Differences in awareness and practice about adverse event reporting among doctors, nurses, pharmacists and post-basic pharmacist assistants in HIV clinical practice in the eThekwini Metropolitan Health district, South Africa

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Abstract

Voluntary reporting of adverse events associated with antiretroviral therapy by healthcare providers is an important part of public health not only for quality of care, but also for efficacy and safety of treatment for patients. This study aimed to determine prevalence of awareness and practice of voluntary adverse events reporting among healthcare providers in public health sector antiretroviral programmes. A descriptive cross-sectional survey was conducted among healthcare providers in public health sector antiretroviral programmes in eThekwini health district, South Africa. Participants consisted of doctors, nurses, pharmacists and post basic pharmacist assistants in HIV clinical practice. Awareness of voluntary reporting was relatively high at 88.0%, 75.9%, 81.6% and 87.5% amongst doctors, nurses, pharmacists, and post basic pharmacist assistants respectively, with no significant difference across the groups (p-value=0.888). Rates of estimated reported adverse events per 100 patients complaining of such effects, in the previous 3 months, were 8.7%, 5.1%, 7.4% and 1.6% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively (p-value<0.001). The most common channels for adverse event reporting included: filling the provincial adverse event reporting form; sending the filled reporting form to the institutional pharmacy or to the pharmaceutical policy and system development at the provincial head office. Future research may investigate barriers and facilitators on uniformity in the reporting process at the healthcare facility level, with emphasis on roles and involvement of nurses and post basic pharmacist assistants in pharmacovigilance activities in the light of new task-shifting at the primary health care platform.

Keywords: Voluntary reporting, adverse event, antiretroviral therapy, healthcare providers, awareness, practice

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Introduction

Data from many countries demonstrated a decline in the overall population mortality following the introduction of highly active antiretroviral therapy (HAART) in communities with a high prevalence of HIV infection (Venter, 2013). Statistics South Africa estimated at 10.6% the total HIV prevalence in the South African population with the highest prevalence of 14.9% found in KwaZulu Natal province (ASSA 2008, 2011). Patients on HAART may have a lack of education or understanding of the potential side-effects they may develop or may interpret adverse events (AEs) as part of symptoms of their HIV infection, thus leading to under or non-reporting of AEs experienced by them. Therefore, voluntary reporting of AEs associated with antiretroviral therapy (ART) by healthcare providers to health authorities is an important part of public health not only for quality of care but also for efficacy and safety of HIV treatment. Healthcare professionals are amongst others key role players in pharmacovigilance activities for public health and medicine registration in a functional healthcare system. In South Africa, reporting suspected adverse drug reactions (ADR) to a competent authority is an ethical duty for healthcare providers, especially in instances of serious AEs or unknown suspected AEs (National Department of Health, 2004). Spontaneous or voluntary reporting of AEs by healthcare providers is one of the methods used to report an AE even though under- reporting is estimated to be high (Santosh et al., 2013).

The lack of awareness about adverse reporting plays a major role in the recording of such events. It is believed that healthcare providers reported fewer ADR to relevant authorities worldwide than experienced and reported by patients; and the degree of under reporting varied by symptom (Justice et al., 2001). The National Department of Health (NDoH) has made the mechanisms for reporting adverse events available in South Africa through the Medicines Control Council (MCC) and the National Pharmacovigilance Programme. The MCC has a system for spontaneous reporting of ADR through the following process: healthcare professionals report AEs by completing and submitting an AE reporting form available on the MCC website (South African Medicines Formulary, 2012; NDoH, 2012). The AE reporting form is then transferred to the National Adverse Event Monitoring Centre (NADEMC) in Cape Town where it is entered into the ADR database, thereafter each AE is given a unique identification number and the reporter will receive an acknowledgement letter with an AE reference number or identity number (South African Medicines Formulary, 2012, NDoH, 2012). The adult ART related AE reporting forms are encouraged to be sent to the Medunsa Pharmacovigilance Centre while child events are supposed to be sent to the Bloemfontein Pharmacovigilance Centre.

This study aimed to determine prevalence of awareness and practice of voluntary AEs reporting among healthcare providers in public health sector antiretroviral programmes. Other studies have reported on ADR from the patient's perspectives while this study focused on views of healthcare providers about commonly prescribed ART regimens, knowledge of AEs reported and awareness about channels of reporting such events.

