# Adverse Event Reporting on Antiretroviral Medicines in KwaZulu-Natal for April 2007 to March 2012

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## Key Words

Adverse event, solicited reporting, antiretrovirals, South Africa, KwaZulu Natal

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## CONTENTS

## List of Figures



## List of Tables

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## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ABC | abacavir |
| ADR | adverse drug reaction |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| ARV | antiretroviral (medicine) |
| AZT | zidovudine |
| CHC | community health centre |
| CNS | central nervous system |
| DDI | didanosine |
| DoH | Department of Health |
| D4T | stavudine |
| EFV | efavirenz |
| HAART | highly active antiretroviral therapy |
| HAST | HIV/AIDS, STIs and TB Department |
| HIV | human immunodeficiency virus |
| IePRS | Integrated Electronic Patient Record System |
| KZN | KwaZulu-Natal |
| LPV | lopinavir |
| MSH | Management Sciences for Health |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| PHC | primary health care |
| PV | pharmacovigilance |
| PTC | Pharmaceutical and Therapeutics Committee |
| RTV | ritonavir |
| SJS | Stevens Johnson syndrome |
| SPS | Strengthening Pharmaceutical Systems |
| 3TC | lamivudine |
| TDF | tenofovir |
| VPPS | Virtual Purple Professional Services |

# EXECUTIVE SUMMARY

The advent of highly active antiretroviral therapy (HAART) has led to significant reductions in morbidity and mortality; however, adverse effects are common, and may lead to discontinuation of therapy, dose interuption, and significant reductions in quality of life. Prompt identification and management of adverse effects are crucial to ensuring adherence to treatment and the success of antiretroviral therapy (ART). The antiretroviral (ARV) treatment programmeprogramme of South Africa advocates the need for pharmacovigilance (PV) as an integral part of its programme. Implementation of active surveillance methods in public health programmes provides an alternate approach for generating information on adverse drug events, especially when spontaneous adverse drug reaction (ADR) reporting is poor.

In May 2007, the KwaZulu-Natal (KZN) Pharmaceutical Services Directorate, in collaboration with the Strengthening Pharmaceutical Systems Program, implemented by Management Sciences for Health, embarked on a project to intensively monitor ARV medicine adverse events (AEs).

## Overview of Solicited Reporting System

"Solicited" reporting refers to the "stimulated" reporting of adverse events whereby the reporting of adverse events to ARVs was linked to a prescriber request to approve a change in the treatment regimen of a patient who had experienced an adverse event. Thus, when solicited reporting was put in place, prescribers were mandated to complete an adverse event report each time a patient's treatment had to be changed. An ARV adverse event report form was developed with guidelines for its completion. If the prescriber did not complete this form, the new prescribed medicines would not be approved and dispensed. Initially, the approval of changes to treatment was centralised at the provincial level. However, because of the increasing number of reports, the approval process had to be decentralised to the health care facility level. Pharmacists were trained to manage the approvals for new ARVs. Completed reports were then sent to the provincial Pharmaceutical Services Directorate to be captured in a centralised database.

## Progress of Adverse Drug Event Reporting

The solicited reporting system was effective in stimulating the reporting of AEs, and the number of reports received from accredited ARV treatment sites increased phenomenally. For the first three years of the ARV programme (April 2004–March 2007), only 430 spontaneous adverse event reports had been submitted. In the three years following implementation of the solicited reporting system (April 2007–March 2010), the system generated 16,367 reports. The total number of reports had increased to 34,209 as of March 31, 2012, but it was not clear whether this was proportional to the increase in the number of patients on treatment.

Although the system was decentralised in October 2009, most health care facilities continued to submit reports to the provincial level. However, of the 91 health care facilities expected to report, the percentage of facilities reporting per annum declined from 89% in 2009–2010 to 58% in 2011–2012. In addition, the quality of reporting and data capture was found to be

suboptimal. There has also been inadequate analysis and use of the data for decision making, as well as poor feedback to health care facilities.

## Overview of Adverse Events from April 2010 to March 2012

Despite limitations in data quality and the validation process, data analysis has yielded valuable information on AEs reported in patients on ART. A total of 18,453 AEs were reported from April 2010 to March 2012. At least 70% of AEs observed were metabolic, followed by neurological AEs (14.6%). A total of 558 central nervous system (CNS) events (3.4% of all events) were reported, with the most common being depression, dizziness, agitation, disturbing dreams, impaired concentration, and sleep disturbances. Two cases of psychosis and one case of insomnia were also reported. Efavirenz (EFV) was reported as the suspected causative drug in 81.3% of the events, and nevirapine (NVP) in 17.4% of cases. Haematological events, anaemia and neutropaenia constituted 1.2% of the events reported. One hundred and three (103) renal events were reported on tenofovir (TDF)-based regimens. These consisted of renal impairment (71) and renal failure (32) cases.

Other notable clinical events reported included pancreatitis (33) and diabetes (79). These events were reported mostly in patients using a stavudine (D4T)-based regimen—85% and 94%, respectively. In addition, 31 cases of Stevens Johnson syndrome were noted, most of which were attributed to a NVP-based regimen (81%). Seven cases occurred in pregnant women.

In addition, a total of 2,166 cases of treatment failure were recorded.

## Successes, Challenges, and Strategies for Strengthening the System

The programme was successful in educating health care professionals on the importance of PV, with the result that the vast majority of health care facilities continued to report AEs despite minimal support. The development of the Bookwise Integrated Electronic Patient Record System (IePRS) is another success, as it is the only system within the public sector that incorporates a module for pharmacovigilance. Despite these successes, however, the system has limitations with respect to data quality and operational challenges in terms of a lack of capacity to manage the system and make use of the information generated. These shortfalls pose a threat to the sustainability of the programme. Effective strategies are needed to strengthen the system. These include:

- Improvement of data quality through continued capacity building of health care providers and effective monitoring and evaluation of the programme at the provincial level

- Increasing capacity for PV through dedicated human resources at central pharmaceutical services, pharmacy and therapeutics committees, and collaboration with the national pharmacovigilance programme

- Improved analysis and use of the information through collaboration with local universities, other research organisations, and the pharmaceutical industry

## Conclusion

The solicited reporting system for ARV AE surveillance is well established in KZN and collects large amounts of valuable data using minimal resources. It is important that the system be effectively managed and that the information generated be used for decision making to guide treatment and improve the overall safety of patients on ART. The system, however, has unresolved challenges and limitations that threaten its long-term sustainability. It is imperative that the gaps are addressed to strengthen the reporting system.

# INTRODUCTION

Pharmacovigilance (PV) in developing countries is becoming increasingly important. Although the risks associated with medicines are well documented in developed countries, these safety profiles cannot necessarily be generalised to developing countries, where the incidence, pattern, and severity of adverse reactions may differ markedly because of local environmental and genetic influences.[1]

The advent of highly active antiretroviral therapy (HAART) has led to significant reductions in morbidity and mortality.[2] However, HAART regimens are complex, and adverse effects are common and may lead to discontinuation of therapy, dose interuption, and significant reductions in quality of life. Furthermore, adherence to treatment may be compromised; adherence is an important determinant of successful antiretroviral therapy (ART).[3] This greatly undermines the success and quality of the antiretroviral (ART) programme. Thus, prompt identification and management of adverse events (AEs) is important for improving the long-term quality of care of patients.

South Africa has a large ARV treatment programme, with an estimated two million patients on treatment, and therefore advocates the need for PV as an integral part of its programmeprogramme. Adverse drug reaction (ADR) reporting is the cornerstone to any PV system, and although South Africa has such a system in place, spontaneous reporting of ADRs on ARVs remains poor. Hence, in the absence of effective passive reporting systems such as spontaneous ADR reporting within public health programmeprogrammes, implementation of active surveillance provides an alternate approach for generating information. Active surveillance not only includes scientific methods such as cohort event monitoring and other observational methods but may also employ less robust methods with the aim of stimulating reporting within a specific focus area.

The Kwazulu-Natal Department of Health (KZN DoH), with the support of the Strengthening Pharmaceutical Systems Program (SPS), implemented by MSH, began implementing a form of active surveillance system for monitoring AEs from ARVs in May 2007. The objective was to systematically collect data on AEs for improving patient safety and enhancing the quality of care of patients on HAART. This system has evolved over the years, through local staff empowerment and capacity building, from one that was enforced centrally by the KZN Pharmaceutical Services Directorate to one that is managed entirely by health care facilities. All ARV treatment sites in KZN routinely collect AEs due ARVs and report these to the provincial Pharmaceutical Services Directorate.

## BACKGROUND

The province of KZN initiated its ARV programme in March 2004. Because of the high burden of HIV in the province and the rapidly increasing numbers of patients being initiated on treatment, there was a need to implement a system for monitoring drug-related toxicities to ARV medicines in line with the South African Comprehensive Care, Management and Treatment plan for HIV and AIDS. In November 2004, the KZN DoH instituted a spontaneous reporting system for ARVs. This was complemented by a series of trainings conducted by SPS in 2006 to increase awareness and knowledge on PV with ARVs. However, this system proved inadequate, as the number of reports being submitted by health care workers was too few in comparison to the number of patients on treatment.

In May 2007, the KZN Pharmaceutical Services Directorate, in collaboration with SPS, embarked on a more active approach for monitoring ARV medicine AEs. Thus, the 'centralised' solicited reporting system was developed. A specific AE report form for ARV medicines was developed, and it became mandatory for clinicians to complete this form in order to seek approval from the Pharmaceutical Services Directorate prior to changing a patient's treatment. This new system proved highly effective in stimulating AE reporting, and the number of AE reports from accredited ARV treatment sites increased tremendously. This 'centralised' approval system remained in effect from April 2007 to September 2009.

With the expansion of the ARV programme, the 'centralised' approval system could not be sustained, because of the high number of AE reports being received and the lack of capacity within the Pharmaceutical Services Directorate to cope with approvals. The turnaround time for approvals increased, which in turn had a negative impact on patient care. Hence, in October 2009, the Pharmaceutical Services Directorate decided to devolve the approval process to the institutional level. With the support of SPS, training was held for the responsible pharmacist from each ART-accredited facility to capacitate them to manage the solicited reporting approval process at the local level. Facilities were then required to submit copies of the approved AE report forms to the Pharmaceutical Services Directorate for data capture. Thus the 'decentralised' solicited reporting system for ARVs was established, and it remains in place to date.

