Evaluation and Potential Cost-Effectiveness of Active Surveillance Pharmacovigilance for First-Line HAART in Namibia

Marita Mann

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Reading Committee:

Andy Stergachis, Chair

Joseph B. Babigumira

Jared Baeten

Program Authorized to Offer Degree:
University of Washington Department of Pharmacy

University of Washington

Abstract

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Marita Mann

Chair of the Supervisory Committee:
Dr. Andy Stergachis
Departments of Pharmacy and Global Health

Background. Active surveillance pharmacovigilance (PV) is a systematic approach to medicine safety assessment and health systems strengthening. These systems can better estimate the burden of adverse events (AEs) and can generate useful information on risk factors of AEs for more effective medicine use, especially in conjunction with introduction of new medicines and/or treatment guidelines. Active surveillance has yet to be implemented on a large scale in low- and-middle income countries. This project aimed to evaluate an active surveillance pilot program for first-line antiretroviral therapy (ART) at sentinel sites in Namibia, project findings to the national level to evaluate potential cost-effectiveness, and demonstrate use of active surveillance data.

Methods. Sentinel sites were outpatient ART clinics at the Windhoek Central Hospital and Katutura Intermediate Hospital. An active surveillance data collection form was developed and placed into patient charts. Adults naïve to ART were enrolled from August 2012-April 2013. Physicians recorded ART and health information during each follow-up visit, including presence or absence of AEs. Following evaluation of this data, a cost-utility analysis from a governmental perspective compared active surveillance PV to spontaneous reporting PV for highly active antiretroviral therapy (HAART) in Namibia. Programmatic data from a sentinel site active surveillance program in Namibia conducted from August 2012-

April 2013 was projected to all HIV-infected adults initiating HAART in Namibia. Costs (PV program, HAART, adverse event [AE] treatment), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs, 2015 U.S. dollars/QALY) were evaluated. Analysis was completed for (1) a cohort analysis in which a single cohort beginning HAART in 1-year in Namibia were followed over their remaining lifetime and (2) a population analysis in which patients continued to enter and leave care and treatment over 10 years. Finally, we examined a potential use of active surveillance data by examining incidence of an AE. Data from the active surveillance forms was used to evaluate the incidence nephrotoxicity in those exposed to the HAART drug tenofovir .

Results. A total of 413 patients were included from August 2012 to April 2013. Average age was 37 years; 51% of patients were at WHO Clinical Stage 1; and mean baseline CD4 count was 216. The most common ART regimen was tenofovir/lamivudine/nevirapine. Presence or absence of AEs was recorded in active surveillance forms for 94% of first follow-up visits. In total, 66 patients experienced 119 AEs of any severity. Incidence of experiencing at least one AE was 33 per 100 person-years. Most common AEs were rash and abdominal pain. On active surveillance forms, demographic variables were missing in 14% of patients and follow-up visits were recorded for 82% of patients. For the cost-effectiveness cohort analysis totals were $28,675,900 and 184,076 QALYs for care and treatment under active surveillance PV versus $23,922,400 and 182,292 QALYs for care and treatment under spontaneous reporting PV, resulting in an ICER of $3,949 for active surveillance compared to spontaneous reporting PV. In the population analysis active surveillance was cost saving. Results were sensitive to quality-of-life associated with AEs. In this study population, incidence of nephrotoxicity was 15 per 100 person-years. However, after adjustment for demographics and comorbidities, nephrotoxicity was not statistically significantly associated with tenofovir exposure.

Conclusions. Completeness of AE recording on active surveillance forms was high.

With improved logistical considerations, such as incorporation of active surveillance forms into medical records, long-term active surveillance programs could be successful. Active surveillance pharmacovigilance was projected to be a highly cost-effective system to improve treatment for HIV in Namibia. Active surveillance PV may be valuable to improve the lives of HIV patients and more efficiently allocate health resources in Namibia. Tenofovir was found to be a generally safe medicine, though results were limited by a small sample size.

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Chapter 1

INTRODUCTION

Pharmacovigilance (PV) is the science and activities relating to the detection, evaluation, understanding, and prevention of adverse events (AEs) associated with medicine use [1]. PV provides information in assessing the inevitable tradeoff between benefits and potential harm from medicine use. This is accomplished through the collection and analysis of information on AEs and communication to those that have the knowledge to interpret the information and act in order to minimize harm to patients [1]. Additional potential benefits of a PV system include improved understanding of the burden of and risk factors for iatrogenic illnesses, a greater understanding of population health, and improved healthcare provision and outcomes. Although some of these population-level benefits are difficult to quantify, it may be feasible to quantify benefits to individual health. For example, if an AE is detected early, a health care provider can alter treatment to minimize negative effects on a given patient's quality of life, improve medication adherence, and/or slow disease progression [2].

Public health systems in low- and middle-income countries (LMICs) traditionally use spontaneous reporting pharmacovigilance systems to identify and report AEs [3,4]. In a spontaneous reporting system, health care providers, pharmaceutical companies and/or patients passively report a suspected AE to a public health or governmental organization via various mechanisms, including phone, internet, or postal systems. Spontaneous reporting systems, though relatively inexpensive to run are useful for signal generation, but lack a well-defined population denominator and, therefore, lack the ability to calculate incidence. Spontaneous reporting systems also suffer from significant underreporting of AEs [5–7].

Active surveillance is a type of PV whereby active measures are taken to detect the presence or absence of adverse events on an on-going basis within a defined group of people.

It involves the on-going systematic collection, analysis, and interpretation of data [3,8–10]. In low- and middle-income countries, health care systems without active surveillance tend not to have the capacity for high quality AE detection. Among other limitations, not enough trained providers are available to detect many AEs. An active surveillance system raises the index of suspicion of AEs and hence raises the potential rate of detection and the treatment of AEs. In addition to enhancing individual level safety, active surveillance methods allow for calculation of population-based rates of AEs [11]. Active surveillance PV can contribute local data by providing estimates of the incidence of AEs and risk factors for medicine-associated AEs, and may allow for more effective and efficient use of resources to reduce the burden of disease [10,12]. Active surveillance methods involve obtaining a denominator of persons exposed to medications of interest, allowing for calculation of population incidence rates of AEs. Active surveillance is especially useful in conjunction with postmarketing safety surveillance for the introduction of new medicines as well as for assessing changes in treatment guidelines. Through active surveillance, potential medicine-associated safety problems and their risk factors can be identified. Active surveillance is particularly well suited for HIV medications, especially when patients are monitored at antiretroviral therapy (ART) clinics and assessed by health care providers on a routine basis.

Data from active surveillance programs can be used to quantify AE risks to the population. For example, the HAART medication tenofovir disoproxil fumarate (TDF), a nucleoside analogue reverse transcriptase inhibitor (NRTI) is a commonly used first-line therapy for people with HIV infection. While generally considered as safe, TDF can cause kidney toxicity through proximal tubule dysfunction either with or without decreased renal function [13]. The reported incidence of TDF nephrotoxicity varies across studies and populations up to more than 20% [13]. While the incidence of kidney injury associated with TDF use may be low, the health risks are serious. Identifying patients who have the greatest risk for nephrotoxicity could improve clinical care and health outcomes by targeting monitoring and selection of alternative NRTI's to those patients. Active surveillance data may be able to be used to understand TDF-associated kidney injury in a specific population, which may allow

the public health community to more effectively allocate resources to improve health.

Despite potential population health improvements and society's willingness to pay for medicine regulation and to avoid AEs [14–18], active surveillance systems have yet to be implemented on a large scale in low-and middle-income countries (LMIC). Active surveillance systems can be complex and costly to implement. While a framework to assess cost-effectiveness of PV has been proposed [19], data have yet to be presented on the health benefits and medical costs of an active PV program at a national level. National level costs and benefits of active PV can be difficult to estimate since the benefits of a national program cut across multiple medicines, indications, and disease areas.

In the Republic of Namibia, the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program supports the implementation of initiatives to improve HIV and AIDS treatment outcomes through strategies that promote pharmacovigilance at the health facility and community levels [20]. The Therapeutics Information and Pharmacovigilance Centre (TIPC), is responsible for the promotion of the rational and safer use of medicines in Namibia. TIPC is part of the Ministry of Health and Social Services (MoHSS), which also administers a network of ART clinics throughout the country. In 2012, SIAPS supported the initiation of prospective sentinel site active surveillance of the safety of antiretroviral medicines. The program, overseen by TIPC in collaboration with the University of Washington, aimed to implement an active surveillance pharmacovigilance system pilot program for first-line antiretroviral therapy (ART) medicines to support the effectiveness of Namibia's ART programs in improving the care and outcomes for persons with HIV/AIDS.

This study had three objectives. First, we prospectively determined the incidence of, and risk factors for, adverse medicine events in persons receiving first-line highly active antiretroviral therapy (HAART) at two sentinel sites in Namibia. The sentinel site activity also aimed to determine quality of data collected through the active surveillance program and identify any gaps in quality that may occur. Second, we evaluated the projected health outcomes and costs of PV in Namibia using first-line HAART as a case study. We assessed the cost-effectiveness of a national active surveillance PV system for HAART, as compared

to a spontaneous AE reporting PV system. The health outcomes and costs of an active surveillance system in Namibia could be used to assess feasibility of active surveillance in other settings, as well as provide information on the potential cost-effectiveness of improving health systems. Third, as a demonstration of use of active surveillance data, we aimed to assess the incidence of and risk factors for TDF-associated kidney injury in Namibia among adults newly placed on HAART using the active surveillance sentinel site data.

Chapter 2

SENTINEL SITE ACTIVE SURVEILLANCE OF SAFETY OF FIRST-LINE ANTIRETROVIRAL MEDICINES IN NAMIBIA

Authors: Marita Mann[1], Assegid Mengistu[2], Johannes Gaeseb[3], Evans Sagwa[3], Greatjoy Mazibuko[3], Jared M. Baeten[4], Joseph B. Babigumira[5], Louis P. Garrison[1], Andy Stergachis[6]

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[1]Department of Pharmacy, University of Washington, Seattle, WA, USA

[2]Therapeutics Information and Pharmacovigilance Centre, Windhoek, Namibia

[3]Systems for Improved Access to Pharmaceutical and Services (SIAPS/Namibia)

[4]Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, WA, USA

[5]Department of Global Health, University of Washington, Seattle, WA, USA

[6]Departments of Pharmacy and Global Health, University of Washington, Seattle, WA, USA

2.1 Abstract

Purpose. Active surveillance pharmacovigilance systems better estimate the burden of adverse events (AEs) and can generate useful information on risk factors of AEs for more effective medicine use, especially in conjunction with introduction of new medicines and/or treatment guidelines. This project aimed to implement an active surveillance pilot program for first-line antiretroviral therapy (ART) at sentinel sites in Namibia.

