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Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga Success & Moving Forward

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This report evaluates the improvement in targeted spontaneous adverse drug reaction reporting and the quality of reports, demographic distribution, regimens implicated, the most commonly reported adverse drug reactions (ADRs) as well as concomitant conditions. Reported cases of ADRs in the Mpumalanga anti retroviral treatment (ART) programme from July, 2011 to February, 2013 were evaluated. A total of 1,756 ADR reports were received from the province. 495 were males (28.9%), 1,057 female (60.19%) and in 204 (11.6%) reports, gender was not reported. 908 were satisfactorily completed, 445 (49%) reported one ADR, 366 (40.3%) two ADRs, and 97 (10.7%) reported three or more. The most commonly reported ADR was peripheral neuropathy and the most prescribed regimen was d4T/3TC/EFV. d4T-containing regimens were the highest suspect drug combinations. Correlations were observed between d4T and the occurrence of peripheral neuropathy and lipodystrophy, nevirapine (NVP) and efavirenz (EFV) with rash while zidovudine (AZT) was observed to be associated with anaemia. Tuberculosis was found to be the most clinically significant concomitant medical condition with the highest frequency (32.3%). The review observed a significant increase in ADR reports as well as ADRs associated with the use of ART. Periodic review of data on the national pharmacovigilance database will reveal interesting trends in future.

Key words: Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), adverse drug reactions (ADRs), pharmacovigilance, decentralized, clusters.

INTRODUCTION

It is well documented that South Africa (SA) has the largest human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) treatment programme in the world, with almost two million people initiated on anti-retroviral therapy (ART) (Mayosi et al., 2012; Johnson, 2012). Mpumalanga province is reported to have an HIV prevalence rate by geographic district of more than 35% on average, with age group 15 to 24 being the highest HIV prevalent group in the province (SA NDOH, 2011). An estimated 111,402 people in the province are on ART (Dheda, 2011). The goal of this therapy is to restore the body's immune system, decrease the viral load, decrease opportunistic infections and, above all, to improve the quality of life of patients initiated on anti-retroviral (ARV) treatment (Dybul, 2002). Therefore, monitoring the safety of this massive treatment programme requires intensive quality assurance in order to ensure optimal patient outcomes, and the prevention and management of side effects. Pharmacovigilance provides one of the best opportunities to achieve this. A robust pharmacovigilance system is crucial in quantifying previously recognized ADRs, identifying unrecognized adverse drug events, evaluating the effectiveness of medicines in real-world situations as well as to decrease mortality and morbidity associated with adverse events (Eguale, 2008). The success or failure of any pharmacovigilance activity

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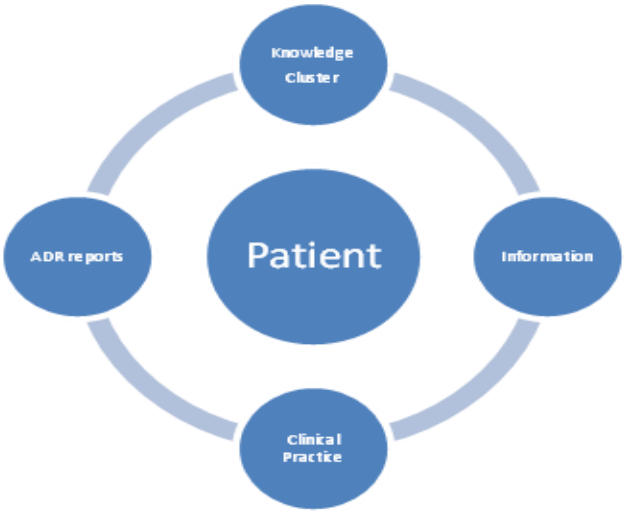

Figure 1. Feedback loop of ADR reports at cluster level.

depends on the reporting of suspected adverse reactions.

SA has relied mainly on spontaneous reporting for its pharmacovigilance which has largely been marred by under-reporting. Further, the overall national pharmacovigilance (PV) approach was not fully designed nor extended to clinical settings to take into consideration the daily management of patients in various healthcare settings.

