



HEALTH
KwaZulu-Natal

Antiretroviral Cohort Adverse Event Monitoring in Kwazulu-Natal

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ANTIRETROVIRAL COHORT ADVERSE EVENT MONITORING IN KWAZULU-NATAL

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CONTENTS

Acknowledgements.....	v
Abbreviations and Acronyms	vii
Introduction.....	1
Background.....	1
Legislative Prescripts.....	1
National and Provincial Policy Objectives.....	2
Methodology.....	5
Study Design	5
Study Period	5
Study Sites and Sampling Method	5
Study Population	6
Selection and Enrolment of Patients.....	6
Data Collection.....	7
Study Duration.....	10
Statistical Analyses.....	10
Confidentiality.....	10
Study Management and Resources	11
Resources Required for the Study	11
Records Maintenance	12
Study Limitations.....	15
Limitations During Implementation	15
Limitations to Study Objectives	17
Primary Objectives	17
Secondary Objectives	17
Findings and Discussion	19
Description of Cohort	19
Summary of key adverse events	28
Report on Study Objectives.....	31
Quality Improvement Opportunities Identified	35
Conclusion	37
Lessons Learned and Recommendations	39
Lessons Learned	39
Recommendations	40
References.....	41
Annex 1. Akademik Steering Committee	43
Annex 2. Electronic Patient Record System (IEPRS/VEMR System)	45
Annex 3: Paediatric Clinical Chart	51
Annex 4. Adult Clinical Chart	59
Annex 5: Grading of Adverse Events	67
Annex 6. Ethics Approval.....	69

Annex 7. Informed Consent Document: English.....	71
Annex 8. Informed Consent Document: Kwazulu-Natal.....	73
Annex 9. Parent Permission Form	75
Annex 10. Assent to Participate in Research.....	77
Annex 11. Manual of Operations.....	79

Tables

Table 1. Sample size at each study site.....	19
Table 2. Distribution Naïve and Non-Naïve Patients per Study Site.....	20
Table 3. Demographic Characteristics of Patients	21
Table 4. Number of Patient Hospital Visits at Each Study Site.....	23
Table 5. Maximum Follow-up Time of Patients at each Study Site.....	24
Table 6. Uncensored Patients per Hospital, %.....	25
Table 7: Summary of HAART Regimens Used by Patients in the Cohort.....	27
Table 8. Summary of Adverse Events Recorded among Naïve and Non-Naïve Patients	29
Table 9: Incidence rate of selected adverse events among naïve patients	31
Table 10: Prevalence of selected adverse events among non-naïve patients.....	32
Table 11. Summary of adverse events among pregnant women	33
Table 12. Potential causal association for adverse events	34

List of Figures

Figure 1. Schematic representation of final sample size.....	19
Figure 2. Mean Age of Naïve and Non-Naïve Patients by Sex	22

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ACADEMIK	Antiretroviral Cohort Adverse Event Monitoring in KwaZulu-Natal
ADE	adverse drug event
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (medicines)
AZT	zidovudine
D4T	stavudine
DDI	didanosine
DoH	Department of Health
EFV	efavirenz
HAART	highly active antiretroviral therapy
HAST	HIV and AIDS sexually transmitted infections and tuberculosis
HIV	human immunodeficiency virus
IePRS	integrated electronic patient record system
IR	incidence rate
KZN	KwaZulu-Natal
KZN PTC	KwaZulu-Natal Pharmacy and Therapeutic Committee
LPV/RTV	lopinavir-ritonavir
NVP	nevirapine
PHC	primary health care
RR	relative risk
SAE	serious adverse event
SOP	standard operating procedure
STG	standard treatment guideline
TDF	tenofovir
WHO	World Health Organization

INTRODUCTION

Background

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.[1] The need for pharmacovigilance emanates from the fact that it is not possible to understand all of the risks and benefits of medicines before they are approved for use in the marketplace. Pre-approval studies use limited number of patients, have narrow indications and generally exclude patients from specific populations (e.g., children, elderly, pregnant women, lactating mothers, patients with renal or hepatic impairment) and those with multiple medical conditions, concomitant medicines and herbal or traditional medicine use. Pharmacovigilance is therefore important for detecting rare or unexpected adverse reactions, chronic toxicity, effects in understudied populations, and determining interactions with other products and diseases. As a result, post-approval safety data collection and risk assessments based on observational data are critical to evaluating and minimizing a medicine's risk profile over its life-cycle and to guide the best use of medicines.[2]

Antiretroviral therapy (ART) which used for the management of HIV and AIDs has been efficacious in decreasing patients morbidity and mortality. However, adverse events (AEs) to ART are common and can potentially affect patient adherence to treatment resulting in poor treatment outcomes and increased resistance. At times they may be life threatening.[3] It is therefore important that AEs are identified, managed, and reported in a continuous systematic manner within antiretroviral (ARV) treatment programmes.

The high burden of HIV and the rapid scale up of ARV treatment program in KwaZulu-Natal provided a unique opportunity to establish a cohort event monitoring system at selected sites within the province. The aim of the cohort event monitoring study was to implement and establish a system of active surveillance that would have resulted in the timely identification, management, and prevention of AEs.

The goal of the Antiretroviral Cohort Adverse Event Monitoring programme in KwaZulu-Natal (ACADEMIK) was to establish an AE surveillance system that would support patient safety, patient adherence to lifelong ART, and enhance quality of patient care in the ARV treatment programme in the province.

Legislative Prescripts

Antiretroviral supply in KwaZulu-Natal (KZN) must be performed in accordance with the following policies and acts, as well as the regulations and rules published in terms of the Acts:

- National Drug Policy (1996)
- National Health Act 61 of 2003
- Medicines and Related Substances Act 101 of 1965, as amended
- Pharmacy Act 53 of 1974, as amended
- Nursing Act 33 of 2005

ARVs must also be supplied in accordance with the provincial standard operating procedures.

National and Provincial Policy Objectives

Because of the to the HIV and AIDS pandemic, the South Africa (SA) Cabinet approved the Comprehensive Plan for the Care, Management and Treatment of HIV and AIDS for SA on the 19 November 2003. The aim of this plan was to adopt a holistic approach to the pandemic based on the pillars of prevention, knowledge of individuals' HIV status, voluntary counselling and testing, nutrition, prevention of mother-to-child transmission, treatment and palliative care. This plan provided a protocol for HIV positive patients who were eligible for Highly Active Antiretroviral Therapy (HAART), as well as provided post exposure prophylaxis with antiretroviral drugs for survivors of sexual assault in South Africa.[4]

The HIV and AIDS and Sexually Transmitted Infection (STI) Strategic Plan for South Africa 2007-2011 originated from the National Strategic Plan of 2000–2005, the Operational Plan for Comprehensive HIV and AIDS Care, Management, and Treatment, as well as other HIV and AIDS strategic frameworks developed for the government and sectors of the civil society in the past five years in SA.[5]

The interventions needed to reach the National Strategic Plan goals are structured under four priority areas:

- Prevention
- Treatment, care, and support
- Research monitoring and surveillance
- Human rights and access to justice

According to the National Strategic Plan, there is a need to conduct regular surveillance by strengthening the active surveillance, reporting, and analysis of AEs in facilities providing HAART.

The KZN Department of Health (DoH) is dedicated to develop and implement a sustainable, coordinated, integrated, and comprehensive health care system.[6] Accelerated implementation of the comprehensive plan on the management of HIV and AIDS has been priority areas for the DoH since 2006.

Rationale for the Programme

KZN has a population of approximately 10.1 million people. The recorded HIV prevalence rate is 16.5 percent with approximately 30 percent of pregnant women between the ages of 15 and 24 years being infected—the highest in SA.[7] The ARV treatment programme was initiated at four accredited sites in March 2004. In November 2004, the KZN Pharmacovigilance Committee decided to implement a paper-based spontaneous reporting system for the reporting of antiretroviral adverse drug reactions.[8] The spontaneous reporting system of reporting yielded 430 reports from 63 sites from November 2004 to April 2007, of which 63 percent of the reports were classified as incomplete because of a lack of pertinent clinical and laboratory information.

The exponential increase in patients being initiated on HAART had resulted in approximately 80,395 patients being initiated on HAART as at 31 March 2007. Because the spontaneous reporting system was ineffective, Pharmaceutical Systems Development department, (now known as Pharmaceutical Services) in collaboration with Management Sciences for Health (MSH) Strengthening Pharmaceutical Systems (SPS) Program, developed the solicited reporting system in KZN which involved mandatory reporting of adverse drug events (ADEs) when changes to the patient treatment regimen were required due to ADEs. This system of reporting had limitations as ADEs that did not require a regimen change such as deaths and AEs due to pregnancy exposures were not being reported. Furthermore, this reporting system did not allow for the calculation of incidence, as accurate information on total population exposed to ARVs were not available (deaths, migrations, and lost to follow ups were not subtracted from the total population numbers deemed to be on treatment). This therefore eliminated a precise denominator to calculate incidence.

In 2008, the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund) had awarded a grant to KZN DoH to enable the province to establish an active surveillance system at selected ARV treatment sites. Since the establishment of a cohort study required financial resources, and the Global Fund award was a once off disbursement, alternate sources of funding were needed to implement and sustain the study. Funding was made available by SPS project through the donation of human and other resources required to maintain the study, for a period of 3 years from June 2009 to June 2012.

Cohort event monitoring is an observational study that does not interfere with the clinical management of individual patients. Data are collected on cohort of patients who are managed in everyday clinical practice unlike highly selected groups of patients in randomized clinical trials who may not represent real world population. In this way, cohort monitoring avoids the problem of generalisability inherent in randomized clinical trials, including many post-marketing safety clinical trials.

Because the data from cohort studies are concerned with events, ADEs or syndromes that are often not suspected of being caused by the drug could be detected. Cohort event monitoring identifies patients with ADEs who can be studied further, for example, in nested case-control studies, to examine risk factors including pharmaco-genetic risk factors. Cohort event monitoring is complementary with other pharmacoepidemiologic methods and can evaluate signals generated in other systems or databases. Similarly, it provides a technique that can generate signals or hypotheses which can themselves be refuted or confirmed by other pharmacoepidemiologic methods.

In a cohort with participants from the varied population and ethnic groups with their genetic differences, diverse traditional, and lifestyle practices, data collected on AEs can serve to determine drug safety issues for improving patient outcomes in the ARV Programme in KZN and for SA. The study could allow population-based trend analysis in terms of safety. In addition, best practice observations and recommendations, as well as programmatic benchmarking information, could be shared as an outcome of this research.

Study Aim

The study aimed to evaluate the incidence of adverse events and the factors associated with their development to improve the identification, diagnosis, management and prevention of drug related morbidity and mortality in HIV-infected patients on HAART in KZN.

Study Objectives

Primary Objectives

- To determine the incidence and severity of adverse drug events (ADEs) in adult and paediatric patients on HAART
- To determine the incidence, severity and outcome of ADEs in pregnant women on HAART
- To determine risk factors and covariates for the development of serious ADEs in adult and paediatric patients on HAART
- To determine the clinical characteristics, management and outcomes of ADEs in adult and paediatric patients on HAART

Secondary objectives

- To identify and develop measures to minimize drug-related morbidity and mortality in HAART patients and to recommend strategies for managing the risks of the ARVs.
- To advise the KZN DOH and the KZN Provincial Pharmacy and Therapeutics Committee (PTC) on issues relating to the safety of HIV and related medications on an ongoing basis to facilitate clinical and safety decision-making.
- To make recommendations for amending treatment regimens and guidelines for the province where appropriate to improve adherence and outcomes in HIV-treated patients.
- To communicate and disseminate information on the safety and management of HIV and related medications to stakeholders provincially, nationally, and internationally.

The implementation plan outlined the structures that were necessary to achieve the above mentioned objectives.

METHODOLOGY

Study Design

This study was a multi-centre, prospective observational cohort study designed to evaluate the incidence of AEs among HIV-infected adult and paediatric patients who were receiving highly active antiretroviral therapy (HAART).

Study Period

The study was intended to be undertaken over a period of three years from June 2009 to June 2012. Participants were to be followed up from enrollment into the study to the last date of follow-up. Since participants were enrolled at different stages, the follow-up time for each participant was expected to be different.

Study Sites and Sampling Method

Study sites were selected using the following criteria.

- Dedicated and committed staff were available at participating study sites.
- Sites had a track record of correct reporting of ADRs verified by the Component of Pharmaceutical Policy and System Development–KZN or generally produced good ADR reports.
- Appropriately trained data entry staff were available who were able to capture data efficiently and effectively
- The site was committed to follow-up on patients for at least 3 years after enrolment.
- A reasonable number of currently followed patients was available on which adequate data are already being collected.
- The site was able to collect data as required and supply the data to the Study Coordinating Office.
- The site was able to implement quality assurance measures.
- The site was able to accept organisation and publication rules of the study.

Additional consideration was given to facilities that had already been using the IePRS programme that was to be used in the study.

The study was designed to be held at seven health care facilities in KZN. However, only five health care facilities commenced the study.

- GJ Crookes Hospital (District Hospital, Ugu district)

- Murchison Hospital (District Hospital, Ugu District)
- Greys Hospital (Tertiary Hospital, Umgungundlovu district)
- Northdale Hospital (District Hospital, Umgungundlovu district)
- Madadeni Hospital (Regional Hospital, Amajuba district)

The two additional sites were excluded because—

- Edendale Hospital's (Regional hospital, Umgungundlovu district) facility management did not fully support the study. Furthermore, this site had infrastructure, network, and server connectivity problems that would have affected the installation of the IePRS.
- St Mary's Hospital (regional hospital, eThekweni district) had initial challenges with the interfacing of the IePRS system and the existing patient information within the hospital. Later, the KZN DoH decided to close down the ARV programme at this site.

The study programme was commenced at facilities using a staggered approach, beginning with Greys Hospital in August 2010. This was followed by GJ Crookes and Northdale in December 2010 and Murchison and Madadeni Hospitals in January 2011.

Study Population

The study population was divided into two groups—

- Naïve patients: Patients who were not previously exposed to HAART at the time of study initiation or who had commenced ARV therapy a maximum of one month before study enrolment.
- Non-naïve patients: Patients who had commenced HAART greater than one prior to enrolment in the study.

The assumption was that inclusion of non-naïve patients would enable the determination of long-term AEs to HAART.

Sample Size

A cohort size of 10,000 was decided on to enable the sample to detect rare cases of AEs and to allow for adequate patient numbers for subgroup analyses. The final sample size (1,815) was dependent on the rate of patient enrolment by each study site.

Selection and Enrolment of Patients

The following criteria were used in the selection of patients.

Inclusion criteria

- ARV-naïve patients entering the HIV treatment programme or existing patients on HAART under active follow-up
- Able and willing to provide informed consent or able to provide parental/legal guardian permission with assent
- Able and willing to provide adequate information for locator purposes
- Not intending to relocate out of the area for the duration of study participation and does not have a job or other obligations that may require long absences from the area
- Possession of an identification number as designated in an official document

Exclusion Criteria

- Patients or parents/legal guardians not willing to provide signed informed consent
- Previous or current participation in a HIV vaccine study
- Active alcohol or substance abuse
- A history of mental illness
- Prisoner status
- Any condition that, in the opinion of the investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

Patients were informed of the study by the clinician or another designated person to ascertain their interest in participating. Upon agreement, an assessment was made to determine whether patient qualified for inclusion. Written permission was then obtained from the patient or parent/legal guardian (in the case of a minor). Patients were then assigned a patient identification number. The patient and eligibility information was then submitted to the study coordinating office for the generation of a study identification number specific to the ACADEMIK study.

Data Collection

Data Collection Tools

The study used both an electronic and manual tools for data collection. The IePRS patient management tool developed by VPPS (annex 2) was upgraded for use in the study. In addition, manual data collection tools (termed clinical charts) were also developed for sites that were unable to do live data capture of patient information in the IePRS. Copies of the manual data collection tools are appended. (annexes 3 and 4)

Data Collection Approach

At all study sites, clinicians and nurses had to capture patient management information either directly onto the IePRS system or on the designated manual clinical charts developed. At sites using the manual charts, an appointed data entry employee had to capture the all information retrospectively from the clinical charts onto the IePRS. At a central level, data was meant to be extracted directly from the IePRS system only. However, some sites failed to use the clinical charts and the IePRS system as intended, resulting in poor recording of patient information according to that required by the protocol. Therefore all study participants hospital files needed to be reviewed to complete missing information as required on the data collection tools. Every effort was made to ensure that all information on study participants (when available) was collected. The study also sought to document changes in the patient's clinical condition and laboratory parameters during each patient visit but the main focus was on the identification of AEs.

Frequency of Data Collection

All study participants visits were recorded at each institution from the time of enrolment. Therefore every visit with the patient was recorded.

Data Collection Variables for Patients

Baseline and Follow-up Data

The following information was required to be captured at enrolment.

ART naïve patients (adults and paediatrics):

- Demographic data
- Date of HIV diagnosis
- Past medical history and medication
- Baseline clinical assessment—WHO staging, reproduction health, TB and nutritional screening, physical examination
- Clinical evaluation for HAART-laboratory assessments, concomitant illness and medication, complementary/traditional medicines, ART medication

ART non-naïve patients (adults and paediatrics) minimum data:

- Demographic data
- Date of HAART initiation
- Past medical history and medication (including previous ART regimens)
- Previous adverse events (if any)
- Current ART medication
- CD4 and viral load

The following data was required to be captured on follow-up assessments

- Clinical examination and vital signs

- Reproductive health (adults)
- TB status
- Laboratory investigations—viral load, CD4, full blood count, liver function tests, creatinine clearance, fasting cholesterol, triglycerides, glucose
- HIV conditions and opportunistic infections
- New traditional/complementary medicines

A complete list of the variables for the study can be found in the data collection tools (annexes 3 and 4).

An AE was defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not it was considered causally related to the product. An undesirable medical condition could be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). The term AE was used to include both serious and non-serious AEs.

Adverse events were required to be diagnosed by the clinician on site as per case definition, or be classified as “to be determined” in the case of uncertainty. Each AE was required to be validated as extracted from the patient’s file on the central database by an independent advisory panel.

