Implementing an TB/HIV Active Surveillance System in Swaziland

Khontile Kunene

November 2016

USAID
FROM THE AMERICAN PEOPLE

SIAPS
Systems for Improved Access to Pharmaceuticals and Services

This document is made possible by the generous support of the American people through the U.S. Agency for International Development (USAID) Cooperative Agreement Number AID-OAA-A-11-00021. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

About SIAPS

The Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SIAPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

Recommended Citation

Kunene, K.N., *Implementing a TB/HIV Active Surveillance System in Swaziland*, November 2016. Submitted to the U.S. Agency for International Development by the Systems for Improved Access to Pharmaceuticals Services (SIAPS) Program. Arlington, VA: Management Sciences for Health.

Key Words

Pharmacovigilance, active adverse drug event surveillance, patient safety monitoring

Systems for Improved Access to Pharmaceuticals and Services
Pharmaceutical & Health Technologies Group
Management Sciences for Health
4301 North Fairfax Drive, Suite 400
Arlington, VA 22203 USA
Telephone: 703.524.6575
Fax: 703.524.7898

CONTENTS

Abbreviations and Acronyms iv

Introduction 1
Background 1
Approach 2
Rationale for Monitoring Medicine Safety in Swaziland 3

Implementing an Active Surveillance System for TB/HIV in Swaziland 5

Key Findings 6
Data Analysis 6
Supportive Supervisory Visits 12
Data Dissemination 14
Challenges at NPVU 14

Information Use and Lessons Learned 15
Review of Data Collection Tool 15
Review SSASSA and DCAT to Align to Changes in Form 15
Strengthen Supportive Visits and Visibility at Facilities 15
Resensitization Meetings 15
Risk Minimization Strategies 15
National Guideline Influence 16
Ministry of Health Decisions 16
PViMS Development 16

Conclusion 17

Annex A. Selection of Abstracts and Presented Work 18

ABBREVIATIONS AND ACRONYMS

ADE	adverse drug event
ADR	adverse drug reaction
AE	adverse event
ART	antiretroviral treatment
ARV	antiretroviral medicines
CNS	central nervous system
DCAT	data collation and analysis tool
DR-TB	drug resistant tuberculosis
HAART	highly-active antiretroviral therapy
HIV	human immunodeficiency virus
MSH	Management Sciences for Health
MOH	Ministry of Health
NPVU	National Pharmacovigilance Unit
PV	pharmacovigilance
PViMS	Pharmacovigilance Information Management System
SIAPS	Systems for Improved Access to Pharmaceuticals and Services (Program)
SSASSA	Sentinel Site-based Active Surveillance System for Antiretroviral and Anti-TB
SPS	Strengthening Pharmaceutical Systems (Program)
TB	tuberculosis
USAID	US Agency for International Development
WHO	World Health Organization

INTRODUCTION

Background

Swaziland has an HIV prevalence of 26% and has one of the highest tuberculosis (TB) burdens globally[1]. The TB incidence rate is 733/100,000, and the drug-resistant TB (DR-TB) prevalence is 7.7% and 33.7% among new and previously treated patients, respectively. The HIV/TB co-infection rate is around 80%, and 66% of TB/HIV co-infected patients are receiving treatment for both diseases[2]. As new essential medicines for HIV/AIDS and DR-TB are being introduced and used in large quantities in resource-constrained countries like Swaziland, the importance of monitoring adverse effects and assuring therapeutic effectiveness is increasing. The burden of adverse drug events (AEs) from poor product quality, adverse drug reactions (ADRs), and medication errors can prevent these new medicines from benefitting users to the fullest potential, as well as pose great challenges for health care systems.

Inadequate monitoring and management of adverse drug events (ADEs) has a negative impact on morbidity and mortality rates. It also increases the burden of disease management on the health system due to both direct cost and indirect costs associated with ADEs, including:

- Loss of confidence in the health system
- Economic loss to the pharmaceutical industry
- Non-adherence to treatment
- Development of drug resistance

A well-integrated, comprehensive pharmacovigilance (PV) system is necessary to reduce the risks associated with ADEs, improve patient management, and provide evidence-based information to inform treatment decisions and promote rational medicine use. Nonetheless, many developing countries still do not have the structures, systems, or resources in place to support PV and medicines safety activities. They also often lack unbiased, evidence-based information to help guide regulatory and patient safety decisions.[3,4]

In addition to passive surveillance, sentinel site-based active surveillance is a key approach to strengthening a country's PV and medicines safety system. Although about 70% of the world's patients on ARVs live in Africa, the continent accounts for just 6% of the ARV-related ADRs reported worldwide.[5] A study on PV in sub-Saharan Africa conducted by the USAID-funded Strengthening Pharmaceutical Systems (SPS) Program in 2011 similarly found that fewer than 30% of the 42 African countries surveyed had legal mandates for post-market safety surveillance

[1] Centre for Disease Control and Prevention. (2013). *Factsheet: CDC in Swaziland.* Centre for Global Health, Atlanta.
[2] Strategic Information Department. (2012). *TB Programme Annual Report 2012*. Ministry of Health, Mbabane.
[3] Olsson, S., ed. 1999. *National Pharmacovigilance Systems*. 2nd ed. Uppsala: The Uppsala Monitoring Centre.
[4] Hughes, M. L., C. M. C. Whittlesea, and D. K. Luscombe. 2002. Review of national spontaneous reporting schemes: strengths and weaknesses. *Adverse Drug Reactions and Toxicological Reviews* 21:231–41.
[5] A Report of the Safety and Surveillance Working Group. (2012). Bill & Melinda Gates Foundation.

reporting[6], meaning that health care workers and marketing approval holders are not compelled to monitor patient safety and report ADRs. Given limited resources and legal authority, as well as lacking PV practices, ADR reporting rates remain low in many developing countries. For this reason, the Swaziland Ministry of Health (MOH) introduced an active surveillance system to complement the existing passive surveillance system (in which there were less than 30 ADRs reported per annum for all disease conditions).

Approach

The Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program supported the MOH in mobilizing key stakeholders from the Swaziland National AIDS Program and the National Tuberculosis Control Program to introduce and implement an active surveillance system for patients on ARVs and anti-TB treatment. SIAPS provided technical assistance to MOH's National Pharmacovigilance Unit (NPVU) to develop the protocol and tools to implement the system, as well as to develop a system for recruiting patients at the HIV and TB sites.

The technical assistance also included the development and implementation of, as well as capacity-building in, electronic tools deployed at the central and facility levels. The Sentinel Site-based Active Surveillance System for Antiretroviral and Anti-TB (SSASSA) is the electronic database that is used to report the ADEs at health facility level, and the data collation and analysis tool (DCAT) system is used for data analysis at the NPVU level. The system documents and quantifies incidence rates of AEs associated with ARVs and anti-TB medicines, and determines risk factors at selected sentinel sites. The HIV/TB active surveillance system was officially launched in May 2013, and subsequently implemented at five hospitals. The system was piloted as a two-year prospective observational cohort study whereby:

- Clinicians in the health facilities enroll treatment-naïve HIV patients and TB patients starting a new regimen. Clinicians follow up with these patients at each visit to determine if they experience any ADEs.

- Relevant patient information is captured in the system (SSASSA) by data clerks, from the paper-based patient files.

- Data is collected monthly and analyzed centrally using DCAT.

A systems approach was used to strengthen PV in Swaziland and establish the active PV system (Figure 1). This approach promotes the intersection of people, functions, and structures at all levels of the health system to arrive at local decisions that prevent medicine-related problems and

[6] Strengthening Pharmaceutical Systems (SPS) Program, *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance*. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. (Arlington, VA: Management Sciences for Health, 2011) Available at: http://apps.who.int/medicinedocs/en/d/Js19152en/

reduce associated morbidity and mortality.[7] This approach highlights the need for building capacity to carry out both passive and active surveillance methods, and highlights the complementary nature of these approaches in ensuring a robust system for addressing medicines safety issues.

