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Decentralized HIV/AIDS pharmacovigilance in South Africa: Mpumalanga as pilot province for national roll-out

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The South African National Department of Health have successfully completed the implementation of a new decentralized patient-centred pilot pharmacovigilance programme in Mpumalanga province. The objective was to integrate the programme into the daily activities of healthcare providers at treatment level. Firstly, we carried out a one-day pre-training site visit to ascertain the training needs and readiness for the programme. Thereafter, we facilitated four one-day interactive pharmacovigilance training sessions for 69 healthcare providers. Further, we provided them with resource materials for successful program initiation at facility level. We then evaluated the effectiveness of the training and program through a before-after study. At baseline, 80 % of the workers reported no previous PV training while 7% reported an initial training when joining the facility, 4% received training at least once a year and 9% gave no response. Further, 67 % of the participants reported that they had no active pharmacovigilance programme at their institutions and only 16 % reported an active programme. The proportion of healthcare workers indicating an increased understanding of pharmacovigilance and awareness of the importance of reporting ADRs increased significantly after the training. A marked improvement in individualized patient management was also observed. We have successfully piloted a decentralized pharmacovigilance program in Mpumalanga province which has resulted in improved pharmacovigilance activities in ARV therapy. Stakeholders in South African pharmacovigilance have endorsed our model to be rolled out to the rest of the country.

Key words: Pharmacovigilance, decentralized, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).

INTRODUCTION

South Africa (SA) has one of the highest prevalence of human immunodeficiency virus (HIV)/acquired immuno-deficiency syndrome (AIDS) infected people in the world and is home to 17.8% of the reported 34 million people living with HIV/AIDS worldwide. This epidemic is a well-documented leading cause of morbidity and mortality in the country. (UNAIDS, 2010, 2011; World Health Organization (WHO), 2006; Medical Research Council of South Africa (MRC SA), 2010) In 2004, the SA government introduced the first guidelines on free anti-retroviral therapy (ART) to treat HIV/AIDS patients in their public health facilities (Allen et al., NDoH, 2004). Today, South Africa has the world's largest ART programme and by the middle of 2011 an estimated 1.9 million people in

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the country were receiving ART (Mayosi et al., 2012; Johnson, 2012; Pillay, 2012). This is approximately one-quarter of the total number of people on ART globally (WHO, 2011). Research has shown that ART increases the physical and emotional quality of life for people living with HIV/AIDS (Wouters et al., 2009; Ruud et al., 2009; Ruud et al., 2010). However, even with ART, HIV/AIDS patients face many challenges. They remain at risk of adverse drug reactions (ADRs) and other complications short and long term (Mehta et al., 2007).

ADRs are common, yet often preventable, are causes of morbidity and mortality (Lazarou et al., 1998; Pirmohamed et al., 2004; McDonnell and Jacobs, 2002). A meta-analysis of 69 prospective and retrospective studies conducted in various regions of the world found that approximately 6.7% of all hospitalisations were as a result of ADRs (Wiffen et al., 2002). Patients with HIV/AIDS and are on ART, are at increased risk due to the effect of the disease as well as the complex drug regimens that they take (Mehta et al., 2007). Consequently, the improved treatment outcomes and quality of life may be negated by ADRs especially at the start of the treatment (Wouters et al., 2009). Many patients have been reported to have toxicity concerns and on many occasions they are reluctant to start or adhere to the treatment (Mascolini et al., 2008; Padarath et al., 2006; Roberts et al., 2000; Weiser et al., 2003; Chesney, 2003). Thus, ADRs may severely jeopardize confidence in the safety of ART thereby altering patient adherence, reducing treatment efficacy and increasing the risk for the emergence of secondary drug resistance. They are a major public health problem and impose a considerable financial and economic burden on health systems (Patel et al., 2007).

Prevention and management of side effects from drugs used to manage HIV/AIDS remains a challenge to clinicians, patients, drug regulators, researchers, governments, healthcare professionals, family members and all those affected. Acute and long-term side effects and mild to severe (and sometimes fatal) reactions continue to affect patients' decisions to start treatment, continue treatment, and adhere to prescribed regimens. New adverse events and toxicities are continuously being identified as people live longer on ART.