Methods. Sentinel sites were outpatient ART clinics at the Windhoek Central Hospital and Katutura Intermediate Hospital. An active surveillance data collection form was developed and placed into patient charts. Adults naïve to ART were enrolled. Physicians recorded ART and health information during each follow-up visit, including presence or absence of AEs.

Results. A total of 413 patients were included from August 2012 to April 2013. Average age was 37 years; 51% of patients were at WHO Clinical Stage 1; and mean baseline CD4 count was 216. The most common ART regimen was tenofovir/lamivudine/nevirapine. Presence or absence of AEs was recorded in active surveillance forms for 94% of first follow-up visits. In total, 66 patients experienced 119 AEs of any severity. Incidence of experiencing at least one AE was 33/100 person-years. Most common AEs were rash and abdominal pain. On active surveillance forms, demographic variables were missing in 14% of patients and follow-up visits were recorded for 82% of patients.

Conclusions. Completeness of AE recording on active surveillance forms was high. With improved logistical considerations, such as incorporation of active surveillance forms into medical records, long-term active surveillance programs could be successful.

2.2 Introduction

Active surveillance pharmacovigilance (PV) involves active measures to detect the presence or absence of adverse events on an on-going basis within a defined group of persons. This approach involves the systematic collection, analysis, and interpretation of information. Ac-

tive PV can provide locally-relevant estimates of the safety of medicines and risk factors for AEs associated with the use of medicines. Active surveillance methods involve obtaining a denominator of persons exposed to medications of interest, allowing for calculation of population incidence rates of AEs. Active surveillance is especially useful in conjunction with postmarketing safety surveillance for the introduction of new medicines as well as for assessing changes in treatment guidelines.

Active surveillance is a key aspect of a systematic approach to medicine safety assessment and pharmaceutical systems strengthening[3,9,21]. Active pharmacovigilance systems better estimate the true burden of AEs and can allow for more effective and efficient use of resources to reduce burden of disease on a national level[10,12]. Despite potential population health improvements and some societal willingness to pay for regulation to avoid AEs[14–18], active surveillance systems have yet to be implemented on a large scale in low- and middle-income countries, largely due to the fact that they can be complex and costly to implement and maintain. Sentinel sites can be utilized to more efficiently perform active surveillance.

In the Republic of Namibia, the Therapeutics Information and Pharmacovigilance Centre (TIPC) within the Ministry of Health and Social Services (MoHSS) is responsible for the promotion of the rational and safe use of medicines in that country. In 2012, Systems for Improved Access to Pharmaceuticals and Services (SIAPS) supported the initiation of prospective sentinel site active surveillance of the safety of antiretroviral medicines. The program, overseen by TIPC in collaboration with the University of Washington, aimed to implement an active surveillance pharmacovigilance system pilot program for first-line antiretroviral therapy (ART) medicines to support the effectiveness of Namibia's ART programs in improving the care and outcomes for persons with HIV/AIDS.

The objective of this study was to prospectively determine the incidence of, and risk factors for, adverse medicine events in persons receiving first-line highly active antiretroviral therapy (HAART) at two sentinel sites. The sentinel site activity also aimed to determine quality of data collected through the active surveillance program and identify any gaps in quality that may occur.

2.3 Methods

2.3.1 Sentinel Site Active Surveillance Procedures

The functions and activities associated with the active surveillance pharmacovigilance activity were conducted at two sentinel ART outpatient clinic sites located at the Windhoek Central Hospital (WCH) and the Katutura Intermediate Hospital (KIH) in Windhoek, Namibia. Staff orientation and training occurred in July 2012. The active surveillance pharmacovigilance activity was implemented in August 2012. Staff at the two sentinel ART sites identified eligible HIV positive adult patients naïve to HAART who were newly placed on a first line HAART regimen. Eligible patients were actively followed during routine care visits over an up to 12-month period. The presence or absence of AEs as well as demographic and clinical information was recorded onto a novel and pre-tested active surveillance data collection form (see Appendix A). Other clinical care information at ART sites is routinely recorded in Patient Care Booklets (PCBs). The PCBs have been shown to have high quality information on therapy, clinical progress notes, and laboratory values[22].

Included in the active surveillance program were patients diagnosed with HIV/AIDS aged 18 years and above, naïve to ART, who received care at one of the sentinel sites and were enrolled for ART initiation. They must have resided in the same location for at least three months and were not planning to relocate out of the area for the duration of the active surveillance follow-up. Pediatric and adolescent HIV/AIDS patients were excluded; as were adult HIV/AIDS patients not naïve to ART; and persons with any condition that, in the opinion of the clinician, would make participation in the activity unsafe, complicate the interpretation of findings, or otherwise interfere with achieving the activity's objectives.

At the baseline, when a patient was first placed on ART, the physician assessed each patient for starting HAART and determined eligibility for the active surveillance activity. The nurse then placed the active surveillance data collection form into the PCB for all eligible patients and placed a sticker onto the PCB that alerted the clinical staff that the patient was included in the active surveillance activity. The nurse completed Part A of the active

surveillance data collection form. The physician then recorded the ART regimen, reviewed other fields in Part A, and prescribed ART as appropriate. The clinic-based pharmacist checked each new patient started on ART for eligibility, and assigned and recorded a unique ID onto a patient enrollment form that was maintained in the pharmacy. During each follow-up visit the physician actively recorded the presence or absence of any adverse events on Part B of the active surveillance data collection form, along with other required fields pertaining to that visit. The active surveillance data collection form stayed with the PCB throughout the PV activity. The TIPC coordinator collected this information on a periodic basis for data entry. No patient identifying information left the ART sites. The TIPC coordinator visited each of the two sentinel sites on a regular basis—typically weekly—to reinforce with the staff the importance of following the procedures set forth for the active surveillance pharmacovigilance activity. Other quality assurance actions included tracking the progress in patient recruitment by sentinel site for the active surveillance pharmacovigilance activity.

The study was approved by the Institutional Review Board at the University of Washington as well as the Ministry of Health and Social Services of Namibia as part of the duties of TIPC.

2.3.2 Statistical Analysis

We assessed baseline values using frequencies for categorical variables and mean and standard deviation for continuous variables. To assess the potential for selection bias, we abstracted data from the PCBs for those who were eligible for the active surveillance pilot program but were not enrolled. We compared these patients to the study population using a multivariate linear regression model adjusted for age, gender, functional stage, WHO stage, starting ART regimen, baseline CD4 count, and weight.

We evaluated the frequency of adverse events in the follow-up period then calculated the unadjusted incidence of AEs using number of persons who experienced an AE during the person-time at risk for an event. We compared the adjusted incidence of adverse events of patients on each ART regimen using a Cox proportional hazard model. For time-to-

adverse event, we used the Kaplan-Meier method to estimate the survival function. The model calculated hazard ratios and 95% confidence intervals (CIs) with adjustment for ART regimen, WHO stage at baseline, age, gender, and CD4 count at baseline.

A sample of more than half of the active surveillance data collection forms was selected to assess data quality of the information collected for this activity. This sample was randomly selected from the full study patient population. For these forms, we abstracted and recorded missing values from the PCB to supplement information in the active surveillance data collection forms. We calculated frequency of missing values for baseline characteristics and follow-up visits. Values may have been missing on the active surveillance forms because they were not filled in on the forms or because they were not collected at all. In order to assess the specificity of missingness in the active surveillance data collection forms, we calculated for each field the number of patients missing the value in the active surveillance data collection form but present in the PCB divided by the total number missing the value in the PCB. For each patient in the quality sample, we abstracted from the PCB any follow up visit that was not recorded in the active surveillance form. We then determined the percentage of the sample that returned for any follow up visits, and for those calculated the percent recorded in the active surveillance data collection forms and mean number of visits and mean follow-up time both recorded in the active surveillance data collection forms and overall. All statistical analyses were completed using Stata version 10.1.

2.4 Results

2.4.1 Patient Recruitment and Follow-Up

Patients were enrolled in the active surveillance pharmacovigilance activity from August 1, 2012 to April 5, 2013. A total of 457 patients were initially included. Of these, 44 were excluded due to ineligibility, leaving a total of 413 patients for the final sample for analysis. The primary reason for ineligibility was not being naïve to ART. Of the included patients, 272 (66%) were from KIH and 141 (34%) were from WCH. No statistically significant differences

were found in demographic or baseline characteristics between patients enrolled at KIH and those enrolled at WCH.

The average duration of follow-up time was of 6.6 months as calculated as time from enrolment through the latest recorded follow-up visit on either the active surveillance form or PCB.

The average age of patients included in this active surveillance PV activity was 37 years; WHO clinical stage was Stage 1 for 51% of patients; and mean CD4 count was 216 (table 2.1). Of the included patients, 12% had concomitant tuberculosis and 15% had anemia. Of the 201 women in the sample, 157 had pregnancy status recorded. Of these, 56 (35%) were pregnant at baseline. The most common ART regimen was tenofovir/lamivudine/nevirapine (TDF/3TC/NVP), accounting for 73% of the regimens in this patient population. Of remaining patients, 16% were on TDF/3TC/efavirenz (EFV), 7% were on zidovudine (AZT)/3TC/NVP, 2% were on AZT/3TC/EFV, and 1% were on other, or atypical, regimens.

2.4.2 Demographics

After the active surveillance activity was completed, 35 additional patients who were eligible for enrolment, but were not enrolled, were identified. Patients enrolled in the PV activity (n=413) were similar to those eligible but not enrolled (n=35) in terms of age (p=0.57), gender (p=0.89), functional stage (p=0.18), WHO stage (p=0.79), starting ART regimen (p=0.77), baseline CD4 count (p=0.95), and weight (p=0.84).

2.4.3 Adverse Events

A total of 66 patients experienced at least one adverse event of any severity over a total follow-up time of 196 person-years. The incidence rate of experiencing at least one adverse event was 33 per 100 person-years. A total of 102 adverse events were recorded among these 66 patients. The most common adverse event recorded overall was rash (n=16), followed by

abdominal pain (n=15), and anemia (n=12) (Table 2.2). Among those who experienced an AE, 35% had a substitution of HAART medication, and 5% stopped HAART.

Table 2.1: Baseline characteristics of the study population (n=413).