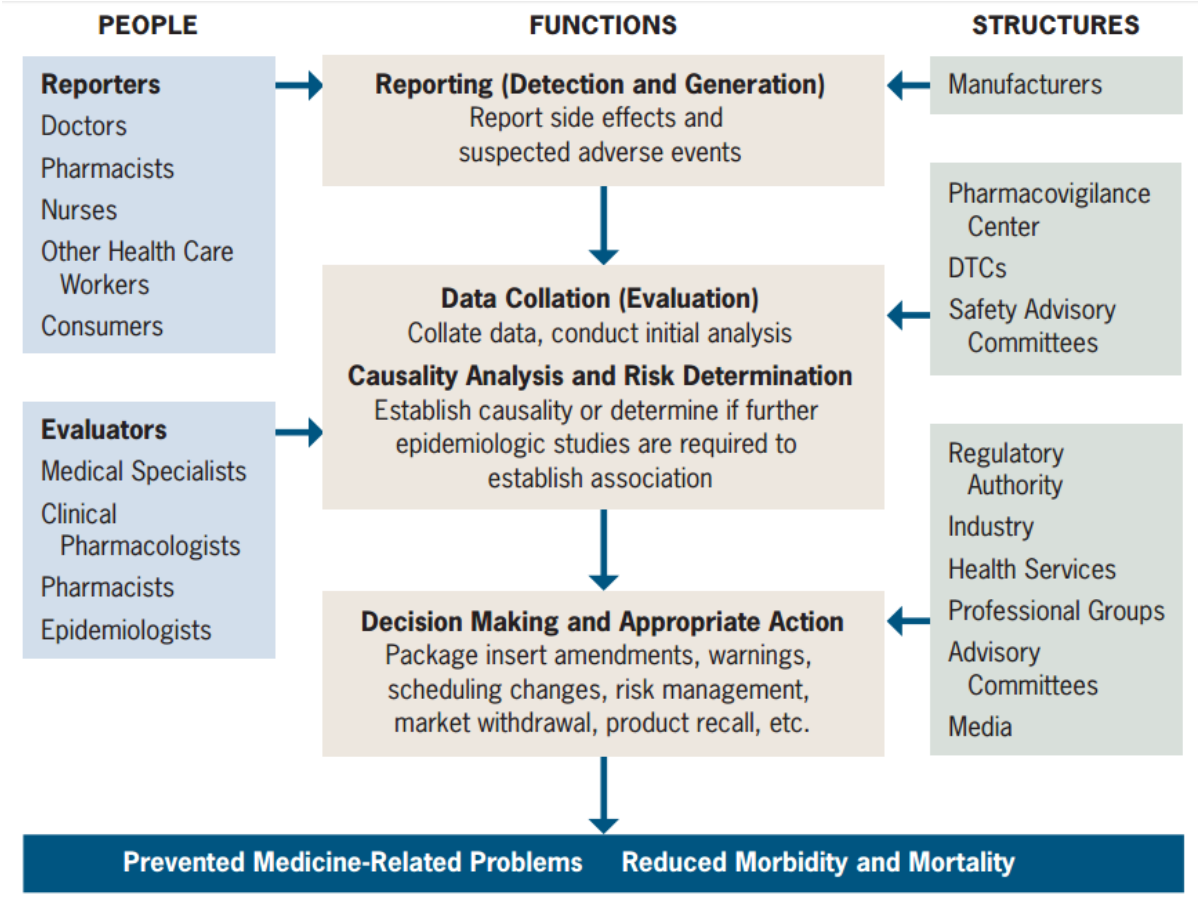


Figure 1: PV framework: relating people, functions, structures, and expected outcome and impact.[8]

Rationale for Monitoring Medicine Safety in Swaziland

There are currently 172,871 (August 2016) people on antiretrovirals (ARVs) in Swaziland. The revisions of the highly active antiretroviral therapy (HAART) eligibility criteria[9] will lead to an

[7] Strengthening Pharmaceutical Systems (SPS). *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective*. Submitted to the U.S. Agency for International Development by the SPS Program. (Arlington, VA: Management Sciences for Health, 2009). Available at: http://apps.who.int/medicinedocs/documents/s18813en/s18813en.pdf

[8] Ibid, 6.

[9] Criteria were revised to take into account people with CD4 count of <500 (changed from CD4 count of <350) and life-long treatment of all people (changed from lifelong treatment for HIV+ pregnant women, regardless of CD4 count)

increase in these numbers. Swaziland also has a very high TB incidence rate (733 per 100,000 people)[10], and TB is the leading killer of HIV-positive people. In the absence of a comprehensive PV system in Swaziland, little was known about the epidemiology of the toxicity or risk-benefit profiles of ARVs and TB medicines in the Swaziland population. Drug-related morbidity and mortality in patients on ARVs, TB, and DR-TB medicines—especially those co-infected and who are on treatment for both—had not been quantified and posed significant challenges to enhancing treatment outcomes.

Given that ADRs are one of the most important factors in determining patient adherence, it is important to monitor, manage, and prevent AEs. Although the SIAPS predecessor program, SPS, supported the implementation of a passive surveillance system and the development of accompanying tools, the passive surveillance system only resulted in about 30 ADRs reported per annum. This prompted the implementation of a complementary active surveillance system to improve patient safety monitoring and ADR reporting rates.

Furthermore, the introduction of new medicines for DR-TB (bedaquiline and delamanid) and shorter DR-TB regimens (in 2015 and 2016, respectively) necessitated that countries have active surveillance systems. Swaziland's establishment of such a system helped eliminate delays in accessing these new medicines and regimens.

[10] WHO-CIDA. *Intensifying TB Case Detection: Swaziland Update 2012*. (WHO-CIDA Global Initiative: 2012) Available at: http://who.int/tb/Swazilandfactsheet_CIDA_Oct2012.pdf

IMPLEMENTING AN ACTIVE SURVEILLANCE SYSTEM FOR TB/HIV IN SWAZILAND

The MOH, supported by SIAPS, established a two-year pilot active surveillance system to monitor the safety, quality and effectiveness of ARVs and anti-TB medicines at selected sentinel sites in Swaziland, starting in June 2013. The goal of this system was to develop, implement, and demonstrate the feasibility of a practical and sustainable PV system at the local level, which could later be scaled up throughout the country. The system was also meant to facilitate capacity building for future active surveillance of other high risk medicines, similar settings, and populations. The results from this activity will help inform future revisions of in-country treatment guidelines and regulatory decisions. The active surveillance system systematically documents and quantifies the incidence rate of AEs associated with ARVs and TB medicines. In addition, the active surveillance system generates local data to provide better estimates of risk-benefit profiles and help prevent and minimize such risks to patients on treatment.

The active surveillance system was implemented at the following five sentinel sites:

- Good Shepherd Hospital
- Hlathikhulu Government Hospital
- Mbabane Government Hospital
- National TB Hospital
- Raleigh Fitkin Memorial (RFM) Hospital

Following the end of the pilot phase, the MOH rolled out the active surveillance system to two additional facilities in August 2015, namely; Matsapha Comprehensive Care Clinic (MSF Matsapha) and AIDS Health Care Foundation (AHF) clinic. In addition to the rates and types of AEs, the SSASSA system allows for data tracking and reporting on adherence levels, the severity of AEs, patient demographics, and reasons for switching regimens.

SIAPS supports the NPVU in conducting monthly data collection from the five sentinel sites, as well as in bi-monthly supportive supervisory visits and the quarterly analysis and dissemination of PV data at the national and regional levels. The supportive supervisory visits also serve as part of the capacity-building activities.

KEY FINDINGS

Data Analysis

The active surveillance data presented in the following table and graphs represents the results for analysis of data recorded from June 1, 2013 to September 30, 2016. The data analysis shows that 4210 patients were enrolled on the active surveillance system between May 2013 and September 2016, and 1224 ADEs were reported (Table 1).

Table 1: Patients enrolled at the 7 sentinel sites

Facility	# of Patients	# of ADEs
MSF - Matsapha	1447	19
National TB Hospital	311	520
RFM Hospital	689	268
Good Shepherd Hospital	518	235
AHF Clinic	261	17
Hlathikhulu Government Hospital	500	21
Mbabane Government Hospital	484	144
Total	**4210**	**1224**

Gender and Age Distribution of Patients Reporting ADEs

Of patients enrolled in the active system who reported ADEs, 58% were female and 42% were male. This is in line with the general enrollment percentages: 44% males and 56% females. Throughout the reporting periods, the reporting rate has consistently remained marginally lower for males than females. The age distribution of the patients who reported ADEs is represented in Figure 2.

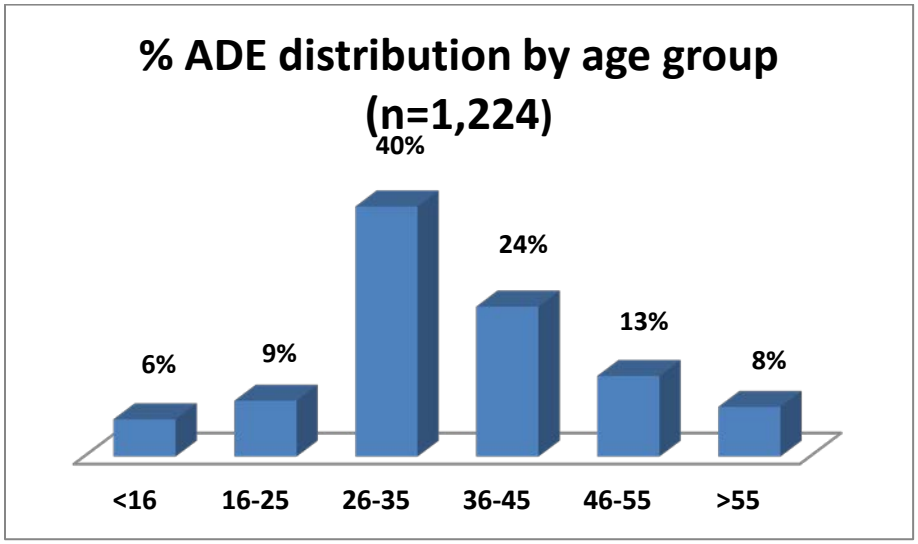


Figure 2: Age distribution of patients reporting ADEs (n=1,224)

Summary of ADEs

Of the enrolled patients, 76% are using ARVs and 24% are using anti-TB medicines. However, 58% of the ADEs were from patients on TB medicines, while 42% were from patients on ARVs. The most prevalent ADEs among all enrolled patients were gastrointestinal effects and peripheral neuropathy, at 17%, followed by central nervous system (CNS) effects, at 11%. A selection of the top reported ADEs for all patients are shown in Figure 3.

