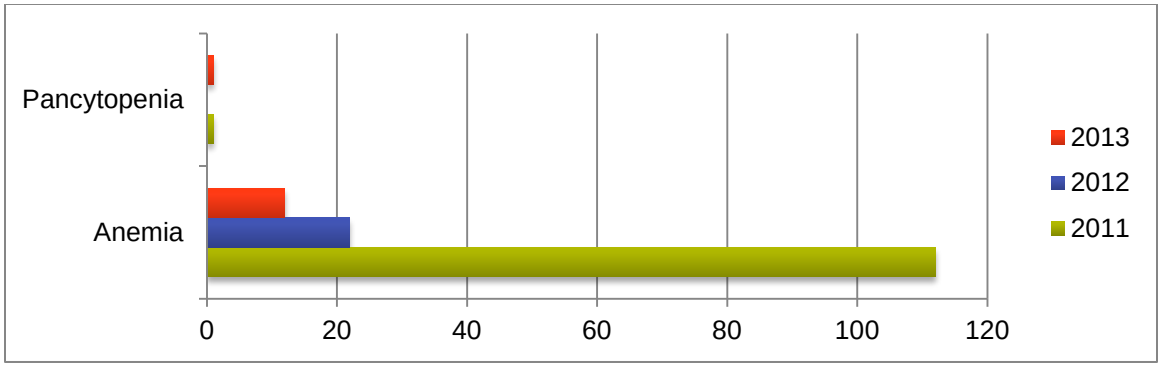


Figure 3. Frequency distribution by PTs for red blood cell disorders

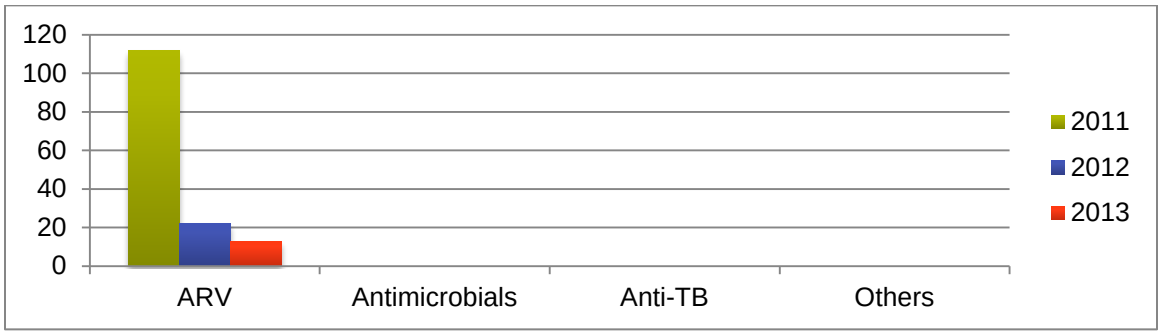


Figure 4. Frequency distribution by treatment categories for red blood cell disorders ; note that data shows 100% ARV causal association

Table 6. SOC 3 − Liver and biliary system disorders (92 events)

PT	EFV*	NVP*	3TC	AZT	AZT/3TC	D4T	AZT/NVP/3TC	D4T/NVP/3TC
Hepatic enzymes increased	✓	✓						
Hepatic function abnormal		✓						
Hepatitis	✓	✓					✓	
Hepatocellular damage		✓						
Jaundice		✓						
SGPT increased	✓	✓					✓	

*81/92 (88%) events were associated with ARVs; 74/81 (91%) of ARV-associated events were caused by NVP . All AEs are linked to the the liver and biliary system. Close monitoring of patients with pre-existing liver disease taking a regiment containing NVP is recommended.

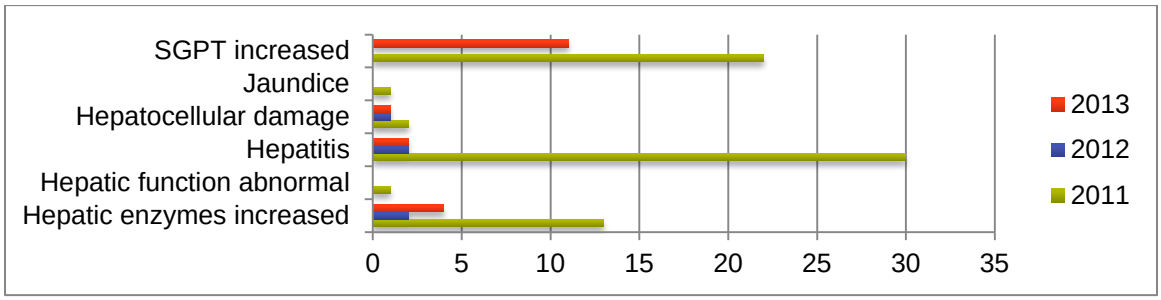


Figure 5. Annual frequency distribution by PT for liver and biliary disorder SOC

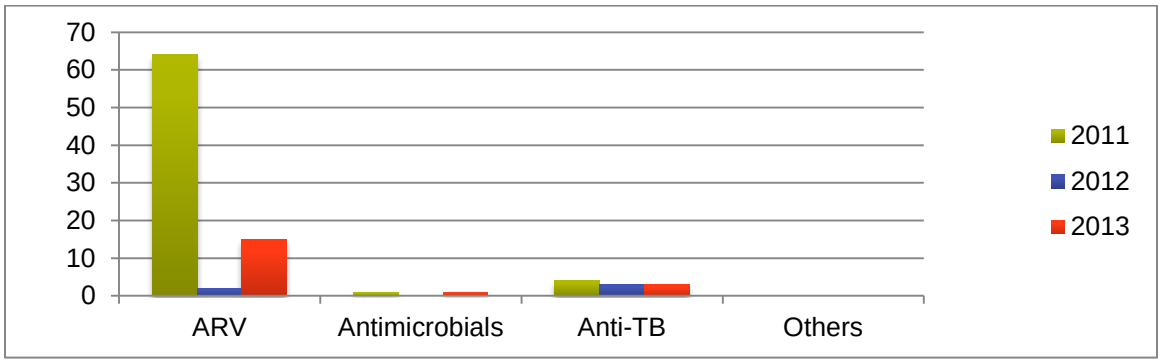


Figure 6. Annual frequency distribution for liver and biliary disorder SOC by treatment categories (Note: 100% ARV causal association)

Table 7. SOC 4 - Central and peripheral nervous system disorders with 46 events and 33% ARV association*

PT	EFV	NVP	3TC	AZT	AZT/3TC	D4T	AZT/NVP/3TC	3TC/TDF
Neuropathy peripheral			✓					
Convulsion								
Hypertonia								
Headache	✓	✓						
Dizziness	✓							

PT	EFV	NVP	3TC	AZT	AZT/3TC	D4T	AZT/NVP/3TC	3TC/TDF
Dyskinesia								
Coma								
Hypokinesia								✓
Meningitis								
Hypoaesthesia					✓			
Dystonia								
Stupor	✓							
Numbness								

*****67% of AEs were non-ARV associated (26% anti-TB treatment association); dizziness was experienced more than other events. Only 2 cases of peripheral neuropathy were associated with 3TC; 8/11 (72%) of ARV-associated events were due to EFV which is known to cause unusual CNS effects.