Methods

Study design and sites

A descriptive cross-sectional survey was conducted among healthcare providers caring for HIV infected patients in public health sector antiretroviral programmes. Five regional hospitals, three specialised hospitals and two district hospitals supplying ART were surveyed between June and August 2013 in eThekwini Metropolitan Health district, South Africa.

Sample size

Using a formula described by Naing et al (2006), a minimum sample size assumption was computed by assuming an expected prevalence of 10% among study participants, with a precision of ±5% (d=0. 05), and 95% confidence intervals. The minimum sample size was 138 participants. Potential sampling bias was minimized by attempting to include a minimum of 138 healthcare providers involved HIV practice. However a total of 120 healthcare providers consented to participate. Recruitment of healthcare providers into the study and data collection took place at respective ART clinics. Healthcare providers consisted of medical doctors, nurses, pharmacists, and post basic pharmacist assistants.

Data collection

The questionnaire was pilot tested prior to data collection. Eight final year pharmacy students collected data; they interviewed healthcare providers as part of their research module. They were responsible for administering the questionnaire which consisting of socio-demographic characteristics of healthcare providers, information on prescribed ART regimens, knowledge about AEs reported or seen in practice, awareness about channels of reporting, numbers of patients seen per day, estimate of reported AEs consistent application and following of standard operating procedures (SOPs) as pharmacovigilance activities when reporting, self-reported channels of reporting AEs, and suggested ways of improving AEs reporting in public health sector.

Statistical analysis

Data were processed and analysed using Stata 13.0 SE (StataCorp, 2013). Ninety-five (95%) binomial confidence intervals were constructed around point estimates e.g. proportion of yes responses to the various dichotomous (yes/no) reporting variables. Significant difference in awareness and practice of voluntary reporting of AEs by sub-group (health care professional type) were assessed using the Kruskal-Wallis equality-of-populations rank test to identify significant mean differences in continuous explanatory variables and the standard Pearson's chi-square ($\chi 2$) test or Fishers exact test was preferred (if expected cell count of less than 5 observation observed) to identify significant differences in categorical explanatory variables. A p-value <0.05 was deemed statistically significant.

Results

Socio-demographic characteristics of healthcare providers

Ninety-four out of 120 healthcare providers who consented to participate completed the questionnaire, yielding a response rate of 78.3%. Table 1 presents socio-demographic characteristics of the healthcare providers There were 25 medical doctors (26.6%), 29 nurses (30.9%), 32 pharmacists (34.1%) and 8 post basic pharmacist assistants (8.5%). The majority

were female 71.3% (67/94); over half 53.2% (50/94) had 1 to 5 years of work experience (and 34.0% (32/94) had experiences of 6-10 years. The overall mean work experience was 5.9 years (standard deviation ±4.4, range 0.4 to 22.0 years).

Table 1- Socio-demographic characteristics of the healthcare providers

Category	**Sub-category**	**Freq. (%)**
Gender	Male	27 (28.7%)
	Female	67 (71.3%)
Professional qualification	Doctor	25 (26.6%)
	Nurse	29 (30.9%)
	Pharmacist	32 (34.0%)
	Post basic pharmacist assistant	8 (8.5%)
Professional experience (years)	Less than 1 year	3 (3.2%)
	1-5 years	50 (53.2%)
	6-10 years	32 (34.0%)
	11-15 years	4 (4.3%)
	16-20 years	4 (4.3%)
	21-25 years	1 (1.1%)
	Mean (standard deviation)	5.9 (±4.4)
	Range (minimum - maximum)	0.4-22.0

Information on prescribed ART regimens

Table 2 presents commonly prescribed ART regimens to patients as reported by healthcare providers in the previous three months of data collection. Commonly prescribed ART regimens were as follows: tenofovir, lamivudine, efavirenz (TDF/3TC/EFV, 42, 28%); stavudine, lamivudine, efavirenz (D4T/3TC/EFV, 41, 27.3%); and stavudine, lamivudine, nevirapine (D4T/3TC/NVP, 10, 10.7%).