## PURPOSE OF THE REPORT

- Provide an overview of the solicited reporting system, including the resources and support required to establish the system
- Report on the progress of ARV AE reporting through the system since its inception
- Provide an overview of medicine AEs reported by health care facilities for the period April 2010–March 2012 and discuss key adverse events of interest
- Highlight both the successes and current gaps/challenges in the system and discuss future strategies for strenghthening and sustainability of the system

## OVERVIEW OF THE SOLICITED ADVERSE EVENT REPORTING SYSTEM

### Description of the Reporting Process

In the AE reporting system, the term 'solicited' means stimulated. The reporting of adverse events to ARV medicines was linked to a prescriber request to approve a change in the treatment regimen of a patient who had experienced an adverse event. Thus, prescribers were mandated to complete the KZN-specific ARV AE report form when seeking to change a patient's treatment regimen. If this form was not completed, the new prescribed medicines would not be approved and dispensed. Once completed, these forms were then sent to the pharmacy within the health care facility for onward transmission to the provincial Pharmaceutical Services Directorate, where they were captured in a centralised database. The objective was to analyse and use the information to optimise the ARV treatment of patients.

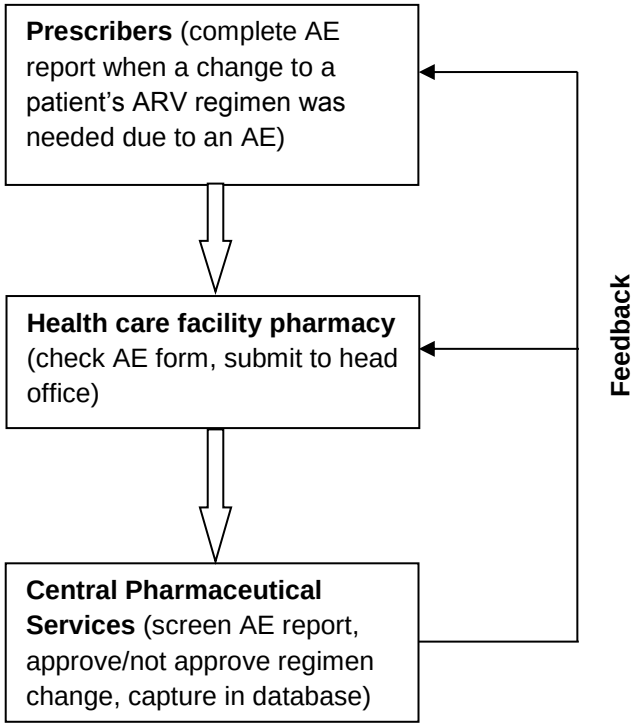


**Figure 1. Schematic representation of the centralized reporting process**

### Centralised versus Decentralised System of Approval

Starting in April 2007 during the initial phase of the system, all completed AE reports and the requests for changes to ARV treatment regimens had to be evaluated and approved by a pharmacist at the provincial Pharmaceutical Services Directorate prior to the new medicines being dispensed by the health care facility. This process was highly effective in validating adverse events and ensuring rational changes to treatment regimens. It also ensured appropriate clinical management of ARV patients, which was facilitated by consultation with key experts within the ARV programme. However, with the growing numbers of patients on

treatment and the increase in the number of AE reports being received for approval, this centralised approval process became inefficient. There was insufficient capacity at the provincial level to cope with screening and approval of AE forms on a daily basis, resulting in a high turnaround time for approvals, which ultimately impacted on dispensing for the patient. As a result, the province decided to decentralise the approval process to health care facilities. Pharmacists at health care facilities were trained on how to evaluate and approve AE reports. However, the approved forms were still required to be transmitted to Pharmaceutical Services for data capture at the provincial level. This decentralised approval system commenced in October 2009 and remains in effect currently.

## Operational Management

### *Tools for Reporting*

In 2007, an ARV-specific AE report form was developed for KZN. The ARV report form differed from the general ADR report form in that it was tailored to collect additional information on AEs pertaining to ART. This was deemed necessary to allow for better characterisation of AEs and to establish their causality with ARVs. In 2009, the form was updated further to include a list of all possible ARV-related adverse events in order to improve the quality of reports and streamline the process of reporting by health care professionals. Guidelines and standard operating procedures (SOPs) for reporting were also developed. The guidelines and AE report are appended (annex A).

### *Resource Requirements*

#### *Human Resources*

The solicited reporting system has been maintained through central data entry staff for capturing of reports as well as the full-time supervision of a pharmacist at provincial Pharmaceutical Services. At inception, a designated pharmacist from within the Pharmaceutical Services Directorate managed this process. However, because of human resources constraints within the directorate, the need for funding support was raised. Subsequently, SPS funded one pharmacist (at a deputy manager level) and one central data capturer for the period July 2010–June 2012.

#### *Budget*

The establishment of the solicited reporting system has required minimal financial resources. The cost to maintain the system was assimilated from the funding of the pharmacist and data capturer posts at the central level. Additional costs incurred were those for administrative support, which include facsimile maintenance, paper for printing, and maintenance of the central database.

#### *Training*

With the support of SPS, a series of training workshops for clinicians and pharmacists was conducted at both the preparatory and implementation phases of the system. Since 2007, six training workshops have been held in KZN and a total of 315 persons have been trained in the solicited reporting system. The training covered diagnosis and clinical management of

AEs relevant to the South Africa ART guidelines, completion of the ARV-specific AE report form, and SOPs for reporting.

### *Database for Capturing Reports*

For the period 2004–2007, all AE report forms were captured in an Excel database that was developed with the assistance of one of the pharmacy managers in the province. This database became inefficient for data capture as the volume of AE reports increased. At the time, a computerised programme called the Bookwise Integrated Electronic Patient Record System (IePRS), developed by the company Virtual Purple Professional Services (VPPS), had been donated to KZN DoH. This programme was being piloted as an ARV patient management system at a few health care facilities in KZN. In December 2008, the Pharmaceutical Services Directorate collaborated with VPPS to develop a PV module, based on the solicited reporting system, within the Bookwise IePRS programme. This programme has since been in use for central data capture of all ARV AE reports received from health care facilities, and has improved the efficiency of data capture and facilitated analysis of AE reports. A brief overview of the programme is appended.

## PROGRESS OF SOLICITED ADVERSE EVENT REPORTING

### Impact of Active Surveillance

The value of a solicited reporting system in a resource-constrained setting was evident, as shown in figure 2. For the first three years of the ARV programme (April 2004–March 2007), prior to the implementation of the solicited reporting system, only 430 AE reports were received. Over the next three years (April 2007–March 2010), the number of AE reports received increased by more than thirty folds

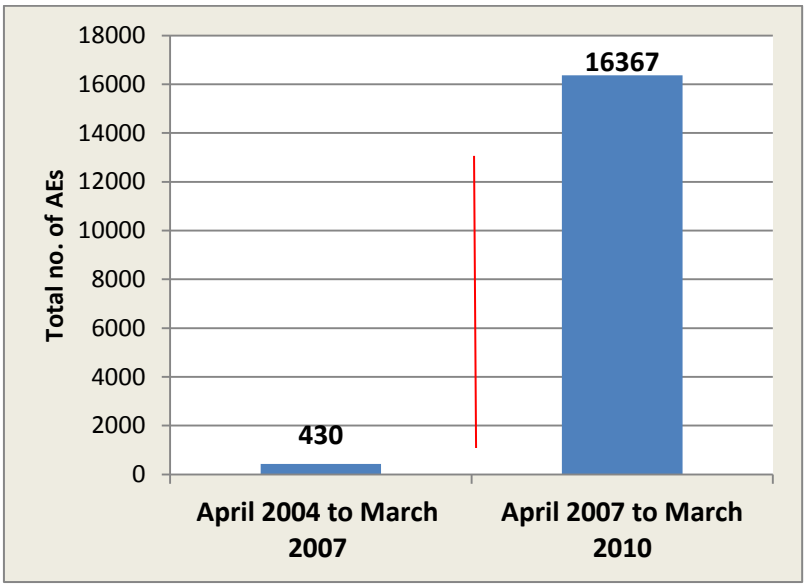


**Figure 2. Impact of active surveillance on the reporting of AEs to ARVs**

The cumulative number of AE reports submitted and captured in the central electronic data capture system as of March 31, 2012, was 34,209 (as shown in figure 3).

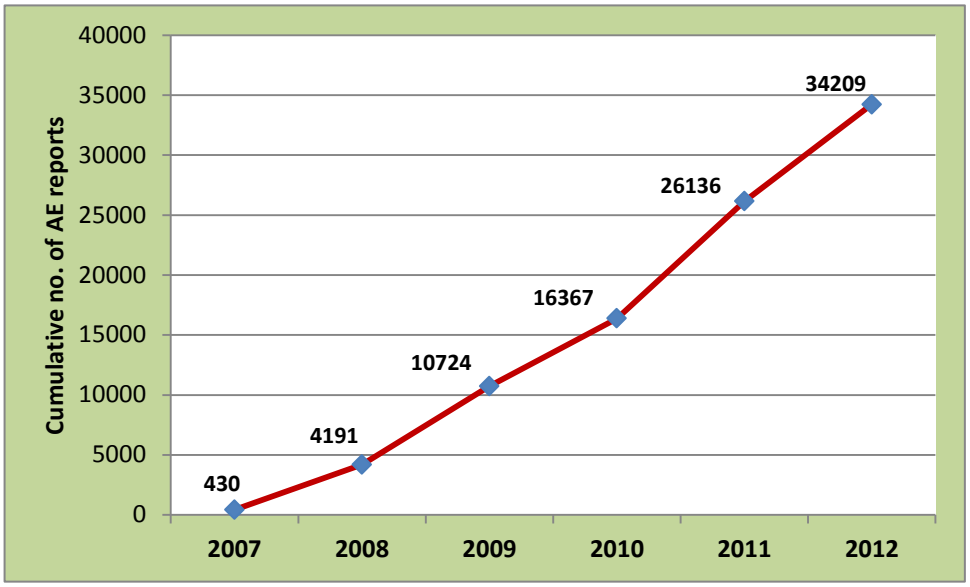


**Figure 3. Cumulative number of adverse event reports as of March 31, 2012**

## Number of Reports Submitted and Number of Health Care Facilities Reporting per Annum

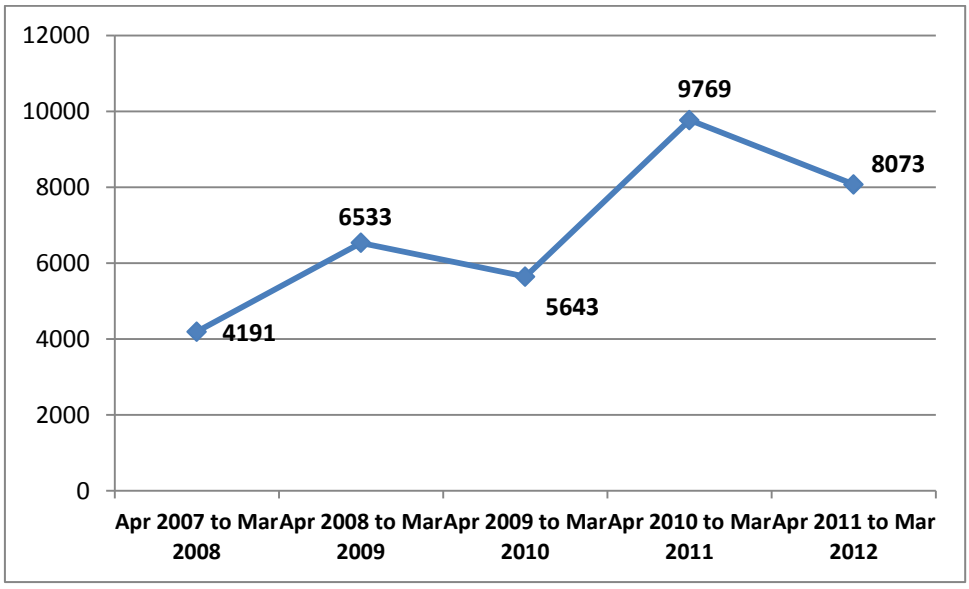


**Figure 4. Number of adverse event reports submitted annually**

The number of AE reports submitted has increased steadily each year (figure 4), although as of March 2012 it had not been determined whether the increase was in direct proportion to the annual increase in the number of patients in the ARV programme. Figure 4 was based on the date of capture of the AE reports into the central database: the number of reports denoted for each year may not be an accurate reflection of the number of reports submitted in that period but rather a reflection of the number of reports captured in the central database in that period. For example, a backlog in data capture at the end of each financial year would have