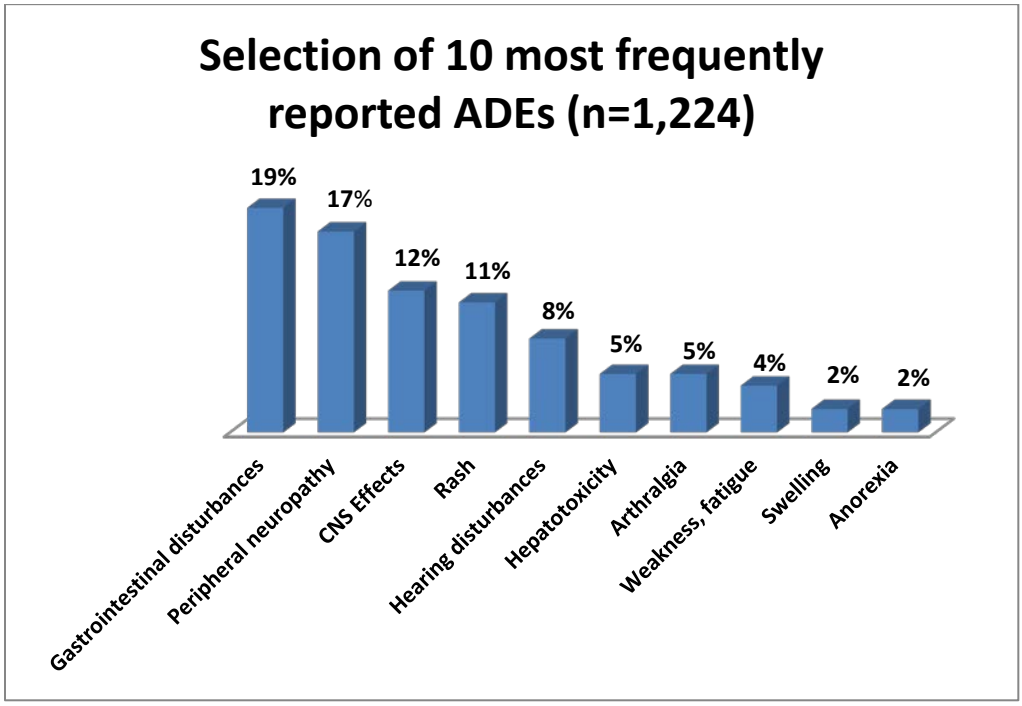


Figure 3: Selection of top 10 ADEs reported by patients on ARVs and TB medicines (n=1,224)

ARV Focus

The leading complaint among patients on ARVs was gastrointestinal disturbances (including nausea, vomiting, diarrhea, and gastrointestinal pain) at 20%. This was followed by rash and peripheral neuropathy, at 14%. CNS effects decreased from 15% to 9% in this reporting period (compared to the last reporting period), while hepatotoxicity reports decreased from 9% to 8%. Gynecomastia increased from 0.3% in the last reporting period, to 4%, which could be due to increased awareness among clinicians as the last newsletter (used to disseminate PV findings) included an alert to health care workers on the increasing incidence of efavirenz-induced gynecomastia, as well as information on how to identify and manage of this condition.

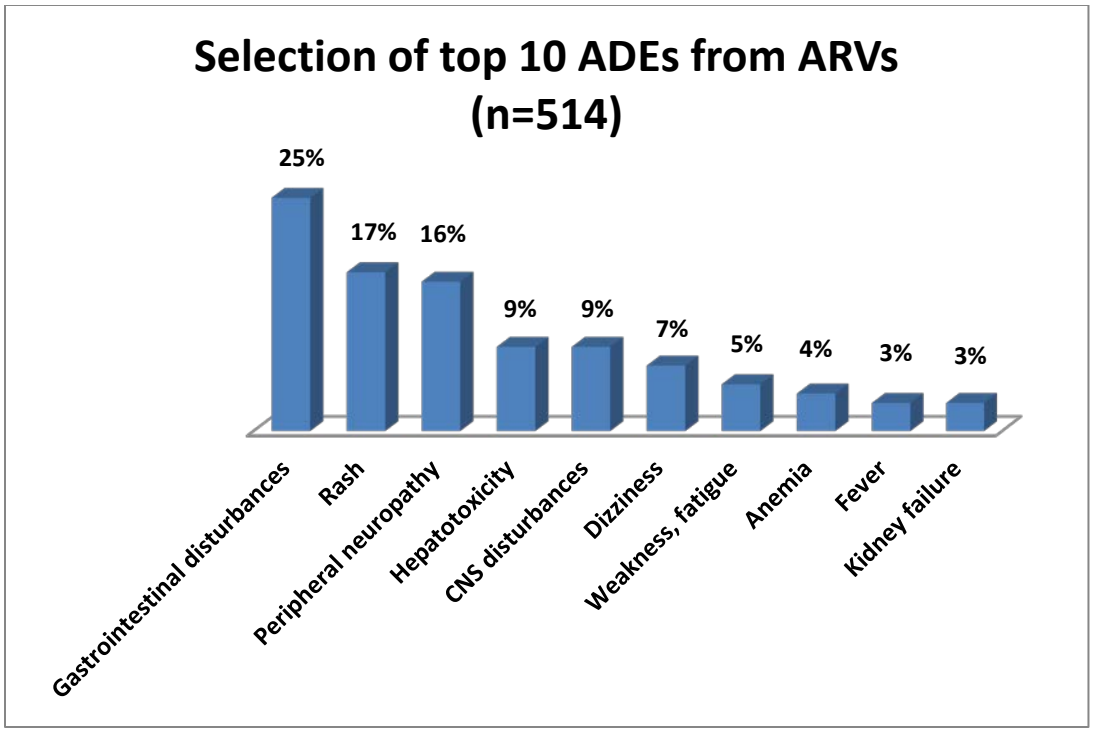


Figure 4: Selection of top 10 ADEs reported by patients on ARVs (n=514)

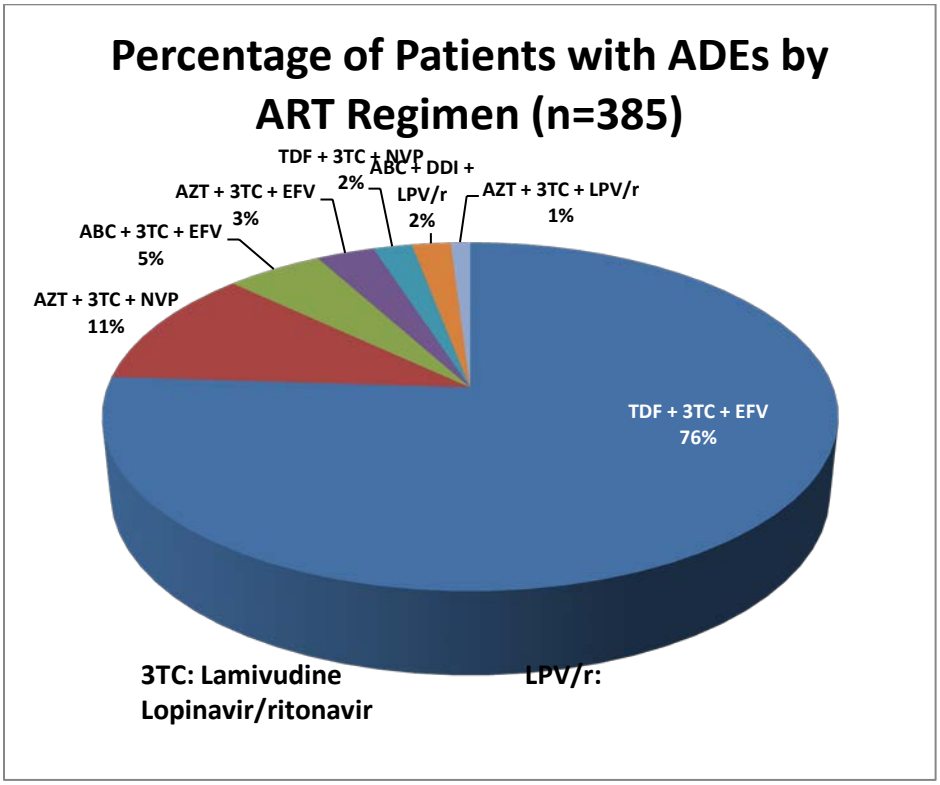


Figure 5: Percentage of patients on ARVs reporting ADEs by regimen (n=514)

The majority of patients reporting ADEs were on tenofovir/lamivudine/efavirenz (TDF + 3TC + EFV), which is to be expected as close to 80% of the patients on ARVs are on this first-line regimen.