Table 2- Commonly prescribed ART regimens listed by healthcare providers for HIV treatment (frequency)

ART regimen	Doctor	Nurse	Pharmacist	PBPA	Cumulative frequency
Stavudine combinations					
D4T/3TC/EFV	19	14	6	2	41
D4T/3TC/NVP	3	6	5	2	57
D4T/3TC/Lop/rit	0	1	0	0	58
Subtotal	22	21	11	4	
Tenofovir combinations					
TDF/3TC/EFV	5	13	20	4	42
TDF/3TC/NVP	1	2	7	0	52
TDF/FTC/EFV	0	0	3	1	56
Subtotal	6	15	30	5	
Zidovudine combinations					
AZT/DDI/Lop/rit	5	2	1	1	9
AZT/3TC/EFV	1	0	0	1	11
Subtotal	6	2	1	2	
Abacavir combinations					

ABC/3TC/Lop/rit	2	0	2	0	4
ABC/3TC/EFV	1	0	3	0	8
Subtotal	3	0	5	0	
Other					
Unsure	0	3	0	0	3
Missing value	4	5	4	1	17
Subtotal	4	8	4	1	
Total*	41	46	51	12	150

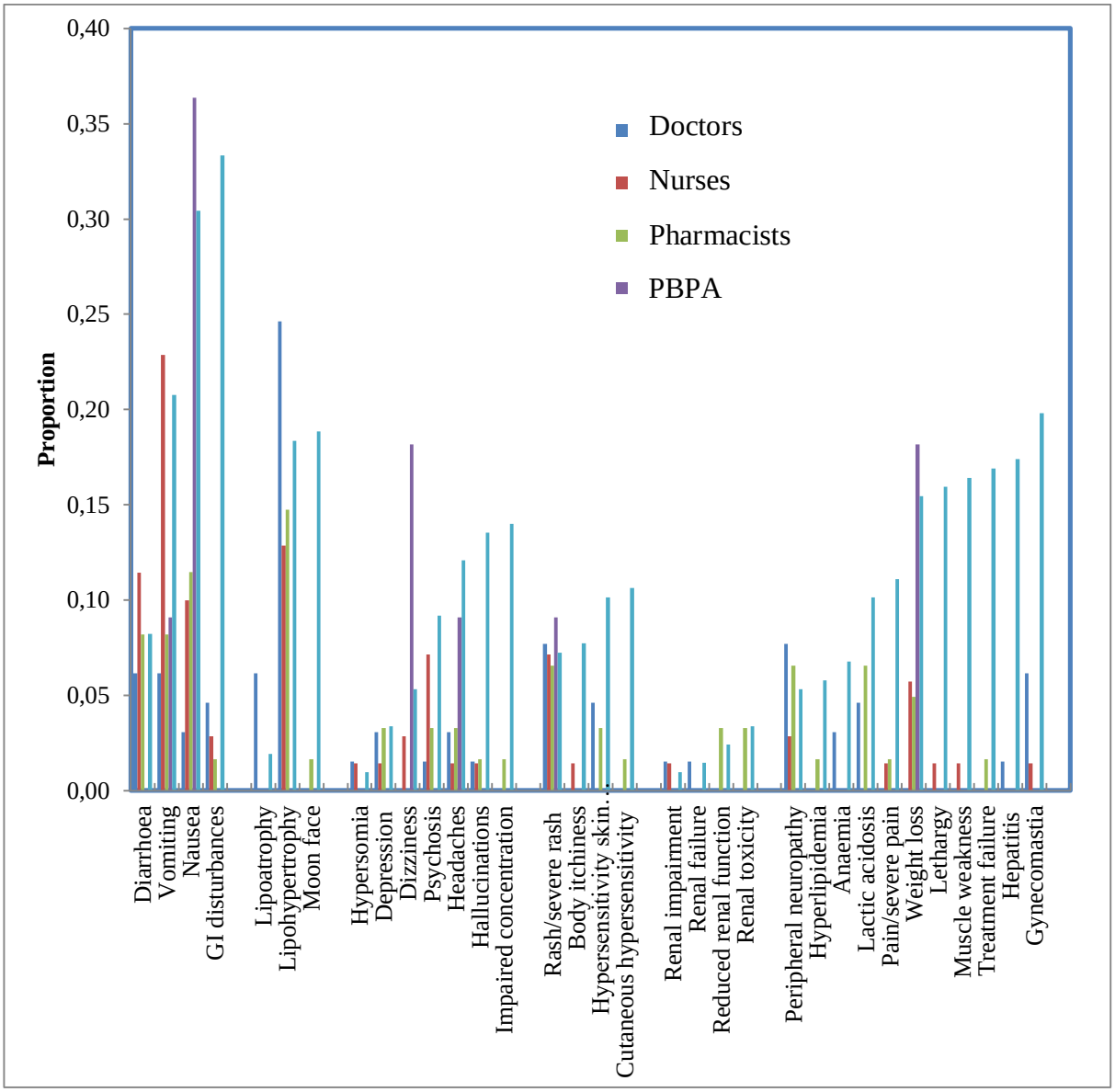
*More than two allowed per participant

Legend: D4T=stavudine, 3TC=lamivudine, EFV=efavirenz, NVP=nevirapine, Lop/rit=lopinavir/ritonavir, TDF=tenofovir, FTC=emtricitabine, AZT=zidovudine,ABC=abacavir, and PBPA=post basic pharmacist assistant

Knowledge about adverse events seen in practice

The most listed AEs reported by patients and seen by healthcare providers in practice included gastro–intestinal adverse effects such as diarrhoea, nausea, vomiting and gastro-intestinal disturbances (33.3% or 69/207), followed by lipodystrophy including lipoatrophy and lipohypertrophy (18.9% or 39/207); central nervous effects (14.0% or 29/207); and skin rash, hypersensitivity skin reactions and body itchiness (10.6% or 22/207). Figure 1 presents comparative frequency of adverse events reported to healthcare providers by patients, with statistically significant differences across professional groups using Fisher exact.

Figure 1- Frequency of common reported adverse events, 2013