resulted in reports from the previous year being captured only in the new financial year. It is also important to note that the design of the database did not provide for capturing the date of the adverse event. This may explain the low number of reports for the period April 2009–March 2010, followed by a sharp rise in the following year. The high number of AE reports post–April 2010 could also be attributed to the change in the ART guidelines in April 2010. Since tenofovir (TDF) was added to the first-line treatment regimen, patients experiencing adverse effects to stavudine (D4T) were being changed to TDF. The 2010 guidelines also introduced new eligibility criteria, which increased access to ART; thus, there was also a rapid rise in the number of new patients initiated on treatment from April 2010.

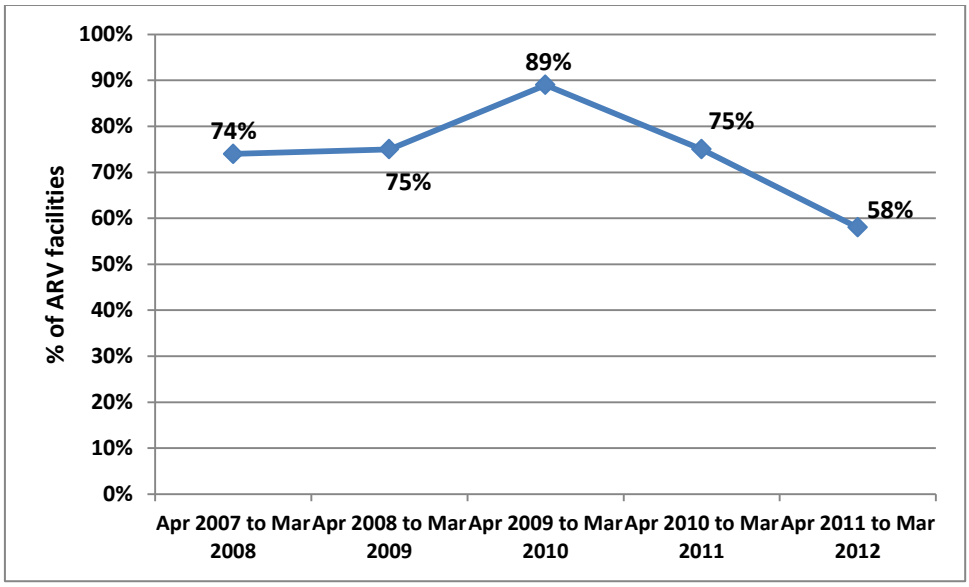


**Figure 5. Percentage of ARV facilities reporting adverse events annually**

At the inception of the ART programme in South Africa, only health care facilities that had been accredited and designated by the DoH as ART sites could initiate patients on ART. A total of 91 ARV-accredited health care facilities (only hospitals and Community Health Centres) had been designated as treatment sites by April 2007. Thus, only these facilities were trained in the solicited reporting system. Since April 2010, the accreditation of ART sites was no longer a requirement and ART sites had extended to primary health care facilities. However, for the purpose of this report, reporting only by the 91 ARV accredited sites is discussed.

The percentage of facilities reporting per annum was 75% in the first two years (April 2007–March 2009) after implementation (figure 5). An increase in the percentage of facilities reporting (89%) was observed during the period April 2009–March 2010. The increased reporting may be attributed to the decentralised solicited reporting training held for health care facilities in October 2009. After March 2010, however, a decline in the number of facilities reporting had been observed. Only 58% of facilities submitted AE reports for the period April 2011–March 2012. It should be noted, however, that no monitoring, support, or feedback had been provided to health care facilities since October 2009. This history indicates that the intervention to decentralise the solicited reporting system was successful but could not be sustained in the absence of feedback and support to facilities.

## Reporting of Adverse Events per District

Figure 6 shows the number of reports submitted by each district for the period April 2007–March 2012. Ethekwini submitted 45% of the total number of reports. This, however, was not due to a good reporting rate for all facilities in eThekwini, but rather the contribution of reports from a few facilities in the district with large ARV programme. The numbers contributed by each district was also dependent on the number of patients on ART in the district. A large number of reports (2,235) could not be categorised by district, and the health care facility name was not indicated on the AE report.

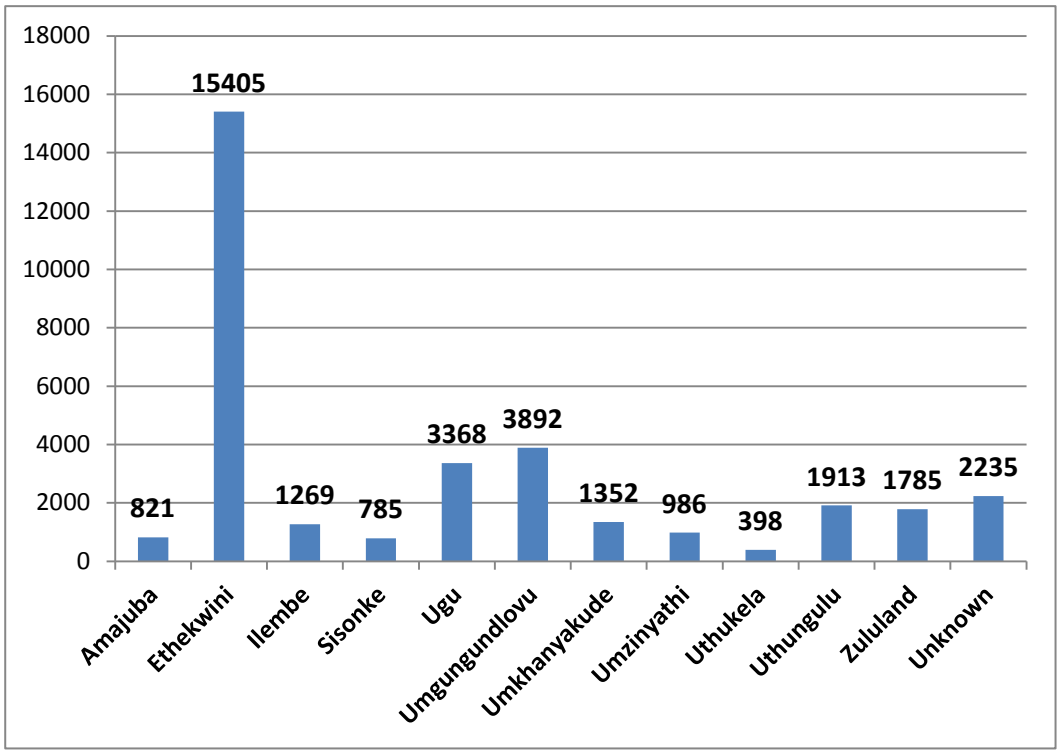


**Figure 6. Number of adverse event reports submitted per district for the period April 2007–March 2012**

## Quality of Reporting

The quality of reporting by prescribers has been found to be suboptimal. Problems included missing information such as the name of the health care facility, the demographic details of patient, and laboratory parameters to confirm AEs. A large percentage of AE reports on the system did not have an AE recorded. It is unclear, however, whether these were errors in data capture or a problem with the database. In addition, many forms were noted showing cautionary changes without an actual event having occurred. This may be a result of the AE report being linked to a change in regimen. Hence, clinicians also submitted an AE report when a change in regimen was made as a preventive measure—for example, cautionary changes from D4T in patients with a high body mass index who were at risk of experiencing an AE or switches from efavirenz (EFV) to NVP in patients who became pregnant. Overall,

the quality of data extracted from the IePRS system seemed to be poor, as a result of incorrect data capture due to misinterpretation of clinical information written on the AE reports.

## Comparison of Reporting during the Centralised versus Decentralised Phase of System Management

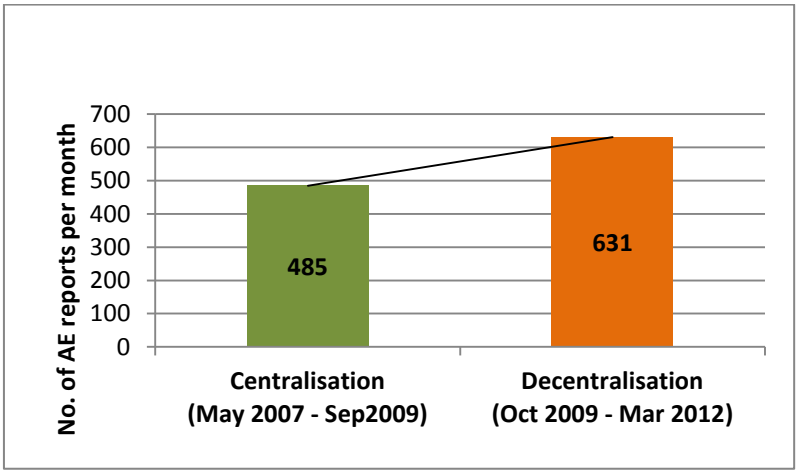


**Figure 7. Average number of reports per month submitted by health care facilities**

The centralised system involved mandatory reporting by health care facilities for a change in regimen, which required authorisation at the provincial level. During this period, the average number of reports being received for authorisation at the provincial level was 485 per month. Because this system was not sustainable, authorisation of changes to regimens was decentralised to health care facilities.