TB Medicines Focus

For patients on anti-TB medicines, the most frequently reported ADEs were peripheral neuropathy (34%) and gastrointestinal disturbances (14%) for drug-susceptible TB patients (Figure 6), and hearing disturbances (19%) and gastrointestinal disturbances (14%) for patients on DR-TB treatment (Figure 7). Injectable-containing regimens account for most ADE reports (54%), followed by the drug-susceptible TB regimen of rifampicin/isoniazid/pyrazinamide/ ethambutol, which accounted for 21% of the reported ADEs (Figure 8).

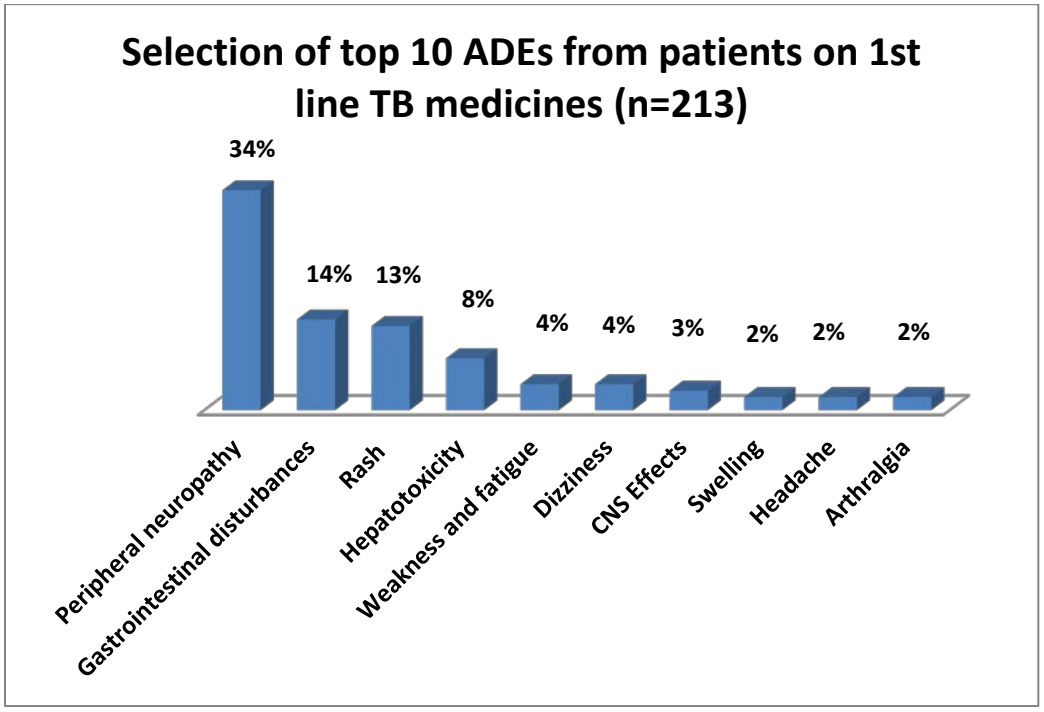


Figure 6: Selection of top 10 ADEs reported by patients on first-line TB medicines (n=213)

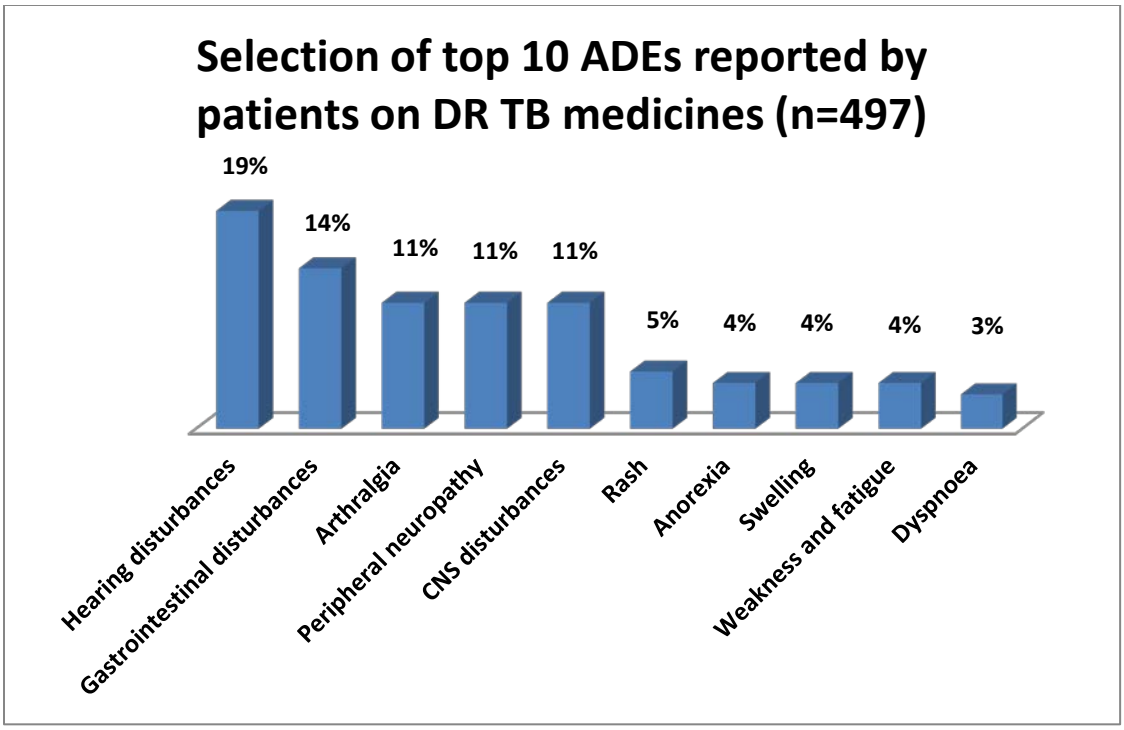


Figure 7: Selection of top 10 ADEs reported by patients on DR-TB medicines (n=497)

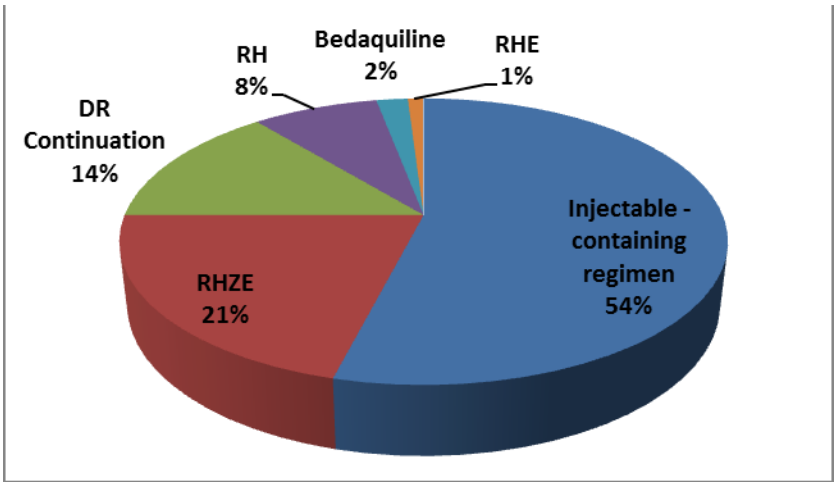


Figure 8: Percentage of patients on TB medicines reporting ADEs by regimen (n=710)

Severity Grading

In terms of severity, the majority (54%) of the ADEs were mild at Grade 1 severity, as can be seen in Figure 9. The ADE grades are defined as follows:

- Grade 1: Mild ADE
- Grade 2: Moderate ADE
- Grade 3: Severe ADE

- Grade 4: Life-threatening or disabling ADE
- Grade 5: Death related to ADE

The most prevalent amongst the ADEs with severity of grades 3-5 were hearing disturbances (20%), gastrointestinal disturbances (14%) and rash (11%).

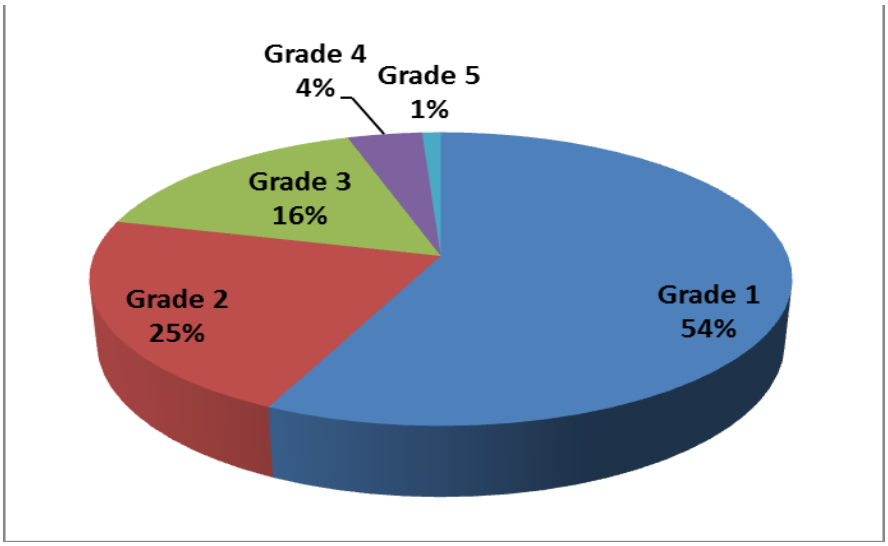


Figure 9: Percentage of ADEs by severity for ARVs and TB medicines (n=1,224)