A serious AE is one that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or existing hospitalisation prolonged
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Any AE identified during follow-up visits were required to be recorded in the clinical charts (annexes 3 and 4) irrespective of whether the event was considered to be drug related or not. The following specific scenarios were specified.

- All new events even if minor
- Changes in a pre-existing condition
- Abnormal changes in laboratory tests that required change in treatment
- Accidents/overdose
- All deaths with date and cause
- Possible interactions with other medicines including over the counter, complementary and traditional medicines, tobacco, and alcohol

Additionally, a description of the event, including its date of onset and resolution, whether it constitutes a serious AE or not; any action taken (e.g., changes to study treatment, other treatment given, and follow-up tests) and outcome; was required along with the investigator’s

assessment of causality and grading of the AE (annex 5). Event descriptions were required to be reviewed by the study coordinating office and the standard AE terminology applied.

Study Duration

The ACADEMIK study had been funded for a period of 24 months (June 2010 to May 2012). However, depending on the availability of funding, the intent was to continue monitoring the study cohort for an additional 18 months.

Statistical Analyses

Ethics Approval

Ethics approval for the study was obtained from University of KwaZulu-Natal and Health-KwaZulu-Natal Provincial Health Research Committee. (annex 6)

Informed Consent

Written informed consent was obtained for each study participant (annexes 7, 8, 9, 10) Participation was voluntary with the right of the patient to opt out at any given time. Patients were assured that only their health care providers and authorized DoH personnel would have access to their treatment records and that patient identity would not be included in published information.

Confidentiality

Data extracted for analysis were coded and all results were intended to be reported in aggregated form. Confidentiality was maintained throughout the study period by the study coordinating office.

STUDY MANAGEMENT AND RESOURCES

Resources Required for the Study

Human Resource Support

Study Coordinating Office

The study coordinating office located at the provincial head office in Pietermaritzburg had the overall responsibility for the study including: formation of a central database; coordination and collection of data from each of the participating sites to the central database; oversight of protocol compliance at participating cohort sites; oversight of clinical site performance; preparation of study material including data collection forms, manuals, and protocols; and review and query of event forms. The study coordinating office also had the responsibility of monitoring study site activities through regular support visits. Staff within the study coordinating office consisted of the principal investigator, study coordinator, data manager and data capturers. The staff employed to manage this study were funded by SPS.

Site Coordinator and Data Entry Personnel

Site coordinators were appointed at each of the participating sites. The site coordinators were generally the ART study managers for the respective sites. Their responsibility was to manage all activities relating to the ACADEMIK Study at an institutional level.

Some study sites required data entry personnel for capturing patient information onto the computerised patient management system.

Study Steering Committee

A study steering committee was appointed to oversee the study and guide decision making during all phases (planning, implementation, and monitoring) The ACADEMIK Steering Committee was comprised of representatives from SPS and academia. The principal investigator, study manager, co-investigators, study co-ordinator, and representatives from the KZN DoH were also committee members. The steering committee was solely responsible for the scientific conduct of the study as well as for decision making regarding site participation or exclusion of a cohort site, if a significant proportion of the core data was unreliably collected. Regular meetings were held to discuss progress and challenges with implementation. The staff at the coordinating office convened and participated in the meetings.

In addition to the steering committee, an independent advisory committee was to be formed to evaluate recorded AEs, to serve as a data monitoring committee, to assist with causality assessment, and to undertake periodic analysis of data to identify problems with the data, but it never materialized.

Technical Support

Technical support for the study's overall design and implementation as well as funding study was provided by SPS. The IePRS developed by the company Virtual Purple

Professional Services (VPPS) was used as the computerised data collection tool for the study, and VPPS provided technical support for updating, installation and maintenance of the system at all sites.

Physical Resources

Functional computers and printers were required at institutional level for the recording of patient information. Some study sites had adequate resources whilst others required new computers and printers to be purchased and installed. These resources were funded by the Global Fund.

Informational resources

An operations manual outlining the standard operating procedures was developed specifically for this study (annex 11). These standard operating procedures were discussed and distributed to all health care workers at the study sites in KNZ.

Financial Resources

The entire study cost approximately 3 million rand. Apart from the initial financial resources provided through the global fund, additional funding was required for the implementation of the ACADEMIK Study. This was provided by SPS.

Training

Training for this study, as well as general pharmacovigilance training was provided to staff from the ART clinics at study sites. SPS and the Global Fund in collaboration with the DoH funded and coordinated the training sessions.

Records Maintenance

Maintenance of Essential Documents and Participant Files

The study coordinating office maintained a record of all participants' consent forms, while the site maintained the manual and electronic records of all patient information.

Manual Records

The manual records are comprised of the baseline/pre-treatment and follow-up questionnaires. Madadeni, Murchison, and Northdale Hospitals collected patient data manually which was then entered into the IePRS by the designated data entry capturer at the site.

Computerised Programme

The IePRS was installed at all study sites. GJ Crookes and Greys Hospitals opted for the direct capture of patient information by the clinicians and other health care workers on the IePRS. This programme used a password protected login system at all sites.

Patient database

All information for the study participants that was captured onto the IePRS were stored onto the facilities' and the provincial servers in a "read only" format to prevent tampering and to ensure security. The data was then backed up to the central server which had clear designations of the origins of the data.

Access to Database

At the central level, only the study coordinating office could access study participant information for purposes of monitoring protocol implementation, quality of data collected and for data review and analysis. Access to the database was password protected.

Maintenance of IePRS and Central Database

Technical support for IePRS at study sites was provided by VPPS on a weekly basis and as requested by the study site to ensure optimal functioning of the system for accurate data capture.

STUDY LIMITATIONS

Limitations During Implementation

Patient Recruitment

The protocol stipulated that 10,000 patients will be recruited over a period of 18 months however the final number enrolled was 1,815, of whom only 1,328 patients were eligible for analysis. Many factors contributed to this.

- Only five of the intended seven healthcare facilities participated in the study
- Because the study started late, it only ran from 1 July 2010 to 30 June 2012 instead of the intended three years.
- There was extensive training on the study. However, due to limited human resources and high burden of patients, staff at sites did not have the time to recruit the expected numbers of patients, and to successfully follow up patients as per protocol.
- Reluctance of patients to participate in the study despite posters being placed in waiting areas explaining the benefits of participating in such a study. At some study sites, patients cited the increased consultation time with clinicians as the reason for non-participation.
- Poor follow-up of patients post-enrolment and loss of consent forms also eliminated patients

Data Quality

A major limitation of the study was the inability to collect quality data for all of the required variables. Reasons for this include—

- Training with regard to the protocol implementation and the ACADEMIK study in general was conducted regularly; however, some sites were not compliant with using the manual or computerised data collection tool (IePRS), which was designed for this study. To ensure that the study was integrated into routine clinical practice and that study sites would not be burdened with separate data collection, the data collection tools (clinical charts with initial assessment and follow up forms) for this study were structured in accordance with the revised National and Provincial Guidelines (April 2010). Further, since some hospitals in KZN were already using a specific ARV patient clinical chart, which was approved by the provincial HIV and AIDS sexually transmitted infections and tuberculosis (HAST) unit, for recording patient information, the steering committee opted to update and utilise the HAST chart as the official data collection tool. However, sites that opted to use a paper-based system failed to consistently use the manual clinical chart for documenting patient information. For some patients the initial assessment would be done using the clinical charts but the follow-up visits would be documented in the official provincial outpatient yellow file. In other instances, only the follow-up forms would be used and not the initial assessment forms. The result was that either baseline or follow-up data was not recorded for many patients, making them ineligible for analysis. In addition,

patient information that was recorded in the official yellow file was either inconsistent with that required for the study or not documented at all. This also proved to be a challenge for the study coordinating office when conducting a review of patient files to update missing variables. The study sites that did use the computerised data collection tool for patients management failed to complete all relevant fields resulting in incomplete patient information.

- For non-naïve patients it was important to have a good baseline history for patients including previous treatments used and AEs encountered. However, only a small proportion of patients' files had all the required information since the start of the patient on HAART. Thus it was difficult to establish a complete clinical history of non-naïve patients resulting in missing information for key variables. Furthermore, when cases of AEs were recorded for non-naïve patients, it was often not possible to determine if it was caused by the current ART regimen or previous regimen due to the lack of adequate patient history.
- According to the study protocol, AEs were to be identified and recorded by clinicians. However, in most cases AEs were not recorded as confirmed events in the patients' notes but rather as a clinical condition. Thus, when the patient notes and laboratory parameters were reviewed, additional AEs were identified and recorded by the SCO. However, the data on clinical symptoms and laboratory parameters was also poorly documented which may have either limited the number of AEs identified or resulted in misinterpretation of AEs.
- This study intended to undertake a causality assessment of AEs. For each AE recorded, the clinician was required to answer a series of questions (in accordance with WHO guidelines) relating to the causality of the AE. For most AEs that were identified, causality assessments were not completed by the clinician. Therefore it was not possible to conclusively determine whether AEs were caused by HAART or by underlying co-morbidities or concomitant medication.
- The study did not commence on the original date as planned which shortened the overall study period from three years to two years. The slow recruitment process also meant that some patients only joined the study a few months before the end of the study period hence these patients did not have an adequate period of follow-up on the study.

Operational Management

- There were several changes to the committee members over the study period. This affected the overall functioning of the committee which resulted in inadequate monitoring and timely decision making around the implementation challenges at study sites.
- Because a clinical advisory committee was never established although it was required by protocol, regular monitoring and review of data for AEs and quality assurance was never implemented.
- The study had an implementation plan but lacked a formal monitoring and evaluation plan. A sound monitoring and evaluation plan would have detected some of the problems with recruitment and data quality much early on in the study and the necessary actions could have been taken.

Limitations to Study Objectives

Due to limitations in the implementation of the study and lack of adequate data for specific analysis, not all study objectives could be addressed. In addition, due to the small number of paediatric patients and few AE cases, data for adults and paediatrics have been combined. Pregnancy cases are included among the adult population. However, data for naïve and non-naïve patients groups have been analysed and reported separately as it is only statistically appropriate for incident rates to be calculated for the naïve group. A period prevalence of adverse events has been calculated for the non-naïve group.

Primary Objectives

The study was unable to achieve the following primary objectives.

Objective 1: In terms of incidence of AEs, incidence was only calculated for naïve patients and prevalence was calculated for non-naïve patients. There was also no separate calculation of incidence (or prevalence) for adults and paediatric patients because of the small number of paediatric patients enrolled. Severity of AEs could also be not determined because of missing data on this variable.

Objective 2: The severity and outcome AEs among pregnant women could not be analysed as data on these variables were not recorded.

Objective 3: Risk factors were limited to demographic characteristics because of a lack of adequate data on other covariates.

Objective 4: The clinical characteristics, management, and outcomes of AEs could also not be analysed as not all health care facilities used the IePRS programme for patient management, and those facilities that did use it, use was inconsistent.

Secondary Objectives

The protocol listed four secondary objectives which were intended to be achieved. However, only objective four which relates to the communication and dissemination information on the safety and management of HIV and related medications to stakeholders was partially achieved through the study—see results and recommendations sections for further discussion.

The objectives relating to disseminating regular information on measures to minimize drug related risks of ARVs and advising and making recommendations for amending treatment regimens and guidelines to improve adherence and outcomes in HIV-treated patients were not achieved at the time of termination of the study. The reason for this was because the independent advisory committee to conduct interim data analysis and to perform routine clinical review of the data was not established during the study period.

FINDINGS AND DISCUSSION

Description of Cohort

Final Cohort Size

The study aimed to enrol 10,000 patients over a period of two years. However, only 1,800 patients were enrolled into the study during the period of 1 October 2010 to March 2012 achieving approximately 20 percent of the target. The low enrolment was due to operational challenges of the study which are discussed later in the report. Of the 1,815 patients enrolled in the study, only 1,328 patients were eligible for analysis. Figure 1 depicts the reasons for exclusion of patients and the final sample size.

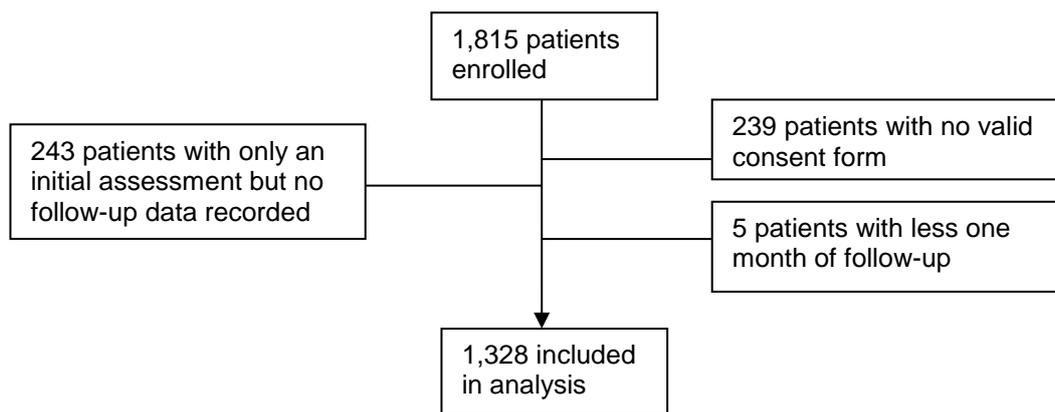


Figure 1. Schematic representation of final sample size

Although the study protocol stipulated that patients should have a minimum of 12 months follow-up, it was decided that all patients who had at least one month of follow-up after treatment initiation could be considered for inclusion in analysis. This would not affect the incidence rate calculation as this is based on actual time period contributed by each person. In addition, it was considered that since most early adverse events occur within the first month to a year of initiating HAART, [9] excluding patients may result in the loss of valuable information on these adverse events.

Table 1. Sample size at each study site

Study site	Number (N = 1328)	Percentage (%)
GJ Crookes	293	22
Greys	387	29
Madadeni	161	12
Murchison	304	23
Northdale	183	14

Table 1 reflects the distribution of the 1,328 patients between the study sites. Twenty-two percent of patients were from GJ Crookes Hospital, 29 percent from Grey's, 12 percent from Madadeni, 23 percent from Murchison and 14 percent from Northdale Hospital.

Characteristics of Study Sample

For each hospital, patients were subgrouped into naïve or non-naïve patients. Naïve patients were those who had no prior exposure to ARV therapy at the time of study initiation or who had commenced ARV therapy a maximum of one month before study enrolment. One month was used as the basis for designation into the naïve group as this seemed a reasonable timeframe within which an accurate baseline history of patients and early adverse effects could be retrieved allowing for subsequent prospective follow-up. All other patients with a previous exposure to ARV therapy were classified as non-naïve. Table 2 indicates the number of naïve and non-naïve patients from each of the hospitals that participated in the study.

Table 2. Distribution Naïve and Non-Naïve Patients per Study Site

	Naïve		Non-Naïve	
	Number	%	Number	%
GJ Crookes	18	4.9	275	28.7
Greys	27	7.3	360	37.6
Madadeni	106	28.6	55	5.7
Murchison	43	11.6	261	27.3
Northdale	177	47.7	6	0.6
Total	371	100.0	957	100.0

The final study sample comprised of 72 percent non-naïve and 28 percent of naïve patients. There is marked variation in the distribution of naïve and non-naïve patients among sites due to differences in the enrolment by each study site. GJ Crookes, Greys, and Murchison Hospitals accounted for 93.6 percent of non-naïve patients whilst Madadeni and Northdale hospitals accounted for 76.3 percent of naïve patients.

Table 3 presents the number of patients in each group, categorized by sex, race, and either paediatric or adult and pregnant women in each hospital. The category of either paediatric or adult was generated based on the WHO definition of a paediatric being aged 14 years or younger and an adult being 15 years and older.

Table 3. Demographic Characteristics of Patients

Demographic characteristics	GJ Crookes		Grey's		Madadeni		Murchison		Northdale		Total (n = 1328)
	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	
Sex:											
Male	0	57	6	79	40	13	5	18	57	4	279
Female	18	218	21	281	66	42	38	243	120	2	1049
Race:											
African	18	270	25	343	106	55	43	260	173	6	1299
Coloured	0	1	0	10	0	0	0	0	2	0	13
Indian	0	4	2	5	0	0	0	1	1	0	13
White	0	0	0	2	0	0	0	0	1	0	3
Age group:											
Adult	18	268	27	359	102	50	32	248	149	4	1257
Paediatric	0	7	0	1	4	5	11	13	28	2	71
Pregnant:											
Yes	1	7	1	4	1	0	0	2	20	0	36
No	15	196	17	275	21	10	1	11	47	1	594
Unknown	2	15	3	2	44	32	37	230	53	1	419

The demographic distribution of patients showed that adults comprised 94.7 percent (1,257) and paediatrics 5.3 percent (71) of the study sample. The number of paediatrics was highest (39.4 percent, n = 28) among naïve patients at Northdale. In terms of race, the majority of patients (98.7 percent) were of African origin with the remainder of the sample comprised of < 1 percent Indian and < 1 percent Coloured patients. Females and males comprised 79 percent and 21 percent of the study sample respectively. These statistics are highly reflective of the high prevalence of HIV amongst adult female population of KZN.[10] Out of 1,049 female patients, 40 percent had missing data on pregnancy. Of the remaining 60 percent (630) of patients with data on pregnancy, only 5.7 percent (36) were noted as being pregnant at some point during the study period. The majority (56 percent, n = 20) of the pregnant women were from amongst the naïve patients at Northdale hospital.

Figure 2 depicts the mean age of males and females amongst naïve and non-naïve groups in each hospital. The mean age of males in the study sample ranged between 18.0 and 44.1 years while that of females ranged between 9.3 and 39.6 years. Among the naïve patients the mean age of the males ranged from 18.0 years (Murchison) to 40.0 years (Madadeni) and the mean for females ranged from 28.6 years (Murchison) to 37.2 years (Greys). Among the non-naïve patients the mean age of males ranged from 22.5 years (Northdale) to 44.1 years (Madadeni) and the mean for females ranged from 9.3 years (Northdale) to 39.6 years (Greys). Overall, the mean age of the entire study sample ranged between 28 and 40.0 years which is representative of a reproductive age group.