The availability of numerous new drugs and drug combinations makes it critical to systematically monitor adverse events linked to ART. The goal of ART 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 treatment (Dybul et al., 2002). Therapy therefore requires intensive quality assurance in order to ensure optimal patient outcomes, and the prevention and management of side effects through pharmacovigilance (PV). South Africa has had a poorly developed PV programme since the inception of the Comprehensive HIV/AIDS Care Management and Treatment plan (CCMT) in 2004 (RSA NDoH CCMT, 2003). At best, ADRs are only intermittently identified and systematic reporting in all provinces is rare (Dheda, 2007). Identification, intervention and effective case management of ADRs especially at treatment level has therefore become a priority in this country as it affects the required comprehensive management, care and support of HIV/AIDS patients. A robust PV system would therefore provide one of the greatest opportunities for improved patient outcomes and quality of life. South Africa is one of the developing countries that has registered its pharmacovigilance with the World Health Organisation (WHO) programme, however, the system remains much less than ideal probably due to the lack of resources, infrastructure and expertise (WHO, 2006; SPS MSH, 2011). It is critical for South Africa to have a well-structured and coordinated pharmacovigilance programme.

Mpumalanga is a province in South Africa which according to the 2007 community survey by Statistics South Africa has a rural population in its 3 districts of Ehlazeni, Nkangala and Gert Sibande of 3,643,435 which constitutes 66% of the provincial total (Statistics RSA, 2007). According to the National Antenatal Sentinel HIV and Syphilis Prevalence survey in SA carried out between 2007 and 2009, Mpumalanga has an HIV prevalence rate averaging 34.7% (RSA NDoH, 2010). In October, 2012, the Mpumalanga provincial government estimated that 111,402 patients were on ART (Mahlangu, 2011). Like the rest of the country, this province has relied on spontaneous reporting by HCPs to the National Pharmacovigilance Centre (NPC) of the National Department of Health (NDoH) as the cornerstone of monitoring medication safety and ADR reporting especially in the HIV/AIDS treatment programme. Spontaneous ADR reporting is a passive approach which is the most practical and cost-effective method widely used in the world. It must however be properly set up and managed, sometimes in combination with other methods in order to get optimal benefits. There are a few other methods used today to report and detect ADRs including cohort studies, analyses from automated databases, randomized controlled trials and Prescription Event Monitoring (PEM).

From the number of reports we have received at the NPC in the past, what is clear is that spontaneous reporting has not worked for SA. HCPs have been expected to spontaneously report ADRs to the NPC and then wait for case management instructions from the NPC of the NDoH. This system of reporting has been marred with underreporting with the focus mainly on medicine safety rather than patient safety. It has too little focus on how side effects should be managed and above

all, the NPC lacks the resources to monitor and attend to cases of side effects reported from all the treatment sites. A dismal number of ADR reports have been received from Mpumalanga and in fact, between July and September, 2006 there were no recorded ADR reports from the province (Dheda, 2007). Previous research has attributed ADR underreporting to unfamiliarity, lack of pharmacovigilance knowledge, diffidence, lethargy, indifference and complacency by HCPs and that medical education and training may promote more effective reporting (Pérez García et al., 2011; Lopez-Gonzalez et al., 2009).

In SA generally and Mpumalanga in particular, the PV approach was neither fully designed, properly strategized nor extended to the clinical setting to take into consideration the daily management of patients in various healthcare settings. There exists insufficient infrastructure to support the PV needs of a rapidly expanding ART programme. Furthermore, most HCPs are not trained in recognising and reporting ADRs. The prevention, detection and management of side effects, establishment of causality and subsequent individual case interventions at facility level have for a long time remained a significantly weak link in ensuring quality of care, quality of life and improved patient outcomes in the SA ART programmes.

In our effort to strengthen the National HIV/AIDS PV activities, we recently successfully completed a decentralized PV pilot programme in Mpumalanga province. We identified this as the pilot province in which to initiate the programme due to the dismal ADR reporting rate and the enthusiasm the HCPs demonstrated to learn about the programme. It was our view that integration of this programme in HCPs daily activities is a missing key component in SA PV that would result not only in improved ADR reporting, but also intervention and effective case management at treatment level with improved patient outcomes. The appropriate monitoring, both clinical and laboratory, can detect ADRs at relatively early stages when they are treatable. Undetected ADRs may result in preventable morbidity and/or mortality.