Legend: PBPA= Post basic pharmacist assistant

Awareness about AE reporting per professional category

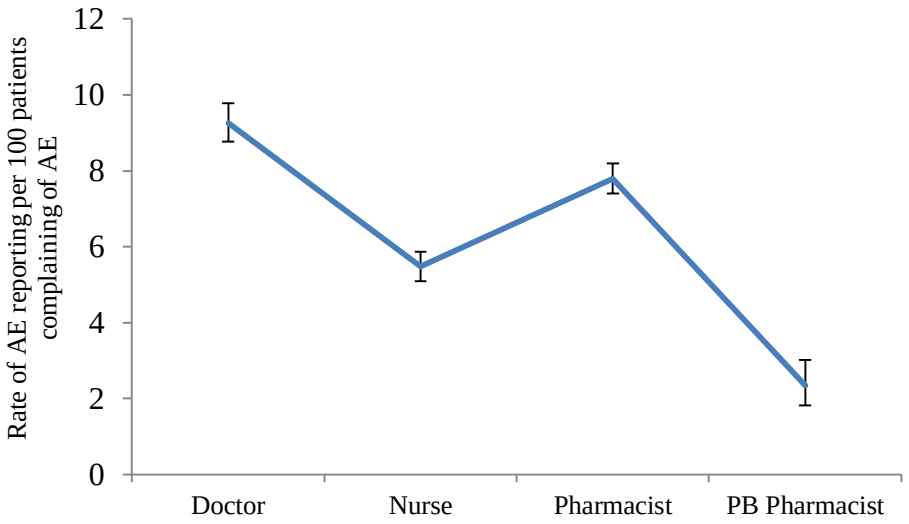
Awareness of voluntary reporting was relatively high at 88.0%, 75.9%, 81.6% and 87.5% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with no significant difference across the groups (p-value=0.888). A higher proportion of doctors had ever reported an adverse event in the past three months at 84.0% compared to 69.0%, 68.8% and 50.0% amongst nurses, pharmacists and post basic pharmacist assistants respectively with no significant difference across the four categories of health professionals(p-value=0.264).

Numbers of patients seen per day and estimate of reported adverse events in the previous three months per professional category

Healthcare providers reported seeing an average number of 50, 53, 151 and 69 patients per day amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively,

with a significant difference across the groups (p-value=0.001). Doctors, nurses, pharmacists and post basic pharmacist assistants, further estimated receiving about 6, 5, 7 and 3 patients complains of AEs per day respectively. An estimate of numbers of AEs reported in the previous three months was given by professional category: 46, 23, 43 and 4 amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with a significant difference across the groups (p-value=0.040). Rates of estimated reported AES per 100 patients complaining of such effects, in the previous 3 months, by professional group are presented in figure 2, namely: 8.7%, 5.1%, 7.4% and 1.6% amongst doctors, nurses, pharmacists and post basic pharmacist assistants, respectively (p-value<0.001).