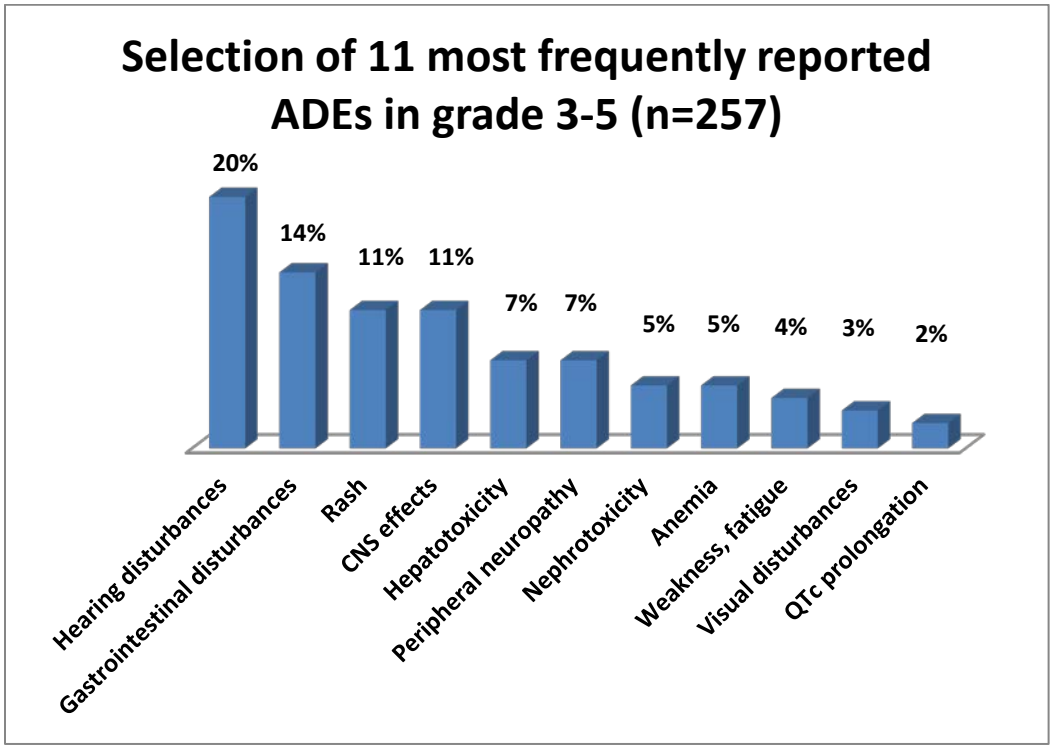


Figure 10: Selection of 11 most frequently reported ADEs in grades 3-5 (n=257)

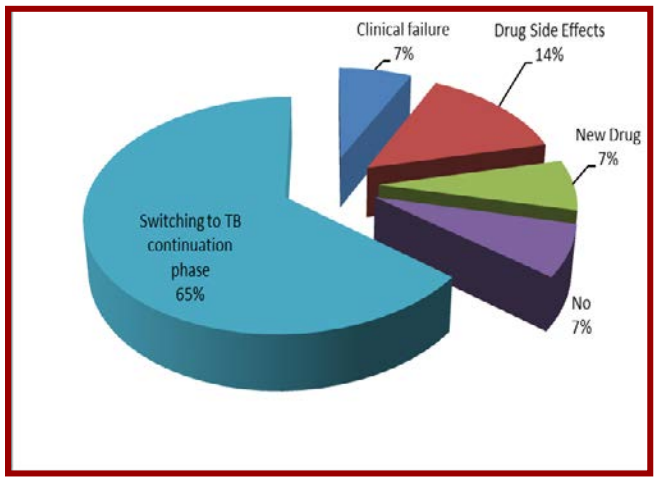


Figure 11: Reasons for regimen change

ADEs accounted for a change in 14% of all regimen changes and clinical failure accounted for 7% of the changes (Figure 11). As expected, the most common reason for changing regimen amongst TB patients was the change to the continuation phase following consecutive negative sputum results, which is in accordance with the treatment guidelines.

Supportive Supervisory Visits

Supervisory visits are conducted by the NPVU on a monthly basis to collect data and to determine if the facilities need any technical support. For new facilities, and for facilities whose data indicates reporting issues, the supportive supervisory visits are conducted every two weeks until all issues are resolved. The visits were conducted every two months in 2013, but this changed to more frequent visits in June 2014 after some of the problems highlighted below were noted.

The supportive visits and data analysis revealed that the patient enrollment rates were below what was expected. Targeted supportive visits were then conducted to identify bottle necks and explore possible solutions to the poor enrolment rates by clinicians and non-entry of data by data clerks. The following issues were identified in the sentinel sites, and were found to be common among all the sites:

- Human resource shortages
- SSASSA only installed on one computer, therefore only one person can capture data at a time
- Clinicians not enrolling patients as planned, due to some trained physicians leaving the facilities

Table 2 shows the critical site-specific issues and the solutions that were carried out to address them.

Table 2: Summary of major findings from supportive supervision visits

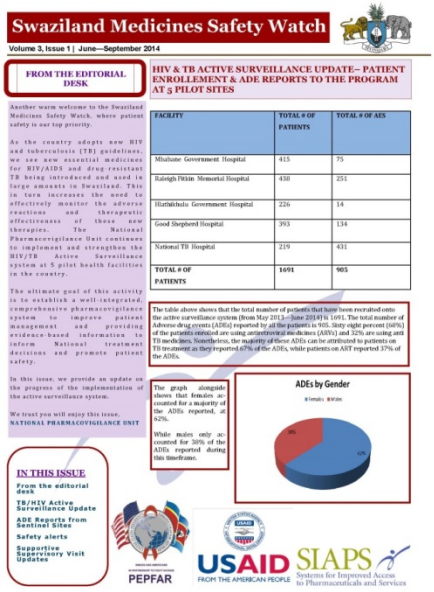
Issue	Causes	Interventions
Non-entry of data into SSASSA (despite presence of completed forms and new data to be entered)	Human resource constraints - Insufficient number of data clerks for work load - Data clerks attrition and remaining data clerks not competent on use of SSASSA	SIAPS engaged a data capturer to rotate among the facilities and assist in addressing issues of data entry back logs and to support capacity building initiatives for facility data clerks
		Conducted re-sensitization meetings and trainings for data entry staff members
Non-entry of data into SSASSA due to system problems	SSASSA being incompatible with operating system in health facility computers.	SIAPS provided technical assistance in updating facility computer operating systems and verification of versions across all facilities.
	SSASSA version incompatibilities (different versions at some facilities)	
	Replacement of servers leading to loss of SSASSA and data	SIAPS supported the re-deployment of database from NPVU back-ups
	SSASSA being deployed on only one computer meaning that only one person can enter data	SSASSA was deployed in multiple computers to enable another data clerk at the TB Unit who could assist in entering the data into SSASSA but was unable to do so because SSASSA was only in one computer.
	Data quality importation issues when importing SSASSA data onto DCAT for NPVU analysis	SSASSA version was updated to align fields that are mandatory for successful importation into DCAT.
		The new version was deployed to all facilities and all users trained on the necessary fields.
		DCAT was also reviewed to eliminate certain gaps identified during data analysis.
		Development of pharmacovigilance information system (PViMS) – a web-based system to eliminate data importation issues emanating from the use of different platforms.
Decreased recruitment and reporting rates	Attrition of trained clinical personnel	SIAPS supported the NPVU to conduct retrospective capturing of patient information to ensure that information on SSASSA was up-to-date and to improve enrolment rates
	ADR monitoring and reporting fatigue by clinicians	The following activities were conducted by the NPVU (supported by SIAPS): • Quarterly data feedback during facility meetings • Annual national stakeholder forum • Re-sensitization meetings for clinicians and data unit staff • Supportive supervision visits (at least bi-monthly, but more frequent when necessary)
	Move of focal staff member from health facility	
	Clinicians view reporting as an extra activity on top of their full schedules	
Slow TB enrollment and ADR monitoring and reporting	Lack of full-time TB doctors leading to few or no patients being enrolled (nurses were not comfortable with conducting the activity in the absence of a clinician)	Re-sensitization meetings conducted. ART clinicians requested to support TB units.
Data collection tool issues	Tool too lengthy (requiring more time)	The tool was revised and condensed, and adopted during a national stakeholder forum.
	Tool too bulky (resulting in thickening patient files)	

Data Dissemination

Newsletter

SIAPS supported the Ministry in the development of the *Medicines Safety Watch*, a quarterly newsletter designed to disseminate information on medicines safety (pictured).

Copies are printed and distributed to all health facilities, and electronic copies are mailed to all stakeholders.