In this programme, our aim was to identify gaps, provide effective training to HCPs as well as identify clusters as decentralized PV centres throughout the province. Further, we aimed at the formation of multi-disciplinary committees in these clusters to meet on a regular basis to discuss individual cases as this would provide a forum at which they could convene and offer different views and expertise as it relates to specific patient cases, in order to improve patient treatment outcomes. We envisage that this programme will realise downstream benefits such as an increased number of HCPs with PV knowledge that would directly benefit both the patients and reporting HCPs.

METHODOLOGY

The training was conducted in three districts, Ehlazeni, Gert Sibande and Nkangala of Mpumalanga Province in South Africa, known for its high prevalence of HIV/AIDS and high number of patients on ART. The province comprises undeveloped and underdeveloped rural villages and farms. Initiation and evaluation of the programme was in three phases namely pre-training, training and continued monitoring and support.

Phase I

During September, 2010, we carried out a one-day pre-training site visit to the province. This visit was an opportunity to liaise with key members and stakeholders in the Provincial Department of Health (PDoH) in order to ascertain their needs and readiness for establishing our proposed PV programme. We conducted a combination of meetings, interviews and discussions with senior members of the PDoH and the districts. The success of the programme centred on maintaining a good relationship and open communication with them. After a review of our pre-training site visit, our overall hypothesis was to set up a well-structured and highly participative decentralized programme that would integrate pharmacovigilance into primary health care practice. Specifically, we envisaged that this could be achieved by firstly providing structured one-day workshops on adverse drug reactions and pharmacovigilance to nurses, pharmacists and physicians. Through these, we would establish multidisciplinary decentralized PV clusters at clinic level who going forward, would hold monthly review meetings where they can discuss suspected and/or confirmed cases of ADRs. This would result in not only an increased number of reports at clinical level, but also a measurable improvement in patient outcomes as these decentralized structures create smaller and more effective safety feedback loops. As part of the larger feedback loop and from the increased number of reports received, the NPC would then be able to monitor trends and generate important safety information which can be fed back to the reporters/clusters.

Phase II

We sent out invitations requesting that at least one doctor, one pharmacist and one nurse per healthcare facility in the province attend the training. Feedback from all facilities was only obtained in May, 2011. The training workshop is designed to be highly interactive including a variety of learning approaches such as lectures, group discussions and case studies. The trainees were introduced to the NPCs planned decentralized approach to PV and the HIV-specific ADR tool with a user guide. The latter is an ADR report form designed for the ART programme. It is used to collect demographic data, medical history, concomitant mediations, suspected/confirmed ADRs (both from clinical examination and laboratory results) and ADR outcomes. The participants also learned about clinical case review with a focus on PV as well as the formation of clusters and selection of committee members. Further, they received materials and literature such as the HIV/AIDS PV orientation and training manual and a copy of the baseline assessment tool (Appendix 1) used to assess their knowledge before the training as reference sources. These sources would assist them to identify co-morbidities and clinical complexity of distinguishing signs and symptoms of ADRs from those caused by AIDS, concomitant therapy capability and early warning indicators

by which to detect potential drug resistance cases. Furthermore, the HCPs were trained to be more proactive about asking their patients of possible ADRs and were encouraged to complete the HIV/AIDS ADR tool and fax the completed tool to the NPC. They were also given the SA ART pocket guide on prevention and management of side effects and drug interactions (Fomundam et al., NDoH, 2005). A fourth one-day training session was offered as a "mop-up" for those facilities or HCPs that were unable to attend the initial session held in their district. Central locations were chosen for the training venues to minimize associated travel and lodging costs.

Training design, instruments and analysis

We administered a structured questionnaire for data collection (available only in English). A before-after study design was employed in which HCPs completed questionnaires prior to, and immediately after the training session.

Measures/questionnaire

Data were collected on the existing infrastructure at their various facilities, staff members' knowledge and prior training in PV, as well as HCPs practice as it relates to reporting ADRs. In addition, data was collected on additional support facilities and HCPs would require from the NPC to increase the success of the programme. Participants were also asked to score on a scale of 1 to 5 (1 being "*Knew nothing about the topic*" and 5 being "*Very knowledgeable*") their confidence and knowledge of pharmacovigilance, reporting and case management.