The National Pharmacovigilance Centre (NPC) recently reported the successful initiation and setting up of a well-structured and highly participative decentralized pharmacovigilance pilot program for ART treatment in Mpumalanga Province (Dheda, 2011). It focuses on patient-centred healthcare safety, prevention and management of side effects, better communication between the various healthcare disciplines providing patient care, proper management of side effects at all levels, while prioritising disease control. This robust patient-focused decentralized PV process in ART in Mpumalanga is the model and platform for roll-out into the rest of South Africa. This roll-out has the potential of achieving the desired cohesive and dynamic system that will meaningfully impact on clinical care and patient safety in the whole country.

Twenty-six (26) PV clusters have been formed in Mpumalanga Province. Their formation was not prescriptive and the provinces, districts, hospitals and clinics decided on what works best for them. Clusters were formed where structures or systems already existed between hospitals and clinics, such as up or down referrals of patients, or where geographic proximity was allowed. The purpose of this decentralization is to bring PV closer to the primary healthcare practice and to increase the general interest in drugs and drug-related problems. Each cluster, consisting of multidisciplinary health care provider (HCP) teams of doctors, nurses, pharmacists, social workers, laboratory technicians and dieticians, meets monthly to discuss effective intervention and case management strategies per individual patient case. These decentralised structures create a smaller and more effective safety feedback loop which allows faster information flow-back to reporters thereby enhancing patient care (Figure 1). In addition to this, the clusters also have the important task of informing other healthcare professionals about ADR with a focus on the reporting. A copy of each individual case report is faxed to the NPC where it is stored in the national database. The report captures data such as demographics, medications, co-morbidities, outcome and suspect drug assessment. Trends are then monitored from this data generating important safety information which is ultimately fed back to the reporters/clusters from the NPC through acknowledgement, ADR information and bulletins describing signals as part of a larger nationwide feedback loop through direct communication with the reporting HCPs or clusters, newsletters, internal memorandums and publication in peer reviewed journals.

The primary endpoints of this interim review were to monitor the change in practice of ADR case reporting manifested through an increased number of reports from the province, their gender and age distribution as well as identify the most commonly observed ADRs. The secondary endpoints were to conduct an interim review of the quality of submitted reports, the regimens implicated in these ADRs as well as the predominating concomitant medical conditions amongst the people on ART in the Mpumalanga population.

METHODOLOGY

This was a retrospective review conducted on PV reports from the ART program in Mpumalanga province from the districts of Nkangala, Ehlanzeni and Gert Sibande. For the primary endpoints, all the 1,756 reports submitted for patients between 27th July, 2011 and 28th February, 2013 were considered. Only the properly completed 908 reports were taken further into the secondary analysis. The following information was collected: gender, age, suspected drug(s), suspected ADR(s), concomitant medical conditions and outcome for the patient. The incidence was calculated by considering the ratio of number of patients with ADRs and total number of patient reports considered. Data for sex and age were analysed using the sample test of proportions for establish proportional differences using STATA10® (StataCorp, 2007). A p value of < 0.05 was considered as statistically significant.

This paper does not report on primary research and all data analysed were collected as part of routine diagnosis and treatment according to national ART treatment guidelines. It does not report the use of experimental or new protocols and was not set up as a study or research project but is part of the South Africa National Department of Health pharmacovigilance programme. The retrospective review was done internally as part of an evaluation, so as to improve patient quality of care. By its very nature, ART in HIV/AIDS treatment exposes patients to a high risk of treatment failure, possible drug resistance and consequently death so it was felt that this vital information should be published in a reputable open source journal. Publication of such information without

Table 1. Patients reported per district in Mpumalanga n = 1,756.

Characteristic	Ehlazeni	Gert Sibande	Nkangala	Total	Incidence (%) = reported/*n*
Gender					
Male	146	292	57	495	28.19
Female	281	652	124	1057	60.19
Unknown	29	149	26	204	11.6

*Unknown: Gender not reported.

Table 2. Age of Patients reporting ADRs in the Mpumalanga province n = 1,756.

Characteristic	Number of ADRs	Number of ADRs	Incidence (%) = reported/*n*	*P* Value
Age (years)				
0 – 17	Male 89 Female 131 Unknown 59	279	15.81	
18 – 30	Male 30 Female 156 Unknown 25	211	12.01	
31 – 40	Male 145 Female 364 Unknown 43	552	31.44	*p* value < 0.001
41 – 50	Male 130 Female 243 Unknown 51	424	24.15	
51+	Male 101 Female 158 Unknown 26	285	16.23	

*Age not reported = 5.

approval by an ethics committee is not unprecedented in operational research. In a similar case, both the WHO Research Council and the Committee on Publication Ethics held decisions in favour of public interest to have such information published as it would probably bring benefits to the people whose autonomy may be harmed by its publication (Gollogly, 2006). The autonomy of the patients in this case is protected because their identity is withheld from the data reviewers. Consequently, neither patient informed consent nor ethics approval was sought because this is an epidemiological review in which it was impossible to identify the patients (Nilstun and Lofmark, 2005).