Variable[7]	Value	Variable	Value
Demographics		Baseline Lab Values	
Male	41%	Mean CD4 (SD)	216 (131)
Mean Age (SD)	37 (10)	Mean Creatinine (SD)	79 (85)
		Mean Alanine Transaminase (SD)	29 (31)
Baseline Characteristics		Mean Blood Sugar (SD)	6.6 (8.1)
Mean Weight kg (SD)	64 (24)	Mean Hemoglobin (SD)	12.0 (2.4)
Functional Stage		Mean White Blood Cells	5.4 (2.9)
Working	92%	Rapid Plasma Reagin	3%
Ambulatory	7%	Hepatitis B	7%
Bedridden	1%	Urine Protein	8%
WHO Stage of Disease			
1	51%	Starting ARV Regimen	
2	17%	TDF/3TC/NVP	73%
3	20%	AZT/3TC/NVP	7%
4	12%	AZT/3TC/EFV	2%
Smoking	6%	TDF/3TC/EFV	16%
Alcohol Abuse	14%	Other	1%
Other Substance Abuse	2%		
Pregnant (among women)	36%		
Concomitant Illnesses			
Diabetes	2%		
Hypertension	6%		
Renal Disease	5%		
Chronic Liver Disease	2%		
Acute Liver Disease	1%		
Anemia	15%		
Tuberculosis	12%		
Cancer	2%		

[7]Abbreviations: standard deviation (SD), alanine transaminase (ALT), antiretroviral (ARV), tenofovir (TDF), lamivudine (3TC), nevirapine (NVP), zidovudine (AZT)

Table 2.2: Number and type of adverse events recorded by ART regimen (n=413).

Type of adverse event[8]	ART Regimen					
	TDF/3TC/NVP	AZT/3TC/NVP	AZT/3TC/EFV	TDF/3TC/EFV	Other/Unknown	Total
Rash	10 (2%)	0	1 (0.2%)	1 (0.2%)	4 (1%)	16 (4%)
Abdominal pain/ discomfort	12 (3%)	3 (0.7%)	0	0	0	15 (4%)
Anemia	4 (1%)	3 (0.7%)	0	0	5 (1%)	12 (3%)
Nausea	6 (1%)	1 (0.2%)	0	0	0	7 (2%)
Elevated LFT	2 (0.5%)	0	0	4 (1%)	0	6 (1%)
Hepatitis	5 (1%)	0	0	1 (0.2%)	0	6 (1%)
Headache	1 (0.2%)	2 (0.5%)	0	2 (0.5%)	0	5 (1%)
Fatigue	2 (0.5%)	1 (0.2%)	0	1 (0.2%)	0	4 (1%)
Serious skin reaction	2 (0.5%)	0	0	2 (0.5%)	0	4 (1%)
Diarrhea	1 (0.2%)	0	0	2 (0.5%)	0	3 (0.7%)
Jaundice	1 (0.2%)	0	0	1 (0.2%)	1 (0.2%)	3 (0.7%)
Elevated creatinine	1 (0.2%)	0	0	1 (0.2%)	1 (0.2%)	3 (0.7%)
Peripheral neuropathies	2 (0.5%)	0	0	0	0	2 (0.5%)
Central nervous system	1 (0.2%)	0	0	1 (0.2%)	0	2 (0.5%)
Renal Failure	0	0	0	1 (0.2%)	0	1 (0.2%)
Other	6 (1%)	1 (0.2%)	0	3 (0.7%)	3 (0.7%)	13 (3%)
Total	56 (14%)	11 (3%)	1 (0.2%)	20 (5%)	14 (3%)	102

[8]Abbreviations: antiretroviral therapy (ART), alanine transaminase (ALT), tenofovir (TDF), lamivudine (3TC), nevirapine (NVP), zidovudine (AZT), liver function test (LFT)

The hazard ratios by covariate after adjustment for ART regimen, age, gender, WHO stage, and CD4 count are presented in Table 2.3. Compared to patients on a TDF/3TC/NVP regimen, those on an "other" atypical regimen had 17.6 times higher risk of experiencing at least one adverse event (p=0.002, 95% CI 2.8-111.8) after adjustment for age, gender, WHO stage, and CD4 count. This difference of atypical regimens may have been due to confounding by indication whereby those patients on an atypical regimen were prescribed such medication due to baseline health or demographic differences that placed them at higher risk. Compared to those with WHO Stage 1 disease at baseline, those with WHO Stage 2 disease had 8.8 times higher risk of experiencing at least one adverse event (p=0.01, 95% CI 1.9-41.2) after adjustment for ART regimen, age, gender, and CD4 count. Age, gender, and CD4 count did not alter risk of experiencing an AE.

Table 2.3: Multivariate regression analysis results of factors associated with experiencing an adverse event.

Covariate[9]	Number of patients	Hazard Ratio	95% Confidence Interval			P-Value
ART Regimen						
TDF/3TC/NVP	296	Reference				
AZT/3TC/NVP	29	1.4	0.2	-	12.1	0.8
TDF/3TC/EFV	65	1.4	0.3	-	7.0	0.7
Other	11	17.6	2.8	-	111.8	0.002
Age (years)	399	0.9	0.9	-	1.0	0.3
Female	201	0.9	0.2	-	3.7	0.9
WHO Stage						
1	186	Reference				
2	60	8.8	1.9	-	41.2	0.01
3	73	1.2	0.2	-	6.3	0.9
4	45	2.4	0.2	-	32.3	0.5
CD4 count (100 cells/mm3)	408	0.5	0.3	-	1.1	0.1

[9]Abbreviations: antiretroviral therapy (ART), standard deviation (SD), alanine transaminase (ALT), tenofovir (TDF), lamivudine (3TC), nevirapine (NVP), zidovudine (AZT), World Health Organization (WHO)

The incidence of the most common AEs: rash, abdominal pain, and anemia; were 8.2, 7.7, and 6.1 per 100 person-years, respectively. Risk of abdominal pain was not statistically different by ART regimen, while risk of rash was higher for those on an atypical ART regimen compared to TDF/3TC/NVP (Hazard ratio 18.1, p<0.01, 95%CI 4.8-68.4), and risk of anemia was higher for those on an AZT/3TC/NVP regimen (Hazard ratio 11.2, p<0.01, 95%CI 2.3-55.8) or an atypical regimen (Hazard ratio 19.2, p<0.01, 95%CI 3.2-115.6).

2.4.4 Data Quality

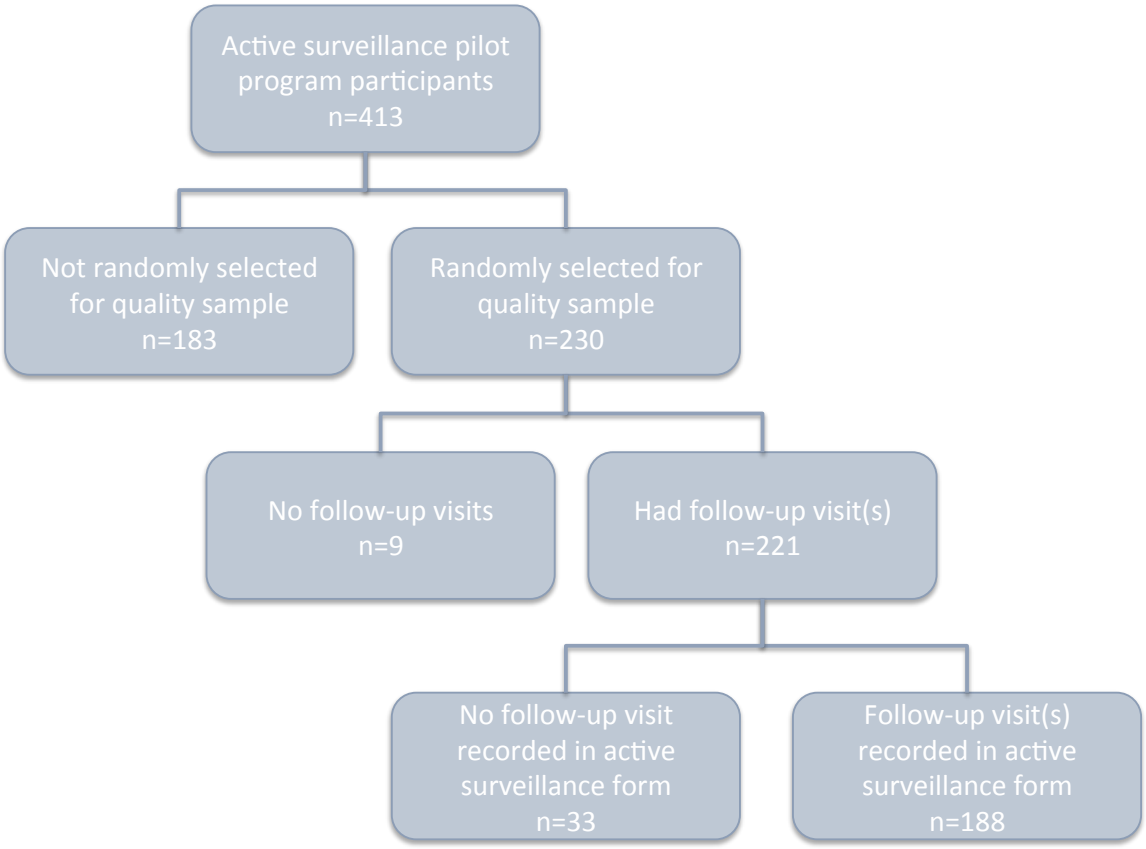

Figure 2.1: Number of patients reviewed for follow-up in the quality sample.

As assessed by evaluating a sample of 230 records (Figure 2.1), data completeness of the active surveillance data collection form varied by data field in the active surveillance data

collection forms (Table 2.4). Age and weight were missing 5% and 14% of data, respectively. Concomitant illnesses or conditions had missing data up to 32% of the time. Height was rarely present in the active surveillance data collection forms (missing 95% of the time). Baseline laboratory values varied from 2% missing for CD4 count, up to 98% missing for blood sugar values. Table 2.4 also shows the percentage missing data based on the first follow-up visit for the same 230 patients. Of the 230 patients, 188 (82%) had at least one follow-up visit recorded in the active surveillance data collection forms (Figure 2.1). Of these 188, there was missing data for each of the variables assessed, ranging from 2% missing the ART regimen to 42% missing other conditions present at first follow-up visit. Specificity of missingness on the active surveillance data collection forms compared to the PCB for recorded versus missing variables was 0.35 for gender, 0.35 for starting ART regimen, 0.53 for WHO stage, 0.43 for functional stage, 0.31 for HIV date of diagnosis, 0.25 for date of enrolment in HIV care, and 0.29 for ART start date.

Of those patients whose records were included in the data quality analysis sample (n=230), records indicated that 221 returned to the ART site for at least one follow-up visit (Figure 2.1). A total of 950 visits were recorded in the active surveillance data collection forms, while 482 visits (34%) were missed. The median number of follow-up visits recorded in the active surveillance data collection form was 5 (interquartile range (IQR) 4-6), with a median of 4 visits (IQR 2-5) not recorded. The active surveillance data collection forms included a median of 7 months (IQR 0-11) of follow-up time per patient, while median total follow-up time per patient was 7 months (IQR 1-11).

Based on the review of 230 patient charts and active surveillance forms, presence or absence of an adverse event was recoded on 94% of the active surveillance forms. The rate of recording AEs on the active surveillance form tended to decrease with subsequent visits. Comparatively, AEs were rarely explicitly recorded in the PCBs.