Phase III

Three months after the training, we conducted a retrospective review of the PV reports from the provincial districts of Nkangala, Ehlanzeni and Gert Sibande. We considered the improvement of reporting patterns, quality and completeness of reports, interventions and effective case management at treatment level in the facilities. This did not involve the use of questionnaires. This paper does not report on 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 brief 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 approval by an ethics committee is not unprecedented in operational research and has previously been allowed especially when it is in 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 and participants in this case is protected because their identity is withheld from the data reviewers. Consequently, neither informed consent nor ethics approval was sought or deemed necessary because this is an epidemiological review in which it was impossible to identify the participants.

RESULTS

Our pre-training site visit revealed that training was required by multidisciplinary teams of HCPs consisting of doctors, nurses and pharmacists, and that they required an on-going support mechanism and communication. It also revealed the requirement of assistance in setting up structured PV programmes, strategies of integrating ADR reporting in their daily activities and intervention and effective case management at treatment level.

For the training, a total of 69 HCPs from the three districts were available. They constituted 20% medical doctors, 44% nurses and 36% pharmacists. At baseline, 67% of the participants reported they had no active PV programme at their institutions and only 16% reported an active programme. Further, 80% of the HCPs reported no previous PV training while 7% reported an initial training when joining the facility, 4% received training at least once a year and 9% gave no response. All 69 HCPs reported previously encountering at least one or more adverse drug reactions. In a simple exercise which did not critically explore linkage to suspected drugs and/or patient outcomes, HCPs were asked whether they had encountered a particular ART ADR (from a list of 25) and their responses recorded. They were then asked whether they had reported the reaction. It was found that the HCPs would report the ADR less than half the time. Figure 1 illustrates the number of adverse drug reactions that have been encountered per HCP versus the number that have been reported.

From the baseline evaluation of additional support needed by the HCPs, we found that 80% of the participants indicated a need for PV training and reference sources. 83% said they required training on ADR intervention and management, 75% needed help with design and use of ADR report forms, 71% agreed to the need for increased communication between the district and provincial levels. 70% of the participants said they wanted feedback on ADRs reported. 67% of the participants required computer training to polish up on their skills (Figure 2)

Twenty-six PV clusters were identified and committees formed to meet on a monthly basis to discuss individual patient cases. The clusters are in the provincial districts, formed by a hospital and its surrounding feeder clinics with a designated hospital/clinic serving as a coordinating facility. Committees consist of multidisciplinary teams of healthcare professionals including doctors, nurses, pharmacists, social workers, laboratory technicians and dieticians. The trained HCPs convened cluster level meetings to introduce our HIV/AIDS and TB tool and the NPC decentralized PV programme and these have since been integrated into the facilities at that level.

After the training, the proportion of healthcare workers indicating an increased understanding of PV and awareness of the importance of reporting ADRs increased. Of the 3 participating districts, the one with more medical doctors present from the facilities came out of the training