Swaziland Medicines Safety Watch

Volume 3, Issue 1 | June—September 2014

FROM THE EDITORIAL DESK

HIV & TB ACTIVE SURVEILLANCE UPDATE– PATIENT ENROLLEMENT & ADE REPORTS TO THE PROGRAM AT 5 PILOT SITES

FACILITY	TOTAL # OF PATIENTS	TOTAL # OF AES
Mbabane Government Hospital	415	75
Raleigh Fitkin Memorial Hospital	438	251
Hlathikhulu Government Hospital	226	14
Good Shepherd Hospital	393	134
National TB Hospital	219	431
TOTAL # OF PATIENTS	1691	905

ADEs by Gender

IN THIS ISSUE

From the editorial desk

TB/HIV Active Surveillance Update

ADE Reports from Sentinel Sites

Safety alerts

Supportive Supervisory Visit Updates

PEPFAR

USAID FROM THE AMERICAN PEOPLE SIAPS Systems for Improved Access to Pharmaceuticals and Services

Facility-Level Data Dissemination

Facility-specific data is disseminated at each health facility on a quarterly basis.

Data Dissemination Stakeholder Forum

There is also an annual stakeholder data dissemination meeting to share findings and PV updates, as well as to chart a way forward in continually strengthening active surveillance implementation.

Conference Presentations

The findings on the medicines risk profiles have been shared at a number of national and international conferences. A selection of abstracts and presentations is included in Annex A.

Uppsala Monitoring Centre Database

SIAPS supported Swaziland in qualifying as a member of the WHO Programme for International Drug Monitoring administered by the Uppsala Monitoring Centre. Consequently, Swaziland qualified as a full member of this international drug safety monitoring network in June 2015. SIAPS continues to support the NPVU to upload Swaziland reports onto the database, Vigiflow.

Challenges at NPVU

The use of different platforms for the databases that were used at the facility level and by the NPVU resulted in some data not being imported into the data analysis system. The facility SSASSA system is based in Microsoft Access®, and the NPVU system (DCAT) is a Microsoft SQL application. Data quality issues meant that some data that did not meet DCAT standards would not be imported into DCAT, meaning that the numbers of patients and ADEs would be lower in DCAT than the numbers in SSASSA.

INFORMATION USE AND LESSONS LEARNED

Review of Data Collection Tool

Feedback from supportive supervision visits and national stakeholder meetings, and lessons learnt from data analysis by the NPVU were used to improve the data collection tool. A version control tracker was also introduced into the tool to ensure that all facilities use the most up-to-date version of the tool, and to more easily disseminate communications.

Review SSASSA and DCAT to Align to Changes in Form

Some of the lessons learnt from the use of SSASSA by health facilities and DCAT by the NPVU were used to improve the versions of SSASSA and DCAT that were initially deployed at the five facilities and the national level, respectively. Consequently, system bugs were fixed and a newer version re-deployed to the five facilities and to new facilities as they were added on.

Strengthen Supportive Visits and Visibility at Facilities

The presence of the NPVU, supported by the SIAPS team, was strengthened with bi-weekly visits by the supervisory team to any new sites and monthly visits to all sentinel sites. This was to maintain the momentum of the activity, and to enable the supervisory team to identify and respond quicker to issues at facility level.

Resensitization Meetings

There were re-sensitization meetings at all the sites to ensure that new personnel are familiar with the tools, thus addressing issues of staff turnover.

Risk Minimization Strategies

SIAPS used the lessons learned from the implementation of the active surveillance system to support the development of prescriber and public risk mitigation material. The findings have been used to revise treatment guidelines and develop job aids for health professionals and patients to facilitate the early identification and management of ADEs, and promote patient safety and adherence. This included the:

- Development of an ADE definition and severity grading job aid to facilitate the uniform identification and severity grading of ADEs so data was more consistent and accurate to enable quality decision-making by programmes and clinicians.

- Development of a reporting cascade job aid for health care workers.

- Development of ADE monitoring and reporting job aid for patients to encourage the reporting of ADEs.

National Guideline Influence

The data has been used to inform the following national decisions:

- The safety profile of DR-TB medicines and associated toxicities in the Swaziland population have been used to inform the revision of national programmatic management of drug-resistant TB guidelines.

- The data is being used to formulate clinical guidance on the adoption and implementation of a shortened multi-drug resistant TB (MDR-TB) treatment regimen.

- The data were used to quantify the country's needs for bedaquiline (factoring in patients who will benefit from bedaquiline due to toxicities on current second-line treatment). The data were also used to quantify the need for raltegravir (an ARV that does not interact negatively with bedaquiline) for those patients who are also taking bedaquiline (i.e., HIV-TB co-infected patients on treatment for both HIV and drug-resistant TB) to avoid undesired interactions between efavirenz and bedaquiline.

Ministry of Health Decisions

The MOH formally established an NPVU in November 2014 to oversee PV activities, including quarterly causality assessments and information sharing. The NPVU is under the Office of the Chief Pharmacist, and SIAPS is providing technical assistance to the unit. This unit will be moved to the medicines regulatory authority upon establishment of the authority.

The strength of the data generated from the system also supported the establishment of a National Patient Safety Monitoring Committee. Furthermore, based on the evidence presented by the data, the MOH expanded the system to two more facilities in 2015, with plans to expand to all hospitals by 2017.

PViMS Development

The challenges faced in implementing the electronic PV tools informed the development of a new system, the PViMS. PViMS is a web-based tool developed by SIAPS that facilitates more streamlined data collection and analysis. This tool will be rolled out in Swaziland in 2017.

CONCLUSION

The active surveillance system has shown the feasibility of systematically documenting the incidence rate of ADEs associated with ARVs and anti-TB medicines to generate local data that will provide better estimates of risk-benefit profiles. This is crucial as PV systems need to meet the demands placed on them by the rapidly increasing access to medicines.

ANNEX A. SELECTION OF ABSTRACTS AND PRESENTED WORK

Oral Presentation given at the 45th Union Conference on Lung Health and Tuberculosis, Barcelona, Spain, October 2014

Enhancing the capacity of TB/HIV providers to promote safety of TB medicines at the community level

Presenter: Khontile Kunene

Authors: Khontile Kunene, Chinwe Owunna, Nomsa Shongwe & Kidwell Metshotyana

45th Union World Conference on Lung Health
Barcelona

USAID FROM THE AMERICAN PEOPLE SIAPS Systems for Improved Access to Pharmaceuticals and Services

INTRODUCTION

- Swaziland has an HIV prevalence of 26% while she remains one of the countries with the highest TB burdens globally.
- The HIV/TB co-infection rate is about 80% and 66% of TB/HIV co-infected patients are receiving treatment for both.
- The continuous introduction of new essential medicines necessitates the concurrent monitoring of their adverse effects.
- The burden of adverse events from poor product quality, adverse drug reactions (ADRs), and medication errors may affect achieving the full benefits of these new medicines

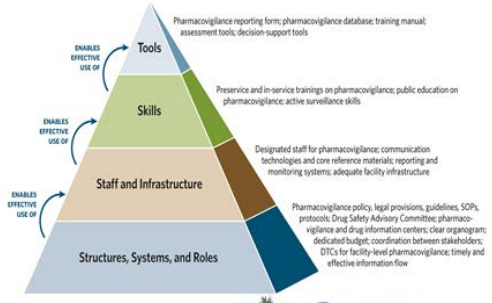
USAID FROM THE AMERICAN PEOPLE SIAPS

INTRODUCTION Cont.

- The recently developed National TB Strategic Plan prioritises the use of new and emerging medicines and technologies to curb TB
  - Introduction of bedaquiline which necessitates the country to take measures to ensure its proper use in order to avoid the development of resistance
    - that the response to treatment is monitored closely,
    - that patients are well informed of both the expected benefits and possible harms of the drug, and
    - that particular attention is given to detect and report any adverse events that develop.
- Thus, the MOH, supported by the USAID-funded SIAPS program implemented by Management Sciences for Health, prioritised the establishment and strengthening of an HIV/TB active surveillance system in order to:
  - help reduce chances of medicine resistance and
  - increase patient compliance
  - improve retention rates
  - improve treatment outcomes
  - inform decisions to improve patient safety and treatment protocols

USAID FROM THE AMERICAN PEOPLE SIAPS

THE APPROACH: Pharmacovigilance capacity building model



USAID FROM THE AMERICAN PEOPLE SIAPS

THE APPROACH Cont.

- **Passive /Spontaneous Reporting**
  - Ongoing
  - ADR Reports using standard form
- **Active Surveillance**
  - Pilot at 5 sentinel sites
  - HIV/TB Focus
  - Electronic tools (SSASSA for facilities and DCAT for Pharmacovigilance unit)
  - Leverage existing M&E structures and resources and built on sustainable platform contributing to other surveillance activities
  - Engage all relevant stakeholders and ensure local ownership
  - Use surveillance data for decision making and improving treatment outcomes

USAID FROM THE AMERICAN PEOPLE SIAPS

RESULTS

FACILITY	TOTAL # OF PATIENTS	TOTAL # OF AES
Mbabane Government Hospital	415	75
Raleigh Fitkin Memorial Hospital	438	251
Hlathikhulu Government Hospital	226	14
Good Shepherd Hospital	393	134
National TB Hospital	219	431
TOTAL # OF PATIENTS	1691	905

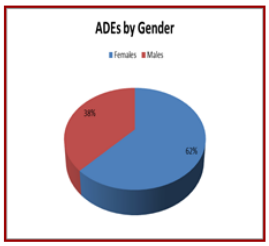
Aggregate Results

- Number of patients recruited = 1691
- The total number of ADEs reported = 905
- 68% of the patients enrolled are using ARVs)
- 32% are using anti TB medicines
- 67% of ADEs – patients on TB treatment
- Patients on ART reported 37% of the ADEs

USAID FROM THE AMERICAN PEOPLE SIAPS

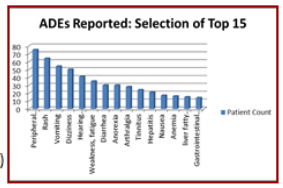
RESULTS Cont.