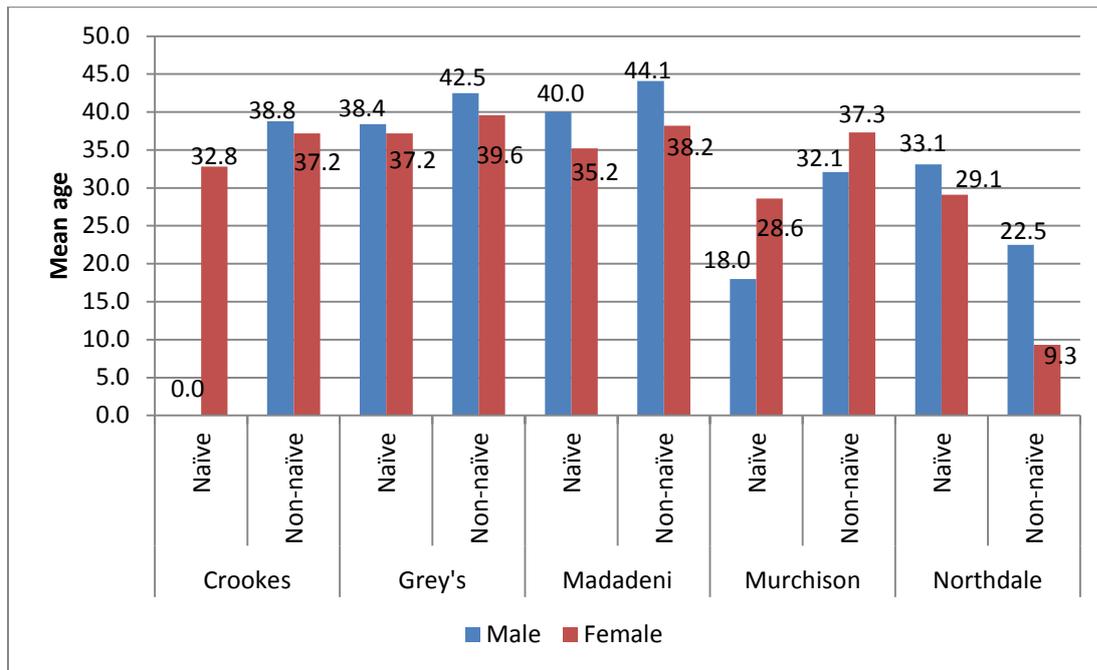


Figure 2. Mean age of naïve and non-naïve patients by sex

Patient Follow-up

Number of Patient Visits

Since this was an observational study, the number of visits with information recorded for each patient differed between patients as this was dependent on the frequency of hospital attendance by patients for monitoring. Most naïve patients would have visited the hospital more than once in a month after starting HAART, depending on their follow-up schedule. It was also possible for patients to have follow-up visits at greater than one month interval for various reasons. However, most stable patients were followed up monthly. The number of hospital visits documented for each patient is reflected in table 4.

Table 4. Number of Patient Hospital Visits at Each Study Site

Visit Number	Crookes			Greys			Madadeni			Murchison			Northdale		
	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total
1	18	275	293	27	360	387	106	55	161	43	261	304	177	6	183
2	17	272	289	27	359	386	106	55	161	38	255	293	176	6	182
3	15	242	257	24	338	362	99	54	153	34	246	280	171	5	176
4	14	191	205	24	318	342	92	51	143	34	231	265	161	4	165
5	8	139	147	19	283	302	84	43	127	29	219	248	157	4	161
6	4	80	84	15	203	218	74	40	114	22	199	221	151	4	155
7	4	59	63	12	143	155	59	24	83	16	176	192	144	4	148
8	3	47	50	9	90	99	37	13	50	12	144	156	135	4	139
9	2	31	33	7	56	63	29	6	35	6	117	123	126	3	129
10	2	25	27	3	30	33	15	4	19	3	96	99	117	2	119
11	1	21	22	0	13	13	7	2	9	2	75	77	107	1	108
12	1	19	20	0	6	6	6	2	8	2	59	61	92	0	92
13	0	12	12	0	5	5	3	1	4	2	42	44	77	0	77
14	0	6	6	0	1	1	1	1	2	0	27	27	55	0	55
15	0	2	2	0	1	1	0	1	1	0	14	14	27	0	27
16	0	1	1	0	1	1	0	0	0	0	8	8	11	0	11
17	0	0	0	0	0	0	0	0	0	0	2	2	4	0	4
18	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1

Table 4 above indicates the number of hospital visits documented for patients at each study site. This actually represents the number of consultations with the physician/healthcare worker, at which point information on the patient had been recorded. As explained previously the time interval between visits as well as the date of visits is different for each patient hence the visits are not comparable between patients and or hospitals. The table does however provide useful information on the variability in the overall number of consultations (data collection time points) contributed by each patient to the study. The number of visits recorded is dependent on many factors such as the time point of enrolment into the study, loss to follow-up, and censorship due to end of study period.

Follow-up Time

This was an open cohort since patients were enrolled at different time points during the study period. Follow-up of patients was thereafter prospective from the date of enrolment and the length of time each patient contributed to the study differs from patient to patient and across the study sites. The duration of follow-up of patients is reflected in Table 5. The length of follow-up is the difference in time (in days) from the date of study recruitment to the last date of a visit record.

Table 5. Maximum Follow-up Time of Patients at each Study Site

	Month	Follow-up (in days)	Crookes				Greys				Madadeni				Murchison				Northdale			
			Naïve	Non-Naïve	Total		Naïve	Non-Naïve	Total		Naïve	Non-Naïve	Total		Naïve	Non-Naïve	Total		Naïve	Non-Naïve	Total	
	1	0-30	2	19	21	0	2	2		2	2	4		6	6	12		3	0	3		
	2	31-60	2	30	32	0	9	9		8	0	8		1	6	7		12	1	13		
	3	61-90	3	28	31	3	6	9		6	3	9		4	12	16		2	0	2		
	4	91-120	1	28	29	0	2	2		3	4	7		7	11	18		4	0	4		
	5	121-150	1	36	37	0	2	2		6	5	11		0	14	14		5	0	5		
	6	151-180	1	30	31	0	17	17		12	10	22		4	47	51		9	0	9		
	7	181-210	1	18	19	0	7	7		21	19	40		3	17	20		5	0	5		
	8	211-240	1	19	20	1	3	4		10	1	11		4	14	18		9	2	11		
	9	241-270	1	26	27	1	7	8		6	5	11		1	14	15		10	0	10		
	10	271-300	0	8	8	2	16	18		6	2	8		4	13	17		5	0	5		
	11	301-330	1	7	8	2	14	16		4	1	5		0	16	16		9	0	9		
	12	331-360	1	1	2	2	60	62		8	0	8		6	27	33		12	1	13		
	13	361-390	1	2	3	3	34	37		14	1	15		2	24	26		29	1	30		
	14	391-420	0	13	13	4	57	61		0	1	1		1	32	33		35	1	36		
	15	421-450	1	6	7	2	27	29		0	1	1		0	4	4		22	0	22		
	16	451-480	0	3	3	3	23	26		0	0	0		0	3	3		5	0	5		
	17	481-510	1	0	1	4	40	44		0	0	0		0	0	0		1	0	1		
	19	511-540	0	0	0	0	28	28		0	0	0		0	0	0		0	0	0		
	20	541+	0	0	0	0	6	6		0	0	0		0	0	0		0	0	0		
	Total number of patients with follow-up period (in months):																					
5 or less			9	141	150	3	21	24		25	14	39		18	49	67		26	1	27		
6 + Months			9	133	142	24	339	363		81	41	122		25	211	236		151	5	156		
12 + months			4	25	29	18	275	293		22	3	25		9	90	99		104	3	107		

Note: A single missing value each for Crookes (292 instead of 293) and Murchison (303 instead of 304)

Table 5 above indicates the actual duration (in days and months) that patients contributed to the study. There is great variability in the length of time contributed by each patient and between study sites because of various factors such as date of patient recruitment into the study, loss to follow-up, and censorship of patients at the end of the study period. Greys Hospital had the longest duration of patient follow-up with six patients having a follow-up of greater than 20 months. This may be because the official start date for commencement of the study at Greys was at least three months prior to the other sites. On the other hand, Madadeni Hospital has the shortest duration of follow-up which may be attributed to it being the final site to join the study.

In total, there were 307 (23.1 percent) patients who had a follow-up of less than six months (81 naïve and 226 non-naïve patients). There were 1,019 patients with a follow-up of 6 months and greater (290 naïve and 729 non-naïve patients). Additionally, only 553 (41.6 percent) patients contributed a time period of 12 months and greater. Of these, 157 were naïve and 396 were non-naïve patients.

Table 6 shows the percentage of uncensored patients for each of the study sites who had a follow-up of less than six months, greater than or equal to six months, and 12 months or more. This represents the percentage of patients enrolled at each study site who did not contribute time to the study beyond these three periods. Hence, it can be deduced from the table that 75.7 percent of Grey's patients had a follow-up time of 12 months or more in the study compared to 9.9 percent patients at GJ Crookes, 15.5 percent patients at Madadeni, 32.7 percent at Murchison and 58.5 percent at Northdale hospital.

Table 6. Uncensored Patients per Hospital, %

Hospital	Period	Group	Number of			Uncensored (%)
			Initial Sample	Censored	Uncensored	
Crookes	5 or less	Naïve	18	9	9	50.0
		Non-Naïve	275	141	134	48.7
		Total	293	150	143	48.8
	6+ Months	Naïve	18	9	9	50.0
		Non-Naïve	275	133	142	51.6
		Total	293	142	151	51.5
	12+ months	Naïve	18	4	14	77.8
		Non-Naïve	275	25	250	90.9
		Total	293	29	264	90.1
Grey's	5 or less	Naïve	27	3	24	88.9
		Non-Naïve	360	21	339	94.2
		Total	387	24	363	93.8
	6 + Months	Naïve	27	24	3	11.1
		Non-Naïve	360	339	21	5.8
		Total	387	363	24	6.2
	12 + months	Naïve	27	18	9	33.3
		Non-Naïve	360	275	85	23.6
		Total	387	293	94	24.3
Madadeni	5 or less	Naïve	106	25	81	76.4
		Non-Naïve	55	14	41	74.5
		Total	161	39	122	75.8
	6+ Months	Naïve	106	81	25	23.6
		Non-Naïve	55	41	14	25.5
		Total	161	122	39	24.2
	12 + months	Naïve	106	22	84	79.2
		Non-Naïve	55	3	52	94.5
		Total	161	25	136	84.5

Hospital	Period	Group	Number of			
			Initial Sample	Censored	Uncensored	Uncensored (%)
Murchison	5 or less	Naïve	43	18	25	58.1
		Non-Naïve	260	49	211	81.2
		Total	303	67	236	77.9
	6 + Months	Naïve	43	25	18	41.9
		Non-Naïve	260	211	49	18.8
		Total	303	236	67	22.1
	12 + months	Naïve	43	9	34	79.1
		Non-Naïve	260	90	170	65.4
		Total	303	99	204	67.3
Northdale	5 or less	Naïve	177	26	151	85.3
		Non-Naïve	6	1	5	83.3
		Total	183	27	156	85.2
	6 + Months	Naïve	177	151	26	14.7
		Non-Naïve	6	5	1	16.7
		Total	183	156	27	14.8
	12 + months	Naïve	177	104	73	41.2
		Non-Naïve	6	3	3	50.0
		Total	183	107	76	41.5

Note: A single missing value (patient) for Murchison, 303 reflected instead of 304

Antiretroviral Treatments Regimens

Patients in the study cohort would have been treated with HAART regimens as per the ARV treatment programme. At the time of study commencement, in 2010, new ARV treatment guidelines were published which advocated tenofovir (TDF) based regimen as first line therapy in new patients as opposed to previous guidelines of 2004 which primarily used stavudine (D4T). Due to the nature of the study and the enrolment of both naïve and non-naïve patients, as well the duration of HAART treatment per patient, the use of a wide range of regimens was noted among the cohort of patients.

Table 7. Summary of HAART Regimens Used by Patients in the Cohort

HAART Regimen	GJ Crookes		Grey's		Madadeni		Murchison		Northdale		Summary		Total
	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-Naïve	Naïve	Non-naïve	
3TC-d4T-EFV	1	2	3	35	3	8	16	74	5	2	28	121	149
3TC-d4T-NVP	0	66	1	17	0	2	4	71	1	0	6	156	162
3TC-AZT-EFV	1	15	1	20	4	5	0	5	4	0	10	45	55
3TC-AZT-NVP	0	35	1	11	0	0	0	15	8	0	9	61	70
3TC-TDF-EFV	11	78	14	57	74	22	11	36	105	2	215	195	410
3TC-TDF -NVP	4	28	2	23	23	9	10	71	25	1	64	132	196
3TC-ABC-EFV	0	2	0	9	3	3	2	3	20	0	25	17	42
3TC-ABC-NVP	0	12	0	1	0	0	0	0	0	0	0	13	13
3TC-d4T-LPV/RTV	0	31	0	1	0	0	1	0	2	0	3	32	35
3TC-AZT-LPV/RTV	1	0	1	23	0	0	1	5	0	0	3	28	31
3TC-TDF-LPV/RTV	0	1	5	97	1	7	2	23	0	0	8	128	136
3TC-ABC-LPV/RTV	0	0	0	1	2	1	2	3	7	1	11	6	17
AZT-DDI-EFV	0	4	0	0	0	0	0	0	0	0	0	4	4
AZT-DDI-LPV/RTV	0	2	0	36	0	0	1	12	0	0	1	50	51
AZT-EFV-LPV/RTV	0	0	0	1	0	0	0	0	0	0	0	1	1
AZT-TDF-LPV/RTV	0	0	0	8	0	0	0	0	0	0	0	8	8
3TC-DDI-LPV/RTV	0	0	0	17	0	0	0	0	0	0	0	17	17
3TC-ABC-DDI-LPV/RTV	0	0	0	1	0	0	0	0	0	0	0	1	1
3TC-AZT-DDI-LPV/RTV	0	0	0	4	0	0	0	0	0	0	0	3	3
3TC-AZT-EFV-LPV/RTV	0	0	0	1	0	0	0	0	0	0	0	1	1
TDF-EFV-LPV/RTV	0	0	1	0	0	0	0	0	0	0	1	0	1
TDF-NVP-LPV/RTV	0	0	0	1	0	0	0	0	0	0	0	1	1
3TC-D4T-TDF	0	0	0	0	0	1	0	0	0	0	0	1	1
EFV-LPV/RTV	0	0	0	1	0	1	0	0	0	0	0	2	2
3TC-AZT-Atazanavir	0	0	0	1	0	0	0	0	0	0	0	1	1
Total	18	276	29	366	110	59	50	318	177	6	384	1024	1408

Table 7 shows the summary of the different HAART regimens used by patients in the entire study in all the five hospitals. Since the study was prospective and followed-up patients over a period of time, some patients had used more than one HAART regimen over time due to changes in therapy. The tenofovir-based regimens (TDF-3TC-EFV or TDF-3TC-NVP) were the most common regimens used across all hospitals accounting for 53% of all regimens used in the cohort (naïve and non-naïve). This is expected and consistent with the 2010 ARV treatment guidelines for adult patients. In addition, stavudine-based regimens accounted for 24.6% of all regimens used in the cohort. This was mainly in the non-naïve patients from Grey's hospital and Murchison hospital who would have been initiated on D4T prior to the change in treatment guidelines in April 2010.

Second line and other treatment regimens comprised at least 6.6% of all the regimens used. The range of use of HAART regimens varied between the groups and hospitals with non-naïve patients at Grey's hospital having the widest range. This is due to Grey's hospital being a tertiary facility and is thus a referral site for the management of patients with advanced disease or complications requiring specialized treatment regimens. Hence all third line regimens were among non-naïve patients at Grey's hospital. A total of 22 different drug combinations of HAART were noted for Greys which included four cases of quadruple HAART therapy.

Summary of key adverse events

Table 8 shows a summary of the key AEs recorded during the study period for both naïve and non-naïve patients across the five hospitals. A total 869 adverse events were recorded. Of these 210 were among naïve patients and 659 among non-naïve patients. Greys hospital had the most number of adverse events recorded. For the in depth analysis, only the following selected adverse events (where relevant) that were documented will be discussed viz. anaemia, diarrhoea, lactic acidosis, peripheral neuropathy, symptomatic hyperlactataemia, lipodystrophy, hypercholesterolaemia, hyperglycaemia, skin reaction, thrombocytopenia, depression, visual disturbance, and vomiting (refer to table 8).