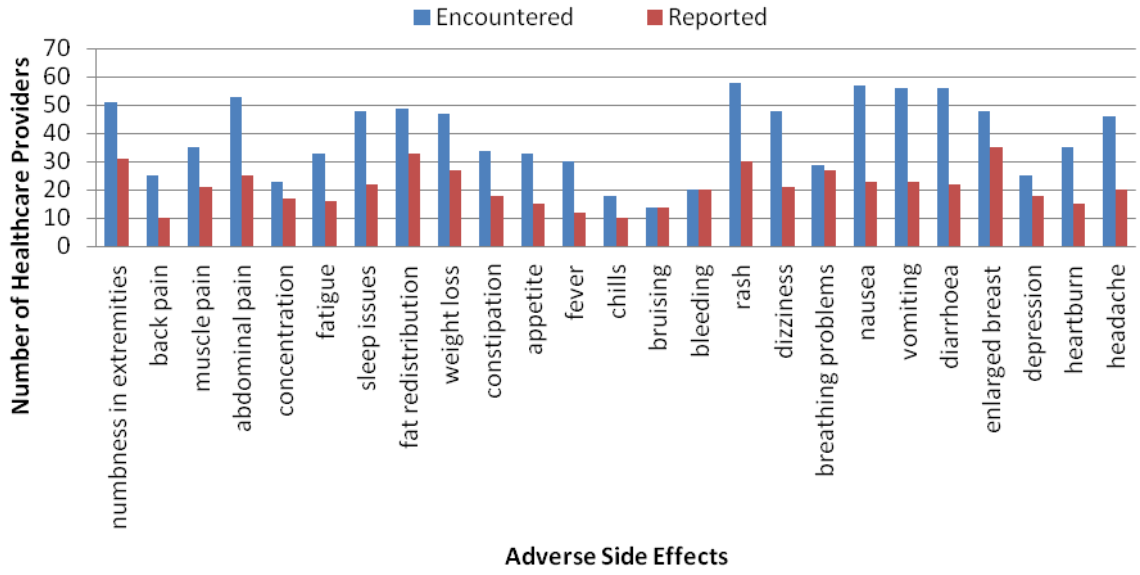

Figure 1. Number of adverse side effects encountered *versus* reported in Mpumalanga. *N* = 69.

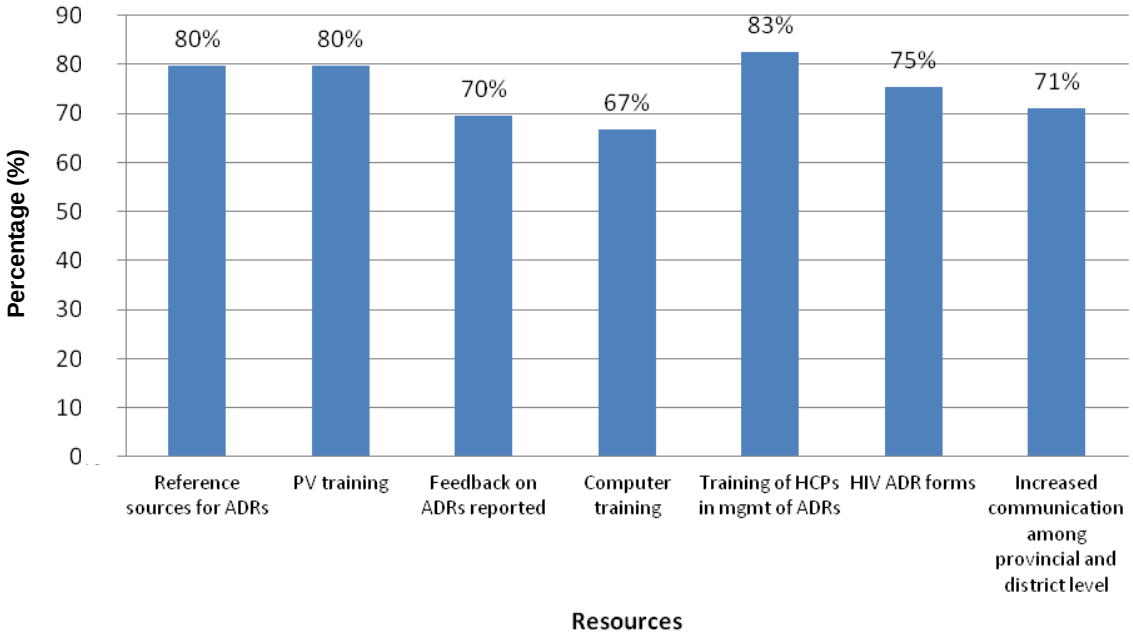

Figure 2. Areas of support needed by the Mpumalanga HPCs for the success of the PV program *n* = 69.

with an overall higher score of 4.16 knowledge gained compared to 3.0 at baseline (Figure 3).