To ensure sustainability of reporting, pharmacy managers were trained to manage the process locally. Through capacity building, this new system appears to have sustained itself with minimal support from the provincial level. Figure 7 shows that, through March 2012, health care facilities continued to report AEs at an average rate of 631 reports per month.

## OVERVIEW OF ADVERSE EVENTS REPORTED

### Comparison of Adverse Event Reporting on Old (April 2004) versus New (April 2010) Treatment Guidelines

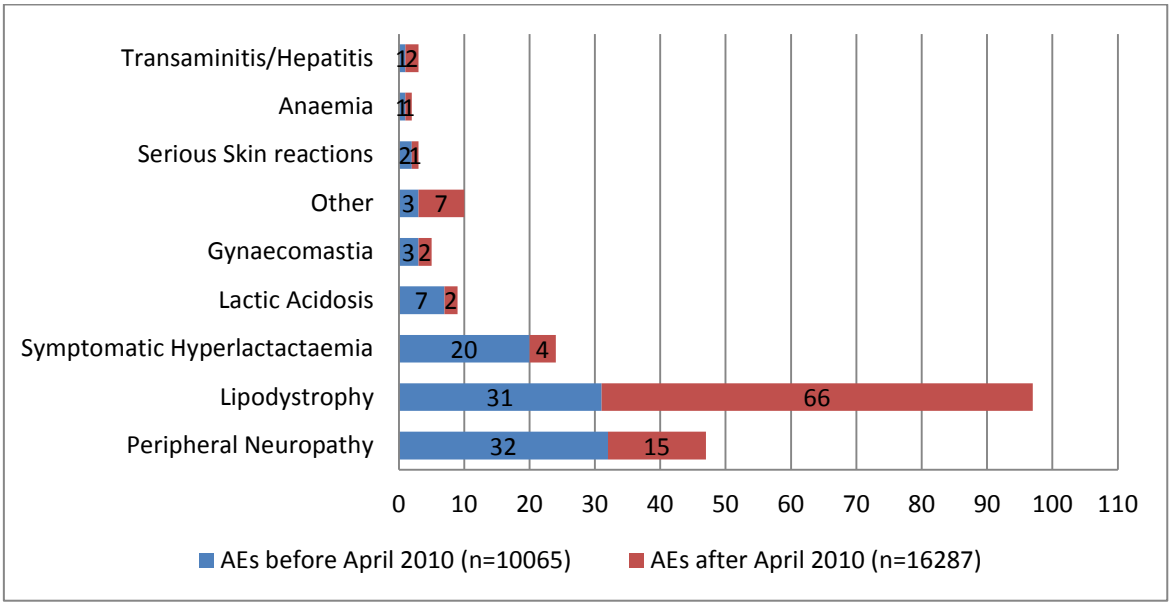


**Figure 8. Frequency of adverse events before and after April 2010**

The new South African ART guidelines came into effect in April 2010. One of the major changes was the inclusion of tenofovir (TDF) as part of first-line treatment. All new patients were henceforth initiated on TDF and existing patients on D4T were switched to TDF if they experienced AEs. This greatly reduced the use of D4T and, as shown in Figure 8, expected declines in the frequency of lactic acidosis (from 7% to 2%), symptomatic hyperlactaemia (from 20% to 4%), and peripheral neuropathy (from 32% to 15%) was observed with the change. The increased reporting of lipodystrophy events post-April 2010 was attributed to the high number of patients who were switched from D4T to TDF as a result of pre-existing lipodystrophy based on the requirement of the new guideline. There was also continued use of D4T/AZT in patients unable to use TDF post–April 2010.

### Analysis of Adverse Events Reported from April 2010 to March 2012

**Table 1. Summary Information for Data Extracted from the IePRS Programme**

| Report Range Extracted Programme | April 1, 2010–March 1, 2012 |
|---|---|
| Total number of forms logged | 17,842 |
| Number of forms with an AE specified | 15,380 |
| Number of forms with **NO** AE specified | 2,462 |
| Total number of AEs | 20,473 |
| Number of forms with a current regimen specified | 17,749 |
| Number of forms with **NO** current regimen specified | 93 |

The total number of AE reports recorded for the period 1 April 2010–31 March 2012 was 17,842 (table 1). Of these, only 86.2% (15,380) reports had an AE recorded. A total of 20,473 AEs were recorded for these 13,250 reports, indicating that multiple AEs were reported for some patients. Based on this, an average of 1.3 AEs per report was calculated.

Because of the large number of reports, not all data could be validated prior to analysis. Hence, only selected reports were validated. These included all reports with renal events (585), the term 'other event' (200), treatment/virologic failure (2,166), haematological events (696), cardiac events (36), Stevens Johnson syndrome (SJS) (31), and congenital abnormality (5). Following this process, only 18,453 valid AEs were noted. This included 16,287 clinical events and 2,166 cases of treatment/virologic failure.

### *Type and Frequency of Clinical Adverse Events by Organ System*

The distribution of clinical AEs by organ system is depicted in figure 9.

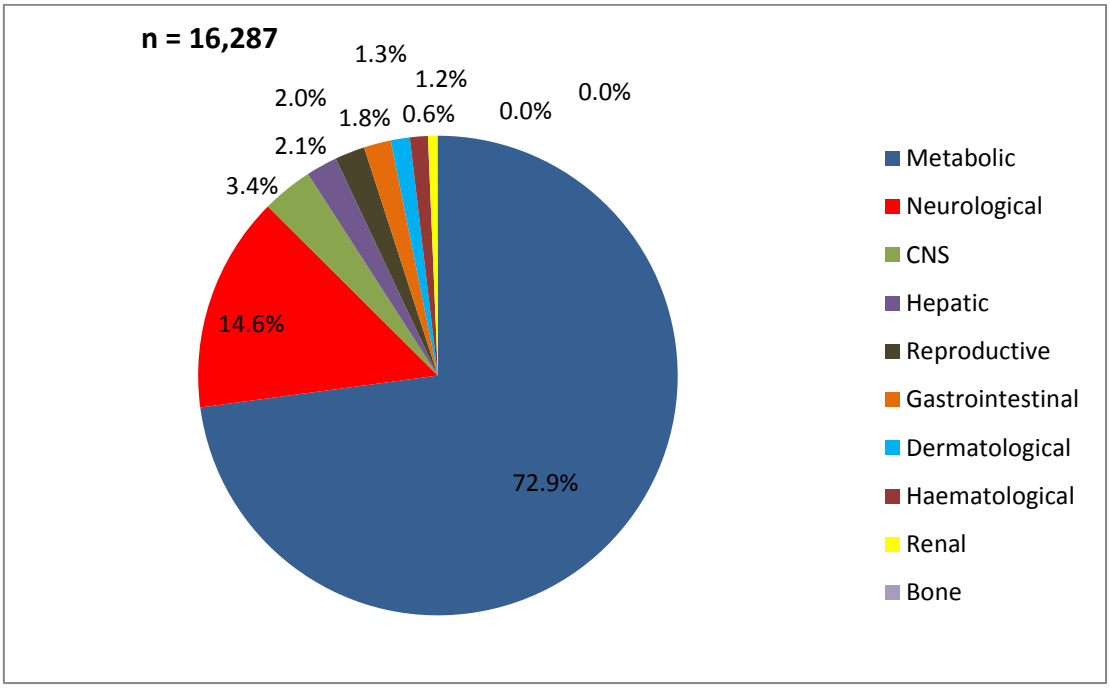


**Figure 9. Distribution of adverse events by organ system**

The most common AEs were metabolic (72.9%) and neurologic (peripheral neuropathy) (14.6%). This is expected, and attributed to the high use of nucleoside reverse transcriptase inhibitors (NRTIs) in first-line treatment regimens. This is followed by central nervous system (CNS) (3.4%), hepatic (2.1%), and reproductive system (2.0%) events mainly due to non-nucleoside reverse transcriptase inhibitors (NNRTIs), EFV and NVP. A total of 103 renal and 5 bone-related events were also reported in this period.

### *Metabolic Events*

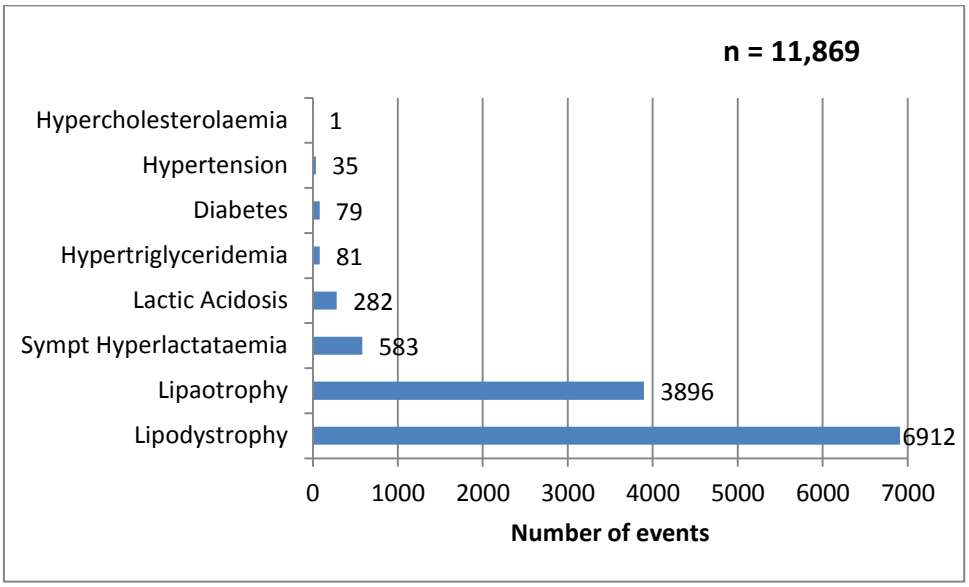


**Figure 10. Summary of the types of metabolic adverse events**

The most common metabolic AE reported was lipodystrophy, accounting for 6,912 (58%) of events (figure 10). Due to the limitation in the ARV AE report form, lipodystrophy included either lipohypertrophy, lipoatrophy, or a combination of both. More specifically, 3,896 (33%) cases of lipoatrophy were reported. Other metabolic AEs reported included symptomatic hyperlactaemia (583), lactic acidosis (282), hypertriglyceridaemia (81), diabetes (79), and hypertension (35).