Table 8. Summary of Adverse Events Recorded among Naïve and Non-Naïve Patients

Adverse Event Type	GJ Crookes			Grey's			Madadeni			Murchison			Northdale		
	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total
Haematological															
Anaemia	2	8	10	3	23	26	3	0	3	0	1	1	3	0	3
Neutropaenia	0	0	0	0	3	3	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	4	7	11	0	0	0	0	0	0	0	0	0
Central Nervous System															
Depression	0	0	0	0	8	8	1	1	2	0	0	0	0	0	0
Dizziness	0	4	4	0	11	11	0	0	0	0	1	1	5	0	5
Epilepsy	0	1	1	0	0	0	0	0	0	1	0	1	1	0	1
Headaches	0	15	15	2	11	13	3	0	3	0	0	0	12	0	12
Sleep Disturbances	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Hepatic															
Hepatitis	0	0	0	2	3	5	0	0	0	0	0	0	2	0	2
Pancreatitis	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0
Splenomegaly	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Renal															
Increased Creatinine	0	0	0	3	19	22	3	2	5	0	0	0	0	0	0
Nephrotoxicity	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0
Renal Failure	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0
Metabolic															
Hypercholesterolaemia	0	2	2	5	55	60	0	0	0	0	0	0	1	0	1
Hyperglycaemia	0	0	0	1	27	28	0	0	0	0	0	0	0	0	0
Symptomatic Hyperlactataemia	0	2	2	1	28	29	0	0	0	0	0	0	0	0	0
Lactic acidosis	0	0	0	1	5	6	0	0	0	0	2	2	1	0	1
Lipoatrophy	2	8	10	0	21	21	0	0	0	1	14	15	1	0	1
Lipodystrophy	0	5	5	0	27	27	0	2	2	1	33	34	1	0	1

Antiretroviral Cohort Adverse Event Monitoring in Kwazulu-Natal

Adverse Event Type	GJ Crookes			Grey's			Madadeni			Murchison			Northdale		
	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total	Naïve	Non-Naïve	Total
Dermatological															
Skin Reaction	1	16	17	7	40	47	11	1	12	2	5	7	44	2	46
Steven Johnson Syndrome	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Gastrointestinal															
Nausea	0	5	5	0	25	25	0	0	0	0	0	0	0	0	0
Vomiting	0	1	1	3	28	31	0	0	0	1	1	2	3	0	3
Diarrhoea	0	5	5	5	35	40	2	0	2	0	0	0	14	0	14
Other															
Peripheral neuropathy	4	46	50	5	57	62	8	7	15	2	13	15	22	0	22
Gynaecomastia	0	0	0	1	2	3	1	0	1	0	1	1	1	0	1
Miscarriage	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Death	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0
Fatigue	1	4	5	0	0	0	0	0	0	0	0	0	0	0	0
Glaucoma	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Visual Disturbances	0	4	4	1	3	4	0	0	0	0	0	0	0	0	0
Total per facility	10	127	137	45	445	490	32	13	45	8	71	79	114	2	116

Report on Study Objectives

Primary objectives

Incidence rate of adverse events among naïve patients

Incidence refers to new cases of an event in patients during a defined period. The incidence rate of AEs was computed as the number of observed cases of new AEs divided by the total person-time (in months) contributed by each patient in the study. The person-time for patients reporting an AE was computed as date of first reported event minus the date of initiation on HAART. In patients who did not experience an AE, the period-time was computed as date of last follow-up minus the date of initiation on HAART

Table 9. Incidence rate of selected adverse events among naïve patients

Adverse Event	Incidence rate per 1000 person-months					
	Crookes	Greys	Madadeni	Murchison	Northdale	Overall
Anaemia	e	10.4	4.0	0	1.7	3.4
Diarrhoea	0	18.4	2.7	0	8.2	6.7
Lactic Acidosis	0	3.4	0	0	0.6	0.6
Peripheral Neuropathy	35.1	17.5	10.9	7.6	13.4	13.5
Lipoatrophy	16.4	0	0	3.7	0.6	1.2
Lipodystrophy	0	0	0	3.7	0.6	0.6
Hypercholesterolaemia	0	0	0	0	0.6	0
Hyperglycaemia	0	3.4	0	0	0	0.3
Increased Creatinine	0	10.9	4.0	0	0	1.9
Skin Reaction	8.7	27.5	15.8	7.6	24.4	20.8
Thrombocytopenia	0	15.3	0	0	0	1.2
Depression	0	0	1.3	0	0	0.3
Visual Disturbance	0	3.3	0	0	0	0.3
Vomiting	0	11.2	0	0	1.7	1.9

Table 9 reflects the incident rates of selected AEs for naïve patients noted during the study period. These have been computed per hospital since certain AEs were not reported for some hospitals. Thus the incidence rates need to be interpreted with caution. Whilst it may be appropriate to consider the overall incidence rate for certain AEs, some incidence rates are specific to individual hospitals. Skin reaction and peripheral neuropathy was most common with overall incidence rates of 20.8 and 13.5 cases per 1000 person-months respectively. This was followed by diarrhoea and then anaemia with overall incidence rates of 6.7 and 3.4 per 1,000 person-months respectively.

Prevalence of adverse events among non-naïve patients

Prevalence of AE was calculated as the number of observed cases AEs among non-naïve patients divided by the total number of non-naïve patients in the study. A total of 957 non-naïve patients were used in the computation.

Table 10. Prevalence of selected adverse events among non-naïve patients

Adverse Event	Prevalence-Non-naïve patients					Overall prevalence
	JG Crookes (N=275)	Greys (N=360)	Madadeni (N=55)	Murchison (N=261)	Northdale (N=6)	
Anaemia	0.0291	0.0639	0	0.00766	0	0.0345
Diarrhoea	0.0182	0.0972	0	0	0	0.0418
Lactic acidosis	0	0.0139	0	0.0077	0	0.0073
Peripheral neuropathy	0.0167	0.1583	0.127	0.0498	0	0.1296
Symptomatic hyperlactataemia	0.00727	0.0777	0	0	0	0.0313
Lipodystrophy / lipoatrophy	0.0473	0.133	0.0364	0.18	0	0.115
Hypercholesterolaemia	0.00727	0.153	0	0	0	0.0596
Hyperglycaemia	0	0.075	0	0	0	0.0282
Increased creatinine	0	0.0528	0.0364	0	0	0.0219
Skin reaction	0.0582	0.1111	0.0182	0.0192	0.333	0.0669
Thrombocytopenia	0	0.0194	0	0	0	0.0073
Depression	0	0.0222	0.0182	0	0	0.0094
Visual disturbance	0.0145	0.00833	0	0	0	0.00732
Vomiting	0.00364	0.0778	0	0.00383	0	0.0313

Table 10 above provides the crude prevalence of AEs amongst non-naïve patients on HAART. The number of cases (n) of AEs for each hospital is derived from table 7. Values in the table need to be interpreted with caution. In some instances it is appropriate to use the overall prevalence whilst in others it may be more accurate to report individual prevalence rates per hospital.

It is noted from the above table that peripheral neuropathy was the most common clinical AE documented for non-naïve patients with an overall prevalence of 12.9%. This was followed by lipodystrophy/lipoatrophy and skin reaction which had overall prevalence rates of 11.5% and 6.7% respectively. For hypercholesterolaemia a prevalence of 6.0% was observed. All other commonly known AEs had overall prevalence rates ranging from 2-4%.

Pregnancy related adverse events

Since the sample of confirmed pregnancies among naïve patients in the cohort was very small and there were very few cases of adverse events noted in this group, calculation of incidence was considered inappropriate. A descriptive summary of pregnancy related adverse events is thus reported.

Table 11. Summary of adverse events among pregnant women

Adverse Event	Non-Naïve patients (N=13)					Overall
	JG Crookes (N=7)	Greys (N=4)	Madadeni (N=0)	Murchison (N=2)	Northdale (N=0)	
Diarrhoea	0	1	0	0	0	1
Symptomatic hyperlactataemia	0	0	0	1	0	1
Peripheral neuropathy	1	1	0	0	0	2
Skin reaction	1	1	0	0	0	2
Thrombocytopaenia	0	1	0	0	0	1
Virological failure	1	1	0	0	0	2
Vomiting	0	1	0	0	0	1
Total	3	6	0	1	0	10

Adverse Event	Naïve patients (N=23)					Overall
	JG Crookes (N=1)	Greys (N=1)	Madadeni (N=1)	Murchison (N=0)	Northdale (N=20)	
Anaemia	0	1	0	0	0	1
Lipodystrophy	0	0	1	0	0	1
Hypercholesterolaemia	0	1	0	0	0	1
Treatment failure	0	1	0	0	0	1
Miscarriage	0	0	0	0	1	1
Total	0	3	1	0	1	5

Table 11 above provides a summary of all the AEs that were recorded for pregnant women. As noted previously in Table 3, there were 36 patients reported as being pregnant, 23 of whom were naïve and 13 non-naïve. There were 10 cases of AEs recorded for non-naïve and 5 cases for naïve patients. Multiple AEs may have occurred in one patient. Of significance is the one case of miscarriage in a naïve patient at Northdale hospital. This occurred in the third trimester of pregnancy. Patient was on TDF-3TC-NVP regimen for a period of 221 days prior together with isoniazid preventive therapy (IPT) and pyroxicline. The cause of miscarriage was not specified.

Two cases of virological failure and one case of treatment failure were also recorded among pregnant women. Poor patient adherence to treatment was cited as the reason.

HAART Regimens and Other Medication on Which AEs Potentially Occurred

Table 12. Potential causal association for adverse events

Regimen	Anaemia	Diarrhoea	Lactic Acidosis	Lipodystrophy	Lipoatrophy	Symptomatic hyperlactataemia	Hypercholesterolaemia	Hyperglycaemia	Increased Creatinine	Peripheral Neuropathy	Skin Reaction	Thrombocytopenia	Depression	Vomiting
3TC-d4T-EFV	0	0	0	14	14	6	7	0	0	18	9	0	0	1
3TC-d4T-NVP	0	0	1	20	8	0	0	0	0	15	8	0	0	0
3TC-d4T-LPV+RTV	0	0	0	1	0	0	0	0	0	0	0	0	0	0
3TC-AZT-EFV	2	0	0	2	0	4	0	0	0	4	6	0	2	0
3TC-AZT-NVP	1	0	1	2	3	1	0	0	0	4	5	0	0	1
3TC-AZT-LPV+RTV	2	4	0	2	1	4	5	3	0	3	1	0	0	3
3TC-TDF-EFV	0	0	1	1	2	2	0	0	6	0	48	0	2	4
3TC-TDF-NVP	0	0	0	0	0	0	0	0	2	0	16	0	0	1
3TC-TDF-LPV+RTV	0	19	0	6	3	1	9	5	9	0	0	0	0	10
3TC-ABC-EFV	0	0	0	2	1	1	0	0	0	0	7	0	1	1
3TC-ABC-NVP	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3TC-ABC-LPV+RTV	0	7	0	1	0	0	1	0	0	0	0	0	0	4
3TC-ddI-LPV+RTV	0	1	0	1	0	1	1	1	0	0	0	0	0	2
3TC-AZT-ddI-LPV+RTV	0	1	0	0	0	0	0	0	0	0	0	0	0	0
3TC-EFV-LPV+RTV	0	0	0	0	0	0	5	0	0	0	2	0	0	1
TDF-EFV-LPV+RTV	0	0	0	0	0	0	1	0	0	0	0	0	0	0
AZT-EFV-LPV+RTV	0	0	0	0	0	0	0	0	0	0	1	0	0	0
AZT-TDF-LPV+RTV	1	1	0	0	0	0	3	0	0	1	0	0	0	2
AZT-ddI-LPV+RTV	1	4	1	2	5	1	6	5	0	3	0	0	0	5
TB treatment/IPT	0	0	0	0	0	0	0	0	0	55	8	0	0	0
Cotrimoxazole	0	1	0	0	0	0	0	0	0	0	10	0	0	1
Streptomycin	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Co-amoxiclav	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Metformin	0	0	0	0	0	0	0	0	0	3	0	0	0	0
Multivitamin tabs	0	0	0	0	0	0	0	0	0	0	0	0	0	1
'Unknown'	37	22	5	15	10	10	25	14	9	58	8	11	5	0

Table 12 reflects the summary of potential causal agents for selected adverse events among patients from all study sites. Lipodystrophy/lipoatrophy and peripheral neuropathy occurred most commonly on stavudine-based regimens. A large number of peripheral neuropathy cases were also associated with TB treatment or isoniazid preventive therapy rather than HAART. Skin reactions were noted primarily with efavirenz and nevirapine-based regimens whilst diarrhoea was most commonly observed in patients on lopinavir/ritonavir based regimens. Skin reactions were also associated with the use of TB medication and cotrimoxazole as well. The term 'unknown' reflects adverse events for which no possible association with any

medication could be linked. However, many of these ‘adverse events’ may also be caused directly by the HIV disease itself or opportunistic infections.

Quality Improvement Opportunities Identified

- Poor maintenance of manual records at healthcare facilities resulted in the inability to find patient files when needed. This often resulted in new patient files being duplicated. In addition, there was no system in place for identification and archiving of patient files that were no longer required. The Study Coordinating Office provided support and mentorship to one of the study sites for the reorganisation of filing rooms at the clerking office. This intervention reduced their ARV patient numbers by approximately 2000 which implied patients who were lost to follow up, demised or transferred out were not being subtracted from the patient numbers. This resulted in inflated patient statistics being submitted to District and Provincial Offices. With the cleaning of the filing rooms, and rearrangement of patient files; correct patient numbers were being computed.
- In general, patient flow at study sites did not follow a logical pathway to streamline overall patient management and therefore was not conducive to the study. With the implementation of the ACADEMIK Study, patient flow pathways were developed for all sites in order to decrease congestion and ensure optimal patient flow. Sites such as Murchison, GJ Crookes and Greys implemented the patient flow process suggested which improved the movement of patients between different departments.
- Some facilities did perform the recommended screening tests for patients as per the ARV treatment guidelines whilst other sites did not adhere to the guidelines when managing patients. As an example; although both TB and STI screening were included as the basic screening tests, only TB screening was performed at some sites while STI screening was not performed on a regular basis (Murchison, Madadeni, and Northdale). Patients were only evaluated for STIs when they presented with symptoms.
- With the use of manual patient record forms, results from routine laboratory investigations were usually misplaced and could not be found in patients’ folders. It is unclear whether these tests were completed and misplaced or were not done at all. The inability to monitor laboratory parameters over a period of time is a serious problem and may result in suboptimal patient management. In addition, this may also result in duplication of tests, thus increasing costs.
- One of the key findings of this study is that the sites (GJ Crookes and Greys) that did use the IePRS for direct capture of patient information had more complete patient records which enabled more information to be documented for the study. Thus a greater number of AEs were identified at these sites. In contrast, procedures at the remaining sites (Murchison, Northdale, and Madadeni) involved the health care workers transcribing patient information on the manual data collection tools. This information was then subsequently captured on the IePRS by a data capturer. This process sometimes resulted in the non-use of the data collection tool to transcribe patient information, and hence the inconsistent recording of patient information on the IePRS.
- At a hospital level, HAART care forms a parallel and not an integrated service. Co-morbidities are managed at other clinics, while ARV care is provided specifically in the ARV clinic. Therefore all patients on HAART have two patient files; a ‘general

outpatient file' and 'ARV clinic file' which prevent patients from being viewed in a holistic manner. For most patients, co-morbidities and concomitant medication were not documented on the ARV patient file. They were only recorded in the outpatient file. Thus the clinician at ARV clinic may not be aware of a pre-existing disease condition or medication that a patient might be taking. A similar situation may arise if patients are admitted as this is usually documented in the general outpatient file. Hence the doctor at the ART clinic may again be unaware of a patient's hospitalisation, unless the patient remembers to inform the doctor.

CONCLUSION

The ACADEMIK cohort study was undertaken with the ultimate aim of establishing and sustaining an active cohort event monitoring surveillance for ARVs within the public health sector in KZN. The main purpose was for the province to be able to collect information on ARV AEs in a more structured and scientifically validated way that would allow for dissemination and use of the information for decision-making purposes. This would have contributed to the existing knowledge on ARVs thereby enhancing quality of care of patients on the ARV programme.

The study did not achieve all of its intended objectives due to the previously cited limitations. The study did however collect some data on AEs from 1,328 ARV patients in KZN. A total of 869 AEs were recorded among the study cohort: 210 amongst the naïve patients and 659 amongst the non-naïve patients. Among the naïve patients, skin reaction and peripheral neuropathy had the highest incidence with overall incidence rates of 20.8 and 13.5 cases per 1000 person-months respectively. Among the non-naïve patients, peripheral neuropathy was the most common AE with an overall prevalence of 12.9 percent. This was followed by lipodystrophy/lipoatrophy and skin reaction which had overall prevalence rates of 11.5% and 6.7% respectively.

Lipodystrophy/ lipoatrophy and peripheral neuropathy occurred most commonly on stavudine-based regimens. Skin reactions were noted primarily with efavirenz and nevirapine-based regimens whilst diarrhoea was most commonly observed in patients on lopinavir/ritonavir based regimens. A large number of AEs were also associated with other concomitant medication such as TB medication and co-trimoxazole as well as manifestations of HIV disease.

The study was also able to highlight both clinical and operational gaps within the ARV treatment programme as a whole (although this was not a study objective) that need to be considered by the HAST directorate in order to improve the quality of service and care to ARV patients. This becomes even more critical as the number of patients on HAART increases which will require greater capacity and more efficient systems and processes for holistic patient management.

Despite the challenges faced with the ACADEMIK study, there are undoubted benefits to implementing active surveillance of AEs within the ARV treatment programme. It should therefore continue to be given importance. The ACADEMIK study can serve as a catalyst for sustainable active surveillance at specific sites. With adequate capacity, hospitals that showed potential for yielding good data may continue to be supported and strengthened in the follow-up of their patients through the use of the IePRS system.

LESSONS LEARNED AND RECOMMENDATIONS

Lessons Learned

Cohort event monitoring is an extremely valuable method for gathering information on AEs to ARVs. However, it is also a very resource intensive method. It is therefore important that before embarking on such a study or study, a thorough situational analysis is undertaken to determine actual resources needed for implementation. In terms of the ACADEMIK study, it underestimated the human resource capacity needs. Capacity was created at the central level for overall coordination and data management but limited capacity was created operationally. The study relied fully on existing clinicians and staff from the health facility for implementation. With high patient burden it was not possible for clinicians at the ARV clinic to adhere completely to the operational guidelines. Training was undertaken a many times during the study period but this proved to be insufficient. The high staff turnover would have required continuous training on the protocol on a weekly/monthly basis. Although a site investigator was appointed at each site, this person held numerous other responsibilities other than stewardship of the project. In most facilities, this person was the ARV programme manager who was also the clinician that attended to patients. Hence, the level of commitment was dependent on the amount of time that could be dedicated to the study between all other responsibilities. In retrospect, it was independent study coordinators for each site should have been appointed.

The study was based on the assumption that if the study was integrated into routine care and used existing tools and systems for the collection of information then one would be able to efficiently gather all of the necessary data for the study. However, the steering committee did not consider that if the existing tools and systems at sites were not functioning optimally, then this would have a negative impact on the study. An example of this was the assumption that if the data collection tools were updated according to the ARV standard treatment guidelines, then patient management practices would follow these guidelines and data would be easy to collect. To the contrary, this proved to be burdensome to healthcare workers.

A study of this magnitude where there is heavy reliance on persons other than the core study team (steering committee) for implementation requires aligning and mobilisation of people to form broader teams. The study failed to create functional teams at the facility level that shared the same vision as the steering committee. Except for communication with the study coordinator on operational issues, there was no engagement of the study sites in monthly steering committee meetings and in major decision-making processes. Hence sites did not take ownership of the study and the level of commitment was very low.