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[10]Abbreviations: antiretroviral therapy (ART), World Health Organization (WHO), adverse event (AE)

Table 2.4: Completeness of data based on review of the active surveillance data collection forms (n=230).

Baseline Visit[10]		First Follow-Up Visit	
Variable	% Missing	Variable	% Missing
Demographics			
Age	5%	ART Regimen	2%
Weight	14%	Other Medicines	4%
Pregnant (among women)	19%	Adverse Events	6%
Sex	23%	Change Regimen	7%
Height	95%	AE Outcome	13%
Clinical Characteristics		Other Conditions	42%
ART Start Regimen	5%		
WHO Stage	18%		
Functional Stage	20%		
Laboratory Values			
CD4	2%		
Serum creatinine	7%		
Hemoglobin	8%		
Alanine transaminase	9%		
White Blood Cells	31%		
Urine Protein	89%		
Blood Sugar	98%		
Concomitant Illnesses			
Hepatitis B	13%		
Tuberculosis	25%		
Anemia	27%		
Liver Disease	28%		
Renal Disease	29%		
Diabetes	30%		
Cancer	32%		

2.5 Discussion

This sentinel site active surveillance program aimed to enroll all eligible patients beginning first-line antiretroviral therapy at two ART sites in Windhoek, Namibia. Completeness of AE recording on the active surveillance forms was high, while completeness of demographic

characteristics varied widely. The incidence of experiencing at least one adverse event was 33 per 100 person-years among the patients included in this active surveillance pharmacovigilance activity. The most common adverse event was rash, followed by abdominal pain. The risk of experiencing an adverse event was higher for those with an atypical ART regimen or with WHO stage 2 disease. Age, gender, and CD4 count did not alter risk of experiencing an AE.

In terms of data quality, AEs were recorded consistently on the active surveillance forms. While demographic variables such as age were reasonably complete on the active surveillance data collection forms, concomitant illnesses or conditions had missing data almost a third of the time. Moreover, for the follow-up Part B of the form, there were missing data for each of the variables assessed ranging from 2% to 42%. While 82% of patients had at least one follow-up visits recorded, 34% of total visits were missed. This demonstrates that physicians were likely recording more visits soon after the patients began ART, and fewer in later months. These results indicate the need for consistent training and follow-up with the doctors by pharmacovigilance staff. Incorporating the active surveillance form into the PCB would likely increase use on follow-up visits. Additionally, physicians would be more likely to continue recording visits in a longer-term program with additional training.

Of the 35.3 million people living with HIV worldwide, 10 million are receiving highly active antiretroviral therapy (HAART)[23]. However, the use of HAART is associated with a variety of AEs ranging from mild to life-threatening[24–27]. It is particularly difficult to accurately determine the risks of AEs associated with HAART use for several reasons. First, the majority of drug safety data is based on information obtained during clinical trials[28]. The patients and clinicians who participate in clinical trials are highly selected and are studied or practice under ideal settings; therefore, results are likely not representative of the true population using the drug under real-world conditions. Second, populations with relatively high HIV prevalence and widespread HAART treatment are not common. It is necessary to assess the real-world performance of HAART in populations with both high prevalence of HIV and high proportion of patients on HAART treatment to assess

medicine safety. Finally, the risk of AE varies between persons and populations. For example, demographic and comorbid conditions such as age, gender, diabetes mellitus, and CD4 cell count influence the risk of AEs[29].

Previous studies of the safety of ART in persons with HIV have reported incidence rates for adverse events up to 52 per 100 person-years[27,30–33], higher than found in the current study. Demographic and treatment practice differences are likely influential in adverse event incidence rate differences. A prevalence as high as 88%[34] and 63%[35] has been found in several studies. However, several studies conducted in Africa reported lower ranges of adverse event prevalence between 11% and 53%[36–41]. It is difficult to reconcile differences in the results among these studies as due to demographics and treatment practices or those due to data collection practices.

Previous studies have reported effavirenz (EFV) to be safer than nevirapine (NVP), particularly in terms of hepatotoxicity and skin reactions[42]. While the numbers are small, our results demonstrate a similar risk of adverse events irrespective of regimen, with the exception of atypical regimens. The atypical regimens may be confounded by atypical baseline or treatment characteristics: therefore, this result may not be applicable to the general population. The results presented here are consistent with several previous studies that found rash to be one of the most common AEs for HAART patients[25,43]. Several studies have also found increased risk of adverse events in women[30,36,38,44], which was not found in this study. Again, a small sample size may account for a lack of significant results.

The results on data quality indicate a high level of quality for recording AEs, and opportunity for improvement in the completeness of the paper-based forms for the active surveillance. It is important to note that much of the data on the first page of the active surveillance data collection form is duplicative with the PCB. Integrating the form into the PCB, which has been proposed as a potential next step if the program is continued, would likely eliminate many missing data issues, as the baseline information would be filled in the PCB itself, and therefore the physician or nurse would not have to fill it in twice. Additionally, practitioners would likely record more follow-up visits as it became standard practice with longer-term

use. This is indicated by the continuity of recording after TIPC staff ended weekly visits to encourage recording.

The World Health Organization has promoted a method of active surveillance known as Cohort Event Monitoring (CEM), in which data is collected for all AEs within a defined patient cohort[45]. All eligible patients should be enrolled into the cohort until the cohort reaches a predefined size. Though CEM has advantages over spontaneous reporting, defining a cohort size can be problematic, and patients not in the cohort will not be covered by active surveillance. Sentinel site active surveillance surveillance is the collection and analysis of data by designated institutions selected for their geographic location, medical practice characteristics, and ability to record and report high-quality data.

The MoHSS is considering expanding active surveillance pharmacovigilance to the national level. The data quality analysis can aid in determining applicability of this pilot program to larger-scale programs. A TIPC coordinator completed periodic site visits throughout the sentinel site program, which likely increased physician engagement and therefore data completeness. In order to scale up the program, the number staff would likely have to be increased to maintain this data quality. Such an analysis could assess the feasibility of ART active surveillance on a larger scale in Namibia, active surveillance for other medicines in Namibia, or active surveillance in other countries. Future work could explore linking active surveillance pharmacovigilance to eHealth initiatives, expand active surveillance pharmacovigilance to the tuberculosis program, or expand active surveillance pharmacovigilance to pregnant women receiving ARVs.

This study was limited by the relatively small sample size as well as relatively short follow-up time. Many adverse events occur in the weeks following initiation of HAART[31,32], therefore, the likely key relevant time points would have been captured in this study. Those AEs with longer exposure or detection time frames would not have been captured. To capture these events would require a combination of longer active surveillance augmented with targeted spontaneous reporting methods. Additionally, sentinel sites may not represent the general population or the incidence of disease; therefore, there are some limitations in

generalizing for national disease patterns and trends. The study population is generally representative of the population of people with HIV in Namibia[46]. As TDF/3TC/NVP is the WHO and Namibia's recommended first-line regimen, this is likely the most commonly prescribed regimen.

The quality of data collected through active surveillance demonstrated potential for high quality pharmacovigilance. With improved logistical considerations such as implementing active surveillance into the medical record, a sustainable national active surveillance program could be successful. The results of the pilot program as well as potential for a national program will provide valuable information for assessing the feasibility of active surveillance and pharmacovigilance health program improvement for low- and middle-income countries worldwide.

Chapter 3

COST-EFFECTIVENESS OF AN ACTIVE SURVEILLANCE PHARMACOVIGILANCE SYSTEM FOR FIRST-LINE ANTIRETROVIRAL MEDICINES IN NAMIBIA

Authors: Marita Mann[1], Assegid Mengistu[2], Johannes Gaeseb[3], Evans Sagwa[3], Greatjoy Mazibuko[3], Joseph B. Babigumira[4], Louis P. Garrison[1], Andy Stergachis[5]

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3.1 Abstract

Background. Active surveillance pharmacovigilance (PV) is a systematic approach to medicine safety assessment and health systems strengthening, but has yet to be implemented on a large scale in low- and middle-income countries.

Methods. A cost-utility analysis from a governmental perspective compared active surveillance PV to spontaneous reporting PV for highly active antiretroviral therapy (HAART)

[1]Department of Pharmacy, University of Washington, Seattle, WA, USA

[2]Therapeutics Information and Pharmacovigilance Centre, Windhoek, Namibia

[3]Systems for Improved Access to Pharmaceutical and Services (SIAPS/Namibia)

[4]Department of Global Health, University of Washington, Seattle, WA, USA

[5]Departments of Pharmacy and Global Health, University of Washington, Seattle, WA, USA

in Namibia. Programmatic data from a sentinel site active surveillance program in Namibia conducted from August 2012-April 2013 was projected to all HIV-infected adults initiating HAART in Namibia. Costs (PV program, HAART, adverse event [AE] treatment), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs, 2015 U.S. dollars/QALY) were evaluated. Analysis was completed for (1) a cohort analysis in which a single cohort beginning HAART in 1-year in Namibia were followed over their remaining lifetime and (2) a population analysis in which patients continued to enter and leave care and treatment over 10 years.

Results. For the cohort analysis, totals were $30,495,344 and 184,076 QALYs for care and treatment under active surveillance PV versus $23,449,976 and 182,292 QALYs for care and treatment under spontaneous reporting PV, resulting in an ICER of $3,949 for active surveillance compared to spontaneous reporting PV. The population analysis resulted in an ICER of $542. Results were sensitive to quality of life associated with AEs.

Conclusion. Active surveillance pharmacovigilance was projected to be a highly cost-effective system to improve treatment for HIV in Namibia. Active surveillance PV may be valuable to improve the lives of HIV patients and more efficiently allocate health resources in Namibia.

3.2 Introduction

Pharmacovigilance (PV) is the science and activities relating to the detection, evaluation, understanding, and prevention of adverse events (AEs) associated with medicine use [1]. PV provides information in assessing the inevitable tradeoff between benefits and potential harm from medicine use. This is accomplished through the collection and analysis of information on AEs and communication to those that have the knowledge to interpret the information and act in order to minimize harm to patients [1]. Additional potential benefits of a PV system include improved understanding of the burden of and risk factors for iatrogenic illnesses, a greater understanding of population health, and improved healthcare provision and outcomes. Although some of these population-level benefits are difficult to quantify, it may

be feasible to quantify benefits to individual health. For example, if an AE is detected early, a health care provider can alter treatment to minimize negative effects on a given patient's quality of life, improve medication adherence, and/or slow disease progression [2].

Public health systems in low- and middle-income countries (LMICs) traditionally use spontaneous reporting pharmacovigilance systems to identify and report AEs [3,4]. In a spontaneous reporting system, health care providers, pharmaceutical companies and/or patients passively report a suspected AE to a public health or governmental organization via various mechanisms, including phone, internet, or postal systems. Spontaneous reporting systems, though relatively inexpensive to run are useful for signal generation, but lack a well-defined population denominator and, therefore, lack the ability to calculate incidence. Spontaneous reporting systems also suffer from significant underreporting of AEs [5–7].