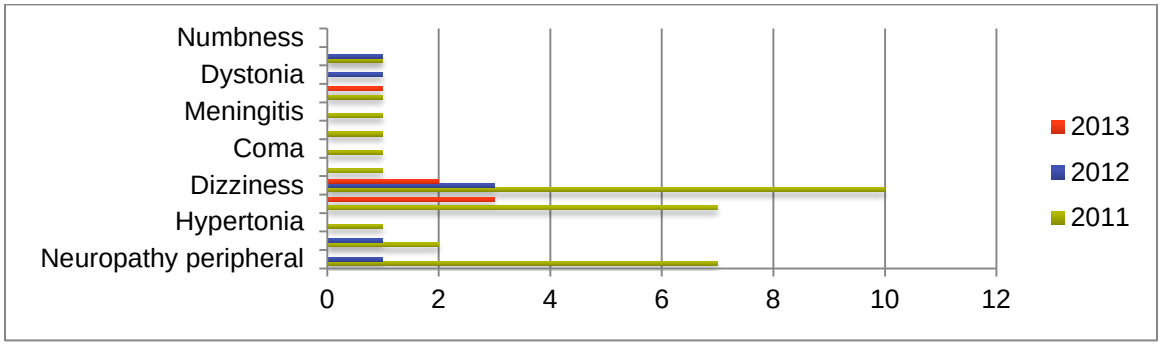


Figure 7. Annual frequency distribution by PT for central and peripheral nervous system disorder SOC

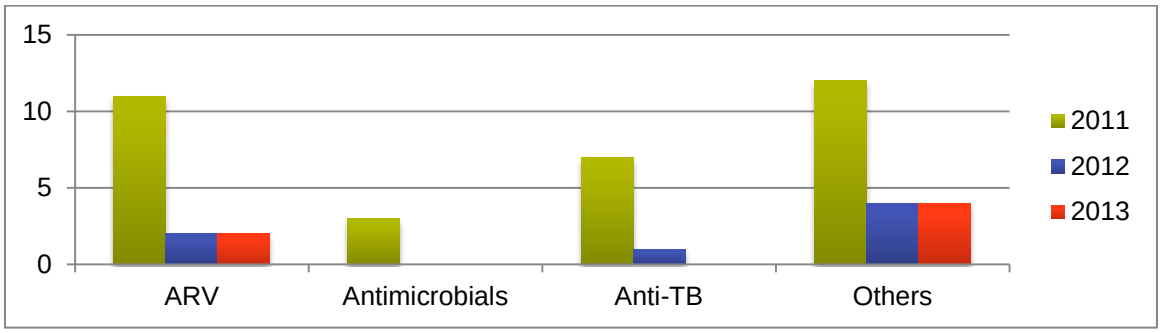


Figure 8. Frequency distribution of treatment association with AE for central and peripheral nervous system disorder SOC

Table 8 SOC 5 – Body as a whole, general disorders with 40 events*

PT	NVP	AZT	TDF	RTV/LPR	AZT/NVP/3TC
Allergic reaction	✓				
Allergy					
Anaphylactic reaction					
Asthenia					
Chest pain				✓	
Death					
Drug reaction paradoxical	✓				

PT	NVP	AZT	TDF	RTV/LPR	AZT/NVP/3TC
Fever					
Leg pain			✓	✓	
Influenza-like symptoms					
Medicine ineffective					
Night sweats					
Oedema mouth (1 death)					✓
Oedema					
Oedema peripheral					
Malaise					
Resistance					

*13/40 (32%) of total reported events were associated with ARVs; 6/13 (46%) of ARV-associated events were caused by NVP; 4/6 (67%) of NVP-associated reactions were allergic in nature, such as mouth oedema, which occur most often in patients with CD4 counts >250 cell/µL

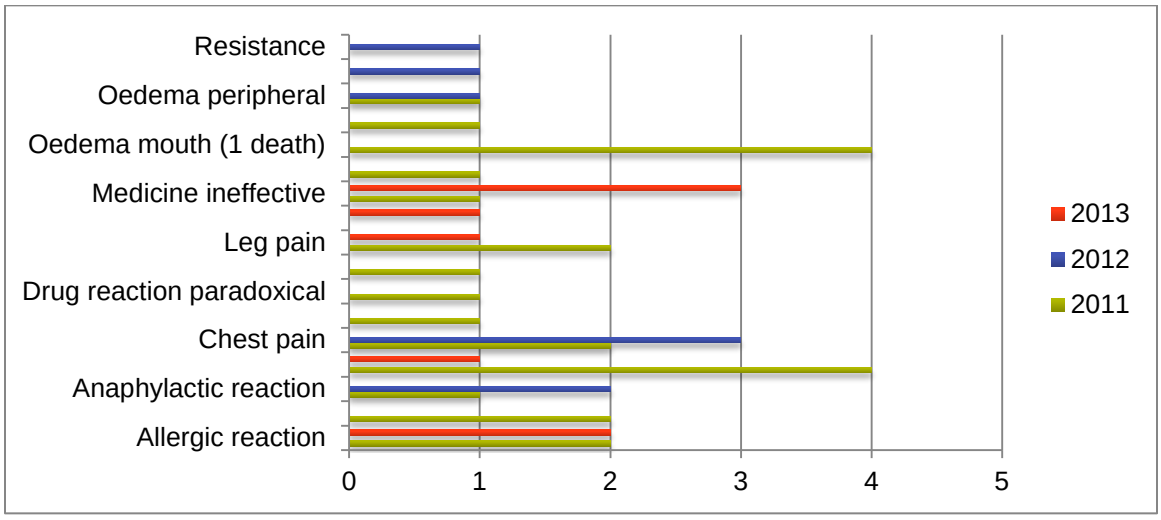


Figure 9. Annual frequency distribution by PT for the body as a whole - general disorders SOC

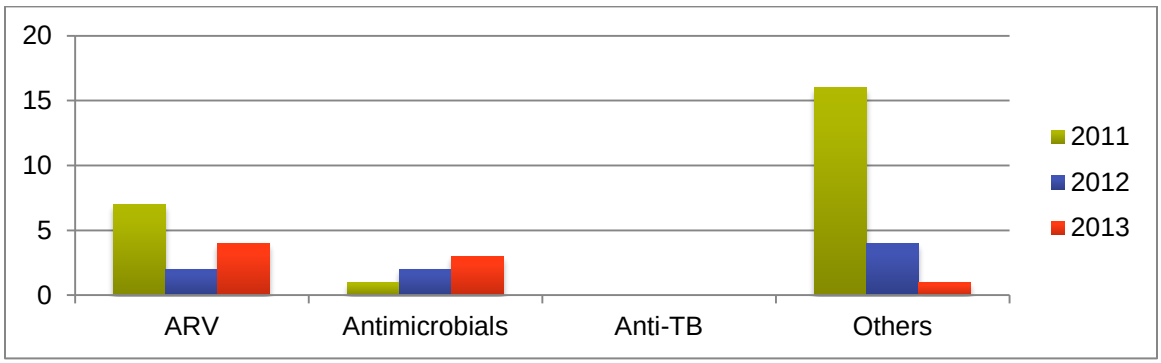


Figure 10. Frequency distribution by treatment category, body as a whole - general disorders SOC