There was overemphasis on enrolment of 10000 patients and hence the focus was on patient recruitment and on increasing numbers rather than on ensuring full readiness of sites prior to commencement. The limited capacity at the study coordinating office did not allow for sufficient monitoring and evaluation of all sites to ensure quality assurance of the process and data collected. In hindsight, because of the challenges being experienced with sites, a decision should have been taken to reduce the number of study sites (perhaps to just 2 or 3 sites) with greater emphasis on monitoring and evaluation of protocol and quality assurance of the data.

Recommendations

Adverse event monitoring forms a key component of the package of care for patients on HAART. Poor identification, management, prevention of AEs does compromise patient treatment outcomes. It may also result in complete treatment failure thus reducing the effectiveness of the ARV treatment programme. Hence it is imperative that management and reporting of AEs by clinicians is integrated into routine care.

National and Provincial authorities need to develop and implement an information system that ensures consistent maintenance of patient information for all patients on HAART. An electronic patient information system would enable efficient management of patients and easy accessibility to patient records over prolonged periods of time. As HIV/AIDS is now considered a chronic disease, patient follow-up would also become easier for clinicians, as they would have faster access to pertinent clinical and laboratory information. This would ensure effective monitoring and evaluation of the quality of care provided at different sites. It would also facilitate the implementation of studies and research activities within public healthcare facilities.

With the continued use of paper-based systems for recording patient information, the adoption of standardised patient record forms at all ARV treatment sites in KZN is of paramount importance. This will ensure consistent and quality care for all ARV patients.

Integration of patient management by different health programmes within public health care facilities is important to ensure holistic patient care as co-morbidities and concomitant illnesses must be considered when monitoring patients on HAART. Innovative ways and systems to promote this should be developed.

New and innovative approaches need to be explored to ensure successful implementation of future surveillance activities. Greater involvement of the pharmaceutical industry in implementation of AE surveillance activities within the public sector can create the necessary capacity that is lacking for effective and sustainable system to be developed. Pharmaceutical companies have the infrastructure, resources and expertise to implement large scale observational studies. Although not legislated in the South Africa as yet, post marketing authorisation safety and efficacy studies are now required by law in the European Union.[11] Hence it is possible that subsidiary companies in SA, given the opportunity, would be willing to invest in such studies within the public sector.

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ANNEX 1. ACADEMIK STEERING COMMITTEE

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ANNEX 2. ELECTRONIC PATIENT RECORD SYSTEM (IEPRS/VEMR SYSTEM)

Overview

Background

VP Health Systems, the developers of the VMER System, was involved with the KwaZulu-Natal Pharmacy Department for over 3 years on a Pharmacovigilance surveillance project and customised and developed additional functionality in the VMER system, specific to the Focussed Antiretroviral Surveillance Project.

The VMER System automates the collection of Adverse Drug reactions encountered at clinic or institution and these in turn are sent electronically to the Provincial Pharmacy office. For those patients on the cohort study who encounter an adverse drug reaction their clinical charts are sent electronically to a central server for analysis.

MSH partnered with the KwaZulu-Natal DOH and VP Health Systems on this project.

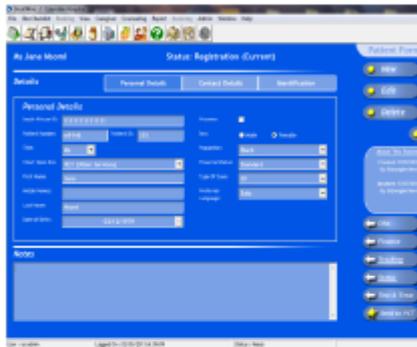
System Modules

- Outpatients Module
- Inpatients Module (Patient Admittance)
- Ward Transfers
- Patient Administration
- Doctor Module
- Nurse Module
- Billing Module
- Maternal Health Module
 - o PMTCT Module
- Paediatric Module
- HCT Module
- Dietician Module
- Pharmacovigilance Component
- Pharmacy Module
 - o Dispensing
 - o Stock Management
 - o Standard Treatment Guidelines (STG's)
- Radiology Module (will need to develop interface)
- Laboratory Module (will need to develop interface)
- Eye Clinic Module
- Paediatric Module
- Chronic Disease Module
 - o ARV
 - o TB
- Link to Wards

System Functions

Patient Registration

The VEMR is an integrated patient management system, which captures complete and relevant patient demographic information.



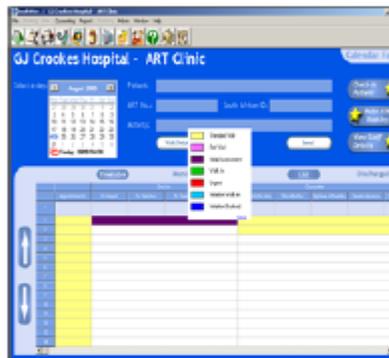
Patient Tracking

The system allows for effective patient tracking which has a significant effect on improving patient flow and provide valuable insight into patient movement that can impact patient care across multiple facilities.



Resource Allocation

Appointment scheduling deals with scheduling of clinical appointments for the patients. The user can view the schedule for a particular clinician; the appointments scheduled for the doctor, the free slots available & blocked slots.



A patient can be moved between the various clinical resources as they become available.



Clinical History

Accurate tracking of patient treatment (including history)



Adverse Drug Reactions



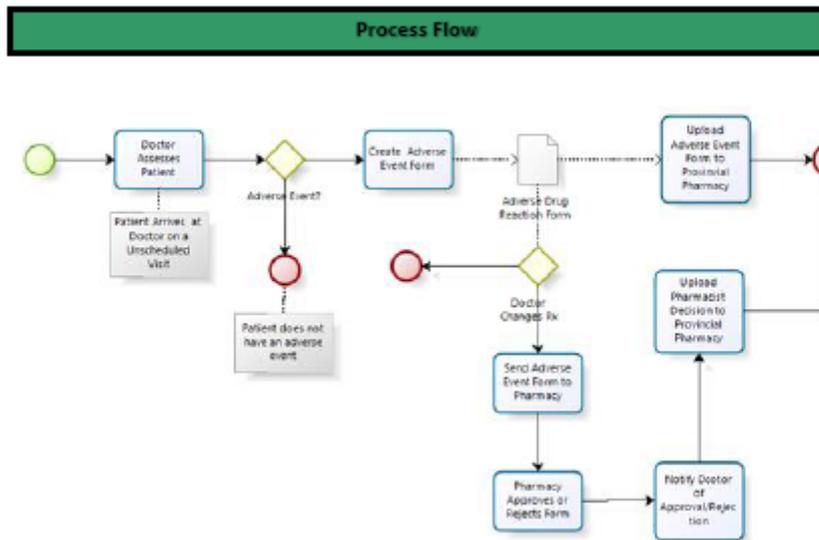
Investigation Record



Adherence Monitoring

An effective computer-based intervention to improve medication adherence among HIV patients.





Solicited Reporting Process

Step 1 – Patient has an unscheduled sick visit **Actor: Registration Clerk**

Patient arrives at the clinic to see the doctor and is checked into the IePRS system by the registration clerk. The patient is scheduled to see the Doctor.

Step 2 – Doctor assesses patient **Actor: Doctor**

The Doctor now assesses the patient and determines that the patient is suffering from an Adverse Drug Reaction. The Doctor logs the details of the Adverse Drug Reaction in the VEMR system against the patient’s visit for the day.

Step 3 – System generates solicited report **Actor: VEMR SYSTEM**

The system generates a solicited report based on the adverse drug reaction logged by the Doctor. All information is defaulted from the patient record.

Step 4 – Solicited report replicated **Actor: VEMR SYSTEM**

The solicited report is replicated overnight onto the Provincial Pharmacy data repository for reporting and data analysis purposes.

Step 5 – Doctor substitutes ARV drug

Actor: Doctor

Due to the adverse drug reaction, the Doctor may substitute an existing ARV drug. If this occurs, the solicited report generated in step 3 is sent to Pharmacy for approval.

Step 6 – Pharmacist approves/rejects report

Actor: Pharmacist

Based on report completeness the solicited report can be approved or rejected by the Pharmacist. This response is replicated up to Provincial Pharmacy for auditing purposes. Due to the automated nature of the solicited reporting, manual processes that involve paper based solicited reports can be updated to use the automated process. This is beneficial as missing reports and delays in processing can now be avoided.

Reporting

<i>Name of Report</i>	<i>Output</i>
<i>Defaulters</i>	Report will produce a breakdown of patients who have been 'Lost to Follow Up', in other word those patients who have not collected drugs in over 90 days. The report will also show all the prescriptions that have been locked due to the fact that the patient has not collected his medication for 14 days as he will have to be re-assessed for possible treatment failure.
<i>TB Suspects</i>	A list of patients that are suspected of having TB.
<i>Missing Labs</i>	The reports highlights those patients whose CD4 and viral load results have not been received and need to be followed up on.
<i>Change in CD4</i>	A list of patients who's CD4 has dropped significantly are produced as it could indicate treatment failure, those patient are followed up on as a matter of urgency.
<i>Drug Usage</i>	A breakdown of the number of drugs that have been dispensed by the institution.
<i>Stock Received</i>	Number of stock that has been received and captured into the system.
<i>Stock at Hand</i>	Current level of stock that is still at hand.
<i>Stock Running Low</i>	Shows which stock items are running low and need to be reordered.
<i>Stock Expiry</i>	Shows stock items that have expired and need to be destroyed.
<i>Regimen Accumulated Statistics Report</i>	A breakdown of the different kinds of regimens that have been issued during a certain time frame.
<i>Patient Status Report</i>	A breakdown of the numbers of patients according their status. I.e. Active vs. Inactive patients.
<i>Initiations Report</i>	A list of patients that are eligible and due to be initiated on ARV's.

Paediatrics Initial Assessment: Page 3

NAME OF PATIENT:		IDENTITY NUMBER:	
5. CLINICAL ASSESSMENT: FIRST VISIT AT THIS CLINIC			
<i>Use this section during your patient's first encounter with HIV / ART services to help decide whether they need HIV or ARV care</i>			
**WHO CLINICAL STAGING:			
If your patient has, OR HAS EVER HAD, any of the illnesses below, and none in stage 4 (except EPTB), and a CD4 count >200, they need HIV ca		your patient has, OR HAS EVER HAD, any of the illnesses below or their CD4 count is <200, they need ARV therapy	
Clinical Features	Date	Clinical Features	Date
Stage 1	Persistent generalised lymphadenopathy	WHO Stage 4 Severe disease (AIDS)	Herpes simplex virus lesions > 1 month
	WHO Stage 2 Recurrent & Varied Disease Presentations		Hepatosplenomegaly
Papular pruritic eruptions		Pneumocystis pneumonia	
Seborrhoeic dermatitis		Kaposi's sarcoma	
Extensive human papilloma virus infection		HIV wasting syndrome/malnutrition	
Extensive molluscum contagiosum		HIV encephalopathy	
Fungal nail infections		Extrapulmonary TB	
Recurrent oral ulcerations		Cytomegalovirus	
Linear gingival erythema (LGE)		Isosporiasis / Cryptosporidiosis	
Angular cheilitis		CNS toxoplasmosis	
Parotid enlargement		Cryptococcal meningitis	
Herpes zoster	CMV retinitis /infection (onset age>1 month)		
Recurrent or chronic RTIs	Extrapulmonary cryptococcosis incl meningitis		
WHO Stage 3 Chronic & Persistent Diseases	Moderate malnutrition not responding to std therapy	Disseminated non TB mycobacterial infection	
	Unexplained persistent diarrhoea (14 days or more)	Candida of trachea, bronchi or lungs	
	Unexplained persistent fever (>1month)	Visceral herpes simplex infection	
	Oral candidiasis (outside neonatal period)	Acquired HIV-associated rectal fistula	
	Oral hairy leukoplakia	Cerebral or B cell non-Hodgkins lymphoma	
	Acute necrotizing ulcerative gingivitis/periodontitis	Progressive multifocal leukoencephalopathy	
	Pulmonary TB	HIV associated cardiomyopathy or nephropathy	
	TB lymphadenopathy (axillary, cervical or inguinal)		
	Anaemia & neutropaenia & thrombocytopenia for >1 month		
	Chronic HIV associated lung disease incl bronchiectasis		
Symptomatic lymphoid interstitial pneumonitis (LIP)			
Severe recurrent bacterial pneumonia			
**TUBERCULOSIS SCREEN			
Previous TB →	Y	N	Outcome
TB symptoms today →	1) Cough > 2 wks Y / N	2) Weight loss Y / N	3) Fever Y / N
			4) Night sweats Y / N
			5) Haemoptysis Y / N
			6) Fatigue Y / N
Smear date			Culture / sensitivity date
Result			Clinical indication of TB Y / N
TB treatment supervisor's name			
**NUTRITIONAL SCREEN			
Date of assessment:	A. Weight: (kg)	B. Height (meters)	Nutritional Risk Score (0-6)
/ /			
HISTORY AND EXAMINATION			
Temperature:	Pulse:	Urinalysis	Respiratory Rate:
PRIOR ARV HISTORY			
**ARVs prior to above start date?		NONE / PMTCT / HAART / PEP	
List ARVs that were used:			

Paediatrics Initial Assessment: Page 4

NAME OF PATIENT:			IDENTITY NUMBER:				
6. CLINICAL EVALUATIONS FOR ARVs OR RE-STARTED ARVs							
<i>If ART therapy is indicated for your patient, use this section to help decide whether there are any medical contra-indications to starting</i>							
BASELINE BLOOD TESTS							
Test	Date	Result	Others:	Test	Date	Result	
**CD4				Haemoglobin (AZT based			
ALT (NVP based regimens)				Creatinine (TDF based Regimens)			
				Glucose			
				Cholesterol			
				Triglycerides			
**TRADITIONAL/ ALTERNATIVE/COMPLEMENTARY MEDICINE							
(If patient is not on Traditional Medication, then the healthcare worker must indicate none)							
Is the patient currently taking Traditional/ Alternative/Complementary Medication: <input type="checkbox"/> Y <input type="checkbox"/> N Indication:							
Name of Product:			Duration of Treatment:				
Did the patient previously take traditional/ alternative/complementary medicines: <input type="checkbox"/> Y <input type="checkbox"/> N							
Name of Product:			Duration of Treatment:				
**CURRENT CONCOMITANT ILLNESSES							
Eg Asthma, including HIV Conditions or other disease conditions (If no current concomitant illnesses, healthcare worker must indicate none.)							
**CONCOMITANT MEDICATION							
Eg Any medication used for concomitant medication (If patient not on concomitant medication, healthcare worker must indicate none)							
ANTIRETROVIRALS AND MEDICATION FOR OPPORTUNISTIC INFECTION							
LIST THE ARVs, DOSES AND DOSING FREQUENCY TO BE INITIATED							
ARV 1							
ARV 2							
ARV 3							
Cotrimoxazole							
Fluconazole							
INH							
Print name:		Signature:		Date: / /			

Adults Initial Assessment: Page 3

NAME OF PATIENT:				IDENTITY NUMBER:			
5. CLINICAL ASSESSMENT: FIRST VISIT AT THIS CLINIC							
<i>Use this section during your patient's first encounter with HIV / ART services to help decide whether they need HIV or ARV care</i>							
**WHO CLINICAL STAGING:							
If your patient has, OR HAS EVER HAD, any of the illnesses below, and none in stage 4 (except EPTB), and a CD4 count >200, they need HIV ca				your patient has, OR HAS EVER HAD, any of the illnesses below or their CD4 count is <200, they need ARV therapy			
Clinical Features		Date		Clinical Features		Date	
WHO Stage 2 <small>Moderate disease</small>	1	Condition:		WHO Stage 4 <small>Severe disease (AIDS)</small>	Herpes simplex virus lesions > 1 month		
		Weights loss <10% body weight			Oesophageal candidiasis		
		Minor mucocutaneous conditions			Pneumocystis carinii pneumonia		
		Recurrent URTI			Kaposi's sarcoma		
	Uncomplicated herpes zoster		HIV wasting syndrome				
	Other:		HIV encephalopathy				
WHO Stage 3 <small>Moderate disease</small>		Weight loss >10% body weight			Recurrent pneumonia		
		Diarrhoea > 1 month			Cytomegalovirus		
		Oral candidiasis			Isosporiasis / Cryptosporidiosis		
		Severe bacterial infections including Pneumonia			Bedridden > 50% / day for most of last month		
		Oral hairy leukoplakia		Cryptococcal meningitis			
		Prolonged fever		Cervical cancer			
	Bedridden < 50% / day for most of last month		Lymphoma				
	Pulmonary TB (current or in the last year)		Other:				
	Other:		Other:				
4		Extra-pulmonary TB					
**REPRODUCTIVE HEALTH							
Pregnant	Y	N	Trimester	1	2	3	Pap smear result: _____ Date: _____
Contraception: _____ Date last used: _____							
none / condom / injection / pill / other							
Signs and symptom of STI today?	1) Urethral discharge/dysuria	2) Vaginal discharge	3) Genital ulcers	4) Genital warts	5) Lower abdominal pain	RPR (date)	Result _____ Treatment completed Y / N
**TUBERCULOSIS SCREEN							
Previous TB	→	Y	N	Outcome			
TB symptoms today	→	1) Cough > 2 wks	2) Weight loss	3) Fever	4) Night sweats	5) Haemoptysis	6) Fatigue
		Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Smear date				Culture / sensitivity date			Clinical indication of TB Y / N
Result				Result			
TB treatment supervisor's name _____							
**NUTRITIONAL SCREEN							
Date of assessment:	/ /	A. Weight (kg)		B. Height (meters)			
HISTORY AND EXAMINATION							
Temperature:		Pulse:		Urinalysis		Blood Pressure:	
PRIOR ARV HISTORY							
**ARVs prior to above start date?		NONE / PMTCT / HAART / PEP					
List ARVS that were used:							
Print name:		Signature:		Date:		/ /	