Figure 2- Adverse event reporting rates per patients complaining of such effects



Legend: PBPA =post basic pharmacist assistant, AE = Adverse event

Perceived common causes of adverse events reported by healthcare providers

In the opinion of healthcare providers AEs were attributed mainly to ART medicines in general (44.3% or 43/97), followed by stavudine containing regimens (12.3% or 12/97), then by other prescribed medication for tuberculosis (TB) treatment and co-trimoxazole (11.3% or 11/97) while interactions of ART with herbal mixtures/traditional medicines accounted for 5.2% or 5/97. Table 3 describes perceived causes of AEs reported by healthcare providers.

Table 3 Perceived causes of adverse events by healthcare providers, 2013

Causes	Doctor	Nurse	Pharmacist	PBPA	Cumulative frequency
ARV drugs	10	15	16	2	43
D4T/3TC/EFV	3	1	0	0	47
D4T regimens	4	3	1	0	55
Other prescribed medicines	3	0	3	0	61
TB medication	4	0	0	0	65
Cotrimoxazole tablets	1	0	0	0	66
Liver impairment and hepatotoxicity	2	1	0	0	69
Renal impairment	1	0	0	0	70
Comorbidities and opportunistic infections	2	0	0	1	73
Impaired drug metabolism, abnormal ADME	3	0	2	0	78
Incorrect use of ARV medication	1	2	1	1	83

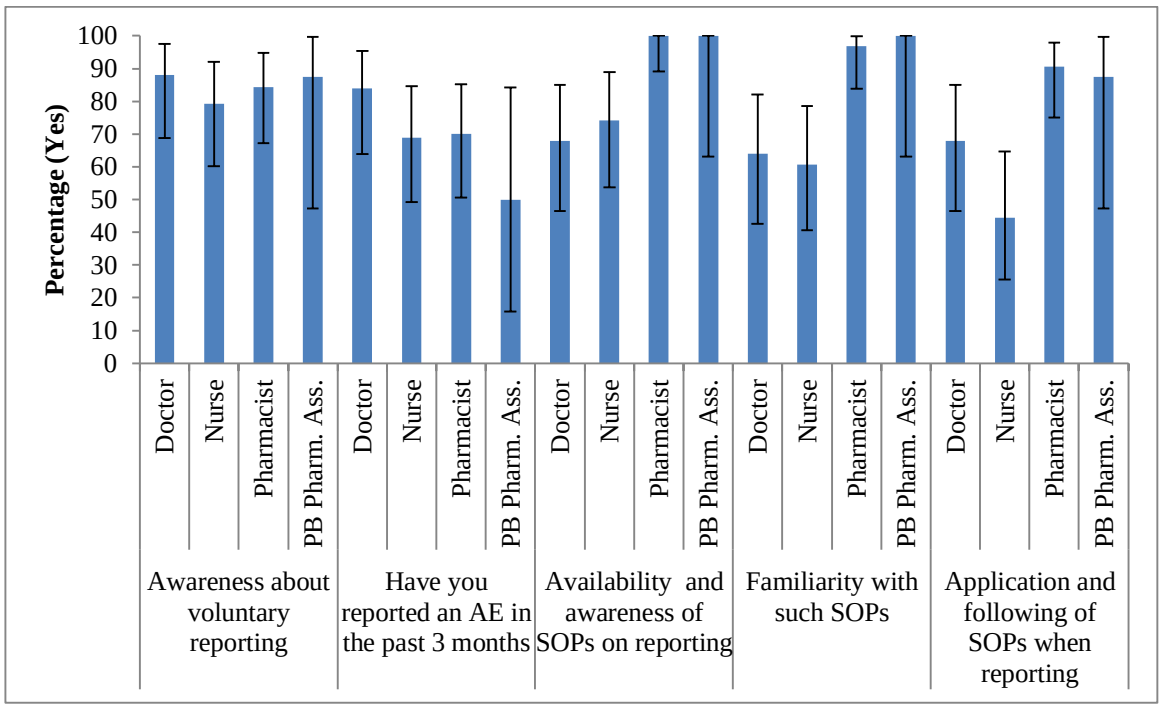
Drug-drug interactions	3	1	1	1	89
Interaction of ARVs with herbal mixtures	3	0	2	0	94
Drug-food interactions	1	0	0	0	95
Poor adherence to HAART	0	1	1	0	97
Total*	41	24	27	5	
*More than one allowed					