Table 9 SOC 6- Endocrine disorders with 36 ARV associated events*

PT	EFV	3TC	AZT	AZT/3TC	D4T	TDF
Adrenal insufficiency						✓
Fat redistribution	✓		✓			
Gynaecomastia	✓				✓	

*31/36 (86%) of AEs were associated with EFV; gynaecomastia (rare AE) occurred in 4/31 ARV-associated AEs

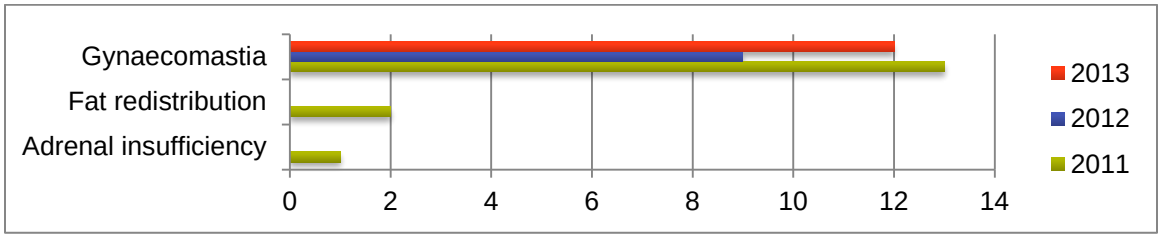


Figure 11. Annual frequency distribution by PT for endocrine disorders SOC

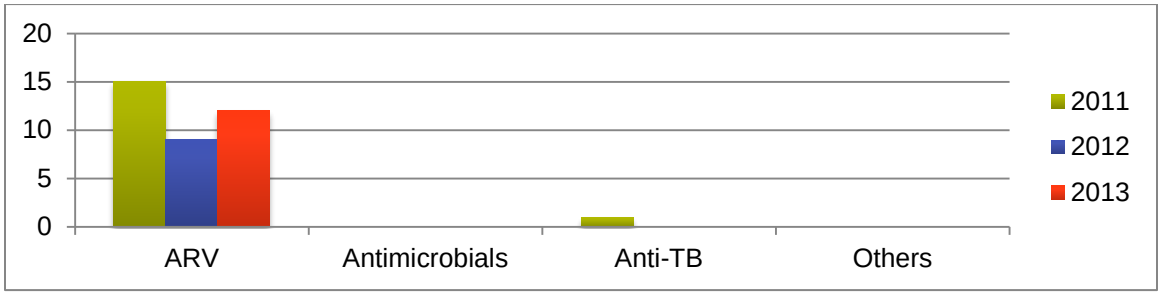


Figure 12. Frequency distribution by treatment category for endocrine disorders SOC

Table 10 SOC 7- Respiratory system disorders*

PT	NVP	D4T/NVP/3TC
Cough		
Dyspnoea	✓	
Epistaxis		✓
Pharyngitis		
Rhinitis		
Respiratory distress		

*Only 2 ARV-associated AEs were reported for NVP and NVP-based regimens

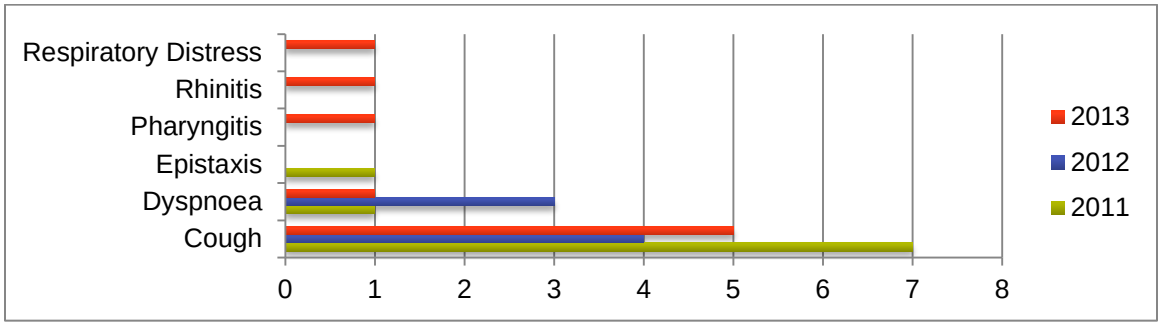


Figure 13. Annual frequency distribution by PT for repiratory system disorders SOC

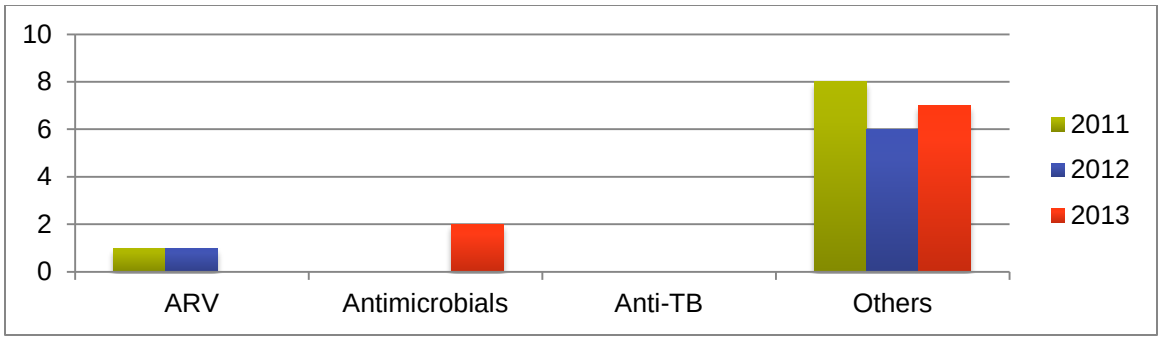


Figure 14. Frequency distribution by treatment category for respiratory system disorders SOC

Table 11 SOC 8- Gastrointestinal system disorders with 17 events

PT	NVP	3TC	AZT	AZT/3TC	3TC/TDF	AZT/NVP/3TC
Abdominal pain	✓		✓			
Diarrhoea	✓					
Dyspepsia						
Gastritis						
Gum hyperplasia						
Haematemesis						
Mouth dry						
Mucositis NOS	✓					
Nausea	✓					
Stomatitis ulcerative			✓			
Tongue discolouration						
Vomiting	✓		✓		✓	
Oesophagitis						
Cheilitis						✓
Lip ulceration	✓					

All treatment categories showed associated AEs to one or more PTs; 14/27 (52%) of total reports were ARV associated. NVPe had the highest frequency of association of AEs. NVP induced lip ulceration is rare. AZT induced stomatitis ulcerative is not a known association.