Active surveillance is a type of PV whereby active measures are taken to detect the presence or absence of adverse events on an on-going basis within a defined group of people. It involves the on-going systematic collection, analysis, and interpretation of data [3,8–10]. In low- and middle-income countries, health care systems without active surveillance tend not to have the capacity for high quality AE detection. Among other limitations, not enough trained providers are available to detect many AEs. An active surveillance system raises the index of suspicion of AEs and hence raises the potential rate of detection and the treatment of AEs. In addition to enhancing individual level safety, active surveillance methods allow for calculation of population-based rates of AEs [11]. Active surveillance PV can contribute local data by providing estimates of the incidence of AEs and risk factors for medicine-associated AEs, and may allow for more effective and efficient use of resources to reduce the burden of disease [10,12]. Through active surveillance, potential medicine-associated safety problems and their risk factors can be identified. Active surveillance is particularly well suited for HIV medications, especially when patients are monitored at antiretroviral therapy (ART) clinics and assessed by health care providers on a routine basis.

Despite potential population health improvements and society's willingness to pay for medicine regulation and to avoid AEs [14–18], active surveillance systems have yet to be

implemented on a large scale in LMICs. Active surveillance systems can be complex and costly to implement. While a framework to assess cost-effectiveness of PV has been proposed [19], data have yet to be presented on the health benefits and medical costs of an active PV program at a national level. National level costs and benefits of active PV can be difficult to estimate since the benefits of a national program cut across multiple medicines, indications, and disease areas.

In the Republic of Namibia, an upper-middle income country, the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program supports the implementation of initiatives to improve HIV and AIDS treatment outcomes through strategies that promote pharmacovigilance at the health facility and community levels [20]. The Therapeutics Information and Pharmacovigilance Centre (TIPC) is the designated national pharmacovigilance program, responsible for the promotion of the rational and safer use of medicines in Namibia. TIPC is part of the Ministry of Health and Social Services (MoHSS), which also administers a network of ART clinics throughout the country.

In this study, we evaluated the projected health outcomes and costs of PV in Namibia using first-line HAART as a case study. We assessed the cost-effectiveness of a national active surveillance PV system for HAART, as compared to a spontaneous AE reporting PV system. The health outcomes and costs of an active surveillance system in Namibia could be used to assess feasibility of active surveillance in other settings, as well as provide information on the potential cost-effectiveness of improving health systems.

3.3 Methods

From August 2012 to April 2013, the MoHSS, through the TIPC, initiated a prospective sentinel site active surveillance activity for first-line highly active antiretroviral therapy (HAART) at two MoHSS ART outpatient clinic sites located at the Windhoek Central Hospital and the Katutura Intermediate Hospital in Windhoek, Namibia - with technical support from the SIAPS program [47]. The study population for this analysis was based on patients included in the sentinel site active surveillance activity, i.e., HIV-infected patients

naïve to HAART who were newly placed on a first line HAART regimen in two publicly financed ART clinics in Namibia. Briefly, patients were 41% male and had an average age of 37 years (Table 3.1). The mean CD4 count was 216 and 51% had WHO stage 1 disease. The most common HAART regimen was tenofovir/lamivudine/nevirapine [47].

Table 3.1: Baseline characteristics of the study population, based on patients included in the sentinel site active surveillance activity, adults initiating on HAART in a publicly financed ART clinic in Namibia, n=413.

Variable[6]	Value
Male	41%
Mean Age (SD), years	37 (10)
Functional Status	
Working	92%
Ambulatory	7%
Bedridden	1%
WHO Stage of Disease	
1	51%
2	17%
3	20%
4	12%
Smoking	6%
Alcohol Abuse	14%
Tuberculosis	12%
Pregnant (among women)	36%
Mean Baseline CD4 (SD)	216 (131)
Starting HAART Regimen	
TDF/3TC/NVP	73%
AZT/3TC/NVP	7%
AZT/3TC/EFV	2%
TDF/3TC/EFV	16%
Other	1%

The costs of a PV system, including care and treatment delivered, were derived from

[6]HAART – highly active antiretroviral therapy, ART – antiretroviral therapy, SD – standard deviation, WHO – World Health Organization, TDF – tenofovir, 3TC – lamivudine, NVP – nevirapine, AZT – zidovudine, EFV - efavirenz

the governmental perspective of MoHSS. This perspective includes costs to the government, including costs to the ART clinics for implementation and management of a PV system and care and treatment associated with managing patients with HIV (Figure 3.1). We compared active surveillance to spontaneous reporting based on two methods, (1) a cohort analysis and (2) a population analysis. First, we used a cohort analysis, in which a single cohort of all patients eligible to begin HAART in one year in Namibia entered care within the PV system and were followed over a lifetime horizon. Because health systems affect not just a single cohort, but the entire catchment population, we also used a second, population-based analysis. In this analysis, patients continued to enter (via beginning HAART) and leave (via mortality) care in the presence of the PV system each year as they became eligible for HAART over a 10-year time horizon. Both costs and health outcomes were discounted at 3% per annum, as recommended [48].

3.3.1 Outcomes

The effectiveness of each PV system is dependent on the probability of detecting an AE in that system. In the active surveillance system, this data were acquired from the sentinel active surveillance activity, which has been described elsewhere [47]. In brief, a specially designed active surveillance data collection form was developed and placed into patient treatment charts, called the ART Patient Care Booklet. Adults naïve to ART were enrolled. Physicians recorded ART and health information during each follow-up visit, including presence or absence of AEs. In the spontaneous reporting system, health care providers are expected to report suspected AEs via fax or mail to the TIPC through the national spontaneous AE reporting system. To avoid the influence of active surveillance on spontaneous AE reports, data for the spontaneous reporting system was acquired from the year prior to the sentinel active surveillance activity.

The health outcomes of each PV system were evaluated in quality adjusted life years (QALYs), which combines morbidity and mortality. Morbidity and quality of life values for patients with and without AEs were defined from existing literature (Table 3.2) [18,49–52].

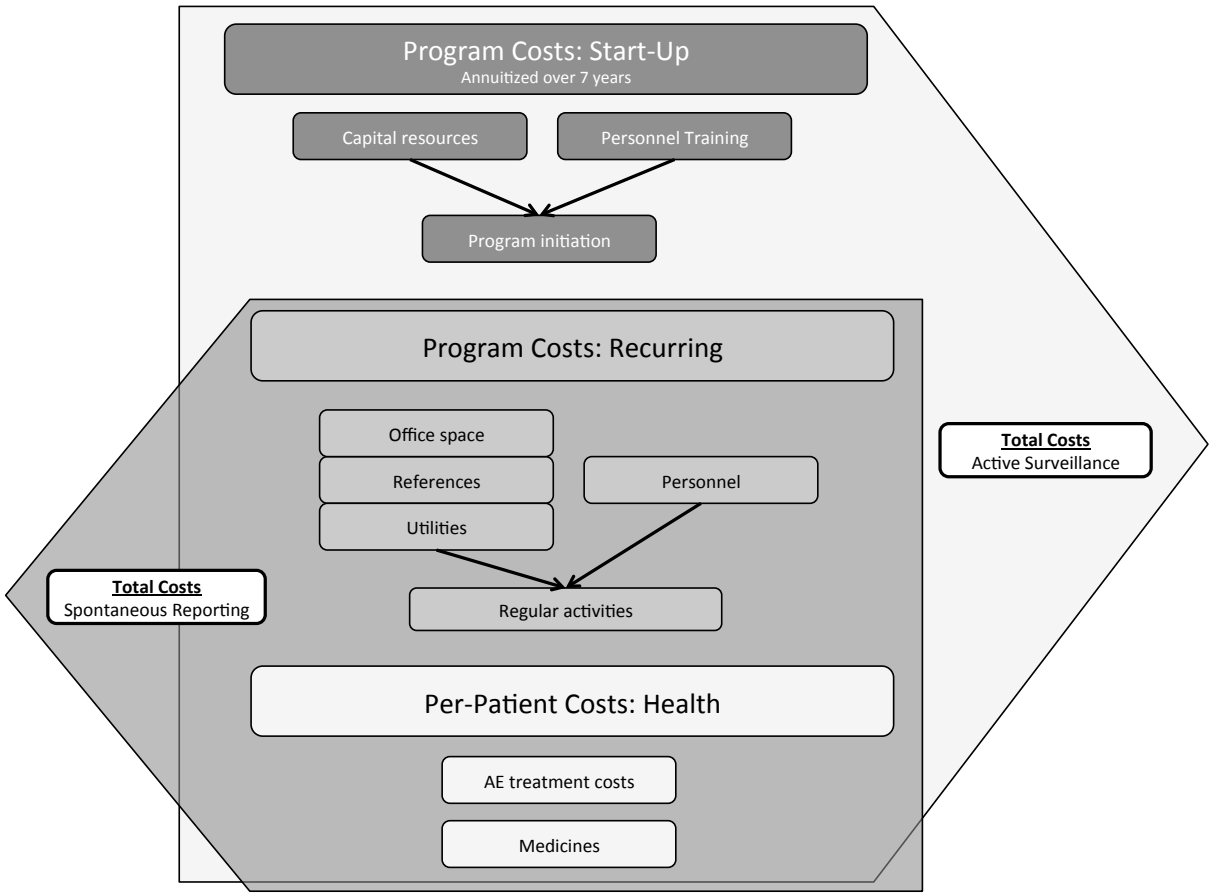

Figure 3.1: Conceptual framework for costs of pharmacovigilance systems, including program costs and per-patient medical costs.

Values from sub-Saharan Africa were used when available.

Costs included two categories: program costs and medical care costs (Figure 3.1). Program costs of an active surveillance system implementation and annually were acquired from the sentinel active surveillance activity and combined with population data to model countrywide estimates [46,53]. For active surveillance, start-up costs were annuitized over the first 7 years of the program. Program costs of a spontaneous reporting system were acquired from TIPC (Table 3.2). The spontaneous reporting system did not have any start-up costs, as it is an existing program. This is a true marginal analysis of a health system in Namibia; therefore we aim to compare active surveillance to the current 'standard of care', in this case,

the steady state spontaneous reporting system that currently exists in Namibia, which does not have start-up costs. Medical care costs, which included HAART and treatment of AEs, for both PV systems were calculated on a per-patient basis based on costs of HAART and inpatient and outpatient care for AEs acquired from TIPC (Table 3.2). All costs are shown in 2015 US dollars (USD).

Table 3.2: Model variable input values for health probabilities, quality of life, pharmacovigilance program activities, and costs: base case and low and high values used in sensitivity analysis.