- **Females - 62%**
- **Males - 38%**



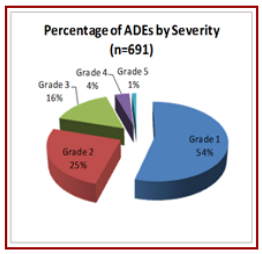
RESULTS Cont.

- **Overall**
  - Most common peripheral neuropathy - 10%
  - Followed by rash - 9%
  - Vomiting & dizziness - 7%
- **Patients on TB treatment**
  - Peripheral neuropathy (12%)
  - Hearing disturbances -8%
  - Rash - 6%



RESULTS Cont.

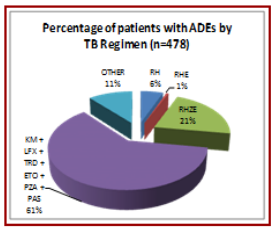
- The most prevalent amongst the ADEs with severity of grades 3-5:
  - hearing disturbances - 14%
  - rash - 14%
  - vomiting - 6%
- The ADE grades are defined as follows:
  - Grade 1: Mild ADE
  - Grade 2: Moderate ADE
  - Grade 3: Severe ADE
  - Grade 4: Life-threatening or disabling ADE
  - Grade 5: Death related to ADE



RESULTS Cont.

ADEs by TB Regimen

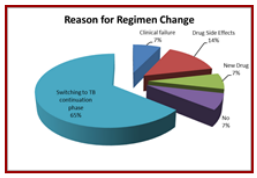
- Kanamycin/levofloxacin/terizidone/ethionamide/pyrazinamide/ para-amisalysilic acid was responsible for 61% of the ADEs
  - Most prevalent ADEs - hearing disturbances at 19% followed by peripheral neuropathy, dizziness and vomiting (6%).
- The next leading TB regimen for which ADEs were reported was Rifampicin/Isoniazid/Pyrazinamide/Ethambutol .
  - Most common ADEs - peripheral neuropathy (27%) and rash (12%)



RESULTS Cont.

Reason for Changing Regimen

- Most common reason amongst TB patients was the change to the continuation phase following consecutive negative sputum results.
- Adverse drug events accounted for a change in 14% of all regimen changes
- Clinical failure accounted for 7% of the changes.



CONCLUSION

- This activity demonstrates the local feasibility of a practical and sustainable pharmacovigilance system that can be used to promote the safety of TB medicines at the community level
- Based on one of the practical issues that affect adherence, quality of life, and treatment outcomes
- Can inform health providers and contribute to the improvement of quality of care

THANK YOU

Abstract for AMREF Health Africa International Health Conference, November 2014

Implementing a HIV/TB active surveillance system in Swaziland

Khontile Kunene

Background

Swaziland has an HIV prevalence of 26% while she remains one of the countries with the highest TB burdens globally. The HIV/TB co-infection rate about 80% and 66% of TB/HIV co-infected patients are receiving treatment for both. The continuous introduction of new essential medicines necessitates the concurrent monitoring of their adverse effects. As such, the Ministry of Health (MOH), supported by the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program implemented by Management Sciences for Health, prioritised the establishment of an HIV/TB active surveillance system in order to help reduce chances of medicine resistance and increase patient compliance and retention rates.

Methods

SIAPS supported the MOH to develop the protocol and tools to operate the *Sentinel Site-based Active Surveillance System for Antiretroviral and Anti-TB (SSASSA)* electronic system.

- The 2-year prospective observational cohort study was introduced at 5 pilot hospitals and 1 clinic in May/June 2013.
- Clinicians enrol (and follow up for 2 years years) treatment naïve HIV patients and TB patients starting a new regimen.
- Relevant patient information is captured onto the system by data clerks.
- Data is collected monthly and analysed centrally using DCAT analysis tool.

Results

A total of 1691 patients have been enrolled from June 2013 to June 2014 and there have been 905 adverse events (ADRs) reported. Peripheral neuropathy (15%) and rash (10%) are the most common, with kidney failure, ototoxicity and death being the most severe. Most of the ADRs were reported by women (55%) and only 2% of 956 regimen switches were due to ADRs.

Conclusion and Recommendations

Active surveillance plays a critical role in ensuring patient safety post the marketing approval of HIV and anti-TB medicines. This activity demonstrates the local feasibility of a practical and sustainable pharmacovigilance system that could later be scaled up throughout the country.

Oral Presentation given at 3rd African Society of Pharmacovigilance Conference, Accra, Ghana, November 2015

Implementing an HIV/TB Active Surveillance System in Swaziland to Improve Patient Safety

Khontile Kunene (Presenter)
Chinwe Owunna, Nomsa Shongwe & Kidwell Matshotyana

27th November 2015
2nd African Society of Pharmacovigilance Conference

USAID FROM THE AMERICAN PEOPLE SIAPS Systems for Improved Access to Pharmaceuticals and Services

Introduction (1/2)

- Swaziland has an HIV prevalence rate of 26% and one of the highest TB incidence rates worldwide
- The TB/HIV co-infection rate is greater than 80%
- 66% of TB/HIV co-infected patients are receiving treatment for both diseases
- The continuous introduction of new essential medicines necessitates the concurrent monitoring of their adverse effects
- The burden of adverse events from poor product quality, adverse drug reactions (ADRs), and medication errors may prevent the full benefits of these new medicines

USAID SIAPS

Introduction (2/2)

The Ministry of Health (MOH), supported by the USAID-funded SIAPS program, prioritized the establishment and strengthening of a TB/HIV active surveillance system in order to:

- Reduce the likelihood of medicine resistance
  - Increase patient compliance
  - Improve retention rates
- Improve treatment outcomes
- Inform decisions for improving patient safety and treatment protocols

USAID SIAPS

The Approach (1/2)

- **Passive/spontaneous reporting**
  - Ongoing
  - ADR reports using standard form
  - For all adverse drug events (ADEs)

USAID SIAPS

The Approach (2/2)

Development of the protocol and tools to operate electronic pharmacovigilance system	• Early stakeholder engagement to ensure local ownership • Integrated into existing structures & built upon sustainable platform contributing to other surveillance activities • Training of healthcare professionals
Pilot at 5 sentinel sites (TB/HIV Focus) in May 2013	• Clinicians enrol TB patients initiating a new regimen and treatment naïve HIV patients. • Relevant patient information is captured onto the electronic system by data clerks
Establishment of a National Pharmacovigilance Unit within the MOH	• Monthly data collection, analysis, causality assessment and supportive supervisory visits • Development of a quarterly newsletter to disseminate pharmacovigilance data and share latest knowledge

USAID SIAPS

Results (1/5)

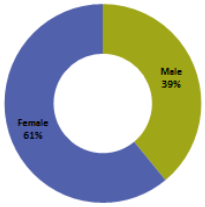
Facility	# of Patients	# of ADEs
Aids Healthcare Foundation Clinic	261	17
Good Shepherd Hospital	518	235
Hlathikhulu Government Hospital	500	21
Mbabane Government Hospital	484	144
Medicines Sans Frontieres - Matsapha	479	2
National TB Hospital	252	390
Raleigh Fitkin Memorial Hospital	512	260
TOTAL	3006	1069

- **Number of patients recruited: 3006**
  - 58% enrolled patients are female & 42% male
  - 65% of enrolled patients are using ARVs
  - 35% of enrolled patients are using anti-TB medicines
- **Total number of ADEs reported: 1069**
  - Patients on TB treatment accounted for 64% of ADEs
  - Patients on ART accounted for 36% of ADEs

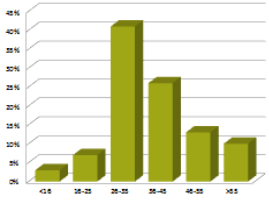
USAID SIAPS

Results (2/5)

% Gender Distribution of ADEs Reported (n=1069)



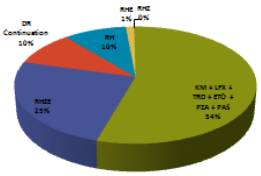
%ADE Distribution by Age Group (n=1069)



Results (3/5)

- **KM + LFX + TRD + ETO + PZA + PAS** accounted for 54% of the TB ADEs reported
  - Hearing Disturbances (19%)
  - Arthralgia (12%)
  - Peripheral Neuropathy (9%)
- **Nephrotoxicity – 3%**
- **Hepatotoxicity – 7%**
- **RHZE** accounted for 25% of the ADEs, with:
  - Peripheral Neuropathy (29%)
  - GI Disturbances (16%)
  - Rash (11%)