### *Central Nervous System Events*

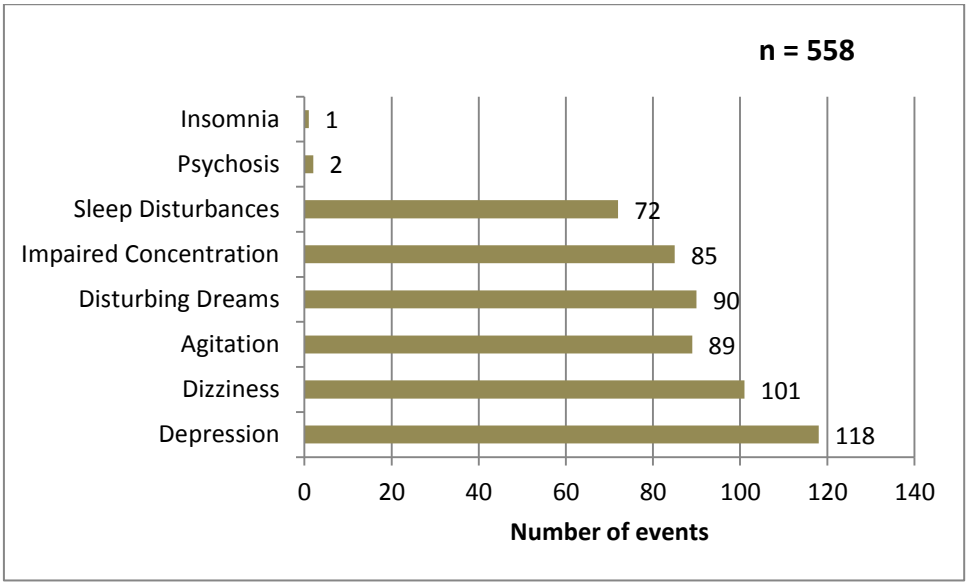


**Figure 11. Summary of the types CNS adverse events**

In total, 558 CNS-related events were reported, with the most common being depression, dizziness, agitation, disturbing dreams, impaired concentration, and sleep disturbances (figure 11). Two cases of psychosis and one case of insomnia were also reported: 68% of reported events occurred in females and 26% in males. Gender was not specified in 6% of cases. Efavirenz was reported as the suspected causative drug in 81.3% of the events, and NVP in 17.4%. Neuropsychiatric disturbances have been reported in 25–70% of patients using EFV.[4] Efavirenz is also more likely than NVP to cause CNS toxicity.[5]

There were also six cases of CNS events reported in adults on the AZT-3TC-LPV/RTV combination.

### *Renal Events*

A total of 103 renal events were reported on TDF-based regimens. These included 71 (69%) cases of renal impairment and 32 (31%) renal failure cases. In 35 (34%) cases, the concomitant use of other nephrotoxic medicines was noted. These included TB medication, co-trimoxazole, enalapril, and hydrochlorthiazide.

### *Dermatological Events*

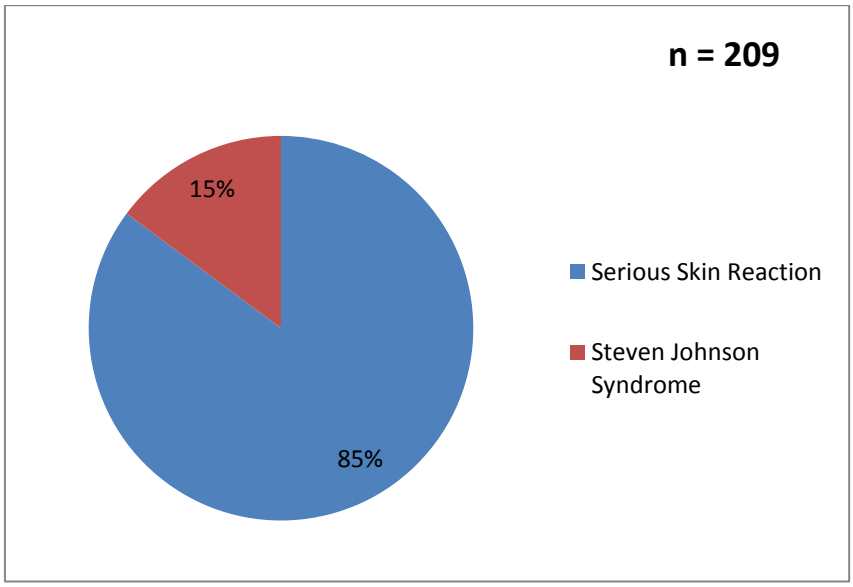


**Figure 12. Distribution of dermatological events reported**

A total of 209 dermatological events were reported. Of these, 178 (85%) were serious skin reaction and 31 (15%) were SJS (figure 12). The gender breakdown of the events was 74.2% in females and 15.3% in males. In 10.5% of cases, gender was not indicated.

For serious skin reactions, the use of a NVP-based regimen was reported in 95 cases, EFV in 70 cases, abacavir (ABC) in seven cases and lopinavir/ritonavir (LPV/RTV) in six cases. Fourteen cases of serious skin reaction were reported in pregnant women.

For Stevens Johnson Syndrome, 25 cases were reported on an NVP-based regimen, three on EFV, and three on ABC. Seven events were reported in pregnant women. NVP has been shown to be associated with a greater risk of skin toxicity than EFV.[5]
Concomitant use of co-trimoxazole or TB medication (fixed-dose combinations) was reported in 26 cases of serious skin reaction and one case of SJS.

### *Hepatic Events*

A total of 226 cases of transaminitis/hepatitis were reported. EFV was the suspected causative drug in 120 cases and NVP in 96 cases. Four cases were also reported on AZT-DDI-LPV/RTV. In six cases, the ART regimen was not recorded.

Hepatic encephalopathy is a condition which occurs secondary to advanced liver disease. Encephalopathy due to fulminant/acute liver failure was reported in 58 cases. The majority of these were reported to have occurred on EFV and NVP—28 and 27 cases, respectively—in combination with 3TC-D4T, 3TC-AZT, and 3TC-TDF. One case on DDI-3TC-LPV/RTV and another on D4T-3TC-LPV/RTV were also reported. In two cases, the ART regimen was not recorded.

Hepatic steatosis is a rare but potentially life-threatening toxicity seen with NRTIs. Twenty-seven cases of hepatic steatosis (non-alcoholic fatty liver disease) were also reported. Eighteen cases were reported on 3TC-D4T, three on AZT, and six on TDF, mostly in combination with EFV/NVP. A triple-NRTI regimen was reported in one case. Information on alcohol use was not available.

Concomitant use of TB medicines and co-trimoxazole was noted in 38% of hepatic cases.

### *Haematologic Events*

A total of 173 events of anaemia and 24 events of neutropaenia were reported.

Both these events were reported on AZT-based regimens. Anaemia and granulocytopaenia affect about 5–10% of patients who receive AZT and are more common in people with advanced HIV disease.[6]

### *Reproductive System Events*

A total of 269 events of 'gynaecomastia' were reported. Of these, 151 events were reported in males and 96 were actually cases of breast enlargement (lipodystrophy) in females. Gender was not specified in 22 cases. EFV was indicated as the suspected causative agent in 241 cases and AZT-DDI-LPV/RTV in two cases. There were also 26 cases reported on D4T-3TC-NVP.

A total of 61 cases of sexual dysfunction were reported. EFV was implicated in 47 cases, AZT-DDI-LPV/RTV in two and D4T-3TC-NVP combination in 12 cases. Sexual dysfunction was reported more in females than males—45 cases and 13 cases, respectively. The gender was unknown in three cases.

### *Peripheral Neuropathy*

A total of 2,375 cases of peripheral neuropathy were reported. A stavudine-based regimen was reported in 91% (2,171) of cases. Additionally, an AZT-based regimen was reported in 107 cases, TDF in 23 cases, DDI in 4 cases, an AZT-DDI combination in 20 cases, and ABC in 4 cases. The complete regimen could not be confirmed in 46 cases. Peripheral neuropathy is a well-documented adverse effect of stavudine. Studies have shown that the proportion of patients diagnosed with peripheral neuropathy on D4T is significantly higher when compared to non-stavudine-based regimens.[7]

A total of 66% of events were reported in females, 23% in males, and in 11% of cases the gender was not recorded. Concomitant use of TB medication (isoniazid, fixed dose combinations) was noted in 141 cases and metformin in two cases.

### *Pancreatitis*

A total of 28 cases of pancreatitis were reported on a 3TC-D4T regimen, two on 3TC-AZT, two on 3TC-TDF, and one on 3TC-ABC with either EFV orNVP. Acute pancreatitis is a relatively infrequent but serious AE documented with the use of NRTIs, including stavudine.[8] Concomitant use of other medicines with a potential for pancreatitis was noted in six cases: five with isoniazid and one with sodium valproate.

### *Diabetes*

Diabetes is a metabolic complication associated mostly with NRTI lipodystrophy. Stavudine in particular has been associated with a high prevalence of dyslipidaemia and hyperglycaemia.[9]

In total, 79 cases of diabetes were reported. Of these, 76 cases were attributed to D4T and two cases to AZT-based regimens. One case of diabetes on AZT-DDI-LPV/RTV combination was also reported.

### *Osteopaenia/Osteoporosis*

Five cases of osteoporosis were reported (four males and one female). Three cases were reported on D4T-3TC-EVF and one case each on D4T-3TC-NVP and AZT-3TC-EFV regimens, respectively. Of the five cases, three were reported in persons over the age of 65 years.

## Treatment Failure and Virologic Failure

Treatment failure was reported in 2,166 patients. The term ‘virologic failure’ was sometimes used interchangeably when reporting, as noted in 50 reports.

There was uncertainty about 72 reports, as the viral loads were indicated were below 100 copies/mL and CD4 counts were greater than 500 cells/uL, with only a single drug switch in the regimen change. Viral loads were not indicated in 409 cases but these were changed to second-line regimens. Data for 2,094 reports are summarised in table 2.

**Table 2. Summary of Regimens Associated with Treatment Failure**

| Regimen | Number of events | Percentage |
|---|---|---|
| 3TC-D4T-NVP | 481 | 22.2 |
| 3TC-D4T-EFV | 1,006 | 48.8 |
| 3TC-AZT-NVP | 64 | 3.0 |
| 3TC-AZT-EFV | 101 | 4.7 |
| 3TC-TDF-NVP | 102 | 4.7 |
| 3TC-TDF-EFV | 202 | 9.3 |
| 3TC-ABC-NVP | 1 | 0.0 |
| 3TC-ABC-EFV | 24 | 1.1 |
| 3TC-DDI-EFV | 4 | 0.2 |
| AZT-DDI-EFV | 2 | 0.1 |
| D4T-DDI-EFV | 3 | 0.1 |
| ABC-DDI-EFV | 1 | 0.0 |
| TDF-D4T-EFV | 4 | 0.2 |
| ABC-D4T-EFV | 1 | 0.0 |
| TDF-AZT-NVP | 1 | 0.0 |
| D4T-NVP-EFV | 1 | 0.0 |
| TDF-NVP-EFV | 2 | 0.1 |
| 3TC-NVP-EFV | 3 | 0.1 |
| 3TC-D4T-TDF | 6 | 0.3 |
| 3TC-D4T-ABC | 3 | 0.1 |
| 3TC-D4T-DDI | 1 | 0.0 |
| 3TC-D4T-AZT | 2 | 0.1 |
| 3TC-AZT-TDF | 1 | 0.0 |
| AZT-DDI-LPV/RTV | 23 | 1.1 |
| 3TC-D4T-LPV/RTV | 13 | 0.6 |
| 3TC-AZT-LPV/RTV | 7 | 0.3 |
| 3TC-TDF-LPV/RTV | 4 | 0.2 |
| 3TC-ABC-LPV/RTV | 2 | 0.1 |
| ABC-AZT-LPV/RTV | 1 | 0.0 |
| TDF-AZT-LPV/RTV | 1 | 0.0 |
| 3TC-EFV-LPV/RTV | 5 | 0.2 |
| 3TC-NVP-LPV/RTV | 1 | 0.0 |
| D4T-EFV-LPV/RTV | 1 | 0.0 |
| Unknown | 20 | 0.9 |
| **Total** | **2,166** | **99.0** |

Note: Due to rounding, percentage may not add up to 100.