Parameter	Base	Low	High	Source
Adverse Event Probabilities				
AE occurrence	0.37	0.28	0.46	[59]
AE severe	0.20	0.15	0.25	[60,61]
AE detected				
Active surveillance	0.89	0.45	1	Sentinel Site Data
Spontaneous reporting	0.19	0.09	0.28	Spontaneous Reporting Data
Health and Utilization Probabilities				
Regimen switch				
Mild/moderate AE	0.10	0	0.5	[60]
Severe AE	1	0.5	1	Assumed
To second line	0.10	0	1	Assumed, [62]
Hospitalization (severe AEs only)	0.28	0	1	[60]
Outpatient visit				
Severe AE	0.56	0	1	Assumed double hospitalization probability
Moderate AE	0.56	0	1	
Death				
Detected AE	0.004	0.0002	0.008	[60]
Undetected AE	0.008	0.0004	0.016	Assumed double detected probability
Annual new HAART patients in Namibia	9413	1936	5808	[63]
Reductions in Quality of Life Due to AE				
In year of event				
Severe AE				
Regimen switched	0.16	0.07	0.24	[60]
Regimen not switched	0.32	0.14	0.48	[60]
Mild/moderate AE				
Regimen switched	0.04	0.02	0.06	[60]
Regimen not switched	0.08	0.04	0.12	[60]
In subsequent years				
Severe AE				
Regimen not switched	0.13	0.00	0.16	[64]
Mild/moderate AE				

Parameter	Base	Low	High	Source
Regimen not switched	0.06	0.00	0.08	[64]
Program Start-Up Activities For Active Surveillance (Weeks Required)				
Design of AE forms	4	3	5	[65]
Printing of AE forms	1	1	1	
Advocacy meetings with key stakeholders	4	3	5	
Advocacy with radio, TV and newspapers	3	2	4	
Website design	4	3	5	
Personnel Training For Active Surveillance (Weeks Required)				
Physician	2	2	3	[65]
Pharmacist	1	1	1	
Nurse	2	2	3	
Clinical pharmacologist	1	1	1	
Epidemiologist	1	1	1	
Personnel (Number Required For Active Surveillance)				
Project coordinator	2	1	4	[65]
Research assistant	2	1	4	
Physician	1	0	3	
Pharmacist	0.5	0	3	
Nurse	2	1	4	
Clinical pharmacologist	0.5	0	3	
Epidemiologist	0.5	0	3	
Driver	2	1	4	
Costs				
Patient Costs				TIPC, [65]
HAART medicine costs per patient per year				
1st line	$117	$88	$146	
2nd line	$469	$352	$586	
Utilization costs				TIPC, [65]
Outpatient visit	$6	$5	$8	
Hospitalization	$996	$747	$1,245	
Program Costs				TIPC, [65]
Supplies (per month)				
Active surveillance	$149	$112	$187	
Spontaneous reporting	$59	$44	$73	
Office space (per square foot per month)	$8	$6	$10	
Utilities (per month)				
Active surveillance	$272	$204	$340	
Spontaneous reporting	$156	$117	$195	
Phone (per person per month)	$25	$19	$31	
Internet (4G per person per month)	$17	$12	$21	
References for active surveillance (per year)	$1,060	$795	$1,325	

Parameter	Base	Low	High	Source
Equipment required for active surveillance (computers, copiers, etc.)	$68,070	$51,053	$85,088	
Personnel (annual salary)				TIPC, [65]
Project coordinator	$42,409	$31,807	$53,011	
Research assistant	$25,198	$18,899	$31,498	
Physician	$16,902	$12,676	$21,127	
Pharmacist	$13,865	$10,399	$17,332	
Nurse	$25,115	$18,837	$31,394	
Clinical pharmacologist	$25,198	$18,899	$31,498	
Epidemiologist	$4,298	$3,223	$5,372	
Driver	$4,298	$3,223	$5,372	

3.3.2 Model

Cost-effectiveness was defined in terms of cost compared to the quantity of the reductions in mortality and morbidity as a result of increased detection and treatment of AEs [54]. In an active surveillance program in a LMIC, we assume that more AEs will be detected, leading to an increase in number of patients switched to other medicines, which improve health but also increase costs for these patients. A percentage of these switches may be to more expensive second-line medicines, while the majority are to alternative first-line medicines. Depending on the PV system and health care provider, detection of an AE may or may not have an influence on treatment. In this model, we assumed that AE detection is by the health care provider and therefore its detection can influence treatment.

We adapted a previously described decision-analytic framework to model costs and outcomes of PV at the national level (Figure 3.2) [19]. We made several simplifying assumptions in the model framework and inputs. We assumed that all AEs can be categorized as either severe or mild/moderate, probability of detection of AE is independent of severity of the AE, and among mild/moderate AEs no death or hospitalizations occur due to the event. We also assumed that if the AE is not detected there would be no healthcare utilization related to the event. We assumed that AEs occur at beginning of the first year of treatment and, if treated, resolve within one year. We assumed that inpatient and outpatient visits do not affect quality of life (i.e., quality of life is only affected by AE severity and switching HAART

regimens). Finally, we assumed that the probability of outpatient visits is independent of switching HAART regimens or severity of the AE, probability of death is independent of inpatient or outpatient visits, and probability of death without switching HAART regimen is double the probability of death with HAART regimen switch. Assumptions were evaluated in sensitivity analyses.

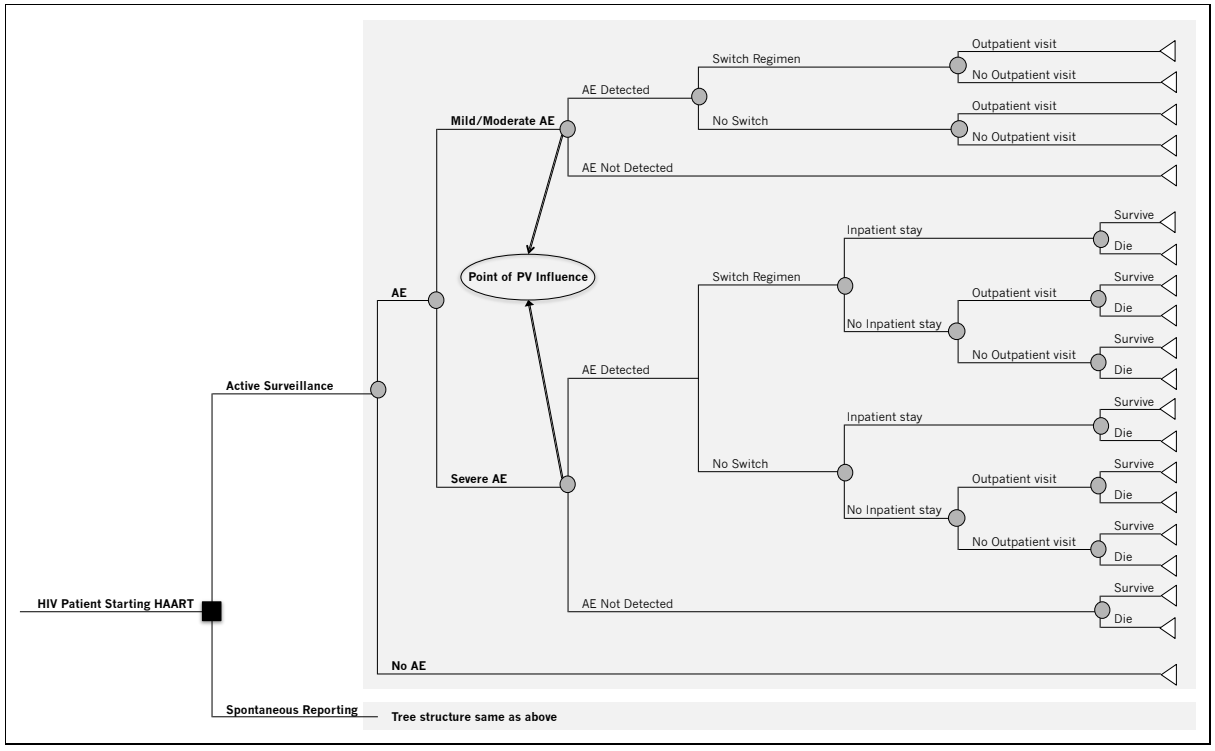

Figure 3.2: Decision analytic framework used to model costs and outcomes comparing active surveillance PV and spontaneous reporting PV at the national level in Namibia.

3.3.3 Analytical Methods

A probability was calculated for the average patient to be in each of the final health states (shown as the white triangles in Figure 3.2). Each health state was assigned a value for QALYs and cost. The probability of being in each final state was applied to the annual incident HAART cohort of 9,413 patients [55] in the 213 existing public ART clinics (in-

cludes main ART sites, Integrated Management of Adulthood Illnesses sites, and outreach sites) [55] in Namibia to calculate population total costs and total QALYs associated with pharmacovigilance.

We applied the per-patient results for medical costs and health outcomes to each of the two methods described above, (1) the lifetime cohort analysis, and (2) the 10-year population analysis. We then calculated an incremental cost-effectiveness ratio (ICER), in which the numerator is the incremental program and medical costs for an active surveillance PV system compared to spontaneous reporting PV system, and the denominator is the incremental QALYs gained due to active surveillance PV compared to spontaneous reporting PV. An intervention is considered cost-effective if the ICER is less than three times the gross domestic product (GDP) per capita, and highly cost-effective if the ICER is under the GDP per capita [56]. The current GDP per capita in Namibia is $9,736 purchasing power parity [53].

To assess uncertainty in the model, we conducted a one-way sensitivity analysis. For this analysis, we evaluated the incremental cost-effectiveness ratio (ICER) results for the cohort-based analysis when each input value was varied from a low to high range, and summarized the input variables that had the greatest effect on ICER a tornado diagram. We also conducted a probabilistic sensitivity analysis.

Data analysis was done using Stata version 10 and Microsoft Excel version 14. The study was approved by the Institutional Review Board at the University of Washington as well as the Ministry of Health and Social Services of Namibia as part of the duties of TIPC.

3.4 Results

3.4.1 Program Costs

The estimated national-level program start-up cost for a nation-wide active surveillance PV program for HAART was determined to be $97,200. There were no start-up costs for the spontaneous reporting PV program (see Methods for explanation). The estimated annual recurring program cost for active surveillance PV was $263,400 versus $49,800 for

spontaneous reporting PV (Table 3.3).

Table 3.3: Annual results for program costs, per patient medical costs including HAART and adverse event treatment, and annual expected QALYs for active surveillance PV and spontaneous reporting PV. Results were combined into a cohort analysis in which 9,413 patients were modeled for their remaining lifetime and a population analysis in which 94,130 patients were modeled over 10 years.