Adults Initial Assessment: Page 4

NAME OF PATIENT:			IDENTITY NUMBER:				
6. CLINICAL EVALUATIONS FOR ARVs OR RE-STARTED ARVs							
<small>If ART therapy is indicated for your patient, use this section to help decide whether there are any medical contra-indications to starting</small>							
BASELINE BLOOD TESTS							
Test	Date	Result	Others:	Test	Date	Result	
**CD4				Haemoglobin (AZT based			
ALT (NVP based regimens)				Creatinine (TDF based Regimens)			
				Glucose			
				Cholesterol			
				Triglycerides			
**TRADITIONAL/ ALTERNATIVE/COMPLEMENTARY MEDICINE							
(If patient is not on Traditional Medication, then the healthcare worker must indicate none)							
Is the patient currently taking Traditional/ Alternative/Complementary Medici <input type="checkbox"/> Y <input type="checkbox"/> N Indication:							
Name of Product:			Duration of Treatment:				
Did the patient previously take traditional/ alternative/complementary medicines: <input type="checkbox"/> Y <input type="checkbox"/> N							
Name of Product:			Duration of Treatment:				
**CURRENT CONCOMITANT ILLNESSES							
Eg Diabetes, Hypertension, Epilepsy, Peripheral Neuropathy, Asthma, including HIV Conditions or other disease conditions (If no current concomitant illnesses, healthcare worker must indicate none.)							
**CONCOMITANT MEDICATION							
Eg Any medication used for concomitant medication (If patient not on concomitant medication, healthcare worker must indicate none)							
ANTIRETROVIRALS AND MEDICATION FOR OPPORTUNISTIC INFECTION							
LIST THE ARVS, DOSES AND DOSING FREQUENCY TO BE INITIATED							
ARV 1							
ARV 2							
ARV 3							
Cotrimoxazole							
Fluconazole							
INH							
Print name:		Signature:		Date: / /			

Follow Up Questionnaires: Page 1

NAME OF PATIENT :		ID NO.	
MINIMUM DATA SET: TO BE COMPLETED AT THE FIRST VISIT WHEN A NON NAÏVE PATIENT IS INITIATED ON THE ACADEMIK PROJECT			
AGE OF PATIENT:		GENDER:	DATE OF HAART INITIATION:
CD4 CELL COUNT AT INITIATION OF HAART:			
Weight		kg	Blood Pressure:
Clinical Notes (If patient is well on HAART, state clinically stable)			
Reproductive Health		Pregnant Y N Trimester 1 2 3	Contraception none/condom/injection/pill/other
STI screen		Urethral Discharge/Dysuria Y N	Genital Ulcers/Warts Y N
		Vaginal Discharge Y N	Lower Abdominal Pain Y N
TB status		Assessment 1. Does the px have a cough Y N	3. Does the px sweat at night Y
		2. Does the px have loss of weight Y N	4. Do you have a fever Y
		If yes to one/more questions, suspect TB	
		If no to all questions, consider IPT (TB Preventive Therapy)	
Date of Diagnosis of TB		TB Suspect Y N No Signs Y N	IPT Started Y N Sputum Collected Y N
List TB Medication		TB Treatment Start Date	
		TB Treatment Start Date	
Investigations & Results			
TB M / C / S		CD4 (every 6 months) (CD4%):	
Viral Load (once a year)		WCC:	
Haemoglobin		ALT:	
Platelets		Fasting Triglycerides:	
Fasting Cholesterol		Creatinine Clearance:	
Fasting Glucose			
Other investigation results (incl. XR)			
HIV Conditions/ Ois (if no HIV Conditions/Ois- indicate none)			
Traditional /Complementary Meds (if no traditional medication indicate none)		Name:	Date Started:
		Date Stopped:	
Co-Morbidities/ Concomitant Medication (if no concomitant medication/illnesses, indicate none)		Name of Medication (Dose, Dosing Frequency)	Concomitant Illnesses
		To be completed by Pharmacist (dispensed quantity, date, signature)	
Antiretroviral/ OI Medication , Dose and Dosing Frequency			
Has the Antiretrovirals being stopped: Y N			
Reason for stopping:		Date:	
Has there been a change of regimen : Y N		Specify reason:	
If patient experienced an adverse event complete pages 2, 3			
Name of Medication (Dose, Dosing Frequency)		To be completed by Pharmacist (dispensed quantity, date, signature)	
Drugs and Doses			
Adherence			
Pill Count			
1. Did the px return the medication containers			
Adherence Rate= Quantity Dispensed- Quantity Returned/ Quantity Expected to be Taken			
>95% =high adherence 75-94= moderate adherence <75%= low adherence			
2. Self Reporting		1. Does the px know the ARVs, doses and times of doses Y N	
2. Do the px take their ARVS at all times Y N		3. Does the patient stop taking their ARVs w hen they feel sick Y N	
If the patient answers no, to one/more questions, investigate adherence.			
Referred		Nights slept in institution	Date:
Date of next visit / /		Sub-clinic	
Signed (Initialed) Nurse/Doctor		Name of Doctor/Nurse:	Data Capturer:

ANNEX 5: GRADING OF ADVERSE EVENTS

Table	Definition of Severity of Adverse Events	
	Severity	Description
Mild		Grade 1 – Does not interfere with the patient’s usual function (awareness of symptoms or signs, but easily tolerated (acceptable)).
Moderate		Grade 2 – Interferes to some extent with the patient’s usual function (enough discomfort to interfere with the usual activity (disturbing)).
Severe		Grade 3 – Interferes significantly with the patient’s usual function (incapacity to work or to do usual activities (unacceptable)).
Life threatening		Grade 4 – Results in risk of death, organ damage or permanent disability (unacceptable)
Death		Grade 5 – Event has a fatal outcome

Note: It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a serious AE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE

ANNEX 6. ETHICS APPROVAL



RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

Website: <http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx>

11 August 2010

Mr Cyril Shabalala
School of Pharmacy and Pharmacology
Westville Campus
University of KwaZulu- Natal

Dear Mr Shabalala

PROTOCOL: Determination of the incidence and severity of adverse drug reactions as well as risk factors and covariates of adverse events HAART patients that are part of the AKADEMIC Cohort Study in KZN. REF:BE159/09.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application dated 28 July 2009.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 01 June 2010 to queries raised on 20 January 2010 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from **11 August 2010**.

This approval is valid for one year from **11 August 2010**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical

Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/ResearchEthics11415.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** at a full sitting of the Biomedical Research Ethics Committee meeting to be held on **14 September 2010**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely



Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

ANNEX 7. INFORMED CONSENT DOCUMENT: ENGLISH



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Private Bag X 9051
PIETERMARITZBURG, 3200
Tel: 033 846 7267, Fax: 033 846 7280
vusi.dlamini@kznhealth.gov.za/viloshini.manickum@kznhealth.gov.za
pharmacy.ho@kznhealth.gov.za

Patient Information and Informed Consent Document: ACADEMIK STUDY

Introduction

You are being given the opportunity to volunteer to participate in a project conducted by the KwaZulu-Natal Department of Health (KZN DOH) and Strengthening Pharmaceutical Services (SPS). The title of the Study is **ACADEMIK – Antiretroviral Cohort Adverse Event Monitoring in KwaZulu- Natal.**

Purpose of the Study

The purpose of the study is to collect data on patients that are on Antiretroviral Therapy, and have experienced adverse drug events/reactions. While Antiretroviral Therapy has improved the well being of patients that are HIV Positive, adverse drug reactions/events are common and sometimes may be life threatening. The data collection will take place every 6 months/ upon occurrence of the adverse event/drug reaction. The data will be the results of routine blood tests and description of your physical health, since the initiation of HAART. The data will be obtained from your medical records, and no additional blood samples or visits at your clinic will be required. In case of death, information on the cause of death will be collected.

Duration of Study

The planned duration of the study is three calendar years, however the study will continue if additional funds are obtained.

Organisation

- The study coordinating office is Pharmaceutical Policy and Systems Development, Department of Health, 121 Chief Albert Luthuli Street, Pietermaritzburg.
- The Study has been approved by the Department of Health Ethics Committee.

Confidentiality

- Only doctors, nurses and personnel authorised by the Department of Health will have access to your records.
- Results from this study will be analysed and may be published in medical journals, but your identity will not be revealed.
- Your participation is voluntary and you can withdraw your consent at any time, by informing the healthcare worker about your decision. This will not influence your future treatment/hospital care.

.....

ACADEMIK STUDY

Patient Informed Consent (Patients older than 16 years)

(If you decide to participate in the project, please sign this form. You will be given a copy of this form to keep)

- The full nature of the ACADEMIK Study has been explained to me. [Y] [N]
- I have read the patient information sheet and have been given the opportunity to ask questions and these have been answered to my satisfaction. [Y] [N]
- It has been explained to me that in the case of death, my next of kin may be approached for additional information pertaining to the death. [Y] [N]
- It has been explained that I can withdraw my consent at any time for any reason. I will inform the healthcare worker that I will no longer be participating in the study. [Y] [N]
- It has also been explained to me that authorised personnel may review my records but that identifiable information under no circumstances will be made publicly available. [Y] [N]
- I consent to enter the above mentioned study. [Y] [N]

If I have any questions about the study, I can contact Ms Viloshini Manickum/Mr Vusi Dlamini on 033 846 7450/7265

Patient Details

Full Name _____ Signature _____
Patient _____ of _____

ACADEMIK Patient Number: _____ Date: _____

ANNEX 8. INFORMED CONSENT DOCUMENT: KWAZULU-NATAL

Antiretroviral Cohort Adverse Event Monitoring in KZN

ZITHOLELE UKUTHI UNGASIZA KANJANI UKUKHUPHULA IZINGA LOSIZO LOHELELO LOKWELASHWA NOKUNAKEKELWA

ISINGENISO

UMnyango Wezempilo ubambisene ne-MSH/SPS kanye nesikole sosokhemesi seNyuvesi yaKwaZulu-Natal ukupha ithuba lokuzibandakanya nocwaningo oluphathelene nokuphepha ekusetshenzisweni kwamakhambi okulapha isandulela-ngculazi (HIV). Lolucwaningo lubizwa ngokufishane ngokuthi yi-ACADEMIK.

INHLOSO YOCWANINGO

Inhloso yalolucwaningo ukuqoqa imininingwane ephathelene nokungaphatheki kahle weziguli emva kokudla imithi ama-ARV's. Lemithi ilusizo olukhulu ezigulini eziphethwe isifo sengculazi kepha kuyenzeka ihambe iziphathe kabi. Leminingwane izoqoqwa lapho isiguli sivela izimpawu zokuphathwa kabi ilemithi noma njalo emva kwezinyanga eziyisithupha. Sizolandela impilo yakho kanye nemiphumela yokuhlolwa kwegazi ohlala ukwenza kusukela waqala ukudla lemithi. Ucwanningo lizoqoqa iminingwane esekhadini lakho. Ukuzubabikho gazi nakuvakasha okuzobakhona ngaphezu kwalokhu okuvele okulindele. Uma ushona sizodinga ukwazi isizathu sokushona kwakho.

UBUDE BESIKHATHI SOCWANINGO

Kulindeleke ukuthi lolucwaningo luqhubeka isikhathi esingangiminyaka emithathu, kodwa kungenzeka kudlule lapho uma zitholakala izimali zokulixhasa.

IKOMKHULU LOCWANINGO

✂-----✂
-----✂

UCWANINGO I-ACADEMIK – Isivumo emva kokuqonda ucwaningo

(Sicela usayine lenchwadi uma uthanda ukuzibandakanya nocwaningo. Uzonikezwa umfanekiso walenchwadi)

Sengichazelwe ngayo yonke imininingwane yalolucwaningo i-“ACADEMIK”. Sengiyifundile noma sengiyifundelwe incwadi yemininingwane yokwazisa iziguli. Futhi nginikeziwe ithuba lokubiza imibuzo ngabe sengenliseka izingcazelo. Ngichazeliwe ukuthi uma ngishona, abomndeni wami bayocelwa ukuthi bazise abezempilo ngemininingwane yokwedlula kwami. Ngichazeliwe ukuthi ngingahoxa kulolucwaningo noma nini ngenxa yanoma yisiphi isizathu. Ngiyokwazisa abezempilo uma sengihoxa kulolucwaningo. Futhi ngichazeliwe ukuthi abezempilo abagunyaziwe bazocwaninga amakhadi kanye nemininingwane yami, kodwa imininingwane engangidalula ayisoze yakhishelwa emphakathini. Uma ngivukelwa imibuzo ngalolucwaningo ngiyothintana noViloshiini Manickum noma uMnu. Vusi Dlamini enombolweni yocingo 033 846 7265/6/7.

Ngiyavuma ukuzibandakanya nalolucwaningo.

Imininingwane yesiguli

Amagama aphelele _____

Isisayino sesiguli _____ Usuku _____

Imininingwane kazoempilo (Imininingwane yelunga lezoMnyango Wezempilo ebelichazela isiguli)

Amagama aphelele kazoempilo _____

Isisayino sikazoempilo _____ Usuku _____

KWABANTU

ABAPHILA NEGCIWANE I-HIV NESIFO I-AIDS

ANNEX 9. PARENT PERMISSION FORM

PARENT PERMISSION FORM: ACADEMIK STUDY

Purpose of the Study

Your child is invited to participate in a research study. The purpose of this study is to study how well HIV/AIDS medicines are working for your child.

Participants

Your child is being asked to participate in the study because your child is taking HIV/AIDS medicines.

Procedures

If you allow your child to volunteer to participate in this study, your child will not be asked to do anything different when they come to the clinic except maybe answer a few extra questions

Benefits of Participation

There *may/may not* be direct benefits to your child as a participant in this study. However, we hope to learn how we can improve our service to you and your child.

Cost /Compensation

There *will not* be financial cost to you to participate in this study. The study is designed around your visit to the clinic.

Contact Information

If you or your child have any questions or concerns about the study, you may contact Mr **Ms Viloshini Manickum/Mr Vusi Dlamini on 033 846 7450/7265** for questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted you may contact **Mr. S. Reddy, Faculty Research Office at UKZN/KZN DOH at 031 2607902.**

Voluntary Participation

Your child's participation in this study is voluntary. Your child may refuse to participate in this study or in any part of this study. Your child may withdraw at any time. You or your child is encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality

All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link your child to this study.

.....
Signature for Research Involving Children

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate.

You will receive a copy of this signed informed consent document.

Name of Parent or Legally Authorized Representative

Date

Signature of Parent or Legally Authorized Representative

Patient Details

Full Name of Child: _____

ACADEMIK Patient Number: _____

Health Care Worker Details (<i>Details of Health Care Worker that explained the nature of the study to the patient</i>)	
Full Name of Health Care Worker _____	Date _____
Designation _____	Signature _____

ANNEX 10. ASSENT TO PARTICIPATE IN RESEARCH

[ACADEMIK STUDY]

7. My name is [*identify yourself to the child by name*].
8. We are asking you to take part in a research study because we are trying to learn more about using HIV/AIDS medicines in our community.
9. If you agree to be in this study you will visit the clinic as usual, but you may answer a few extra questions.
10. There are no risks in this study.
11. We can use the results we get from this study to make our services better in terms of helping you and managing your treatment.
12. Please talk this over with your parents/guardian before you decide whether or not to participate. We will also ask your parents/guardian to give their permission for you to take part in this study. But even if your parents/guardian say “yes” you can still decide not to do this.
13. If you don’t want to be in this study, you don’t have to participate. Remember, being in this study is up to you and no one will be upset if you don’t want to participate or even if you change your mind later and want to stop.
14. You can ask any questions that you have about the study. If you have a question later that you didn’t think of now, you can call me (*Name of Healthcare Worker*)_____ *Tel No:*_____ or ask me next time. If I have not answered your questions or you do not feel comfortable talking to me about your question, you or your parent can call the Study Coordinating Office at KwaZulu Natal Pharmaceutical Policy and Systems Development at 033 846 7267
15. Signing your name at the bottom means that you agree to be in this study. You and your parents/guardian will be given a copy of this form after you have signed it.

Print your name

Date

Sign your name

ANNEX 11. MANUAL OF OPERATIONS

ANTIRETROVIRAL COHORT ADVERSE EVENT MONITORING IN KWAZULU-NATAL (ACADEMIK)

MANUAL OF OPERATIONS



HEALTH
KwaZulu-Natal

SOP Number	PSD-SOP5/2009/1.0
Date Written	6 July 2010
Compiled by	Viloshini K Manickum
Input given by	
Date of Implementation	
Date of review	When policy changes occur
Date reviewed	

Standard Operating Procedure:

Employment Practices for staff employed by Management Sciences for Health with respect to Focussed Antiretroviral Surveillance

Objective:

- To outline the correct procedures to be followed for staff employed for the FASS Study.

Responsibility:

- Principal Technical Advisor: Monitoring and Evaluation
- Deputy Manager: Focussed Antiretroviral Surveillance
- Data Manager: : Focussed Antiretroviral Surveillance
- Data Capturer: Focussed Antiretroviral Surveillance
- Site Investigator at Institutional level
- Antiretroviral Project Manager
- Pharmacy Manager

Legislative Prescripts:

- Public Finance Management Act (1/1999).
- 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)

Principles:

- Staff employed for the FASS Project must adhere to the principles of Batho Pele, code of conduct of the Department of Health, and Management Sciences for Health.

Signing of Attendance Register

- All staff must sign the attendance register at the Pharmaceutical Policy and Systems Development/ Institutional pharmacy daily.

Work Conditions: Staff at Pharmaceutical Policy and Systems Development

- The Deputy Manager, Data Manager and Data Capturer will be stationed at Pharmaceutical Policy and Systems Development, Trizon Towers.
- Staff are expected to commence and terminate duty at 7.45am and 16h30 respectively. Lunch break is limited to 45 minutes.
- The minimum hours to be worked per day are 8 hours. If time off is taken for emergencies, there is a need to work the time taken, claim for the actual hours worked for that particular day.
- If the data manager/data capturer require requires time off/leave/sick leave, the data capturer must contact the Study Coordinating Officer, Ms Viloshini Manickum(033 8467267/0716852906) or Mr Vusi Dlamini (033 846 7265/
- Vacational leave is 20 days per year, while sick leave is 10 days per year. If vacational leave is not approved before going on leave, the respective staff member will receive no salary for those days. In addition if the respective staff member does not call to inform the Deputy Manager/ Principal Technical Advisor (Monitoring and Evaluation) that he/she is sick, this would result in leave without pay.