Treatment failure occurred mostly on dual-NRTI and -NNRTI first-line regimens (92.7%). The vast majority of these occurred on 3TC-EFV-based regimens. An additional 1.9% of treatment failure cases occurred on other dual-NRTI and -NNRTI regimens. Treatment failure to second-line regimens with dual-NRTI and LPV/RTV accounted for the 2.7% of cases. A few cases of treatment failure on triple NNRTI, triple NRTI, and dual NNRTI were also reported. In 20 reports, the regimen failed was not identifiable from the data.

# DISCUSSION

## Programme Implementation

The introduction of the solicited reporting system in April 2007 greatly improved the reporting of ARV AEs compared to the reporting of AEs using a spontaneous reporting system. A total of 34,209 reports were received as of March 31, 2012. Although a fair number of reports are received annually, this may not be proportional to the number of new patients being initiated on treatment. There has also been a decline in the number of reporting facilities (hospitals and CHCs) since March 2010, and as of March 31, 2012, only 58% of 91 facilities were reporting. This may be due to the long absence of training, mentorship, and support to facilities at the programme level as well as the lack of feedback and communication to prescribers on the findings of the programme. Futhermore, since the introduction of the nurse-initiated ART policy, a large number of ARV patients are being managed at the primary health care (PHC) level. However, PHC facilities have not been formally incorporated into the overall reporting system and it is unclear whether there is any reporting of AEs by nurses at PHCs and whether such reports are being submitted via the supporting hospital/Community Health Centre (CHC).

All districts were reporting; however, it seemed that the reporting was not optimal. With the number of patients on ART per district unknown, the number of reports received could not be correlated to the number of patients to validate this assumption.

## Analysis of Adverse Events

The data analysis has yielded some important information on the ART programme and type and frequency of AEs observed since April 2010. A total of 18,453 AEs were reported from April 2010 to March 2012. At least 70% of AEs observed were metabolic, followed by neurological AEs (14.6%). These accounted for more than 80% of the total AEs recorded. This was due to the use of NRTIs. As per the April 2010 ART guidelines, these medicines continued to be used as part of first-line treatment in patients unable to use TDF. A large number of AE reports were also stimulated by the introduction of TDF as first-line treatment, as prescribers were advised to complete an AE report form when switching patients from D4T to TDF due to toxicities.

A total of 558 CNS-related events (3.4% of all events) were reported, with the most common being depression, dizziness, agitation, disturbing dreams, impaired concentration, and sleep disturbances. Two cases of psychosis and one case of insomnia were also reported. EFV was reported as the suspected causative drug in 81.3% of the events, and NVP in 17.4%. This is consistent with a recent systematic review and meta-analysis by Shubber et al., which shows that EFV is more likely than NVP to cause CNS toxicity.[5] Haematological events, anaemia, and neutropaenia constituted 1.2% of the events reported.

One hundred and three (103) renal events were reported on TDF-based regimens. These consisted of renal impairment (71) and renal failure (32) cases. The concomitant use of other nephrotoxic medicines was noted in 35 cases. Other notable clinical events reported included pancreatitis (33) and diabetes (79). These events were reported mostly in patients using a D4T-based regimen—82% and 94%, respectively. In addition, 31 cases of SJS were noted

and were attributed mostly to a NVP-based regimen (81%). Seven events were reported in pregnant women.

A total of 2,166 cases of treatment failure were recorded. Treatment failure occurred on mostly on dual-NRTI and -NNRTI first-line regimens (92.7%). The vast majority of these were on 3TC-EFV-based regimens.

Several limitations in terms of data analysis are acknowledged. Firstly, all data used for the analysis were extracted directly from the IPRS programme and since AE reports are not validated prior to data capture, inappropriate interpretation and recording of AEs in the programme is possible. Errors in data capture were also found to be a problem.

Furthermore, it was not possible to validate all information generated from the IePRS programme at the time of analysis as a result of the large number of AE reports on the system. However, all events recorded as 'other' were validated using the manual AE report forms and the actual event (if applicable) was recorded. Many of these were found not be AEs but actually reports submitted for changes to treatment as a cautionary measure; for example, switching from EFV to NVP when a patient becomes pregnant or the reporting of creatinine clearance when initiating a patient on TDF. In addition, several other events were cross-checked with manual records. These included renal and cardiac events as well as specific key events of interest such as osteoporosis, SJS, virologic/treatment failure, and congenital abnormality.

## SUCCESSES

- Once the system had been established and decentralised to the health care facility level, it required minimal capacity and resources thereafter for implementation of related activities at the provincial level.

- Implementation of the system also provided the opportunity for capacity building of health care professionals in PV. It increased awareness and understanding of the need for and importance of PV, especially for ARVs.

- The system has been adopted by the vast majority of secondary and tertiary health care facilities as policy for ARV AE reporting within KZN. This is evidenced by the continued reporting of AEs through the system even after the process was decentralised and the lack of continued training after October 2009.

- The computerised programme developed for data capture is a valuable tool that increased the efficiency of the system. It allows for electronic data capture and recording of adverse events as well as enables various reports to be produced. With optimum use, the programme can provide a data resource for scientific research.

- Finally, despite limitations, the analysis has demonstrated that solicited reporting is a valuable method for generating information on AEs within a public health programme, especially in an environment where spontaneous reporting is poor.

## CHALLENGES AND STRATEGIES FOR STRENGTHENING AND ENSURING SUSTAINABILITY OF THE SYSTEM

### Improve the Quality of Reporting and Data Capture

Operationally, the system was not functioning optimally, as not all intended health care facilities were reporting AEs. The quality of reporting was also suboptimal, with incomplete information being provided by prescribers. The adverse event report form has a few limitations in terms of the clarity of information required in specific fields as well as some duplication. This has been a contributing factor to the somewhat-limited quality of information being reported. The submission of reports via facsimile poses a problem, as the forms are sometimes not legible. Gaps in the IePRS programme have been identified, such as missing fields and other minor technical issues. This has had an impact on both the efficiency of the data capture process and the quality of information recorded.

Health care facilities have a high staff turnover, and continued in-service training and mentorship are vital to ensuring that those reporting AEs are familiar with the guidelines of what to report and how to adequately complete the ARV AE report. Further amendments and validation of the ARV AE report form are also necessary to ensure accuracy of the information being submitted. This includes elimination of any ambiguity as well as any duplicated fields. It is also important to ensure that only the most updated version of the report is used, consistently, by all health care facilities. The IePRS programme will also need to be enhanced to address current gaps and to ensure ease of data capture and accuracy of information captured. As a long-term strategy, the use of electronic reporting mechanisms needs to be explored. This will improve both the efficiency of the system and eliminate the need for manual data capture centrally.

### Creating Focal Pharmacovigilance Capacity within Pharmaceutical Services

Currently, there is a lack of internal and dedicated capacity for PV within the Pharmaceutical Services Directorate. More specifically, the lack of data capturers results in huge backlogs of uncaptured reports. This inadvertently results in poor analysis and use of the information for decision making and a lack of timely feedback to health care facilities. Specific PV capacity is important for sustainable and timely data capture as well as improved supervision of the solicited reporting system. Having human resource dedicated to PV will address the current challenge of ongoing backlogs with data capture and improve monitoring and evaluation of the system.

### Strengthen Pharmaceutical and Therapeutics Committees

Over time, the system has not succeeded in stimulating the reporting of adverse events which do not require a change in regimen—for example, deaths, adverse pregnancy outcomes—despite intensive training and changes to the design of the original form. This is partially due to the initial policy of the system, which linked AE reporting to centralised authorisation for a regimen change. There is thus a need for continuous monitoring of AEs at an operational level.

Medicine safety monitoring is one of the key functions and responsibilities of Pharmaceutical and Therapeutics Committees (PTCs). Although KZN has a functional provincial PTC, it is important to support the establishment of PTCs at districts and institutions and to encourage medicine safety monitoring activities at the operational level, which will improve efficiency of the programme. This will also facilitate the implementation of new policies and guidelines developed by the province.

## Expansion of the System to Support Reporting from PHC Facilities and Other Disease Programmes

Since April 2010, the ARV programme has been decentralised to the PHC level. As a result, large numbers of patients are being initiated and managed on ART by nurses at that level. Although PHC facilities are supported by hospitals, no specific activities have been undertaken to strengthen ARV safety monitoring at the PHC level. It is therefore critical that PHC facilities are capacitated and formal mechanisms are established for reporting of AEs.

As a long-term strategy, it is important for the province to prioritise other areas of PV, especially where treatments for other disease conditions may have an impact on ARV medicine safety. As an example, the high prevalence of HIV/TB co-infection implies that there are large numbers of ARV patients who are simultaneously on anti-tuberculosis medicines. The combined use of ARVs and anti-TB medicines is known to potentiate AEs in patients. It therefore becomes important to monitor AEs to anti-TB medicines as well.

## Improve Analysis and Use of Information

Analysis and use of information are important for providing regular feedback to stakeholders and for timely decision making. The use of more sophisticated methods for data mining, validation, and analysis is necessary to ensure maximum use of the information collected. Collaboration with local universities and other research organisations could assist with data mining, validation and analysis. Collaboration with the pharmaceutical industry may also be explored, as postmarketing medicine safety surveillance is an integral component of medicine regulation.