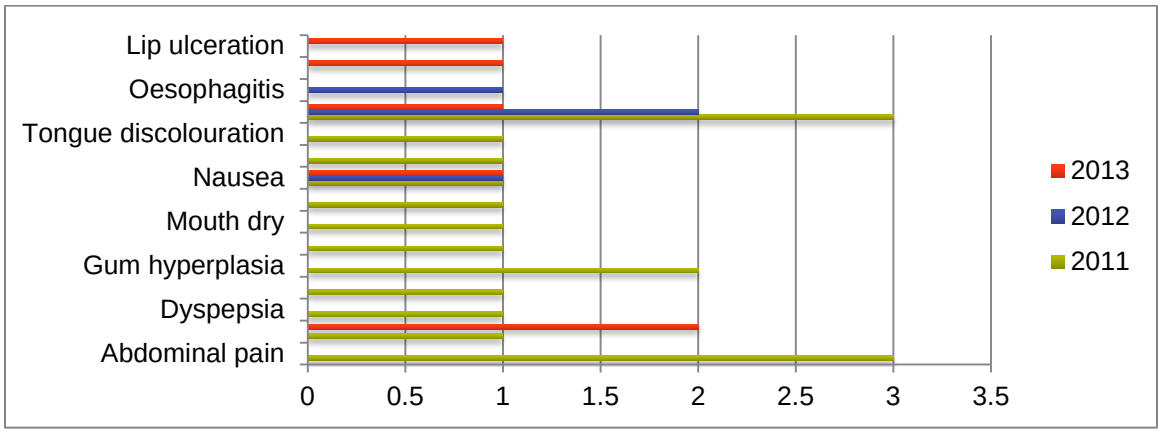


Figure 15. Annual frequency distribution by PT for repiratory system disorders SOC

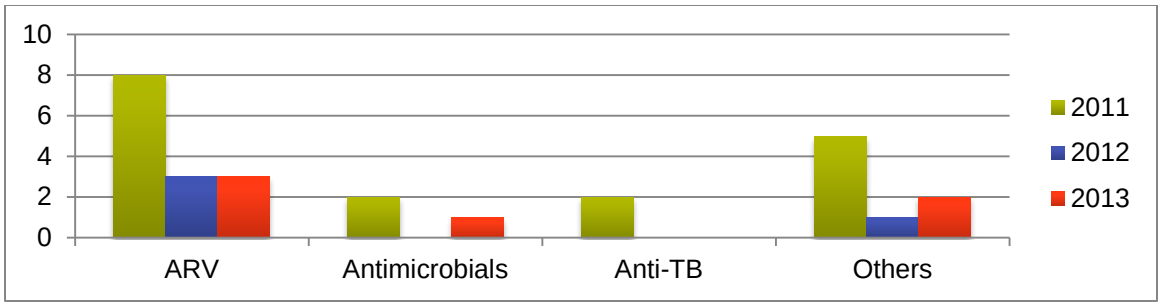


Figure 16. Frequency distribution by treatment category for metabloc and electrolyte disorders SOC

Table 12. SOC 9- Metabolic and nutritional disorders with 16 events

PT	D4T	3TC/D4T	AZT/NVP/3TC
Acidosis lactic	✓		
Electrolyte abnormality			
Lipodystrophy	✓	✓	✓

Table 12 shows that 20/21 (95%) AEs were ARV associated. D4T accounted for 18/20 (90%) of the ARV-associated AEs. The most frequent of these AEs was lipodystrophy, which was highly asscociated with the use of D4T (16/18 or 88% of AEs). A less toxic regimen was recommended because of the high prevalence of lipoatrophy, which is more common in women treatedfirst-line regimens containing D4T. Lipoatrophy is also caused by AZT to a lesser extent. One unrelated ARV associated AE was due to an anti-TB agent.

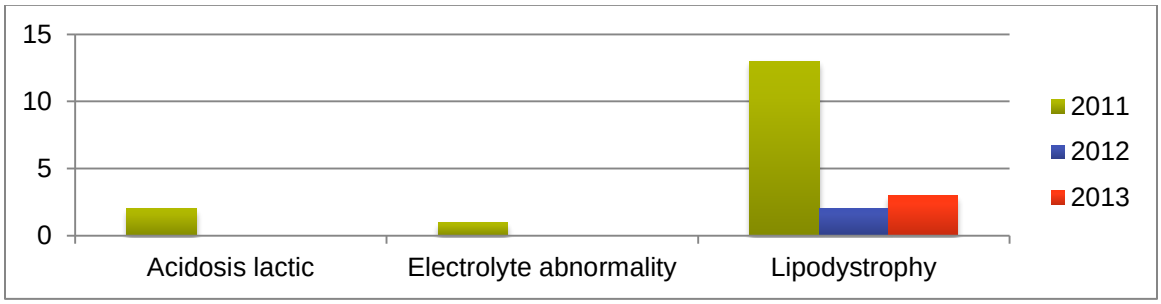


Figure 17. Annual frequency distribution by PT for metablic and electrolyte disorders SOC

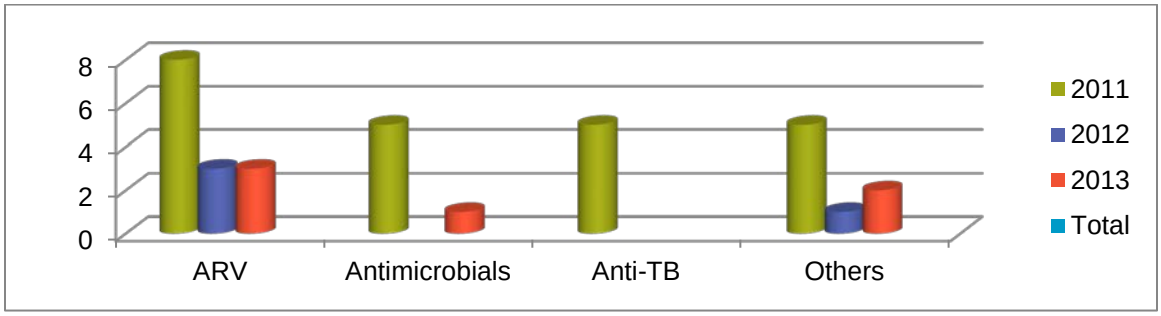


Figure 18. Frequency distribution by treatment category for metabloc and electrolyte disorders SOC

Table 13. SOC 10 - Urinary system disorders with 19 reports and 14 ARV-associated events*

	EFV	NVP	3TC	AZT	TDF	3TC/TDF
Creatinine clearance decreased	✓	✓				✓
Renal function abnormal			✓			✓
Haematuria				✓		
Renal failure acute				✓		
Face oedema						
Azotaemia				✓		
Renal failure acute						
Renal failure chronic					✓	✓
Polyuria						
Nephropathy toxic						✓

*14/19 (74%) reports were associated with ARVs; events are distributed among NVP, 3TC, AZT, and TDF