- MSH closes for the Christmas/New Years break; therefore it is essential that all vacational leave is not taken before the end of the year. In the event of all 20 days of vacational leave being taken, then relevant staff member will receive leave without pay.
- Time sheets are to be updated weekly, as these sheets must be submitted to Management Sciences for Health by the 21st of each month. If time sheets are not submitted, salaries will not be paid to the respective staff member.

Work Conditions: Staff at Institutional Level

- The data capturer will be working in the ART Clinic, and would be accountable to the Manager, at the ART Clinic.
- The data capturer must start work at 8am, and end at 16h30.
- Tea break is 15 minutes, and lunch break is 30 minutes
- The time sheet must be completed daily, and submitted weekly to the Study Coordinating Office.
- If the data capturer requires time off/leave/sick leave, the data capturer must contact the Study Coordinating Officer, Ms Viloshini Manickum (033 8467267/0716852906) or Mr Vusi Dlamini (033 846 7265/0823325629)). The minimum hours to be worked per day are 8 hours. If time off is taken for emergencies, there is a need to work the time taken, claim for the actual hours worked for that particular day
- Vacational leave is 20 days per year, while sick leave is 10 days per year. If vacational leave is not approved before going on leave, the data capturer will receive no salary for those days. In addition if the data capturer does not call to inform the Deputy Manager/ Principal Technical Advisor (Monitoring and Evaluation) that he/she is sick, this would result in leave without pay.
- MSH closes for the Christmas/New Years break; therefore it is essential that all vacational leave is not taken before the end of the year. In the event of all 20 days of vacational leave being taken, then relevant staff member will receive leave without pay.

Communication

- Open, transparent communication is required between the Study Coordinating Office, and the staff employed for the FASS project.
- If communication problems are being experienced at sites, there is a need to inform the Data Manager/ Study Co-ordinator timeously.
- Written reports, explaining the problem must also be emailed to the Study Coordinating office.
- Meetings will be held with site staff to resolve the problem.

Respect and Professionalism

- Staff employed for the FASS Project must ensure that respect and professionalism is maintained to all internal and external stakeholders, as well as patients at all times.

Placement of Data Capturers

- Data Capturers will be placed at sites, in accordance with the needs of the project. This may also result in a data capturer being placed at a specific site, and thereafter being relocated to another site, due to the workload. (All sites have not been allocated data capturers, due to financial constraints.

Understanding of FASS Project

- Data Capturers will be trained with respect to the FASS Project.

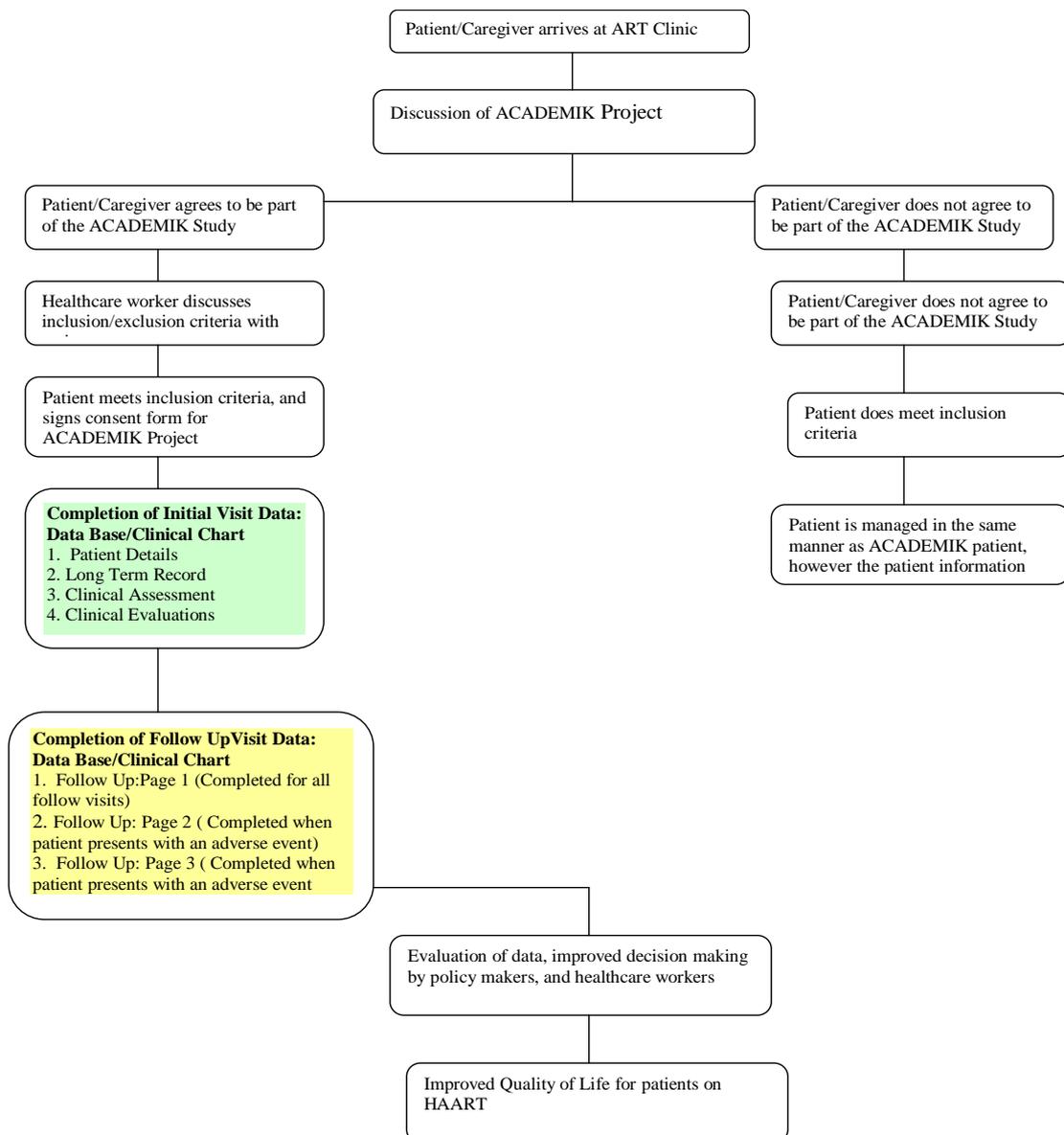
- Data Capturers are requested to read, understand the training notes, and communicate to the Study Co-ordinator/ Principal Technical Advisor/ Data Manager, in the event of difficulties associated with understanding.

Job Descriptions/Workplans

Each employee employed for the FASS Project must function within the context of the job description, and corresponding workplan. Performance Agreements will be signed between the employers and employees, and quarterly performance assessments will be completed by the relevant manager. The key result areas specified in the job description have been subdivided into objectives, activities, indicators and time frames. Therefore each category of staff, Study Co-ordinator, Data Manager and Data Capturer will adhere to specific workplans, as indicated by the following annexures:

- Annexure 1: Workplan for Study Coordinator
- Annexure 2: Workplan for Data Manager
- Annexure 3: Workplan for Data Capturer

Patient Flow: ACADEMIK Project



Completion of Paediatric Clinical Charts and Follow up Forms

Objective:

- To outline the correct procedures to be followed when completing clinical charts and follow up forms

Responsibility:

- Hospital Manager
- Medical Manager
- ARV Programme Manager at Accredited ART site.
- Doctors at the ART Clinic
- Nurses at the ART Clinic
- Data Capturers at the ART Clinic
- Counselors at the ART Clinic
- Administration Officers at ART Clinics

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.
- National Antiretroviral Guidelines, 2004
- Nursing Act 33 of 2005 as amended
- National Strategic Plan (2007-2011)

Principles:

- The National Strategic Plan (2007-2011) identifies research, monitoring and evaluation as the 3rd priority. According to the National Strategic Plan (2007-2011), there is an urgent need to “strengthen the active surveillance, reporting and analysis of Adverse Drug Reactions in accredited facilities providing ART”.
- KwaZulu-Natal Department of Health/ Strengthening Pharmaceutical Systems/ University of KwaZulu-Natal, is embarking on Focused Antiretroviral Surveillance in KwaZulu-Natal.
- Focused Antiretroviral Surveillance/ active surveillance refer to the active follow up of new and existing patients on HAART.
- Patients on HAART will be evaluated for adverse events on a 6 monthly basis.
- Adverse Events will be documented by healthcare workers.
- Patients will be followed up 6 monthly basis

Initial Visit

- When the paediatric patient presents at the initial visit the following information must be completed by the data capturer/ administration clerk:

Inclusion/ Exclusion Criteria: (Completed by Data Capturer/ Administration Clerk)

ACADEMIK STUDY: PATIENT ELIGIBILITY CRITERIA		
INCLUSION CRITERIA	Yes	No
1. ARV naïve patients entering the HIV Treatment Programme or existing patients on HAART under active follow-up with ART history available. Antiretroviral Naïve Patient		
2. Able and willing to provide informed consent or able to provide parental/legal guardian permission with assent.		
3. Consent form Completed/ Signed		
4. Able and willing to provide adequate information for locator purposes.		
5. Not intending to relocate out of the area for the duration of study participation and does not have a job or other obligations that may require long absences from the area.		
6. Possession of an identification number as designated in an official document.		
Notes to Health Care workers : If the patient has answered yes to the criteria specified above, then the patient is eligible for the study.		
EXCLUSION CRITERIA	Yes	No
1. Patients or parents/legal guardians not willing to provide signed informed consent.		
2. Previous or current participation in a HIV vaccine study.		
3. Active alcohol or substance abuse.		
4. A history of mental illness.		
5. Prisoner status.		
Notes to Health Care Workers : If the patient has indicated yes to any of the exclusion criteria indicated above, then the patient must not be initiated in the study		

- Caregivers must be clearly informed by healthcare workers about the nature of the study, as well the benefits of the study.
- If the answers to the inclusion criteria are no, the paediatric patient MAY NOT BE INITIATED ON THE ACADEMIK PROJECT.
- If the answers to the exclusion criteria are yes, the paediatric patient MAY NOT BE INITIATED ON THE ACADEMIK PROJECT

1. Patient Details (Completed by Data Capturer/Administration Clerk)

Referral clinic:		Current Clinic:	
1. PATIENT DETAILS		Date: / /	
First name	_____	Folder #	_____
Surname	_____	Phone #	_____
DOB / /	Sex: M / F	Allergies: <i>(Please write allergies in red)</i>	
ID Number	_____		
ACADEMIK: PERSONAL IDENTIFICATION NUMBER:			
Address:			
Directions to Pxs Home:			
Next of kin: name, address and contact no. (2 contacts compulsory)	Name of Community Based Worker: _____ Address: _____ Cell Number: _____		Name: _____ Address: _____ Cell Number: _____
2. LONG-TERM RECORD		<i>Use this section to maintain an ongoing summary of your patient's health. If another clinician sees this patient for the first time five years from now, s/he should be able to ascertain the major features of the clinical course of disease from this page.</i>	
mm/yy HIV Diagnosed	ARV start date at this or transferring clinic	/ /	Transfer-in (Date - ART only) / /
<i>Note: Patient can only be considered transferred in if this record can be completed in full from the date of the original start. If there is prior treatment with incomplete treatment history, the patient should be considered a new patient with prior HAART exposure</i>			
ARVs prior to above start date?	NONE / HAART / PEP	Details:	
Past medical history		<i>Record here significant medical events that occurred before this patient record was started</i>	

- Data Capturers must capture the above mentioned fields.
- Address of patient and directions to the patients home must be completed in detail (for locator purposes)
- Data Capturers must ensure the patient's/next of kin cell numbers are correct.

2. Long Term Record (To be completed by the Nurses/ Doctors)

- This section relates to the use of previous Antiretroviral Therapy. There is a need to indicate the following:
 - Date of diagnosis of HIV
 - ART Start Date
 - Date of Transfer into the clinic
 - The presence of any allergies, including food/medication
 - Past Medical History

3. Clinical Assessment: First Visit at the Clinic (To be completed by the Nurses/ Doctors)

- The following sections must be completed by the nurse/doctor:
 - WHO Clinical Staging
 - Tuberculosis Screen
 - Nutritional Risk Score
 - History and Examination

3. Clinical Assessment: First Visit at the Clinic

ACADEMIK: PERSONAL IDENTIFICATION NUMBER:													
3. CLINICAL ASSESSMENT: FIRST VISIT AT THIS CLINIC													
<small>Use this section during your patient's first encounter with HIV / ART services to help decide whether they need HIV or ARV care</small>													
Presents from: TB clinic / VCT / GP / other ART clinic / primary care clinic / in-patient / other													
WHO CLINICAL STAGING:													
<small>If your patient has, OR HAS EVER HAD, any of the illnesses below, and none in stage 4 (except EPTB), and a CD4 count >200, they need HIV care</small>						<small>If your patient has, OR HAS EVER HAD, any of the illnesses below, or their CD4 count is <200, they need ARV therapy</small>							
Clinical Features			Date			Clinical Features			Date				
WHO Stage 1 Asymptomatic	Persistent generalized lymphadenopathy					WHO Stage 4 Severe disease (AIDS)	Severe wasting/ malnutrition						
							Pneumocystis pneumonia						
					Recurrent severe bacterial infection								
					Chronic herpes simplex >1 month's duration								
					Extrapulmonary TB								
					Kaposi's sarcoma								
					Oesophageal candidiasis								
					CNS toxoplasmosis (outside the neonatal period)								
					HIV encephalopathy								
					CMV retinitis/ infection (onset age >1 month)								
					Extrapulmonary cryptococcosis incl meningitis								
WHO Stage 2 Recurrent & Varied Disease Presentations	Hepatosplenomegaly												
	Papular pruritic eruptions												
	Seborrhoeic dermatitis												
	Extensive human papilloma virus infection												
	Extensive molluscum contagiosum												
	Fungal nail infections												
	Recurrent oral ulcerations												
	Lineal gingival erythema (LGE)												
	Angular cheilitis												
	Parotid enlargement												
Herpes zoster													
Recurrent or chronic RTIs													
WHO Stage 3 Chronic & Persistent Diseases	Moderate malnutrition not responding to std therapy												
	Unexplained persistent diarrhoea (14 days or more)												
	Unexplained persistent fever (>1 month)												
	Oral candidiasis (outside neonatal period)												
	Oral hairy leukoplakia												
	Acute necrotizing ulcerative gingivitis / periodontitis												
	Pulmonary TB												
	TB lymphadenopathy (axillary, cervical or inguinal)												
	Severe recurrent presumed bacterial pneumonia												
	Anaemia &/or neutropenia &/or thrombocytopenia for >1 month												
	Chronic HIV-associated lung disease incl bronchiectasis												
	Symptomatic lymphoid interstitial pneumonitis (LIP)												
											CD4 result		
TUBERCULOSIS SCREEN													
Ever had TB before?		Y	N	If YES	Year	Extra-pulmonary or pulmonary TB			Treatment outcomes				
Current TB		Y	N	Pulmonary or extra-pulmonary	Date commenced treatment:			Regimen 1 / Regimen 2 / MDR / XDR					
TB symptoms today		1) Cough > 2 wks Y / N		2) Failure to thrive Y / N		3) Fever Y / N		4) Night sweats Y / N		5) Haemoptysis Y / N		6) Fatigue Y / N	
Smear date	Culture / sensitivity date			X-ray date		Clinical indication of TB Y / N							
Result	Result			Result									
TB treatment supervisor's name													
NUTRITIONAL RISK SCORE (Note: Must refer to dietician and nutritional programme, if score is above 3 for support)													
Date of assessment:		A. Weight: (kg)			B. Height (meters)			C. Nutritional Risk Score (0 to 6)					
HISTORY AND EXAMINATION:													
Temperature: Heart Rate: Respiratory Rate:						PLAN:							
						CD4 > 200 AND stage 1-3 or extra-pulmonary TB <input type="checkbox"/>							
						CD4 < 200 OR stage 4 (excl. extra-pulmonary TB) <input type="checkbox"/>							
						Cotrimoxazole: Y / N							
						Fluconazole: Y / N							
						Other: Y / N							
Tuberculin Skin Test:		Date given	Date read	Results									
Screened for INH:		Y	N	Qualifies for INH		Y	N	Started INH		Y	N		
Date:				Date:				Date:					
Screened for cotrimoxazole:		Y	N	Already on cotrimoxazole		Y	N	Qualifies / started		Y	N		
Date:				Date:				Date:					
Screened for other / fluconazole		Y	N	Already on other / fluconazole		Y	N	Qualifies / started		Y	N		
Date:				Date:				Date:					
Print name:				Signature:				Date: / /					

4. Clinical Evaluations for ARVs or Restarted ARVs

ACADEMIK: PERSONAL IDENTIFICATION NUMBER:								
4. CLINICAL EVALUATIONS FOR ARVs OR RE-STARTED ARVs								
<i>If ART therapy is indicated for your patient, use this section to help decide whether there are any medical contra-indications to starting</i>								
PRIOR ARV HISTORY								
<i>If your patient has ever had ARVs before, detail the period when taken, ARV changes and reasons:</i>								
BASELINE SAFETY BLOODS								
Test	Date	Result	Others:	Test	Date	Result	Notes:	
CD4				Lactate				
Viral Load				Creatinine				
FBC				Glucose (fasting)				
Haemoglobin				TG or Cholesterol (fasting)				
ALT								
CONCOMITANT DISEASE CONDITIONS / MEDICATION								
TRADITIONAL/COMPLEMENTARY MEDICINE								
Is the patient taking traditional/ Complementary Medicines? Y / N				Name:				
				How long (months)				
TB WORK-UP								
Symptoms suspicious of TB? Y / N			If YES: Perform TB work-up, record results in daily clinic record sheet					
NUTRITIONAL ASSESSMENT								
Symptoms Nausea / Vomiting / Diarrhoea / Growth Failure / Difficulty swallowing						Developmental Quotient		
CLINICAL NOTES								
CLINICAL FACTORS INFLUENCING REGIMEN CHOICE								
1. On TB treatment? Y / N			PLAN:					
			1st Line (6 months up to 3 years)		(a)			
2. Has had more than 1 month of ARVs Y / N			1st Line (> 3 years and > 10 kg)		(b)			
			2nd Line (6 months up to 3 years)		(c)			
3. Body surface area in m ²			2nd Line (> 3 years and > 10 kg)		(d)			
4. Other (state the details)			Cotrimoxazole - needed		Y / N			
			Fluconazole - needed		Y / N			
COMMENCING ARVs								
Psychosocial readiness / support (see section 7) Y / N			Clinically ready		Y / N			
Regimen factors (clinical factors influencing choice) Y / N			Regimen		(a) , (b) , (c) or (d)			
ASSESSMENT OF OVERALL READINESS FOR ARVs								
Signature:					Date: / /			

- The nurse/doctor must complete the above mentioned fields:
- Prior ARV History
- Baseline Blood Tests
- Traditional/Complementary Medicine
- TB Work Up
- Nutritional Assessment
- Concomitant Illnesses/Medication
- Clinical Notes

- Clinical Factors Affecting Regimen Choice
- Commencing ARVs

Follow Up Form- Page 1

This form must be completed by the nurse/doctor, **AT EVERY FOLLOW UP VISIT.**

The following fields must be completed:

- Weight
- Developmental Quotient
- Height
- Head Circumference
- Nutritional Score
- Puberty Stage
- Antiretroviral Therapy
- Notes (Optional)
- Reproductive Health
- STI Screen
- TB Status
- TB Treatment
- Investigations
- HIV Conditions/OIs
- Traditional/ Complementary Medicines
- Co-morbidities/Concomitant Medication
- Drugs and Doses
- Adherence
- Adverse Event

Follow Up Form: Page 2

This form must be completed by the nurse/doctor, **ONLY WHEN THE PATIENT PRESENTS WITH AN ADVERSE EVENT.**

The following fields must be completed:

- Adverse Event to be ticked, as per different organ system
- Description/Laboratory Values on Diagnosis
- Description/ Laboratory Values on Resolution of Symptoms
- (In the event of multiple adverse events being diagnosed tick the appropriate columns, and complete the relevant description/laboratory values).