RESULTS

Primary outcomes

Number of reports, gender and age distribution

During the period under review, a total of 1,756 ADR reports were received from the province. Of these, 495 were males (28.9%), 1,057 female (60.19%) and in 204 (11.6%) of the reports, the gender was not given. The number of ADRs was higher in the female population compared to that found in the male population (Table 1). The reports were categorised into five age groups namely 0 to 17, 18 to 30, 31 to 40, 41 to 50 and 51+. Overall, the incidence of ADR reports per age group was found to be 15.81% (279), 12.01% (211), 31.44% (552), 24.15% (424) and 16.23% (285), respectively (Table 2). The highest number of ADRs was reported from the age group 31 to 40 years with the majority, like the overall proportions given in Table 1, being females (364/552, 65.94%). A strong correlation between female sex and ADRs was found to be statistically significant (*p* value < 0.001).

Commonly reported ADRs

From our reports, the top 10 most commonly reported

Table 3. Top 10 most commonly observed ADRs.

ADR	Number
Peripheral neuropathy	358
Fat and weight loss	234
Lipidystrophy and fat redistribution	327
Weight loss	122
Breast enlargement and/or gynaecomastia	183
Rash	109
Dizziness	101
Fat gain	65
Vomiting	52
Headache	50

ADRs were peripheral neuropathy, fat loss (lipoatrophy), lipodystrophy, weight loss, breast enlargement and/or gynaecomastia, rashes, dizziness, fat gain, vomiting and headache (Table 3).

Secondary outcomes

Although a total of 1,756 reports came from the province, a review of each individual report revealed that only 908 were satisfactorily completed in all fields including patient details and demographics, ART regimen, ADRs, laboratory results, adverse reaction outcome, relevant clinical history, early warning for drug resistance and reporting HCP. The 848 incomplete reports ranged from those that indicated ADR symptoms but no suspected drug, suspected drugs with no ADRs reported or neither symptoms nor suspect drugs, no report of intervention/ treatment outcome carried out and no information on initial regimen among others. They were not considered further because they did not have important key data for the secondary endpoint analysis.

Number of ADRs reported and treatment failures

Of the 908 properly completed reports, 445 (49%) developed one ADR, 366 (40.3%) developed two ADRs, and 97 (10.7%) reported three or more ADRs (Figure 2). One patient on zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) regimen was reported to have a total of 16 ADRs including peripheral neuropathy, back pain, muscle pain, abdominal pain, unusual fatigue, weight loss, unusual bleeding, rash, dizziness, nausea, vomiting, diarrhoea, depression, heartburn and headache. This patient was among a total number of 103 reported as ART virological, immunological and clinical progression treatment failures. Most of the treatment failures were virological and patients were given iterative intensive adherence management to counter re-suppression and/or changed to Lopinavir/Ritonavir (LPV/r)-based second line ART.

Reported ARV regimens administered

At the time of this report, the ART programme in Mpumalanga was following the SA National ARV Treatment Guidelines of 2010 (Table 4) (SA NDOH, 2010). All new patients were given Tenofovir (TDF), 3TC, NVP/Efavirenz (EFV). Those currently on Stavudine (D4T)-based regimen with no expected D4T ADRs remained on the drug if well tolerated otherwise it was substituted with TDF. It is noteworthy to mention at this point that the South African Anti-retroviral treatment guidelines for 2013 were implemented after the review of data for this report was completed (1st of April, 2013) and will be discussed in detail in future reports (NDOH, 2013).