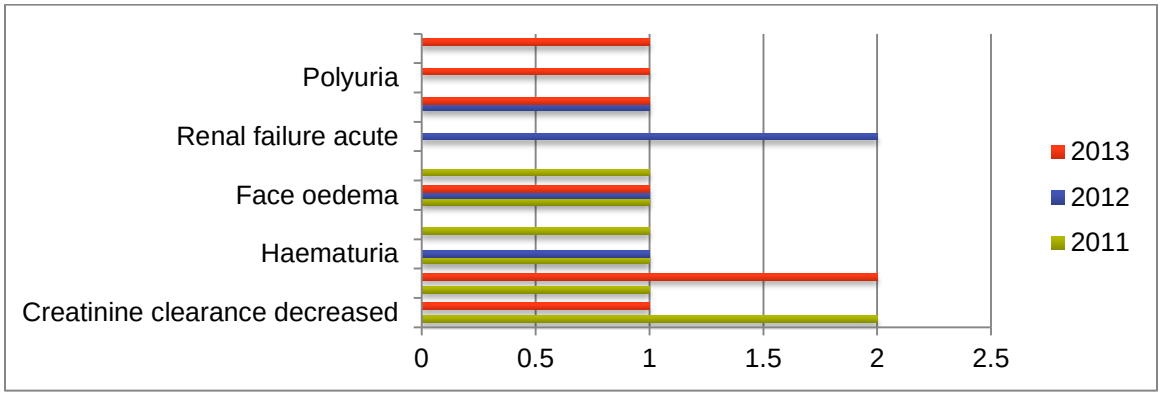


Figure 19. Annual frequency distribution by PT for urinary system disorders SOC

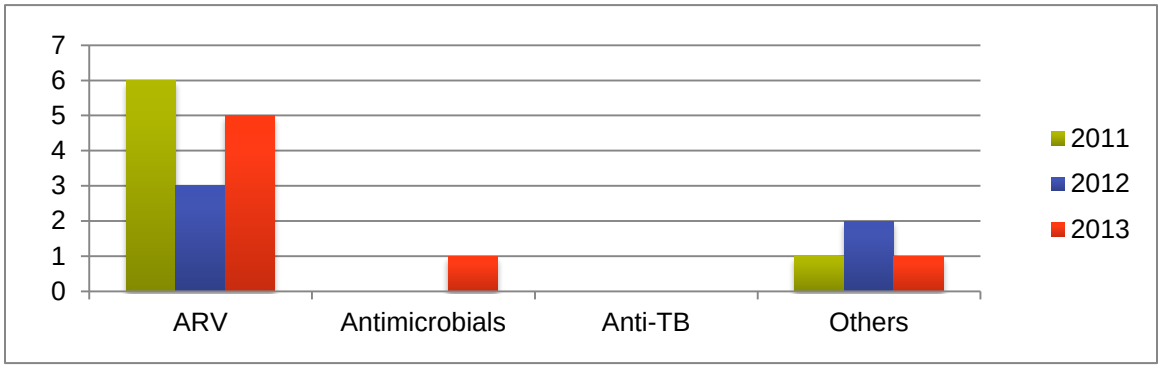


Figure 20. Frequency distribution by treatment category for urinary system disorders SOC

Table 14. SOC 11 - Psychiatric disorders with 15 AE reports*

PT	EFV
Confusion	✓
Delirium	✓
Depression	

PT	EFV
Dreaming abnormal	✓
Impotence	
Sleep disorder	✓
Somnolence	
Paroniria	
Hallucination	✓
Insomnia	✓
Anorexia	

*All events were reported in 2011 and 2013. No AE reports for this SOC in 2012. ARV-associated events were 6/15 (40%) with 100% EFV association. EFV is known to cause severe CNS effects. The highest frequency of events occurred in the "other" treatment group.

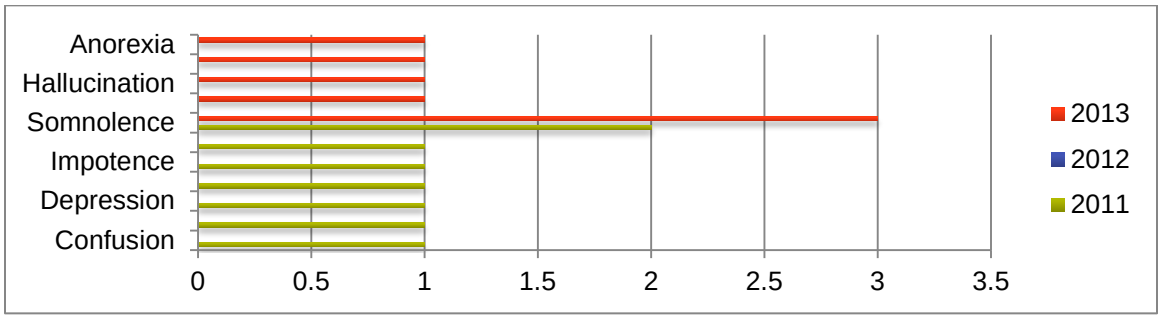


Figure 21. Annual frequency distribution by PT for psychiatric disorders SOC

Table 15 Total AE per treatment category for SOC 11

Treatment	2011	2012	2013	Total
ARV	**4**	No reports	**2**	**6**
Antimicrobials			**1**	**1**
Anti-TB				
Others	**4**		**4**	**8**

Table 16. SOC 12: Musculo-skeletal system disorders with 10 AE reports*

PT	NVP	D4T/3TC	D4T	AZT/NVP/3TC
Arthralgia		✓		
Myalgia		✓		
Arthropathy	✓			✓
Muscle weakness				

*No reports for this SOC in 2012. Arthralgia and myalgia were most frequently experienced Arthropathy was most frequent linked to NVP and NVP/AZT/3TC.

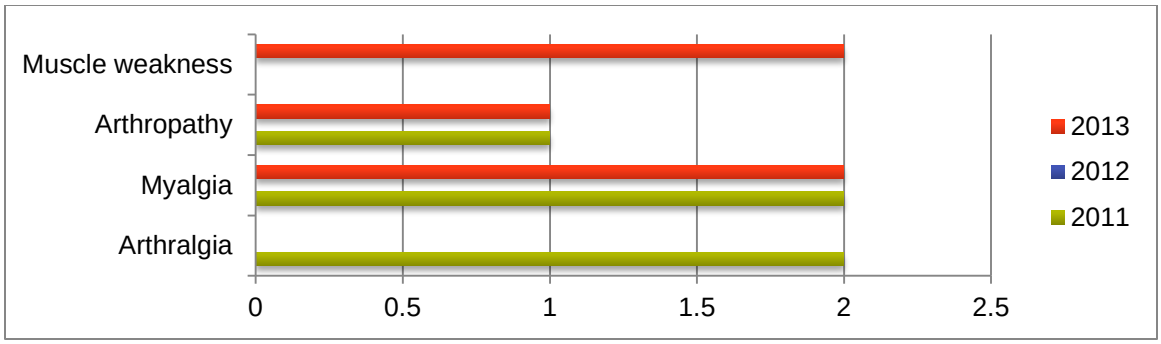


Figure 22. Annual frequency distribution by PT for musculo-skeletal system disorders SOC