## Collaboration with the National Pharmacovigilance Programme

In 2010, the National Pharmacovigilance Unit and the Comprehensive Care Management and Treatment programme embarked on a decentralised model of ARV pharmacovigilance to be implemented in provinces. In this model ADR reporting is linked directly to patient care whereby ADRs are identified and managed by expert teams within districts. These are then documented and reported to the national PV programme for programmatic decision making. Although the model of reporting differs in KZN, the large number of reports collected over time contains valuable information that needs to be linked with other data sources to inform decision making at the national level. It is therefore imperative that efficient systems are created for the transfer of data from the provincial to the national level. This also provides an opportunity for the province to harness support from the national level for strengthening the KZN reporting system. This may include support for new training and for technical assistance in implementing a patient-oriented approach that encourages use of the information at a local level.

## CONCLUSION

The purpose of this report is to provide an overview of the solicited reporting system established in KZN and the progress made with implementation since its inception in April 2007 up to March 2012. Analysis of the data generated through the system was also undertaken, providing insight on the quality and type of information collected. This analysis can also be used to provide feedback to the health care facilities and programme managers with information on ARV AEs that have been observed since inception of the ARV treatment programme in KZN.

The solicited reporting system was established in KZN in April 2007 with the support of SPS and VPPS. The aim of the system was to strengthen the reporting of AEs to ARVs. With regards to programme implementation, the system greatly improved the reporting rate of AEs when compared to the previous spontaneous reporting system that had been implemented. Decentralising the system to the health care facility level alleviated the burden of administrative work at the provincial level and reporting of AEs was sustained.

As of March 31, 2012, a total of 34,209 AE reports had been captured on the database at the provincial level. It was not established whether the reporting rate was proportional to the number of patients on HAART. Analysis of the data shows that the quality of information submitted on the manual AE report form and during data capture is suboptimal. Despite these limitations, a descriptive analysis of the data has highlighted key AEs observed since the start of the ARV programme in 2004. The data showed a decline in fatal toxicities such as lactic acidosis when D4T was replaced with TDF as the preferred first-line NRTI in April 2010. However, metabolic AEs were still the most common AE observed (72.9%) post–April 2010. Renal toxicities due to TDF accounted for only 0.6% of all AEs.

The solicited reporting system for ARV AE surveillance has been well established in KZN and collects large amounts of data using minimal resources. These data can be a valuable source of information for signal generation of ARV AEs and for improving overall patient safety within the ARV programme if they are used effectively. The system, however, has limitations and unresolved operational challenges that threaten its long-term sustainability. It is thus imperative to investigate these further and to explore resourceful avenues to address the current gaps and to strengthen the reporting system.

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## ANNEX A. FORMS AND SOPS

**Switching Patients Circular**

HEALTH
KwaZulu-Natal

PHARMACEUTICAL POLICY AND SYSTEMS DEVELOPMENT
Capital Towers
121 Chief Albert Luthuli Street, Pietermaritzburg, 3201
Private Bag X 9051, Pietermaritzburg, 3200
Tel: 033 846 7267 Fax: 033 846 7280
medicalchambers.pharmacy@kznhealth.gov.za
www.kznhealth.gov.za

Enquiries: Ms V Manickum Reference: 17/6/1 Date: 26 February 2010-01-2009

**TO: HOSPITAL and PHARMACY MANAGERS**

**CC: AREA and DISTRICT MANAGERS**
**DISTRICT PHARMACY COORDINATORS**

**URGENT**

**RE: SWITCHING OF PATIENTS IN ACCORDANCE WITH THE REVISED ANTIRETROVIRAL GUIDELINES**

### 1. OBJECTIVE

The objective of this circular is to inform health care workers about the processes to be followed when switching patients to the revised National ART Regimens.

### 2. BACKGROUND

The revised Antiretroviral Treatment Guidelines were approved by the National Health Council on 5 February 2010.

Pharmaceutical Policy and Systems Development, in collaboration with the HAST Department, has implemented the solicited system of reporting for adverse drug events. This system involves the prescriber completing the adverse drug reaction form, and requesting authority to purchase a non-standard drug.

### 3. FACTS

Processes need to be followed when reporting adverse drug events associated with the revised regimens, as tenofovir and zidovudine are now constituents of regimen 1. Although approval is no longer required, there is a need to continue reporting of adverse drug events.

***PROCESS OF REPORTING OF ADVERSE DRUG EVENTS/REACTIONS***

The adverse drug reaction reporting form must be completed by the prescriber, and forwarded to Pharmacy with the prescription. The pharmacist must review the form in accordance with Tables 1 and 2. Incomplete forms must be sent to prescribers for completion. If the necessary information is not specified on the form, then pharmacist will **NOT** be able to dispense the prescription. Tables 1 and 2 indicate the information that is required when reporting adverse drug events/reactions.

## Table 1. Reporting of Adverse Drug Reactions: Revised Regimens

| Activity | Responsible person who fills out ADE/R form | Parameters to be specified on ADE monitoring form |
|---|---|---|
| Initiation of new patients on TDF, 3TC/FTC, and EFZ/NVP | Not applicable | Not applicable |
| Switching existing patients from D4T to TDF because of adverse drug events | • Doctor completes form<br>• Pharmacist reviews form | • Laboratory/clinical parameters confirming the adverse event (table 2)<br>• Serum creatinine clearance > 50 mL/min<br>• Tenofovir contraindicated in patients < 50 mL/min |
| Switching existing patients from D4T to AZT because of adverse drug events | | Laboratory/clinical parameters confirming the adverse event (table 2) |
| Failing on a D4T- or AZT-based first-line regimen; use of TDF, 3TC/FTC, and LPV/r | | • Previous viral load<br>• Current viral load<br>• Previous CD4 cell count<br>• Current CD4 cell count<br>• Adherence rate<br>• Date of stepped-up adherence<br>• Serum creatinine clearance > 50 mL/min<br>• Tenofovir contraindicated in patients < 50 mL/min |
| Failing on a TDF-based first-line regimen; use of AZT, 3TC, and LPV/r | | • Previous viral load<br>• Current viral load<br>• Previous CD4 cell count<br>• Current CD4 cell count<br>• Adherence rate<br>• Date of stepped-up adherence |

## Table 2. Laboratory Parameters Required: Confirmation of Adverse Drug Events

| Adverse event | Baseline information (laboratory tests to be performed before the patient is initiated on HAART) | Laboratory parameters when the adverse event was diagnosed | Laboratory parameters after the adverse event has subsided |
|---|---|---|---|
| Neutropaenia | | Neutrophil level | |
| Anaemia | Haemoglobin (Hb) level | | |
| Peripheral neuropathy | Pre-existing peripheral neuropathy – specify grade | Grade | |
| Serious skin reaction | | Grade | |
| Transaminitis/hepatitis | Alanine aminotransferase (ALT) level | | |
| Pancreatitis | | Amylase (amy) level | |
| Symptomatic hyperlactaemia/lactic acidosis | | Lactate, bicarbonate/$CO_2$, anion gap, pH | |
| Renal impairment | Creatinine clearance | | |

### 4. REQUEST

The ART/Medical Managers at each site must ensure that this circular is brought to the attention of all stakeholders.

_____ _____

**MR C. B. SHABALALA** **DATE**
**CHIEF TECHNICAL ADVISOR**
**PHARMACEUTICAL POLICY AND SYSTEMS DEVELOPMENT**
**DEPARTMENT OF HEALTH**
**KWAZULU-NATAL**

**SOP 1. Reporting Serious and Unusual Adverse Events in Patients on HAART**

HEALTH
KwaZulu-Natal

## STANDARD OPERATING PROCEDURE FOR:

# 1. REPORTING SERIOUS AND UNUSUAL ADVERSE EVENTS IN PATIENTS ON HAART

## Objective

- To outline the correct procedures to be followed when recording and screening adverse events.

## Responsibility

- District Manager
- District Pharmacy Manager
- Hospital Manager
- Medical Manager
- ARV ProgrammeProgramme Manager at ART site.
- Pharmacy Manager
- Antiretroviral Pharmacist

## Legislative Prescript

- Public Finance Management Act (1/1999).
- Pharmacy Act 53 of 1974 as amended.
- Medicines and Related Substances Act 101 of 1965 as amended.
- Comprehensive Plan for the Care, Management and Treatment of HIV and AIDS for South Africa.
- Clinical Guidelines for the Management of HIV/AIDs in adults and Paediatrics, 2010 National Strategic Plan (2007-2011)
- Nursing Act 33 of 2005 as amended


## STANDARD OPERATING PROCEDURE FOR:

# 1. REPORTING SERIOUS AND UNUSUAL ADVERSE EVENTS IN PATIENTS ON HAART

**Principles**

- Increasing access to antiretroviral therapy is an imperative component of the Antiretroviral ProgrammeProgramme; however, the safety associated with the use of these drugs must be also be prioritised.
- Pharmacovigilance/drug safety is an integral component of the monitoring and evaluation of the Antiretroviral ProgrammeProgramme.
- The National Strategic Plan (2007–2011) identifies research, monitoring, and evaluation as the third priority. According to the National Strategic Plan (2007–2011), there is an urgent need to "strengthen the active surveillance, reporting and analysis of adverse events in facilities providing ART".
- The above statement highlights the need for the correct recording and reporting of adverse drug events associated with HAART.

An **adverse drug reaction** (ADR) is a response to a drug which is noxious and unintended (abbreviated WHO definition).

***Suspected* adverse events** are events that occur in patients where the contribution of the patient's medication in causing the event cannot be ruled out.

This document provides you with guidance on how to report adverse events in patients on antiretroviral therapy, the procedures to be followed when requesting authority to switch antiretrovirals due to adverse events, and the screening of adverse event forms.

**What should be reported:**

- ***Serious*** or ***unusual*** adverse events that occur in patients on HAART and HIV-related medications. This includes events that require hospitalisation.

HEALTH
KwaZulu-Natal

## STANDARD OPERATING PROCEDURE FOR:

## 1. REPORTING SERIOUS AND UNUSUAL ADVERSE EVENTS IN PATIENTS ON HAART

- Events for which there is only a remote suspicion that the medication may have been responsible. This will allow the detection of any new or unusual reactions and drug interactions that may not yet be well understood/documented.
- Special areas of interest—e.g. drug abuse, pregnancy, lactation.
- Events occurring from overdose/medication error.
- Lack of efficacy or quality defects associated with antiretovirals.

**When in doubt as to whether or not to report, it is better to submit a report.**

Report events associated with **any** medicine (i.e. not just antiretroviral medicines).
This is a reporting system for **all** medicines being used in patients who are being treated with antiretroviral medicines.

**A serious adverse event is an event that:**

- results in death
- is life-threatening
- requires hospitalisation or prolongs hospitalisation
- results in permanent disability or incapacity
- is related to a congenital anomaly or birth defect
- warrants a change in one or more drugs

Medical judgement should be used when deciding if other situations are serious.

**Adverse events** that should be reported are specified in Tables 1 and 2.

Exposures to antiretroviral medicines during **pregnancy** should be reported as soon as possible, so that the pregnancy/baby can be followed up.