Legend: ADME=absorption, distribution, metabolism and elimination, PBPA=post basic pharmacist assistant, TB=tuberculosis, HAART=highly active antiretroviral therapy

Application and following of SOPs when reporting

The proportion who responded "Yes" to the "following SOPs when reporting" was at 68%, 44%, 91%, and 88% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with a significant difference across the groups (p-value=0.001). The proportion who responded "Yes" to the "availability and awareness of SOPs on reporting" was relatively high at 100% for pharmacists and post basic pharmacist assistants compared to 68%, 74% amongst doctors, and nurses respectively, with a significant difference across the groups(p-value=0.001) while those who responded "Yes" to the "familiarity with such SOPs" were at 64%, 61%, 97%, 100% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with a significant difference across the groups (p-value<0.001). Figure 3 illustrates the differences in estimated numbers of reported adverse events by respondent type; the application and following of standard operating procedures properly and consistently when reporting among the four categories of healthcare providers.

Figure 3- Comparison of awareness of voluntary reporting, estimated numbers of reported AE in the previous 3 months, knowledge of existence of SOPs on reporting, and application or following of SOPs when reporting (95% confidence intervals)

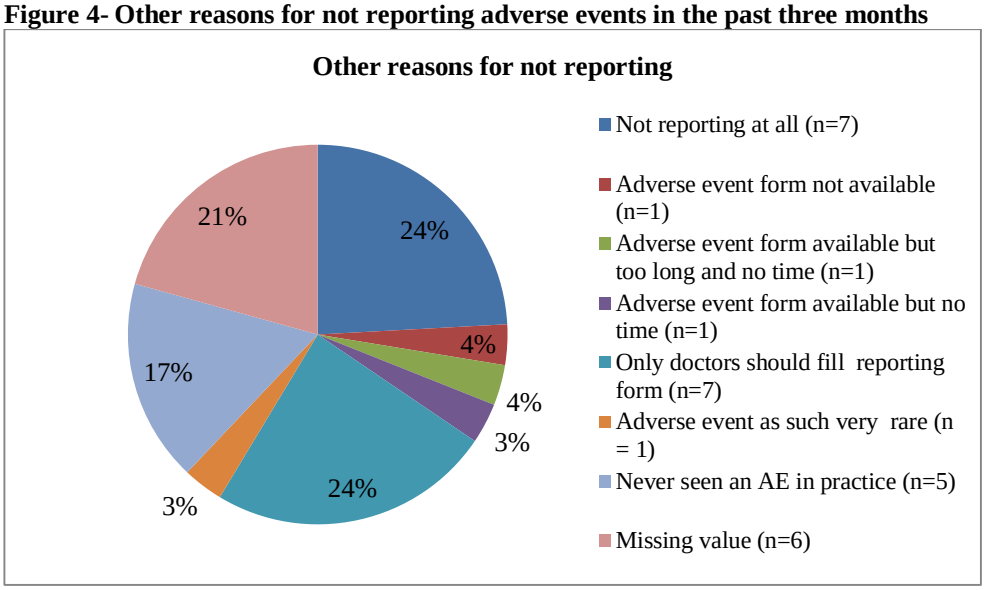


Legend: PBPA = post basic pharmacist assistant, AE=adverse event, SOPs=standard operating procedures

Reasons for non-application and not following of SOPs when reporting adverse events

Twenty–nine out of 94 respondents (30.85%) indicated factors associated with non-application and not following SOPs when reporting (i.e. conversely under-reporting of adverse events) which included reasons such as: lethargy or other non- specific reasons (n=18, 62.06%); never seen and never reported an AE in the past three months (n=5, 17.24%); no training on SOPs (n=2, 6.90%); no uniform system in place for reporting adverse events (n=2, 6.90%); and no access to forms only medical doctors to fill such forms (n=2, 6.90%). Figure 4 illustrates other reasons for not reporting.