	Active Surveillance PV[7]	Spontaneous Reporting PV	Difference	ICER
Program Results				
Start-Up Costs	$97,200	$0		
Annual Recurring Costs	$263,400	$49,800		
Per-Patient Results				
Annual Costs	$130	$118		
Annual QALYs	0.964	0.953		
Cohort Analysis Results				
Costs	$30,495,344	$23,449,976	$7,045,368	$3,949
QALYs	184,076	182,292	1,784	
Population Analysis Results				
Costs	$203,078,416	$194,695,363	$8,383,053	$542
QALYs	1,625,266	1,609,803	15,463	

3.4.2 Per-Patient Costs and Health Outcomes

In the year the patient entered the program, per-patient total medical costs including HAART and treatment of AEs, incurred in an active surveillance PV system were $140 versus $119 within a spontaneous reporting PV system (Table 3.3). In an active surveillance system, more adverse events are assumed to be detected; therefore more patients are switched to alternative drugs, which should provide better health outcomes. The mean expected QALYs per patient in the first year of active surveillance PV was 0.96 versus 0.95 in spontaneous

[7]HAART – highly active antiretroviral therapy, QALYs – quality adjusted life years, PV – pharmacovigilance

reporting PV (Table 3.3).

3.4.3 Cohort Analysis

For the cohort analysis, the total costs included program costs for PV as well as HAART costs and costs for treatment of AEs for 9,413 patients [55] who began HAART and therefore entered the PV system at the same time. Data for these patients were modeled for their remaining lifetime, over which time total costs for the cohort including PV program, HAART, and associated medical costs were $30,495,344 for active surveillance PV versus $23,449,976 for spontaneous reporting PV (Table 3.3). Over their remaining lifetime, this cohort accumulated 184,076 QALYs within an active surveillance PV system versus 182,292 QALYs within a spontaneous reporting PV system. This resulted in an ICER of $3,949 per QALY for active surveillance PV compared to spontaneous reporting PV. This is considered highly cost-effective.

3.4.4 Population Analysis

For the population analysis total costs included program costs for PV as well as HAART costs and costs for treatment of AEs for 94,130 patients (9,413 entering the PV system each year for 10 years). These patients' costs and outcomes were modeled over 10 years, over which time total costs including program, HAART, and associated medical costs were $203,078,416 for care and treatment under an active surveillance PV system versus $194,695,363 under a spontaneous reporting PV system (Table 3.3). Over 10 years, these patients accumulated 1,625,266 QALYs within an active surveillance system versus 1,609,803 QALYs within a spontaneous reporting system. This resulted in an ICER of $542 per QALY for active surveillance PV compared to spontaneous reporting PV. This is considered highly cost-effective.

3.4.5 Sensitivity Analysis

ICERs were most sensitive to the quality of life for a patient with an AE, number of new HAART patients per year in Namibia, and probability an AE is detected in an active surveillance PV system (Figure 3.3). Results were robust to probabilistic sensitivity analysis. Active surveillance PV was projected to be more likely to be cost-effective than spontaneous reporting PV at a willingness-to-pay threshold of $4,100 per QALY in the cohort analysis (Figure 3.4). Based on the current GDP per capita in Namibia [53], active surveillance had a 97% probability of being highly cost-effective in the cohort analysis (Figure 3.4).

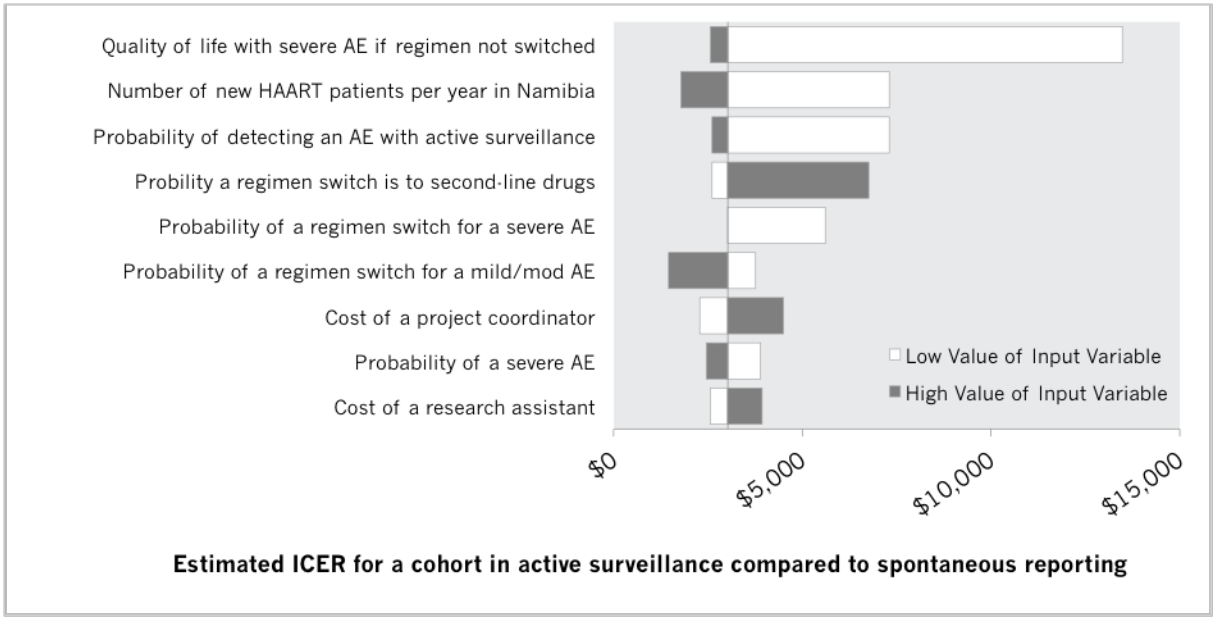

Figure 3.3: Tornado diagram for sensitivity of the ICER comparing active surveillance to spontaneous reporting for a cohort of patients in a PV system in Namibia.

3.5 Discussion

The ICER for a single cohort of 9,413 patients over their lifetime for active surveillance PV compared to spontaneous reporting PV was $3,949 per QALY, which would be considered highly cost-effective based on the current GDP of $9,736 per capita in Namibia. For the

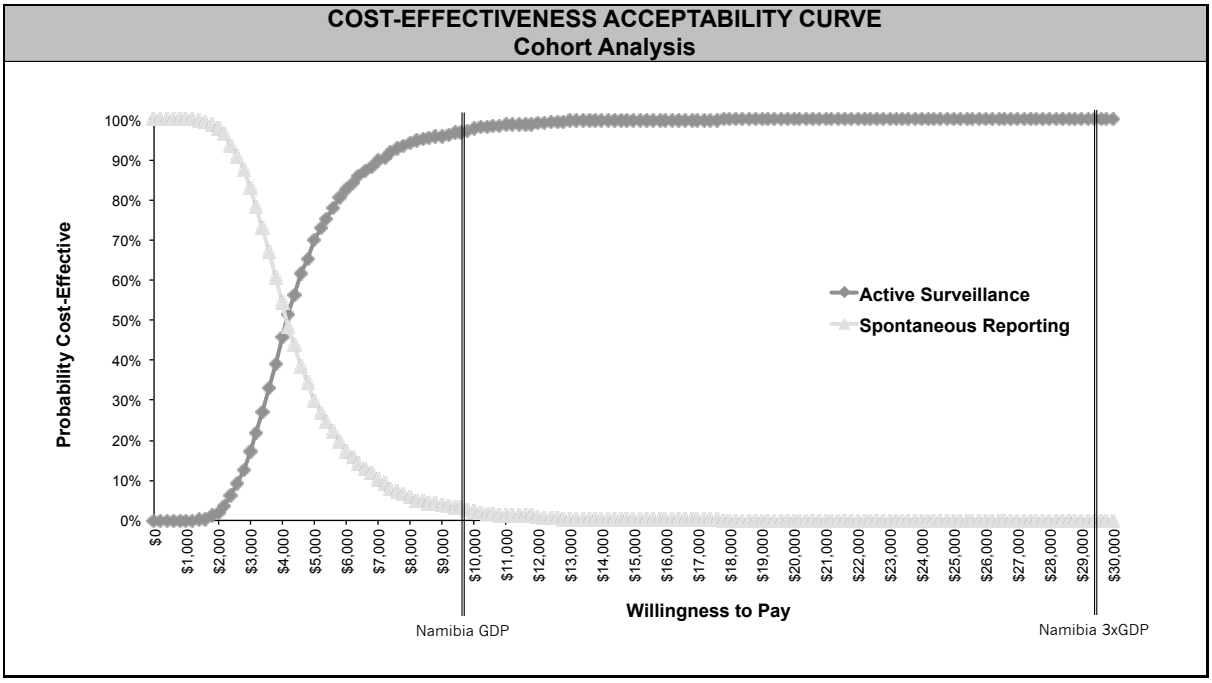

Figure 3.4: Cost-effectiveness acceptability curves for active surveillance PV versus spontaneous reporting PV at varying levels of willingness-to-pay for one QALY based on probabilistic sensitivity analysis for a single cohort over the remaining patient lifetime.

entire population of 94,130 patients beginning HAART in Namibia over 10 years, the ICER was only $542. Although the cost of active surveillance PV system was projected to be higher than that of spontaneous reporting for a single cohort of patients, active surveillance would save more lives and improve patient quality of life over time, resulting in a cost-effective program.

The population analysis results presented here represent a program analysis over a 10-year time horizon. We chose this approach in order to provide useful population-level information about potential program implementation in Namibia. Under the assumptions discussed above, we conclude that an active surveillance PV system would be projected to be highly cost-effective in Namibia. This is one of the first studies of the cost-effectiveness of an active surveillance PV system. The analytic methods used here may also be applied to other health systems or other settings to assess potential cost-effectiveness of these health system

improvements.

This study had several limitations. One limitation of our approach is the assumption that active surveillance leads to a higher rate of detection and treatment of AEs in LMIC. If this assumption is incorrect, the validity of the model is decreased. A second limitation of our method is a lack of inclusion of morbidity and mortality outcomes that occur after 10 years in the population analysis. An additional limitation of this model is the lack of inclusion of other medicines, indications, and disease areas. The existing spontaneous reporting system in Namibia includes all medicines, though we have modeled the PV system only for HAART. In contrast, a national active surveillance program might only have the capacity to evaluate HAART.

The cost-effectiveness results presented here were sensitive to the input values used for quality-of-life [57] reductions associated with an AE. Unfortunately, a paucity of high quality data on quality of life exists in this area. This is an important limitation of our results. If incorrect disutility values were used, it could change the estimated cost-effectiveness of active surveillance. Although we performed a wide range of sensitivity analyses around these values, it will be important for future work to address this area. Additionally, the data inputs for detection of AEs were limited by the relatively small sample size of the active surveillance sentinel site activity.