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## STANDARD OPERATING PROCEDURE FOR:

# 1. REPORTING SERIOUS AND UNUSUAL ADVERSE EVENTS IN PATIENTS ON HAART

**What should not be reported**:

Immune reconstitution phenomena (the patient's condition actually deteriorates after the initiation of ARVs), which are indirectly caused by antiretrovirals, do not need to be reported.

**The ADR/request for change in regimen/ARV form should be completed to**:

- Report an adverse drug reaction
- Request for authority to change regimen/antiretroviral

**Strategies to ensure that the form is completed:**

If an ADR is suspected, the attending doctor must ensure that an ADR form is placed in the patient's folder.

**This form can be completed when the ADR has been treated, and subsequently when the proposed new regimen has been decided.**

## SOP 2. Completion of the Adverse Event Reporting Form

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### STANDARD OPERATING PROCEDURE FOR:

### 2. THE COMPLETION OF THE ADVERSE EVENT REPORTING FORM

**Mandatory Completion of the Adverse Event Reporting Form**

The most recent version of the form "Serious Adverse Events for Antiretrovirals and Request for Authority to Switch Antiretroviral Drugs/Regimens must be completed by the prescriber on diagnosis of an adverse drug event. The following fields must be completed on the form:

1. Reason for report: circle the required option
2. Demographic data: name, identity number, weight, height, gender, pregnancy status
3. Medication history:
   - Antiretroviral drug/dosing frequency
   - Dates started and stopped
   - Number of months on HAART
   - Concomitant medication and disease conditions, dates started and stopped, number of months on treatment
4. Adverse event:
   - Tick the appropriate event as indicated in Tables 1 and 2, specifying the relevant laboratory parameters as well.
   - Assess drug interactions in accordance with Table 3.
5. Laboratory markers:
   - Serum creatinine clearance – to be indicated for all patients requiring tenofovir. (Tenofovir is contraindicated in patients with a serum creatinine < 50 mL/min.)
   - Most recent viral load to be indicated for all patients requiring a regimen change.
6. Outcome: circle the appropriate option
7. Proposed new regimen: indicate all the antiretrovirals, doses, and dosing frequencies
8. Details of reporter/pharmacist: names and cell phone numbers of the prescriber and pharmacist must be supplied.

## SOP 3. Requesting Authority to Switch Antiretrovirals due to Adverse Events/Screening of Adverse Event Forms

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### STANDARD OPERATING PROCEDURE FOR:

### 3. REQUESTING AUTHORITY TO SWITCH ANTIRETROVIRALS DUE TO ADVERSE EVENTS/SCREENING OF ADVERSE EVENT FORMS

**Screening Process**

- The pharmacist must refer to Tables 1, 2, and 3, when screening forms. In addition, it is the responsibility of the pharmacist to ensure that all the relevant information fields on the form, has been completed by the prescriber.
- Once the evaluation is completed by the pharmacist, and the pharmacist is comfortable that all the relevant information has been indicated on the form, the pharmacist may proceed to dispense the medication.
- The pharmacist must tick the “dispensed” column, indicate the date and sign the form.
- The pharmacist that is evaluating the form must indicate their name (clearly in block capital) and sign the form.
- If the evaluating pharmacist dispenses the medication, in the absence of information indicated in Table 1 and 2, the evaluating pharmacist and pharmacy manager will be accountable for their actions.

**Incomplete Forms**

- Incomplete forms must not be processed by the evaluating Pharmacist and must be sent back to the prescriber for completion of the relevant fields.
- The Pharmacist must tick the “not dispensed” column, and indicate the reasons for “not dispensing” under comment.

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KwaZulu-Natal

## STANDARD OPERATING PROCEDURE FOR:

### 3. REQUESTING AUTHORITY TO SWITCH ANTIRETROVIRALS DUE TO ADVERSE EVENTS/SCREENING OF ADVERSE EVENT FORMS

**Recording Adverse Drug Events**

- The pharmacy must fax the forms to **Pharmaceutical Policy and Systems Development**, Head Office, once a week. The name of the institution should be clearly indicated.
- Each request or batch of requests must be sent with a batch tracking sheet as the cover sheet.
- Each batch tracking sheet must be given a unique "batch number" in the format "Hospital Abbreviation dd/mm/yy-"sheet number" – e.g. IALCH 01/04/09-1.
- Each individual request form should be annotated with the batch number and corresponding line number, in proper format, from the batch tracking sheet Pharmaceutical Policy and Systems Development will record all adverse drug events.
- Each "Serious Adverse Drug Events for Antiretrovirals and Request for Authority to Switch Antiretroviral Drugs for Switching Regimens/Regimen 2 Drugs on a Named-Patient Basis" (Annexure 1) form will be allocated a record number that will be unique to that particular request (patient and adverse drug event).
- Adverse drug events which have been processed by the hospital pharmacist will be evaluated by Pharmaceutical Policy and Systems Development. Reports will be forwarded on to pharmacy managers for review and comment. Reports will also be published on the intranet, indicating the number of completed and incomplete reports received for each site.
- The captured forms will **not** be faxed back to the relevant institution. The forms will be stored at Capital Towers and will be used for audit purposes.
- The pharmacy must maintain a manual or computer record of all requests and record numbers.

HEALTH
KwaZulu-Natal

## STANDARD OPERATING PROCEDURE FOR:

### 3. REQUESTING AUTHORITY TO SWITCH ANTIRETROVIRALS DUE TO ADVERSE EVENTS/SCREENING OF ADVERSE EVENT FORMS

Requests must not be re-faxed unless Pharmaceutical Policy and Systems Development is advised and the batch tracking sheet is clearly endorsed.

**Referrals**

If a patient is transferred to another institution for continuation of treatment, the relevant details (current regimen/changed regimen) must be endorsed on the transfer letter. However, there is no need to complete a form when patients are transferred.

**Annexures**

**Annexure 1.** Reporting Form – Serious Adverse Events for Antiretrovirals and Request for Authority to Switch Antiretroviral Drugs/Regimens

**Tables**

Table 1. Classification of Adverse Events in Accordance with Laboratory Parameters and Possible Causative Agent
Table 2. Case Definitions for Adverse Events
Table 3. Drug Interactions

## Serious Events Reporting Form

| **SERIOUS ADVERSE EVENTS REPORTING FORM FOR ARVS & REQUEST FOR AUTHORITY TO SWITCH ARV DRUGS ON A NAMED-PATIENT BASIS** | | | | |
|---|---|---|---|---|
| From: | | Fax no.: | | Date: |
| **REASON FOR REPORT: (PLEASE CIRCLE THE CORRECT OPTION)** | | | | |
| Death due to ADR | Regimen change due to ADR | | Regimen change due to treatment failure | |
| Patient's name and surname: | | ID no.: | | Gender: |
| Weight: | Height: | Pregnant: Y | N | Race: |

**MEDICATION HISTORY: INDICATE ALL MEDICATIONS THAT THE PATIENT IS CURRENTLY TAKING (circle the suspected medicine and provide brand names where available)**

| **Antiretroviral drug/dosing frequency (circle the possible causative agent)** | Date started | Date stopped | Number of months on HAART |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**CONCOMITANT DISEASE CONDITIONS**

| Concomitant medication (doses/dosing frequency) (e.g., anti-TB meds, antidiabetic medicines/antihypertensives, traditional/complementary) | Months on treatment | Date started | Date stopped | Concomitant diseases/conditions |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

**ADVERSE EVENT (INDICATE WITH A TICK AND COMPLETE THE CORRESPONDING LABORATORY VALUES)**

| **Adverse drug event (tick)** | **Laboratory values on diagnosis of the event/clinical investigations** | **Adverse drug event (tick)** | **Laboratory values on diagnosis of the event/clinical investigations** |
|---|---|---|---|
| **Breast disorders/ reproductive system** | | **Hepatic** | |
| Gynaecomastia | | Hepatitis | ALT level: |
| Sexual dysfunction | | Hepatic steatosis | ALT level: |

| | | | |
|---|---|---|---|
| **Bone disorders** | | Hepatic encephalopathy | ALT level: |
| Osteopaenia/osteoporosis | Bone-mass density value | Pancreatitis | Amylase level: |
| **Cardiovascular** | | **Metabolic** | |
| Arrhythmia | Confirmatory ECG [Y] [N] | Lactic acidosis | Lactate level: HCO3: |
| Coronary artery bypass/graft | Cardiac enzymes: | | Anion gap: pH: |
| Coronary angioplasty | | Symptomatic hyperlactaemia | Lactate level: HCO3: |
| Myocardial infarction | | | Anion gap: pH: |
| **CNS effects** | | Hypertriglyceridaemia | LDL: HDL: |
| Agitation | | | Triglycerides level: |
| Depression | | Lipodystrophy | |
| Disturbing dreams | | Lipoatrophy | |
| Dizziness | | Diabetes mellitus | Blood glucose level: |
| Impaired concentration | | Hypertension | BP: |
| Sleep disturbances | | Stroke | BP: |
| **Dermatological** | | **Neurological** | |
| Serious skin reactions | Grade: | Peripheral neuropathy | Grade: |
| Stevens Johnson syndrome | | **Renal** | |
| **Haematological** | | Nephrotoxicity | |
| Anaemia | Hb level: | Renal failure | Creatinine clearance: |
| Neutropaenia | Neutrophil count: | **Other events (specify)** | |
| **Gastrointestinal** | | | |
| Nausea | | | |
| Vomiting | | | |
| Diarrhoea | | | |

**LABORATORY MARKERS**

| | | | |
|---|---|---|---|
| Serum creatinine clearance: | Most recent viral load: | Most recent CD4 cell count: | Other (specify): |

**TREATMENT FAILURE**

| | | | |
|---|---|---|---|
| Preceding data: | Date: | CD4 count: | Viral load: |
| Current data: | Date: | CD4 count: | Viral load: |
| Date when stepped-up adherence initiated: | | Adherence rate (%) | |

**OUTCOME (must be circled)**

| | | | | | |
|---|---|---|---|---|---|
| Death | Not yet recovered | Recovered | Recovered without changing treatment | Permanent damage | Unknown |

| **PROPOSED NEW REGIMEN: INDICATE ALL ARVS THAT THE PATIENT WILL BE TAKING (to be completed by prescriber and pharmacist)** | | | | | |
|---|---|---|---|---|---|
| **Antiretroviral drug/doses and dosing frequency** | | | | **Name** **Cell Mobile number** | **Signature** |
| | | | Prescriber | | |
| | | | Consultant | | |
| | | | Pharmacist | | |
| | | | | | |
| FOR PHARMACY USE | Not Approved | Approved | Date | Signature: | |
| FOR HEAD OFFICE USE | Not Approved | Approved | Date | Signature: | Record number: |