Suspected ADR causing ARV drugs

The most prescribed regimen was D4T/3TC/EFV and d4T was the most suspected drug implicated in causing ADRs especially in cases of peripheral neuropathy and lipodystrophy with 144 and 173 cases from the total of the 908 reports, respectively. The top 10 ADRs reported for d4T are given in Table 5. Other selected suspect drugs and ADRs implicated in the reports are given in Table 6

ARV regimens correlation to the most commonly observed ADRs

Figure 3 indicates strong correlation between use of D4T-regimens and the occurrence of peripheral neuropathy amongst the Mpumalanga population on ART. Figure 4 indicates strong correlation between use of AZT or combinations containing it, and the occurrence of anaemia amongst the Mpumalanga population on ART. Figure 5 indicates strong correlation between use of AZT or combinations containing it, and the occurrence of lipodystrophy amongst the Mpumalanga population on ART. The frequency of rashes (Figure 6) suggests a correlation between NVP and EFV to rash. However, the ADR descriptions suggest a few of the events could be attributed to Stevens Johnson's syndrome.

Reported conditions concomitant to ADRs reported

Tuberculosis (TB) was the clinically significant concomitant medical condition with the highest frequency

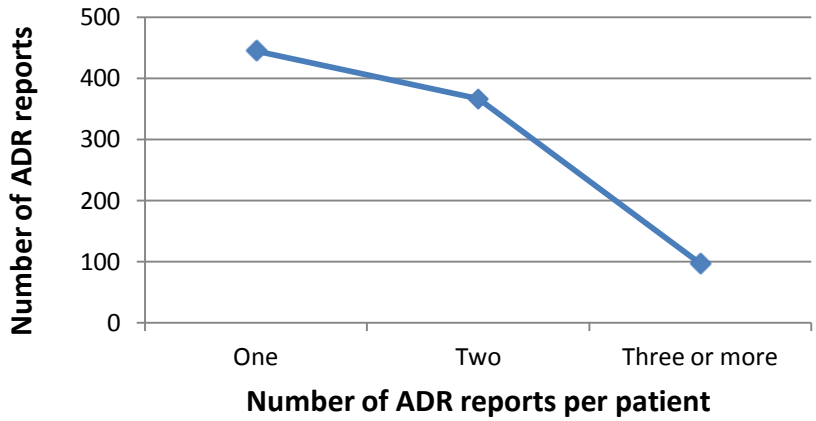

Figure 2. Number of ADRs reported per patient.

Table 4. Standardised SA national ART regimens for adults and adolescents.

First line		
All new patients needing treatment	TDF+3TC/FTC+EFV/NVP	For TB co-infection EFV is preferred. For pregnant women or women of child bearing age, not on reliable contraception, NVP is preferred.
Currently on d4T-based regimen with no side effects	d4T+3TC+ EFV/NVP	Remain on d4T if well tolerated. Early switch with any toxicity. Substitute TDF if at high risk of toxicity (high BMI, older, female, TB treatment).
Contraindication to TDF: renal disease	AZT+3TC+EFV/NVP	
Second line		
Failing on a d4T or AZT-based 1st line regimen	TDF+3TC/FTC+LPV/r	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains >1000 in 3 months despite adherence intervention, switch.
Failing on a TDF-based 1st line regimen	AZT+3TC+LPV/r	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains > 1000 in 3 months despite adherence intervention, switch.

(32.32%, 128/365) followed by hypertension (26.01, 103/365), menopause (13.89%, 55/365), and pregnancy (12.63%, 50/365). Others included diabetes and epilepsy (Table 7).

DISCUSSION

A total of 1,057 (60.19%) reports were recorded from females while 495 were males (28.9%). Categorised by age group, it was observed that the majority of ADRs to ART were in the age group 31 to 40 years and with more reports in females than males with 65.94 and 26.26%, respectively. Gender was not reported in 7.79% of the reports for this age group. The correlation between female sex and higher frequency of reported ADRs was found to be statistically significant (p value < 0.001). It is not clearly understood why gender difference exists in ADRs not only to ART but other therapies as well. Factors cited in similar data reviews include differences in weight and body mass index, hormonal changes unique to females, and the effect of these changes on drug metabolism (Tran et al., 1998; Rodenburg et al., 2011; Anderson, 2005, 2008; Soldin and Mattison, 2008; Zelinkova et al., 2012). Other possible factors include differences in fat composition (thereby affecting drug distribution) and genomic differences influencing the level of enzymes involved in drug metabolism (Harris et al., 1995).

All the patients showed at least one ADR and where the suspect drug was identified, this was discontinued and replaced by another anti-retroviral drug. From all the reports received, including those not properly completed, the most common ADRs were lipodystrophy (327) and

Table 5. ADRs suspected to be caused by D4T.