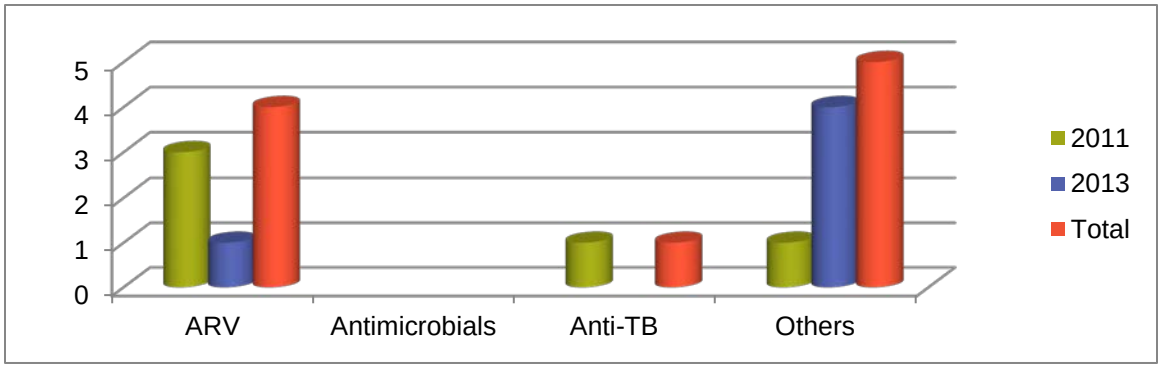


Figure 23. Frequency distribution by treatment categories for musculo-skeletal system disorders SOC (no treatment reports in 2012)

Table 17 SOC 13 Female reproductive disorders with 9 events and 2 ARV-associated events*

PT	EFV
Uterine perforation	
Vaginal haemorrhage	✓
Vaginitis	
Menorrhagia	✓
Pregnancy unintended	
Intermenstrual bleeding	
Moniliasis	

*The suspected drug for both AEs was EFV; both are uncommon.

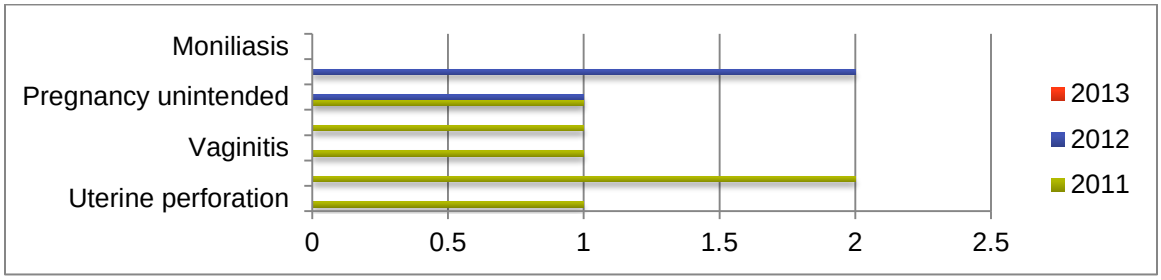


Figure 24. Annual frequency distribution by PT for female reproductive disorders SOC

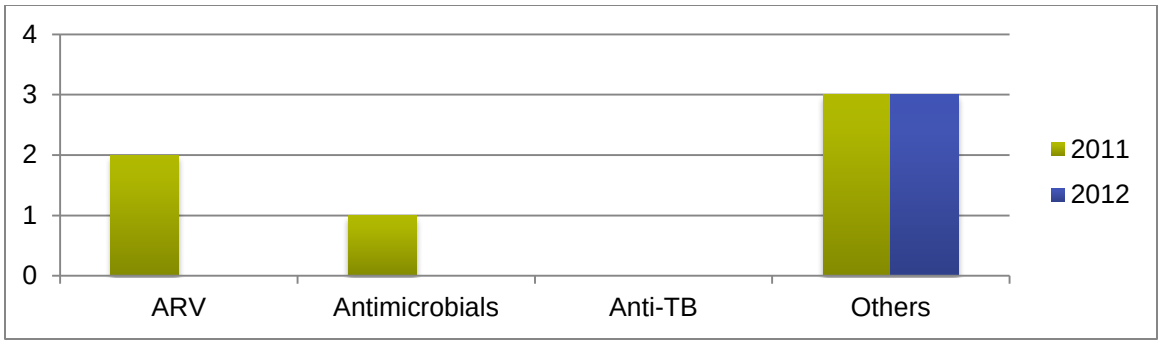


Figure 25. Frequency distribution by treatment category for female reproductive disorders SOC (no ARV treatment-associated AE reports in 2012)

Table 18 SOC 14- Heart rate and rhythm disorder with 8 AE reports*

Palpitation	
Bradycardia	No suspected ARV association
Tachcardia	

*7/8 (87.5%) AEs were associated with other treatment; one AE (palpitation) was associated with the anti-TB agent clarithromycin, a rare reaction with use of this agent.

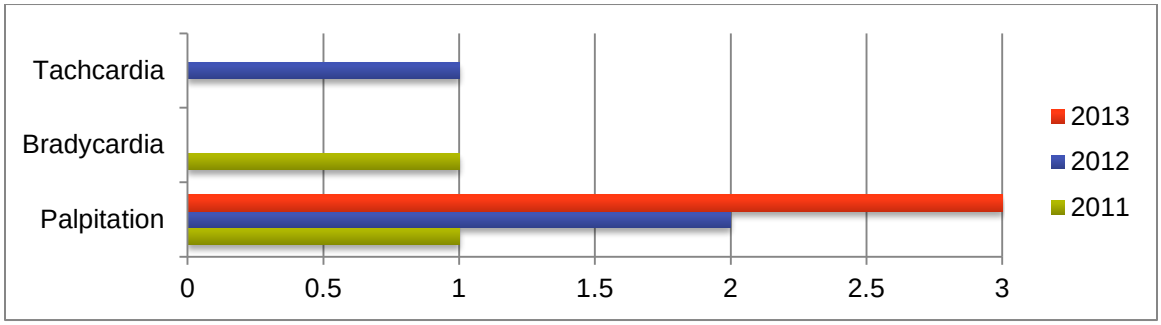


Figure 26. Annual frequency distribution by PT for heart rate and rhythm disorders SOC

Table 19 Total AEs per treatment category for SOC 14*

Treatment	2011	2012	2013	Total
ARV				
Antimicrobials				
Anti-TB			1	1
Others	2	3	2	7

*Frequency distribution of AEs by treatment category for heart rate and rhythm disorders SOC
No treatment associated AE report for ARV

Table 20. SOC 15-Hearing and vestibular disorders with 6 reports and no ARV association*

PT	2011	2012	2013
Hearing decreased	3	0	0
Deafness	3	0	0
Total	6	0	0

*All events in 2011 caused by anti-TB agents. No events were reported in 2012.

Table 21. SOC 16-Vision disorders*

PT	NVP
Blindness color	
Vision abnormal	
Eye pain	
Conjunctivitis	2

*2/2 (100%) reported AEs for conjunctivitis (2011 and 2013) associated with NVP; no events were reported for 2012. NVP is known to cause severe to life threatening conjunctivitis.

Table 22 SOC 17-Platelet, bleeding, and clotting disorders*

PT	2011	2012	2013
Thrombocytopenia	4	0	0
Total	4	0	0

*Annual frequency distribution by PT for platelet, bleeding, and clotting disorders SOC; 2/4 reported AEs were associated with AZT.