Figure 4- Other reasons for not reporting adverse events in the past three months



Self -reported channels of reporting adverse events

Awareness as to whom to report the occurrence of AEs differed among all categories of healthcare professionals. The most common channels for AE reporting indicated included: filling the provincial AE reporting form; sending the filled reporting form to the institutional pharmacy or to the pharmaceutical policy and system development at the provincial head office; reporting to the supervising doctor, the sister in charge, the pharmacy supervisor, or the district office and pharmacy and therapeutics committee. The proportion who responded "Yes" to the "familiarity with the NDoH ADR and product quality problem report form or MCC form also available through NADEMC in Cape-Town" was relatively high at 80%, 71%, 97%, 75% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with a significant difference across the groups (p-value=0.033). However the proportion who responded "Yes" to the "have you used the NDoH or MCC form" was relatively low at 56%, 18%, 38%, 50% amongst doctors, nurses, pharmacists and post basic pharmacist assistants respectively, with a significant difference across the groups (p-value=0.027). Channels of reporting and utilisation rate of the MCC adverse drug reaction and product quality problem report are presented in table 4.

Table 4 Self-reported channels of adverse event reporting and utilisation of the MCC adverse drug reaction and product quality problem report form in HIV clinical practice

Question	Category		Doctor	Nurse	Pharmacist	PBPA	P-value
To whom you report adverse event?	Fill the provincial adverse event reporting form		9	3	0	0	N/A
	Send the filled form to the institutional pharmacy		8	4	0	0	
	Send the filled form to pharmaceutical policy and system development at the provincial head office		1	1	11	2	
	Send the filled form to the district office		4	0	2	0	
	Report to the supervising medical doctor		0	12	9	1	
	Report to the sister in charge		0	3	1	0	
	Report to the pharmacy supervisor		0	0	4	5	
	District office and PTC		0	0	1	0	
	Report to the DOH		0	0	5	0	
	Two or more channels (doctor/sister in charge)		0	1	4	1	
	Total of frequency		22	24	37	9	
Do you know the NDoH or MCC ADR and product quality problem report form?		Yes	20	20	30	6	0.033
		No	5	9	2	2	
		Total	25	29	32	8	
Have you ever used the NDoH or MCC ADR and product quality problem report form?		Yes	14 (56)	5 (17.24)	12(37.50)	4 (50)	0.027
		No	11(44)	24 (82.7)	20 (62.50)	4 (50)	
		Total	25 (100)	29 (100)	32 (100)	8 (100)	

Legend: i:=Fishers exact test, PTC=Pharmacy and Therapeutics committee, DOH=KwaZulu-Natal Department of Health, NDoH= National Department of Health, MCC=Medicines Control Council.

Suggested ways of improving adverse event reporting in public health sector

Respondents indicated that ways of promoting AE reporting in the public health sector could potentially be achieved by: offering more training and workshops on pharmacovigilance (n=28, 29.80%); easier and faster online submission (n=18, 19.14%); increased staff and more time with patients (n=14, 14.90%); uniformity of reporting channels (n=7, 7.45%), missing values (n=27, 28.72%).

Discussions

Adverse events listed by healthcare providers were reported to them by patients. Gastro-intestinal adverse effects were the most reported. Patients reported selectively AEs to each category of health care workers. This finding suggests, on one hand that, there is a good communication with patients about AEs; on the other hand, it implies that the reporting program of the provincial Department of Health seems to bear fruits. Indeed, the KwaZulu-Natal provincial Department of Health implemented a solicited or stimulated reporting programme in 2007. This program documented 3923 approved ADR reports for the period 1May2007 to 31May 2008 prior to regimen change in the province (Manickum and Suleman, 2012). This centralised system was changed from October 2009 to a facility based decentralised

reporting system where pharmacists were trained to evaluate and approve AEs reports (Fyzoo, 2014). However, there was a decline in the quality of reporting, data capturing of AEs and the percentage of facilities reporting per annum from 89% in 2009–2010 to 58% in 2011–2012 after the decentralisation of this system in October 2009 (Fyzoo, 2014). Prescribed ART regimens were conforming to changing guidelines in KwaZulu-Natal and South Africa in general.

Healthcare professional-patient interaction takes 10 to 12 minutes per patient, except for patients for initial patient evaluations, patients with more complex situations and outpatient procedures (Tietze, 2011). Based on the above interaction 35 patients per day per respondent category should be reasonably acceptable for sufficient quality of care. Estimated numbers of patients seen per day by respondent category of healthcare providers in this study may be relatively higher than the estimated 35 patients per day. In South Africa there are 5.4 doctors to 10 000 population while this ratio is at 36.1 for nurses and 2.3 for pharmacy personnel (Matsoso and Strachan, 2012). Estimated reported AEs per patients complaining of such events were fewer than expected; this finding was in line with other studies which indicated that healthcare providers reported fewer adverse events than experienced by patients (Santosh et al., 2013; Justice et al., 2001).