In the three months following the training and formation of PV clusters and committees, the NPC received 314 completed ADR reports compared to no reports for a similar period in 2006. Of the 314 reports, 47 patients had concomitant health conditions and complications (Table 1). These conditions are becoming increasingly important as a consequence of increased life expectancy resulting from effective ART. Preventing or managing these conditions in ART often involves poly-pharmacy and hence the increased risk of drug-drug interactions. 86% of all the ADR reports were received from medical doctors from the districts. The management of these

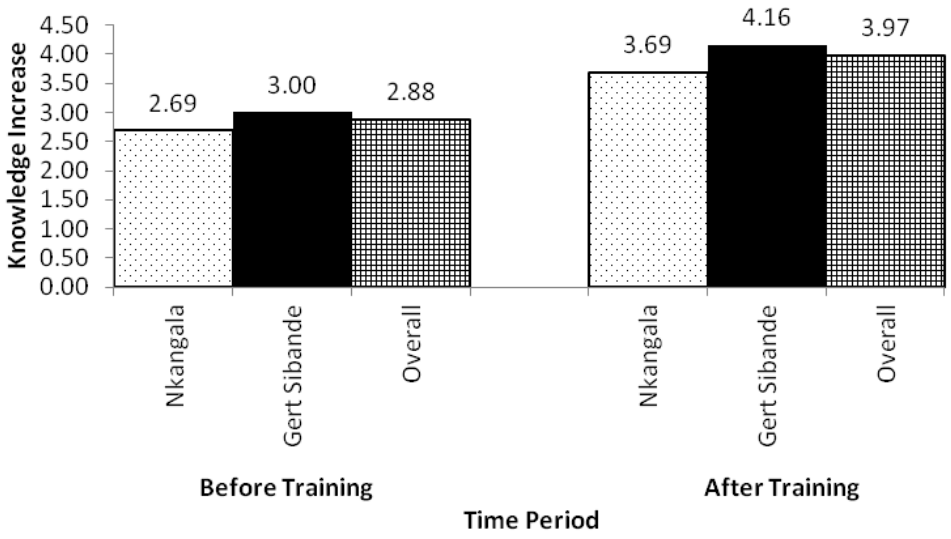

Figure 3. Increase in knowledge amongst the HCPs after training *n* = 69.

Table 1. Patients reported with concomitant health conditions and complications from Mpumalanga. *N* = 47.

Concomitant conditions	Frequency	Percent (%)
Hypertension	14	29.2
Pregnancy	15	31.3
Tuberculosis	6	12.5
Diabetes	4	8.3
Hepatitis	4	8.3
Kaposi's Sarcoma	1	2.1
Cryptococcal meningitis	1	2.1
Haemorrhoids	1	2.1
Lower Respiratory tract infection	1	2.1
Lymphoma	1	2.1
Total	48	100.0

N = 47 One patient was pregnant and had hepatitis.

ADRs should be based on the ADR/side effect, concomitant medications, concomitant disease/condition, interactions (drug–drug and drug–condition interactions), convenience, co-morbidities, and adherence. Consequently, we trained all HCPs on how to individualise treatment to enhance adherence and improve treatment success. This was facilitated by working through actual cases from various ART sites.

DISCUSSION

All HCPs have a role to play in maintaining the balance between a medicines benefit and risk. At baseline we found that 80% of the participants had no previous PV training and 67% said there was no active PV programme at their institutions. This could be a reflection of the statistics for the rest of SA and may be an indication of poor knowledge, attitude and practice amongst HCPs. Further, we found that the number of ADRs reported was very low compared to those encountered highlighting the extent of under-reporting with the spontaneous reporting system which as discussed above has been the cornerstone of the existing SA PV system.

Our baseline assessment of additional support required by the HCPs and their institutions is suggestive of, and is a confirmation of our suspicion that they suffer from the lack of resources to report, monitor and attend to ADRs.

This corroborated by our observation that understanding and reporting of ADRs increased after the training supports the argument that training, on-going support, and decentralizing PV and integrating it into HCPs daily activities can improve practices with regards to reporting ADRs as well as intervention and effective case management at treatment level. This is particularly important in HIV/AIDS management programmes. The potential value of this decentralized programme is that it may result in the establishment of “mini “ PV centres or clusters and this will have a positive downstream effect through increased numbers of HCPs with knowledge and increased PV bias. Consequently, both the patient as well as the reporting HCP at treatment level will benefit.