Suspected drug	ADRs	No of cases reported
D4T	Abdominal pain	19
	Peripheral neuropathy	144
	Rashes	9
	Backpain	7
	Muscle pain	16
	Unusual fatigue	8
	Lipodystophy	173
	Weight/fat loss	181
	Unusual fat gain	38
	Breast enlargement	35

Table 6. Other significant suspect drugs implicated in reported cases of ADRs.

Suspected drug	ADRs	No of cases reported
NVP	Rashes	25
	SJS	3
	Itching	1
3TC	Peripheral neuropathy	1
	Fatigue/muscle weakness	3
AZT	Peripheral neuropathy	11
	Anaemia	11
EFV	Abdominal pain	4
	Peripheral neuropathy	6
	Rashes	14
	Breast Enlargement	29

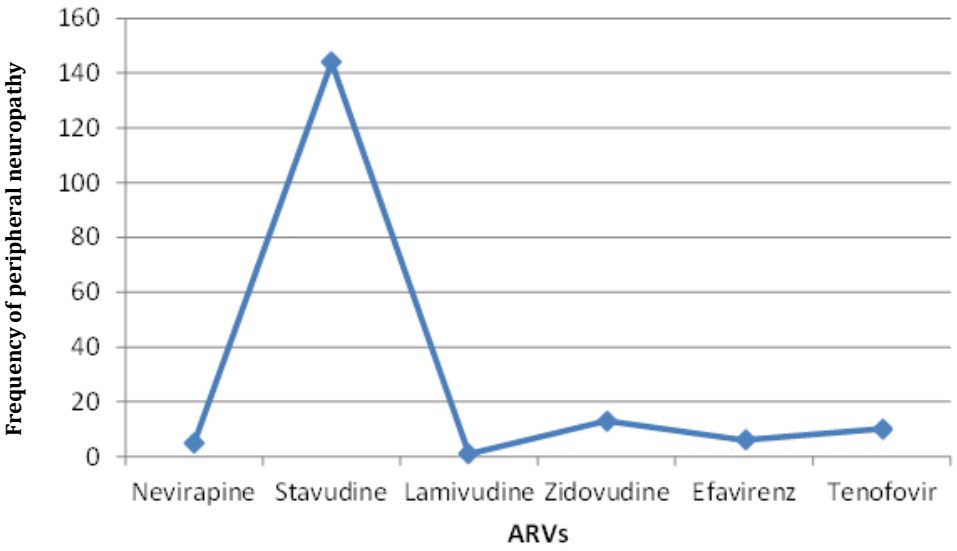

Figure 3. Frequency of occurrence of peripheral neuropathy in reported ARVs.

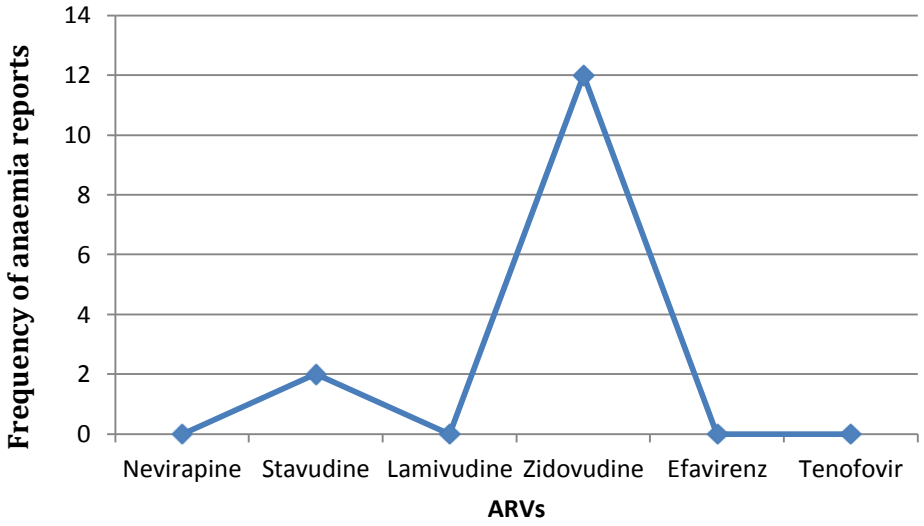

Figure 4. Frequency of occurrence of anaemia in reported ARVs.