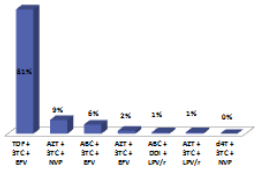
% of Patients with ADEs by TB Regimen (n=684)



Results (4/5)

- Expected since 85% of patients are on **TDF+3TC+EFV**
  - Rash (19%)
  - Peripheral Neuropathy (15%)
- All ARV Regimens
  - **Hepatotoxicity – 9%**
  - **Gynaecomastia – 7%**
  - **Nephrotoxocity – 3%**

Number of Patients with ADEs by ART Regimen (n=385)



Results (5/5)

Actions Taken From Active Surveillance Data

- The data on ADEs for TB patients on 2nd line treatment was used to quantify the number of patients who will require bedaquiline due to toxicities.
- Development of an ADE definition and severity grading job aid
  - to facilitate the objective and uniform identification and severity grading of ADEs
  - to improve data quality for better decision-making by clinicians and programmes
- Evidence for scale up; active surveillance scaled up to 3 additional facilities
- Development of reporting cascade job aid for healthcare workers
- Development of ADE reporting job aid for patients

Future Plans for Active Surveillance Data Use

- Develop an ADE management guideline that is aligned to the Swaziland Essential Medicines List
  - to improve the management and
  - limit out-of-pocket patient expenditure on medicines.
- Generate a risk profile of patients on ARVs and TB medicines to inform treatment guidelines for co-infected patients.

Other Achievements & Conclusion

Achievements:

- Full Uppsala Monitoring Centre Membership – June 2015
- Causality Assessment of most ADRs in system
- Latest newsletter (Medicines Safety Watch) – disseminated August 2015
- Process of establishing a National PV Advisory Committee

Swaziland PV System:

- Demonstrated the local feasibility of a practical and sustainable pharmacovigilance system that can be used to promote the safety of patients on ARVs and anti-TB medicines
- Addresses practical issues that affect adherence, quality of life, and treatment outcomes

THANK YOU

Poster presented at International AIDS Conference 2016, Durban, South Africa, July 2016

Improving Adherence to Treatment and Patient Safety by Implementing an HIV/TB Active Surveillance System in Swaziland

Authors: Khontile Kunene[1], Kidwell Matshotyana[1], Nomsa Shongwe[2]
[1]Systems for Improved Access to Pharmaceuticals and Services (SIAPS), Management Sciences for Health, Mbabane, Swaziland; [2]Ministry of Health, Mbabane, Swaziland

BACKGROUND

Because Swaziland is burdened with an HIV prevalence rate of 26%, a TB incidence rate of 733 per 100,000, and an HIV/TB co-infection rate of more than 80%, the country has mounted a forceful response, focusing on high-impact interventions, including treating over 80% of people living with HIV. The high number of people on antiretrovirals (ARVs) and the toxicity associated with these medicines accentuate the need to monitor and manage their adverse drug events (ADEs) for improved patient safety and adherence. Timely and effective management of ADEs reduces the ill effects experienced by patients that may lead to non-adherence.

DESCRIPTION

The Ministry of Health, with support from the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, established an HIV/TB active surveillance system to improve ADR management and inform decision making. The two-year prospective observational cohort study was introduced at five pilot hospitals providing HIV/TB services. The process included:

- Developing protocols and tools, including an electronic pharmacovigilance (PV) database
- Training health care professionals
- Enrolling treatment-naïve HIV patients and TB patients starting a new regimen (and monitoring their ADRs for an initial period of two years)
- Collecting data monthly, analyzing it, doing a causality assessment, and conducting supportive supervisory visits
- Developing a quarterly newsletter to disseminate PV data and share latest knowledge

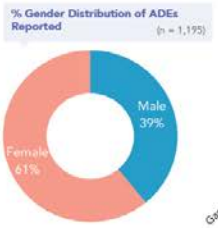
RESULTS

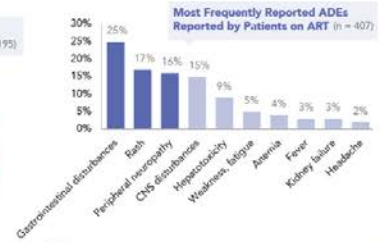
There are presently 3,759 patients enrolled in the active surveillance system (June 2013–May 2016) (52% females and 48% males).

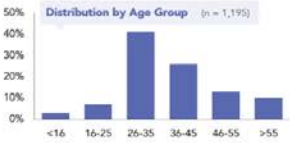
Facility	# of Patients	# of ADEs
AHF Clinic	261	17
Good Shepherd Hospital	518	235
Hlathikhulu Government Hospital	500	21
Mbabane Government Hospital	484	144
MSF - Matsapha	1,030	2
National TB Hospital	311	516
RFM Hospital	655	260
TOTAL	**3,759**	**1,195**

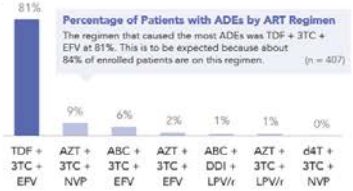
ADE flyer for patients

68% of enrolled patients are using ARVs
32% of enrolled patients are using anti-TB medicines
Patients on TB treatment accounted for 67% of ADEs
Patients on ART accounted for 33% of ADEs









LESSONS LEARNED

- The evidence from the active surveillance activity supported the subsequent expansion of the system to three more facilities in May 2015, and active surveillance of ADEs for patients on ARVs has been adopted as part of the standard of care.
- The data was used to quantify raltegravir for those patients who are also taking bedaquiline (that is, co-infected patients on treatment for both HIV and drug-resistant TB) so as to avoid undesired interactions between efavirenz and bedaquiline.
- The findings have been used to revise treatment guidelines and develop job aids for health professionals and patients to facilitate early identification and management of ADEs to promote patient safety and adherence.
- The MOH formally established a National Pharmacovigilance Unit to implement PV activities, including quarterly causality assessment and information sharing.
- The strength of the data generated also supported establishment of a National Patient Safety Monitoring Committee.
- The challenges faced with implementing electronic PV tools informed the development of a new system, the PV information management system, which is a web-based tool that facilitates streamlined data collection and analysis.

CONCLUSION

Swaziland has established an effective, integrated PV system (synchronizing passive and active surveillance) to improve the identification and management of ADEs and their associated risks.

PEPFAR USAID FROM THE AMERICAN PEOPLE SIAPS Systems for Improved Access to Pharmaceuticals and Services

AIDS 2016 DURBAN, SOUTH AFRICA

Abstract presented at 47th Union Conference on Lung Health and Tuberculosis, Liverpool, United Kingdom, October 2016

PD-888-28 Strengthening patient-centered care through implementing a TB/HIV active surveillance system in Swaziland

Authors: Khontile Kunene
[1]Systems for Improved Access to Pharmaceuticals and Services (SIAPS), Management Sciences for Health, Mbabane, Swaziland.
[2]Ministry of Health, Mbabane, Swaziland.

Background and Challenges to Implementation

Swaziland has a tuberculosis (TB) incidence rate of 733/100 000 with drug-resistant TB prevalence of 7.7% and 33.7% among new and previously treated patients, respectively. Compounding the challenge is an HIV prevalence of 26% and TB-HIV co-infection rate of 80%. The country's forceful response to the dual-burden resulted in accelerated access to treatment necessitating the establishment of a robust pharmacovigilance (PV) system. The Ministry of Health established an active surveillance system, in June 2013, focusing on patients initiating new TB regimen and antiretrovirals (ARVs). Nonetheless, with staff rotation, attrition and fatigue, the quantity of patients enrolled on active surveillance and quality of adverse drug event (ADE) reports declined. There was also need to use the available information to improve patient care.

Intervention

The Ministry of Health (MOH), with support from the USAID-funded Systems for Improved Access to Pharmaceuticals and Services program (SIAPS) formally established a National Pharmacovigilance Unit within the MOH, which:

- Reviewed the PV system tools to make them more comprehensive.
- Conducts re-sensitization trainings and monthly supportive supervision visits to implementing facilities.
- Conducts quarterly data analysis, causality assessment and information dissemination.
- Developed three job aids to improve reporting rates and standardize the identification and grading of ADEs.
- Developed ADE management guidelines aligned to the Swaziland Essential Medicines List to improve ADE management and limit patient out-of-pocket medicines-expenditure.

Results and lessons learnt

- Comparing pre-implementation (August 2014–February 2015) and post-implementation findings (March 2015–September 2015), the patient enrolment rate onto the system increased by 58% and the ADE reporting rate increased by 83%.
- Causality assessment showed improved ADE reporting quality, with 95% of ADEs reported being probably/possibly caused by the medicines (an increase from 90% in February 2015).

Conclusion

Swaziland effectively established an integrated pharmacovigilance system to reduce the risks associated with ADEs, improve ADE management and patient safety. Due to improved data accuracy, the data on ADEs for TB patients on 2nd line treatment was used to quantify the number of patients who will require bedaquiline due to toxicities. The results are also being used to generate a risk profile to inform treatment guidelines for co-infected patients.