Table 23 needs a title AE distribution by type of medicine

Treatment	2011	
ARV	AZT	2/50%
Antimicrobials	RBV	1/25%
Anti-TB	RMP	1/25%
Others		-

Total AE distribution per treatment category for SOC 17

Table 24. SOC 18-Cardiovascular disorders, general with 3 AE reports*

PT	2011	2012	2013
ECG abnormal specific	1	0	
Hypertension		0	
Heart disorder	1	0	1
Total	2	0	1

*2 events were associated with TDF and AZT

Table 25. Total AE per treatment category for SOC 18

Treatment	2011		2012	2013	Total
ARV	TDF	1	No report		2
	AZT	1			
Antimicrobials					
Anti-TB					
Others				PER	1

SOC 19 – White cell and reticuloendothelial disorders: 2 reports

Two events, granulocytopenia and leucopenia, occurred in 2011 with no ARV association. Both AEs were associated with the antimicrobial agent Peg-α2.

SOC 20 - Fetal disorders: 2 reports

Two reports of fetal deaths that occurred in 2012 were associated with levonorgestrel.

SOC 21 – Myo, endo pericardial and valve disorders: 1 report

One report of angina pectoris with no ARV association. Suspected drug was clarithromycin (anti-TB medication).

SOC 22 - Resistance mechanism disorders: 1 report

No association with ARVs, anti-Tb, or antimicrobial medicines. The suspected drug was for "other" treatment.

SOC 23 - Neonatal and infancy disorder: 1 report

One event in 2013 (cyanosis neonatal) was associated with an antimicrobial agent.

SOC 24 – Neoplasm: 1 report

No association with ARV, anti-TB, or antimicrobial medicines. The suspected drug was for "other" treatment.

DISCUSSION

From 2011 to 2013, 840 AEs were submitted to the TIPC database. Of these, 549 (65.4%) were reported in 2011, 135 (16.1%) in 2012, and 158 (18.8%) in 2013, showing a significant decline in reporting rate after 2011. Skin and appendage disorders (SOC 1) were most frequently reported, followed by red blood cell disorders (SOC 2) and liver and biliary disorders (SOC 3). The decline in reporting rate may explain the significant decline in the total number of reported events. In 2013, the most significant drop was seen in SOC 3. In 2011, 76.4% of total events in SOC 2 (red blood cell disorders) were reported; 99% was due to anemia. In 2013, it fell to 8.7%, mostly anemia. The significant reduction in the occurrence of AEs, may also be indicative of increased awareness and the implementation of AE preventive measures.

For ARVs, the most common reactions occurred in SOC 1 (skin and appendage disorders). Patients were more likely to develop skin rash and Steven Johnson Syndrome (SJS). Reports from drug analysis showed SJS accounted for 22.5% of all the cases in the SOC, while rash was 21.9%. Seventy percent of the total reports for this class of disorders was associated with NVP (53% rash, 35% SJS).

In 2012, there were 20 cases of skin rash and 17 cases of SJS rash. NVP attribution to these cases was 45% (9/20) and 82% (14/17). Total NVP associated events for 2012 was 41. Thus, in 2012, 51% of reported NVP associated AEs were due to rash (22%) or SJS (34.1%). Little change is seen in 2013 with 51 cases of reported NVP associated events (rash, 43.5%; SJS, 33.3%). Skin and appendage disorders accounted for 76.5% of the total. In addition, the two deaths reported in 2011 due to SJS were suspected of being caused by NVP. Comparison of this result with that of developed countries shows an elevation in NVP-associated skin reactions and increased risk as developed countries show an absence of fatalities. The recommended requirement for the initiation of treatment for patients on NVP to reduce the risk and/or the severity of the rash is to give a 2-week lead-in dose (200 mg NVP once daily).

Among the 22 cases of non-ARV suspected rash, 59% were associated with co-trimoxazole use and 32% were associated with the anti-TB agents isoniazid (INH) and INH/ethambutol (EMB)/pyrazinamide (PZA)/rifampicin (RMP). Significant skin reactions in patients on anti-TB treatment have been reported with regimens containing, and RMP, INH, and PZA.

Twenty-four percent of the total of reported NVP-associated events were due to liver and biliary disorders. The greatest association was found in 2011, which accounted for 82.4% of all reported NVP-associated events for this class. Although 2012 showed a significant decrease with only 1 event due to NVP, 12 NVP-related events occurred in 2013. However, this class showed 10 cases of AEs associated with anti-TB medicines,7 (70%) of which were due to the single agent INH. Hepatotoxicity is common during treatment of TB patients and is exacerbated with the concurrent use of ARVs.

All reported events for anemia were associated with the use of ARVs, the most common being AZT and AZT-based regimens. Out of 107 reported events due to AZT, 90% were related to anemia. Females disproportionately accounted for 61% of the AZT-suspected anemia cases. The

AE occurred mostly among adults in the age range 18-65 years. Only 5 reported events occurred in children (5-11 years) and 1 event in a 4-month-old infant. This finding correlates with most reports which demonstrate a greater percentage of AZT-induced anemia and the need for regular hemoglobin monitoring of all patients on AZT-based ART regimens.[1]

One reported gastrointestinal disorder "stomach ulcer" was associated with the use of AZT (table 11). This AE is not a known side effect of AZT. Ulcers occur in 10% of adults (common) and are usually caused by *helicobacter pylori*. A full clinical history and laboratory investigations would help ascertain the exact cause of the reported AE.

Among the central and peripheral nervous system disorders, dizziness was experienced more than any other AE and was largely caused by EFV. Results for peripheral neuropathy show fewer reports. Long-term treatment with nucleoside reverse-transcriptase inhibitors causes varying degrees of myopathy and neuropathy. Only three cases of peripheral neuropathy were reported between 2011 and 2013; two of the cases were associated with the use of 3TC (2011) and one case associated with a 3TC-based regimen (2012). Most events within this class were due to concomitant treatment of co-morbidities (67.4%). As such, 25.8% were due to TB treatment; six AE reports were associated with a regimen containing INH (single agent or in combination with EMB/PZA/RMP), and two AE reports were associated with the use of capreomycin. Peripheral neuropathy is a known complication with ARV use, especially with TB treatment.

A total of 37 reports of gynaecomastia, a rare AE, were reported. The highest number of events (16 AE reports) occurred in 2011 (table 9); 2012 and 2013 had 9 and 12 reports, respectively. All cases of gynaecomastia reported in 2012 and 2013 were associated with the use of EFV or EFV-based ART regimens. Gynaecomastia was also associated with AZT, D4T, and TDF in 2011, but this could be due to missclassification especially because these drugs are combined with EFV in the regimen. Temporary breast enlargement has been documented for a small proportion of males on ARVs. Adrenal insufficiency is most commonly associated with males. Though some studies have seen this disorder with the use of nucleoside analogs, it is a rare emerging AEs that has been tagged for further investigations. Some of the patients in these studies had concurrent lipid and glucose abnormalities. It is recommended to discontinue therapy with suspected drugs or substitute agents within the same class that are less likely to cause gynaecomastia and tell the patient to reduce alcohol consumption.

There were 21 cases of lipodystrophy of which 76% were reported in 2011 with 88% associated with D4T, 10% in 2012 (all associated with D4T), and 14% in 2013 (all associated with D4T). One event was seen with an AZT/NVP/3TC regimen and one was due to an anti-TB agent (capreomycin). All reported events occurred in adults with almost even sex distribution (slightly higher in females). Studies and reports have suggested a strong association with lipodystrophy has been associated with AZT and a much higher association (3×) in patients taking D4T or a D4T-based regimen. Early initiation of HIV management before a decline in CD4 count below 200 cells/mm^3 has been reported to help prevent lipodystrophy. Resource-limited areas are being urged to use less toxic and more affordable ART regimens.