This study found a relatively high proportion of healthcare providers being aware of voluntary reporting when compared to levels of awareness of AE reporting described e in Nigeria where 42.9% of medical doctors, 35% of nurses, and 50% of pharmacists reported AEs (Fadare, 2011). Awareness about reporting to the pharmacovigilance centre/unit of the hospital in Nepal was relatively lower at 20.1% while in developed countries with well-established ADR monitoring system 40-70% of physicians do report ADRs (Santosh et al., 2013).

In this study, although healthcare providers noted AEs reported to them, this did not translate in them appraising and reporting these AEs to the pharmacovigilance centers. This leads to under-reporting of AEs into the national pharmacovigilance system. Data from literature indicate that factors associated with under-reporting include ignorance (only severe ADRs need to be reported) in 95%; diffidence (fear of appearing ridiculous for reporting merely suspected ADRs) in 72%; lethargy (an amalgam of procrastination, lack of interest or time to find a report card, and other excuses) in 77%; indifference (the one case that an individual doctor might see could not contribute to medical knowledge) and insecurity (it is nearly impossible to determine whether or not a drug is responsible for a particular adverse reaction) in 67%; and complacency (only safe drugs are allowed on the market) in 47% of studies (Lopez-Gonzalez et al., 2009). In this study, lethargy was the most common reason for not reporting AEs as well as the misconception that only medical doctors can report to the pharmacovigilance centre.

Although attribution of causality of adverse events is difficult in HIV-infected patients, especially those with complex, advanced disease in greatest need of new treatments and enrolled in ARV clinical trials (Marcus et al, 2012), majority of respondents in this study attributed AEs to prescribed antiretroviral drugs. Indeed, most antiretroviral drugs produce gastro-intestinal adverse effects during the start of treatment (Malangu, 2011).

Strengths and limitations of the study

An acceptable response rate was achieved in this study; a 60% response rate is generalised accepted (Finchman, 2008). Although the sample size was relatively small, this study reported information collected among four categories of healthcare providers in public health sector ART programmes. Involvement of doctors and pharmacists in AE reporting seems evident to most stakeholders in public health sector; however, the roles of nurses and post basic pharmacists assistants may go unnoticed. Nurses and post basic pharmacist assistants are included in this study with regard to their role in the specialist support team being prioritised by the South African NDoH for the re-engineering of primary health care services and especially given the emphasis on the role of nurses in nurse-initiated management of antiretroviral therapy (NIMART) with its new task-shifting guidelines and expansion and mainstreaming of antiretroviral services to the primary health care platform (Naledi et al., 2011).

As part of the limitations no attempt was made to access database and adverse event reporting forms at the sites which may have delivered other findings. views and experiences of other healthcare providers such as social workers, psychologists, dieticians and lay counsellors were not assessed, despite of them being part of a multidisciplinary team caring for patients. We could not generalise the results of this study to the entire public health sector HIV practice.

Conclusions

Adverse events listed by healthcare providers were reported to them by patients. Gastro – intestinal adverse effects were the most reported. Reported numbers of patients seen in practice by each category of healthcare providers were relatively higher than the expected norms, with a workload allowing less time spent with patients. This may have a negative impact in implementing pharmacovigilance activities as one of the prioritised health care interventions. Awareness of AE reporting was relatively high among doctors, nurses and post basic pharmacist assistants, but estimated numbers of reported AE were relatively low and differed among the four categories with a higher proportion of doctors reporting more AEs than the other three categories of healthcare providers. Application and following of SOPs when reporting were relatively low among nurses. Different channels of reporting existed in practice.

More training and workshops on pharmacovigilance activities for healthcare providers, easier and faster online reporting process were suggested as ways of improvement of voluntary reporting by healthcare providers. Future research may investigate barriers and facilitators on uniformity in the reporting process at the healthcare facility level; roles and involvement of nurses and post basic pharmacist assistants in a healthcare facility based pharmacovigilance unit/centre need to be redefined in the light of new task-shifting guidelines and expansion and mainstreaming of antiretroviral services to the primary health care platform.

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