With continued support from the NPC to the Mpumalanga facilities via follow-up phone calls, faxes, emails or through phone calls as issues arise, the programme will show benefits with regards to establishing causality of medications and ADRs, if required and summarising reported cases for discussion, as necessary. The new practice now is that upon completion and review of monthly PV meetings at cluster or treatment level, all ADRs are being forwarded to the NPC. This information will be reviewed for trends within the clusters, districts, and/or provinces. Should unique trends in the data provided come to the attention of the NPC, this information will be communicated to the treatment centre and appropriate feedback given. Further, the NPC will review trends and identify potential cohort studies to address specific safety concerns. General practice recommendations will be made to the programme directorates and the NDoH and other key organisations. Specific drug related safety concerns requiring regulatory considerations will be reported to the Medicines Control Council (MCC).

A strength of our brief analysis and conclusions is that the post-training assessment was done a reasonable three months after the training. We plan to have continuous interactions with the clusters to ensure the retention of knowledge and skills acquired during the training. Like the other provinces, Mpumalanga province is part of South Africa’s Nurse initiated Management of Antiretroviral Therapy (NIMART) initiative intended to provide patients with a comprehensive continuum of care. Consequently, we will continue to train more nurses as well as other HCPs from various professional backgrounds such as pharmacists, laboratory technician and counsellors to mention but a few.

One limitation of the before-after design we have reported herein is that confounding is hard to rule out. In addition, one of the challenges in operational health service-based research and programmes such as ours is logistic limitations imposed by day-to-day service delivery obligations, which interfere with careful design of the assessment of a programme or intervention. (Theobald et al, 2009). Nonetheless, the improved ADR reporting patterns we have experienced, the improved knowledge amongst HCPs and better case management we have now observed at treatment level is reassuring.

In summary, participants who underwent the training reported improved knowledge of ADR reporting and a greater confidence in identifying and managing ADRs after the training in comparison to baseline. The effects of the training were similar for all the professions of HCPs that participated.

CONCLUSION

This is the first time that such a decentralized PV programme has been introduced in South Africa to address shortfalls in the existing PV activities. The field of HIV/AIDS and TB PV/ADR management provides one of the greatest opportunities for improving patient outcomes and quality of life. We have successfully made PV an integral part of the daily activities of HCPs in Mpumalanga and as observed from the improved reporting patterns, this is expected to foster a culture of prioritizing patient safety at treatment level. This decentralised PV model constitutes a patient-centred approach by which to prevent and manage side effects. It works to establish better communication between the various healthcare disciplines providing care for each patient, capacitating the NDoH in collating aggregate data, trending of reported cases and giving valuable feedback to treatment sites, the regulatory authorities and the HIV/AIDS and TB directorates. It emphasises proper management of side effects at all levels, while prioritising disease control. A meeting that had most of South Africa’s key players and stakeholders in PV in attendance has recently endorsed our model as ideal to roll-out to other provinces of South Africa. It remains our vision to cascade and expand this programme to all the other provinces, as well as to the correctional services and to the military healthcare services.

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Appendix 1. Section of the baseline assessment tool giving example of assessment questions.

NATIONAL PHARMACOVIGILANCE CENTER:
DECENTRALISED HIV/AIDS & TB PHARMACOVIGILANCE
TRAINING PROGRAMME PRE-TEST

INSTRUCTIONS: This test will establish your current level of knowledge about pharmacovigilance and adverse drug reactions. This will help to guide the tutors to ensure that you receive the most appropriate training to enable you to function optimally in your expanded role.
WHERE RELEVANT SELECT THE BEST RESPONSE GIVEN.

1. What do you understand about pharmacovigilance?

2. Which objective of pharmacovigilance is most important? (select one only)

- ☐ To identify the safety of drugs
- ☐ To calculate the incidence of Adverse Drug Reactions (ADRs)
- ☐ To identify predisposing factors to ADRs.
- ☐ To identify unrecognized ADRs.

3. Which regulatory body is responsible for monitoring ADRs? (select one only)

- ☐ National Comprehensive Care, Management and Treatment HIV/AIDS & TB Programme (CCMT)
- ☐ Medicines Control Council
- ☐ Health Professions Council of South Africa
- ☐ South African Pharmacy Council
- ☐ South African Nursing Council
- ☐ South African Medical Council
- ☐ National HIV/AIDS Sexually Transmitted Infections and TB Programme Unit (HAST)
- ☐ National Pharmacovigilance Center
- ☐ National Adverse Drug Event Monitoring Center