[1] Balakrishnan A, Valsalan R, Sheshadri S, et al. Zidovudine-induced reversible pure red cell aplasia. Indian J Pharmacol. Jun 2010; 42(3): 189–191; http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2937323/

ARV-induced arthralgia was associated with 3TC/D4T and arthropathy with AZT (table 16), which is similar to 3TC/D4T. However, studies have shown rare association with D4T. Hence, it can be assumed that this case of arthralgia may be due to the 3TC base and not D4T. Studies have shown a high relationship of arthropathy to patients on AZT.

A major concern with concurrent use of anti-TB medicines is their association with hearing and vestibular disorders. As is seen in this SOC, all AEs were due to anti-TB medicines (all occurred in 2011 with no reports for 2012 and 2013). One report was associated with each of the following anti-TB agents: ETA, EMB, KAN, CAP, STM, and INH/EMB/PZA/RMP. One case of palpitation was associated with clarithromycin. A study conducted in the US showed that only 1.25% of patients on clarithromycin developed palpitation within a month of initiation.

Seventy-five percent of AEs were reported in 2011 (29% life-threatening events), 12% in 2012 (27% life-threatening events), and 13% in 2013 (16% life-threatening events). The majority (93%) of the reports received in 2011 were associated with adults (58% females and 37% male) in the age range 18-69 years; 13 cases were reported in children (age range 5-11years) and 5 cases in the elderly (age range 70-77 years).

Adults accounted for 84% of events reported in 2012 (age range 21-69 years), most of whom (75%) were females. In that same year, 5 cases were reported in children, 1 for an 8-day old neonate. There was no reported case for an elderly person. In 2013, 95% of reported cases were for adults (age range 21-69 years) with 69.4% female association. This data shows that most of the AE events in Namibia were reported for adults, particularly females.

CONCLUSIONS

AE reporting to Namibia's national pharmacovigilance center (TIPC) showed a drastic decline from 2011 to 2013. This could have been cause by reported fatigue or disinterest, or by a real decline in the occurrence of AEs in the patient population. Commonly, the reported AEs were rash, SJS, anemia, and liver problems. Concomitant ARV treatment and anti-TB medicines contributed significantly to the occurrence of some AEs.

Most of the AE reports were from adult females. HIV clinical trials and studies suggest that sex differences may have an impact on adverse reactions to ART. This is being further investigated. Some mechanisms, such as hormonal changes, differences in body weight, and body mass index may affect the distribution of medicines and play a role in the outcome. Nevertheless, the cause for sex differences in AEs to ARVs is still uncertain.

The reports do not represent all patients on ARV management in Namibia, and the true incidence and prevelence rates cannot be estimated based on the TIPC data of spontaneous reports. In addition, the lack of important clinical information such as past and present medication history, drug rechallenge, and dechallenge; make it difficult to ascertain which drug caused a specific reaction. However, the routine collection and analysis of AE reports can help increase awareness and provide useful information that can guide decisions for improvement in the management of patients in a public health treatment program, such as in HIV and TB treatment.

ANNEX 1. CODES FOR NON-ARV AGENTS USED IN ANALYSIS

ALLO: Allopurinol
α-MD: Methyl Dopa
ACT: Artemether/Lumefantrine
AML: Amiloride
AMI: Amitriptyline
AMP: Ampicillin
Amp-B: Amphotericin
ATN: Atenolol
CMZ: Carbamazepine
Cap: Capreomycin
CAM: Chloramphenicol
Clari: Clarithromycin
CPZ: Chlorpromazine
Clotrimazole
CP/PCM/IBP: Mybulen-Codeine phosphate/Paracetamol/Ibuprofen
CCS: Cycloserine
CYA: Cyclosporin
DAB: Dabigatran
DEM: Dabigatran Etexilate Mesilate
DDS: Dapsone
DIC: Diclofenac - Nonsteroidal anti-inflammatory drug
EPI/LC-HCL: Epinephrine/Lidocaine hydrochloride
ERY: Erythromycin
ETA: Ethionamide
FNM: Fluphenazine
FRS: Furosemide
FTC-ST: Salmeterol/Fluticasone
GG: Guaifenesin
GlcA: Heparin
HP: Haloperidol
HZT/AML-H: Hydrochlorothiazide/Amiloride hydrochloride
HZT/M-HCT: Hydrochlorothiazide/Telmisartan
IBP: Ibuprofen
IND: Indometacin
INH/EMB/PZA/RMP: Isoniazid/Ethambutol/Pyrazinamide/Rifampicin
INH: Isoniazid
ISD-D: Isosorbide dinitrate OR Isordil
LVG: Levonorgestrel
Kan: Kanamycin
MediBPG: Benzyl penicillin G
MPA: Medroxyprogesterone acetate
MET-HCL: Metformin hydrochloride
MTP-HCL: Methylphenidate hydrochloride

NEE: Norethisterone enantate
IPM: Indapamide
MMR-vac: Mumps vaccine/Rubella vaccine/Measles vaccine/Varicella zoster vaccine
PAS: Para-aminosalicylic acid
PBT: Phenobarbitone
PCM: Paracetamol
PNT: Phenytoin
Pegylated interferon-alpha-2a
PER: Perindopril – BP
PMP: Phenoxymethylpenicillin
PMPP: Polio Vaccine
PV: Phenoxymethylpenicillin potassium
PTD: Pethidine
RBV: Ribavirin
RSP: Reserpine
RV: Rabies vaccine
SALB: Salbutamol
SVA: Snake venom antiserum
SUL: Sulpiride
STM:Streptomycin
TMD:Tramadol
TMP-SMZ: Sulfamethoxazole-Trimethoprim, co-trimoxazole, Bactrim
TZM: Tocilizumab OR Actemra
VPM: Verapamil
ZOL: Zoledronic acid

ANNEX 2. BREAKDOWN OF ANALYSIS TABLES

Annual distribution of serious AEs segregated by age range/group and sex

2011 Serious events distribution (357 total serious events)

Age group	Adolescent		Adult			Child		Infant		Neonate	Elderly	
Age range	12-15		19-69			5-11		32 dy-2 yrs		0	70-77	
No. of events	5		334			13		4			5	
Sex	F	M	F	M	U	F	M	F	M		F	M
Sex distribution	4	1	195	125	14	8	5	3	1		5	0

2012: Serious events distribution (55 total serious events)

Age group	Adolescent		Adult			Child	Infant	Neonate	Elderly
Age range	12-16		21-69			5-11	23 mths	8 days	0
No. of events	2		46			5	1	1	
Sex	F	M	F	M	U	F	M	F	
Sex distribution	1	1	27	18	1	5	1	1	0

2013 Serious events distribution (62 total serious events)

Age group	Adolescent		adults			Child	Infant	Neonate	Elderly
Age range	12		21-69			0	4 mths	0	0
No of events	2		59				1		
Sex	F	M	F	M	U		F		
Sex distribution	1	1	41	17	1		1		0

U, sex unknown; F, female; M, male