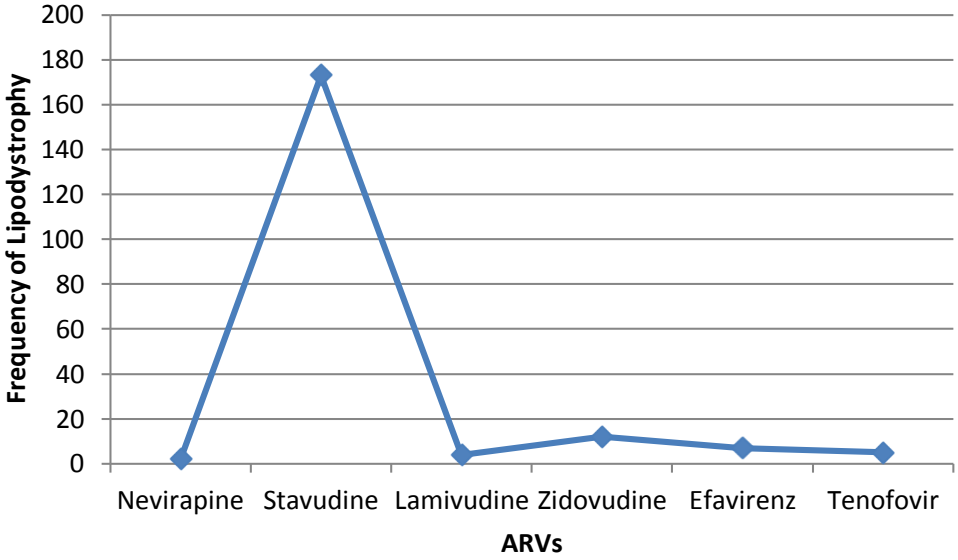

Figure 5. Frequency of occurrence of lipodystrophy in reported ARVs.

peripheral neuropathy (358 cases), mainly with d4T-containing regimens. It was discontinued and replaced with TD4. While peripheral neuropathy is linked to almost all the nucleoside reverse transcriptase inhibitors (NRTIs), it can be seen that d4T-containing regimen is most commonly suspected drug in cases of peripheral neuropathy; or occurring as concomitant medication in some cases. This is in keeping with other ART studies where d4T has been linked to severe peripheral neuropathy (Coetzee et al., 2004; Nomathemba et al., 2011; Simooya, 2012; Bleeker-Rovers et al., 2000; Cornejo-Juárez et al., 2003). This finding supports the World Health Organization (WHO) recommendation to discontinue the use of d4T-based regimens in adolescents and adult patients due to associated adverse effects.

Although our findings have not been subjected to elaborate statistical analysis and the numbers reported were not significant, an association has been observed between NVP and EFV (fewer and milder cases than NVP) containing regimen and hypersensitivity reactions manifested by pruritus, rashes with indications of Steven Johnsons Syndrome (SJS) in the clinical notes.

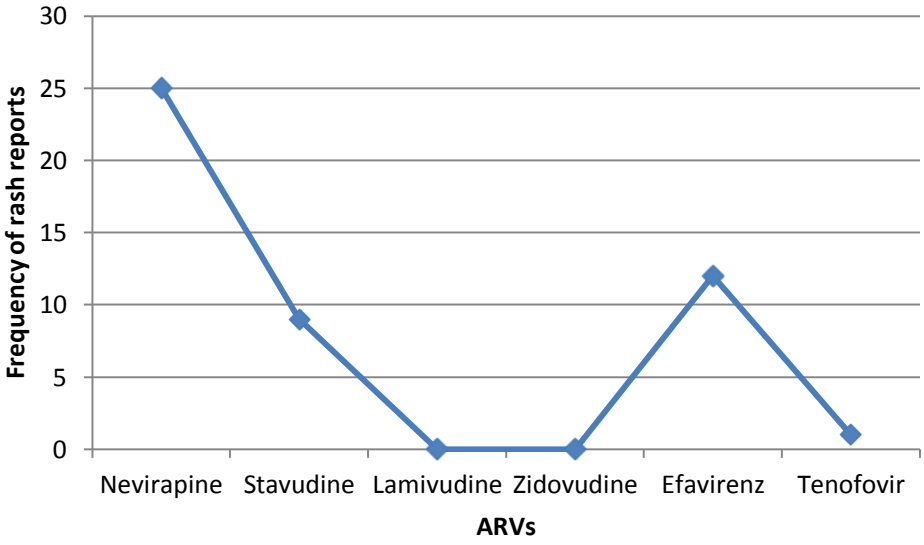

Figure 6. Frequency of occurrence of rash in reported ARVs.