Follow Up: Page 3

This form must be completed by the nurse/doctor, **ONLY WHEN THE PATIENT PRESENTS WITH AN ADVERSE EVENT.**

The following fields must be completed:

- Date of Onset of Symptoms
- Date of Resolution of Symptoms
- **History and Examination**
- Answer the following questions:
- Describe the nature of reaction
- Did the reaction occur within a reasonable time relationship in relation to the administration of the drug?
- Is the reaction a known reaction?
- Are there any other medication/concomitant disease conditions that may have caused the reaction?
- Did the patient recover after the possible offending agents were withdrawn?
- List the possible causative agents
- Adverse Events
- Indicate the status, severity and outcome of the event by ticking the appropriate column.

Follow Up: Page 3

NAME OF PATIENT :		ID NO.	
ACADEMIK PROJECT:PERSONAL IDENTIFICATION NUMBER:			
History and examination	Adverse Drug Events		
	Date of Onset of Symptoms :	Date of Resolution of Symptoms :	
	1. Nature of Reaction:		
	2. Did the reaction occur within a reasonable time relationship in relation to the administration of the drug		
History and examination	3. Is the reaction a known reaction:		
	4. Are there any other medication/concomitant disease conditions that may have caused the reaction		
	5. Did the patient recover after the possible offending agents were withdrawn?		
	6. List the possible causative agents		
Adverse Events	Status of Adverse Drug	Tick the	Answer the Questions
	Ongoing		Was the adverse event drug related [Y] [N]
	Resolved		Is the event an allergy to medicine [Y] [N]
	Intermittent		Has the event been reported by the patient [Y] [N]
	Severity		Has the event been reported by the physician [Y] [N]
	Mild		Is the adverse event related to HIV [Y] [N]
	Moderate		
Life Threatening			
Fatal			
Outcome	Not Yet Recovered	Permanent Damage	Death
	Recovered	Hospitalised	Recovered without changing regimen
	Recovering	Unknown:	
	(Circle the appropriate option)		
	Date	/ /	Sub-clinic
Signature of Nurse/Doctor		Name of Doctor/Nurse:	Da

Completion of Adult Clinical Charts and Follow up Forms:

INITIAL VISIT

- When the patient presents at the initial visit the following information must be completed by the data capturer/ administration clerk:

Inclusion/ Exclusion Criteria: (Completed by Data Capturer/ Administration Clerk)

ACADEMIK STUDY: PATIENT ELIGIBILITY CRITERIA		
INCLUSION CRITERIA	Yes	No
1. ARV naïve patients entering the HIV Treatment Programme or existing patients on HAART under active follow-up with ART history available. Antiretroviral Naïve Patient		
2. Able and willing to provide informed consent or able to provide parental/legal guardian permission with assent.		
3. Consent form Completed/ Signed		
4. Able and willing to provide adequate information for locator purposes.		
5. Not intending to relocate out of the area for the duration of study participation and does not have a job or other obligations that may require long absences from the area.		
6. Possession of an identification number as designated in an official document.		
Notes to Health Care workers : If the patient has answered yes to the criteria specified above, then the patient is eligible for the study.		
EXCLUSION CRITERIA	Yes	No
1. Patients or parents/legal guardians not willing to provide signed informed consent.		
2. Previous or current participation in a HIV vaccine study.		
3. Active alcohol or substance abuse.		
4. A history of mental illness.		
5. Prisoner status.		
Notes to Health Care Workers : If the patient has indicated yes to any of the exclusion criteria indicated above, then the patient must not be initiated in the study		

- Patients must be clearly informed by healthcare workers about the nature of the study, as well the benefits of the study.
- If the answers to the inclusion criteria are no, then the patient **MAY NOT BE INITIATED ON THE ACADEMIK PROJECT.**
- If the answers to the exclusion criteria are yes, then the patient **MAY NOT BE INITIATED ON THE ACADEMIK PROJECT**

3. Clinical Assessment: First Visit at the Clinic

Surname:		First Name:	
3. CLINICAL ASSESSMENT: FIRST VISIT AT THIS CLINIC			
<i>Use this section during your patient's first encounter with HIV / ART services to help decide whether they need HIV or ARV care</i>			
Presents from: TB clinic / PMTCT / VCT / GP / other ART clinic / primary care clinic / in-patient / correctional / work / other			
WHO CLINICAL STAGING:			
If your patient has, OR HAS EVER HAD , any of the illnesses below, and none in stage 4 (except EPTB), and a CD4 count >200, they need HIV care		If your patient has, OR HAS EVER HAD , any of the illnesses below, or their CD4 count is <200, they need ARV therapy	
Clinical Features	Date	Clinical Features	Date
1	Condition:		
WHO Stage 2 Moderate disease	Weights loss <10% body weight		
	Minor mucocutaneous conditions		
	Recurrent URTI		
	Uncomplicated herpes zoster		
	Other:		
WHO Stage 3 Moderate disease	Weight loss >10% body weight		
	Diarrhoea > 1 month		
	Oral candidiasis		
	Severe bacterial infections including Pneumonia		
	Oral hairy leukoplakia		
	Prolonged fever		
	Bedridden < 50% / day for most of last month		
	Pulmonary TB (current or in the last year)		
Other:			
WHO Stage 4 Severe disease (AIDS)	Herpes simplex virus lesions > 1 month		
	Oesophageal candidiasis		
	Pneumocystis carinii pneumonia		
	Kaposi's sarcoma		
	HIV wasting syndrome		
	HIV encephalopathy		
	Recurrent pneumonia		
	Cytomegalovirus		
	Isosporiasis / Cryptosporidiosis		
	Bedridden > 50% / day for most of last month		
Cryptococcal meningitis			
Cervical cancer			
Lymphoma			
Other:			
Other:			
4	Extra-pulmonary TB		CD4 result
REPRODUCTIVE HEALTH			
Pregnant	Y N	Trimester	1 2 3 Grav Para Pap smear result: Date:
Contraception:		Date last used:	
none / condom / injection / pill / other			
Signs and symptoms of STI today?	1) Urethral discharge / dysuria Y / N	2) Vaginal discharge Y / N	3) Genital ulcers Y / N
		4) Genital warts Y / N	5) Lower abdominal pain Y / N
		RPR (date)	Result Treatment completed Y / N
TUBERCULOSIS SCREEN			
Ever had TB before?	Y N	If YES	Year Extra-pulmonary or pulmonary TB Treatment outcomes
Current TB	Y N	Pulmonary or extra-pulmonary	Date commenced treatment: Regimen 1 / Regimen 2 / MDR / XDR
TB symptoms today	1) Cough > 2 wks Y / N	2) Weight loss Y / N	3) Fever Y / N
		4) Night sweats Y / N	5) Haemoptysis Y / N
		6) Fatigue Y / N	
Smear date	Culture / sensitivity date	X-ray date	Clinical indication of TB Y / N
Result	Result	Result	
TB treatment supervisor's name			
NUTRITIONAL SCREEN (Note: If BMI is less than 18.5 must refer to dietician and nutritional programme)			
Date of assessment:	A. Weight: (kg)	B. Height (meters)	C. BMI = $\frac{\text{Weight (A)}}{\text{Height (B)} \times \text{Height (B)}}$
/ /			
HISTORY AND EXAMINATION:		PLAN:	
Temperature: Heart Rate: Respiratory Rate: BP:		CD4 > 200 AND stage 1-3 or extra-pulmonary TB <input type="checkbox"/>	
		CD4 < 200 OR stage 4 (excl. extra-pulmonary TB) <input type="checkbox"/>	
Blood Pressure:		ARVS: Dates:	
		Cotrimoxazole:	
		Fluconazole:	
		Other: _	
Tuberculin Skin Test:	Date given	Date read	Results
Screened for INH: Date:	Y N	Qualifies for INH Date:	Y N
Started INH Date:		Y N	
Screened for cotrimoxazole: Date:	Y N	Already on cotrimoxazole Date:	Y N
Qualifies / started Date:		Y N	
Screened for other / fluconazole Date:	Y N	Already on other / fluconazole Date:	Y N
Qualifies / started Date:		Y N	
Print name:	Signature:	Date:	/ /

- The following sections must be completed by the nurse/doctor:
 - WHO Clinical Staging
 - Reproductive Health
 - Tuberculosis Screen
 - Nutritional Screen
 - History and Examination

4. Clinical Evaluations for ARVs or Restarted ARVs

Surname:			First Name:				
4. CLINICAL EVALUATIONS FOR ARVs OR RE-STARTED ARVs							
<i>If ART therapy is indicated for your patient, use this section to help decide whether there are any medical contra-indications to starting</i>							
PRIOR ARV HISTORY							
<i>If your patient has ever had ARVs before, detail the period when taken, ARV changes and reasons:</i>							
BASELINE BLOOD TESTS							
Test	Date	Result	Others:	Test	Date	Result	Notes:
CD4			Others:	Haemoglobin			
Viral Load				Creatinine			
ALT				Glucose			
				Cholesterol			
				Triglycerides			
TRADITIONAL/ ALTERNATIVE/COMPLEMENTARY MEDICINE							
Is the patient currently taking Traditional/ Alternative/Complementary Medicines:			<input type="checkbox"/> Y	<input type="checkbox"/> N	Indication:		
Name of Product:			Duration of Treatment:				
Did the patient previously take traditional/ alternative/complementary medicines:			<input type="checkbox"/> Y	<input type="checkbox"/> N	Duration of Treatment:		
Name of Product:			Duration of Treatment:				
TB WORK-UP							
Symptoms suspicious of TB? Y N			If YES: Perform TB work-up, record results in daily clinic record sheet				
NUTRITIONAL ASSESSMENT							
Symptoms Nausea / Vomiting / Diarrhoea / Severe loss of weight / Difficulty swallowing					Baseline BMI		
CONCOMITANT ILLNESSES							
1			2				
3			4				
5			6				
CONCOMITANT MEDICATION							
1			2				
3			4				
5			6				
CLINICAL NOTES							
CLINICAL FACTORS INFLUENCING REGIMEN CHOICE							
1. On TB treatment? Y / N		5. Has had more than 1 month of ARVs? (excluding PMTRCT) Y / N		PLAN: (Drugs/ Dosing Frequency)			
2. Pregnant? Y / N		6. BMI > 27.5 Y / N		ARV 1			
3. Has severe peripheral neuropathy? Y / N		7. Other Y / N		ARV 2			
4. Has a history of psychiatric illness? Y / N		8. Other Y / N		ARV 3			
				Cotrimoxazole			
				Fluconazole			
				INH			
COMMENCING ARVs							
Psychosocial readiness (see section 7) Y / N			Clinically ready Y / N				
Regimen factors (clinical factors influencing choice) Y / N			Regimen Y / N				
ASSESSMENT OF OVERALL READINESS FOR ARVs							
Signature:				Date: / /			

- The nurse/doctor must complete the following fields:
- Prior ARV History
- Baseline Blood Tests
- Traditional/Complementary Medicine
- TB Work Up
- Nutritional Assessment
- Concomitant Illnesses/Medication
- Clinical Notes

- Clinical Factors Affecting Regimen Choice
- Commencing ARVs

Follow Up Form- Page 1

This form must be completed by the nurse/doctor, **AT EVERY FOLLOW UP VISIT.**

The following fields must be completed:

- Weight
- Blood Pressure
- Antiretroviral Therapy
- Notes (Optional)
- Reproductive Health
- STI Screen
- TB Status
- TB Treatment
- Investigations
- HIV Conditions/OIs
- Traditional/ Complementary Medicines
- Co-morbidities/Concomitant Medication
- Drugs and Doses
- Adherence
- Adverse Event

Follow Up: Page 2

Name of Patient		ID:	Date:
ACADEMIK PROJECT:PERSONAL IDENTIFICATION NUMBER:			
Adverse Event	Tick	Description/Laboratory Values on Diagnosis	Description/Laboratory Values on Resolution of Adverse Event
Breast Disorders /Reproductive System			
Gynaecomastia			
Sexual Dysfunction			
Bone Disorders			
Osteopenia/ Osteoporosis		Bone Mass Density Value:	
Cardiovascular			
Arrhythmia		Confirmatory ECG [Y] [N]	
Coronary Artery by Pass - Grating			
Coronary Angioplasty			
Myocardial Infarction		Confirmatory ECG [Y] [N] Cardiac Enzymes	
CNS Effects			
Agitation			
Depression			
Disturbing Dreams			
Dizziness			
Impaired Concentration			
Sleep Disturbances			
Psychotic Episodes (eg hallucinations)			
Dermatological			
Serious Skin Reactions		Grade:	
Steven Johnson Syndrome			
Haematological			
Anaemia		HB Level:	HB Level:
Leucopaenia eg Neutropaenia		Neutrophil Count:	Neutrophil Count:
Thrombocytopenia		Platelet count	Platelet count
Hepatic			
Hepatitis		ALT level: Bilirubin Level	ALT level: Bilirubin Level
		ALT level: Bilirubin Level	ALT level:
Hepatic Steatosis		Need to confirm with a biopsy	
Hepatic Encephalopathy		ALT level: Bilirubin Level	ALT level: Bilirubin Level
Pancreatitis		Amylase Level:	Amylase Level:
Metabolic			
Lactic Acidosis		Lactate level: HCO3: ph:	Lactate level: HCO3: ph:
		Anion Gap: ph:	Anion Gap: ph:
Symptomatic Hyperlactatemia		Lactate level: HCO3: ph:	Lactate level: HCO3: ph:
		Anion Gap: ph:	Anion Gap: ph:
Hypertriglyceridemia		LDL: HDL: Triglycerides Level :	LDL: HDL: Triglycerides Level :
Hypercholesterolaemia		Blood Cholesterol Level: LDL level: HDL level	Blood Cholesterol Level: LDL level: HDL level
Lipodystrophy			
Lipoatrophy			
Diabetes Mellitus		Blood Glucose Level:	Blood Glucose Level:
Hypertension		BP:	BP:
Stroke		BP:	BP:
Neurological			
Peripheral Neuropathy		Grade:	
Renal			
Nephrotoxicity		Urea:	Urea:
Renal Failure		Creatinine Clearance	Creatinine Clearance
Other : (List)			

Follow Up: Page 3

This form must be completed by the nurse/doctor, **ONLY WHEN THE PATIENT PRESENTS WITH AN ADVERSE EVENT.**

The following fields must be completed:

- Date of Onset of Symptoms
- Date of Resolution of Symptoms
- **History and Examination**
- Answer the following questions:
- Describe the nature of reaction
- Did the reaction occur within a reasonable time relationship in relation to the administration of the drug?
- Is the reaction a known reaction?
- Are there any other medication/concomitant disease conditions that may have caused the reaction?
- Did the patient recover after the possible offending agents were withdrawn?
- List the possible causative agents
- Adverse Events
- Indicate the status, severity and outcome of the event by ticking the appropriate column.

Follow Up: Page 3

NAME OF PATIENT :		ID NO.	
ACADEMIK PROJECT:PERSONAL IDENTIFICATION NUMBER:			
History and examination	Adverse Drug Events		
	Date of Onset of Symptoms :	Date of Resolution of Symptoms :	
	1. Nature of Reaction:		
	2. Did the reaction occur within a reasonable time relationship in relation to the administration of the drug		
	3. Is the reaction a known reaction:		
History and examination	4. Are there any other medication/concomitant disease conditions that may have caused the reaction		
	5. Did the patient recover after the possible offending agents were withdrawn?		
	6. List the possible causative agents		
Adverse Events	Status of Adverse Drug	Tick the	Answer the Questions
	Ongoing		Was the adverse event drug related [Y] [N]
	Resolved		Is the event an allergy to medicine [Y] [N]
	Intermittent		Has the event been reported by the patient [Y] [N]
	Severity		Has the event been reported by the physician [Y] [N]
	Mild		Is the adverse event related to HIV [Y] [N]
	Moderate		
Life Threatening			
Fatal			
Outcome	Not Yet Recovered		Permanent Damage
	Recovered		Hospitalised
	Recovering		Unknown:
	(Circle the appropriate option)		
Date	/ /	Sub-clinic	
Signature of Nurse/Doctor	Name of Doctor/Nurse:		Da