Table 7. Concomitant medical conditions and frequency of occurrence.

Concomitant conditions	Frequency	%
Hypertension	103	26.01
Pregnant	50	12.63
Tuberculosis	128	32.32
Hepatitis	5	1.26
Diabetes	36	9.09
Epilepsy	6	1.52
PCP	2	0.51
Karposi sarcoma	4	1.01
Haemorrhoids	1	0.25
Lower respiratory tract infection (LFTI)	1	0.25
Lymphoma	1	0.25
Cryptococcal meningitis	2	0.51
HIVAN	1	0.25
Menopause	55	13.89
Scoliosis	1	0.25
Total	365	100.00

Association of NVP with SJS is well documented (Metry et al., 2001; Rotunda et al., 2003; Namayanja et al., 2005).

Generally, from a review of the treatment outcomes and changes in treatment regimens, it is clear to see that ART in Mpumalanga is consistent with the South African Anti-retroviral treatment guidelines for 2010. The 2013 guidelines have recently been released (1st of April, 2013) and changes from the preceding guidelines will be discussed in more detail in the next report.

D4T-containing regimens were the highest suspected drug combinations. 3TC, EFV, AZT and NVP were also reported as having caused a number of ADRs. Compared to the frequencies reported on sources such as Medscape, these frequencies are much lower and numbers of associated, expected and/or reported ADRs are fewer (Medscape, 2013). However, it is envisaged that as this programme expands, more reports will be received, comprehensively capturing all ADRs associated with and unique to ART in South Africa.

TB was the most common clinically significant concomitant medical condition reported, with 128 cases from

the 908 completed reports. Although ART can reduce the incidence of TB, people on ART still have higher TB incidence rates (Lawn et al., 2006). This may be due to delayed initiation of ART or the fact that patients present with advanced TB or both (Nunn et al., 2005). Routine screening among people living with HIV/AIDS (PLWH) offers the opportunity to identify those without TB, prevent TB by chemoprophylaxis as well as to diagnose and promptly treat those who are infected. However, co-administration of ART along with anti-TB therapy presents several management challenges, including drug-drug interactions, overlapping drug toxicities and immune reconstitution syndrome. Generally, for all patients who experienced ADRs, preventive measures were prescribed and administered to patients as well as instructions given to avoid ADRs by providing medication counselling to each patient.

One limitation of this review is that minimal statistical analysis has been performed. However, statistical analysis of spontaneous reports itself suffers severe limitations with regards to data reliability in that there is no data collection protocol, adverse reports vary from period to period by drug type and ADR type. Furthermore, there is no certainty that a reported reaction was causal and there may be duplicates in the reports and if undetected, these can severely bias estimated drug-event associations. Spontaneous report data also involves extensive data cleaning as the number of reports increase. There are also many possible non-causal reasons for associations, and interpretation of comparator groups is difficult. We are however focusing on systematic analytical approach, as spontaneous reports are one of the few ways to learn about rare ADRs. They can also form a cornerstone of hypothesis generation and/or a secondary data source for comparisons.

CONCLUSION

This is the first retrospective review of reported ADRs in HIV-positive patients using ART in Mpumalanga by the NPC. The review observed the significant ADRs associated with the use of ART in the local provincial population. In 2011, there were 111,402 people reported to be on ART in the province. At the end of February, 2013, we received a total of 1,756 ADR reports. This number may appear to be only a small fraction of the total (1.6%, 1756/111402) of the estimated total number of patients on ART in the province. However, it should be noted that the decentralised pharmacovigilance program was only launched 19 months ago whereas the ART program has been in existence since early 2004. We therefore expect that in the next few years, the number of reports received will rise towards a number more reflective of the reality.

Although the 1,756 reports seems minimal compared to the provincial total, and the data has not been subjected to elaborate statistical analyses, these findings demonstrate that our model of decentralised pharmacovigilance reporting of ADRs is capable of producing good epidemiological safety data in HIV patients on ART. They also underscore the importance of pharmacovigilance as a tool which can yield information applicable and relevant to the South African public health sector. ART related ADRs are evident in patients on ART, and this decentralised pharmacovigilance reporting is a good model for roll-out to the rest of South Africa and will help to obtain a complete profile for ADRs due to ARV medicines and inform policy decisions. It is a practical and low cost method that utilises existing financial and human resources.

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