There are potential benefits to active surveillance PV system that, though they cannot be incorporated in a model, would likely be important for improving health. Active surveillance PV may improve treatment guidelines and policies to include improve health by including medicines with a lower incidence or severity of AEs [58]. Active surveillance PV could also lead to identification of incidence rates of and risk factors for adverse events, which improves knowledge of medicine safety. Additionally, data from active surveillance PV could be used to guide high-quality studies of risks associated with HAART and other treatments in Namibia. Finally, an active surveillance program is a health system—the implementation of which could strengthen the existing network of health systems

Active surveillance pharmacovigilance was projected to be a highly cost-effective system

to improve safety of HIV treatment in Namibia. Knowledge of costs and benefits of a health program prior to implementation is of particular importance when resources are limited. Using the results presented here, along with the motivation and government support to improve health systems in Namibia, it may be feasible to improve medicine safety for HIV patients and more efficiently allocate resources for pharmacovigilance in Namibia.

Chapter 4

INCIDENT KIDNEY INJURY AMONG PATIENTS BEGINNING HIGHLY-ACTIVE ANTIRETROVIRAL THERAPY IN NAMIBIA

Authors: Marita Mann[1], Bryan Kestenbaum[2], Andy Stergachis[3]

4.1 Abstract

Background. Acute kidney injury is associated with mortality and progression to chronic kidney disease. The highly active antiretroviral therapy (HAART) medication tenofovir is a World Health Organization recommendation for first-line HAART, but can cause kidney toxicity. We aimed to describe the incidence of kidney injury among adults newly placed on HAART in Namibia.

Methods. Patients beginning HAART and enrolled in a prospective pharmacovigilance cohort study in Windhoek, Namibia from August 2012 to April 2013 were included. Kidney injury was defined as a >25% decline in estimated glomerular filtration rate (eGFR) from baseline as measured by the CKD-EPI equation. We analyzed baseline characteristics and incidence of kidney injury.

Results. Of 172 patients with complete data availability, 94% were exposed to tenofovir. Kidney injury occurred in 19 patients (11%), 13 of who had a subsequent increase in eGFR. Incidence rate of kidney injury was 15 per 100 person-years (95% confidence interval 10-24).

[1]Department of Pharmacy, University of Washington, Seattle, WA, USA

[2]2Division of Nephrology, University of Washington, Seattle, WA, USA

[3]Departments of Pharmacy and Global Health, University of Washington, Seattle, WA, USA

Tenofovir exposure was not statistically significantly associated with nephrotoxicity.

Conclusions. This study found high incidence of nephrotoxicity among patients beginning first-line HAART in Namibia, the majority of whom were exposed to tenofovir. Our results indicate a need for consistent, reliable, and accurate creatinine testing in countries where tenofovir use is prevalent. This would likely lead to earlier detection of kidney injury, which could improve health outcomes and population health.

4.2 Background

Acute kidney injury is associated with mortality and progression to chronic kidney disease[66]. The highly active antiretroviral therapy (HAART) medication tenofovir disoproxil fumarate (TDF), a nucleoside analogue reverse transcriptase inhibitor (NRTI) is a commonly used first-line therapy for people with HIV infection. The excretion of TDF is primarily through the kidneys. TDF is generally considered as safe, and is included in the World Health Organization recommendation for first-line HAART regimens[67]. However, TDF can cause kidney toxicity through proximal tubule dysfunction either with or without decreased renal function [13].

The reported incidence of nephrotoxicity among patients exposed to TDF varies across studies. Though TDF was considered safe following clinical trials, later epidemiological studies found significantly increased incidence of acute kidney injury [68]. The D:A:D (Data collection on Adverse events of antiretroviral Drugs) prospective cohort study reported that 2% of patients on TDF developed an estimated glomerular filtration rate (eGFR) <70 mL/min, and 0.6% developed an eGFR <60 mL/min. These levels indicate that renal interventions may be necessary, and indicate moderately severe kidney disease, respectively [29]. In the observational DART (Development of AntiRetroviral Therapy in Africa) study in Africa, 2.8% of patients had a severe decrease in eGFR following initiation of TDF [69], while additional studies in Africa found 1.6% and 1% developed kidney injury [70,71]. Multivariate analysis of post marketing data showed that advanced age, low body weight, higher serum creatinine levels before starting TDF treatment, comorbidities (i.e. diabetes, hypertension,

HCV coinfection) concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS), and, in some studies, male sex, were identified as risk factors for TDF-induced eGFR reduction [13].

While the incidence of kidney injury associated with TDF use may be low, the health risks are serious. Acute kidney injury interferes with the metabolism of other medications, increasing the risk of additional adverse events. Acute kidney injury can cause nausea, vomiting, and swelling of the lower extremities. Drug interactions are of particular importance for HIV patients, who routinely take 5 or more different medications. Moreover, TDF causes injury to the proximal tubule of the kidneys, the central mechanism for renal excretion of most drugs. If TDF is not stopped, acute kidney injury can progress to chronic kidney disease (CKD), a major risk factor for premature cardiovascular disease and resulting in the need for chronic dialysis [72].

Early identification of patients who experience kidney injury could improve clinical care and health outcomes by targeting selection of alternative NRTI's to those patients. An understanding of kidney injury among populations with high TDF use may allow the public health community to more effectively allocate resources to improve health, such individualizing treatment recommendations. In this study we aimed to measure and describe the incidence of kidney injury among adults newly placed on HAART in Namibia.

4.3 Methods

We conducted a prospective cohort study among HIV-infected adults newly started on first line HAART in two ART clinics in Windhoek, Namibia, located at Windhoek Central Hospital (WCH) and Katutura Intermediate Hospital (KIH) [73]. Patients consisted of those enrolled in first-line HAART between August 1, 2012 and April 5, 2013 and had a creatinine test at time of enrollment and at least one additional creatinine test during the study time period. Exposure was defined by the HAART regimen dispensed at baseline, which was dichotomized as those with a TDF-based regimen and non-TDF-based regimen.

Cases were defined as those who developed kidney injury during the follow up period

August 1, 2012 – April 5, 2013. Kidney injury was defined as nephrotoxicity based on the eGFR, incorporating serum creatinine, age, and sex using the CKD-EPI equation [74]. The CKD-EPI equation has been validated in an African population [75]. It has been shown to provide more accurate estimates for eGFR values in the normal range than either the Modification of Diet in Renal Disease Study or Cockoft-Gault equation when compared to a direct measure of GFR by iohexol clearance [76]. The outcome of interest was kidney injury as defined by >25% decline in eGFR from baseline [77].

The two ART sites identified eligible HAART-naïve HIV-infected adults newly placed on first-line HAART. Patients were actively followed to record the presence or absence of adverse events and selected additional information using an Active Surveillance Data Collection Form (Appendix A). This active surveillance pharmacovigilance form consisted of two parts, Part A consisted of identification numbers, date of enrolment, date of birth, date of HIV diagnosis, patient status at start of HAART, baseline lab values at start of HAART, comorbid conditions at start of HAART, and initial HAART regimen, and was filled out once at first visit. Part B consisted of a table to be filled in at each subsequent visit including date, medicines, adverse events, and outcomes of adverse events. Data were acquired from the active surveillance forms for use in this study.

We analyzed baseline demographics and comorbidities of the population at the time they began HAART, including eGFR. We then assessed incidence of nephrotoxicity using change in eGFR from baseline. We evaluated the risk for kidney injury in those exposed to TDF compared to those not exposed, then evaluated this risk after adjusting for demographics and comorbidities. A logistic regression model was used to evaluate the effects of age, gender, weight, WHO stage of disease, CD4 count, diabetes, hypertension, and cancer on the development of nephrotoxicity. All patients with complete data from HAART regimen, age, gender, and creatinine testing were included in the analysis.

4.4 Results

Of the study population of 455 patients, 401 patients had complete HAART regimen data recorded in the active surveillance forms. Of these, 361 patients were placed on TDF and 40 were placed on non-TDF HAART regimens. Of those exposed to TDF, the mean age was 36, 62% were female, and 52% had WHO stage 1 disease (Table 4.1). Among those not exposed to TDF, mean age was 43, 33% were female, and 45% had WHO stage 1 HIV disease.

Table 4.1: Baseline characteristics of the study population.

	Exposed to TDF[4] n=361	Not exposed to TDF n=40
Mean Age (SD)	36 (10)	43 (10)
Female	62%	33%
Mean Weight (SD)	64 (26)	61 (9)
WHO stage		
1	52%	45%
2	18%	8%
3	20%	30%
4	11%	18%
Mean CD4 (SD)	218 (129)	206 (149)
Diabetes	1%	6%
Hypertension	5%	22%
Cancer	2%	0%

A total of 179 patients had a baseline and follow-up creatinine measurements as well as complete information on HAART regimens, age, and gender. Seven patients were excluded due to pregnancy or baseline eGFR<60 (which is an indication of chronic kidney injury). Of the remaining 172 patients, 161 (94%) were exposed to TDF for a total of 117 person-years.

Kidney injury occurred in 11% (n=18) of those exposed to TDF and 9% (n=1) of those unexposed (Table 4.2). The median time to kidney injury was 149 days (mean 149 days,

[4]Abbreviations: TDF – tenofovir disoproxil fumarate, HAART – highly active antiretroviral therapy, SD – standard deviation, WHO – World Health Organization

standard deviation 75 days) days. The incidence of kidney injury was 15 per 100 person-years (95% confidence interval [CI] 10-24) (Table 4.2). Among those who experienced kidney injury, mean baseline eGFR was 121 (standard deviation 32) (Figure 4.1). Of the 19 who experienced kidney injury during the study follow period, 13 (68%) patients (1 who was exposed to TDF) then had a subsequent increase in eGFR, and 6 of the 19 patients had a regimen switch (Figure 4.1). There were no statistically significant changes in average creatinine measurements over calendar time.

Table 4.2: Kidney injury during follow-up as defined by greater than 25% decline in eGFR (by CKD-EPI equation) from baseline.

	Kidney Injury[5]	No Kidney Injury	Incidence per 100 person-years (95% CI)
Exposed to TDF n=161	18 (11%)	143 (89%)	15 (10-24)
Not exposed to TDF n=11	1 (9%)	10 (91%)	13 (2-90)
Total n=172	19 (11%)	153 (89%)	15 (10-24)

The unadjusted odds of experiencing kidney injury were not statistically different in those exposed to TDF than those not exposed to TDF (odds ratio 95% CI 0.2-10.4, p-value 0.83). After adjustment for age, gender, weight, WHO stage, CD4 count, diabetes, hypertension, and cancer, TDF exposure was not statistically significantly associated with nephrotoxicity (Table 4.3). Only age was significantly associated with nephrotoxicity, with the odds of nephrotoxicity being 1.09 higher for each additional year of life (SE 0.05, 95% CI 1.0-1.2, p-value 0.05).

[5]Abbreviations: TDF – tenofovir disoproxil fumarate, CI – confidence interval

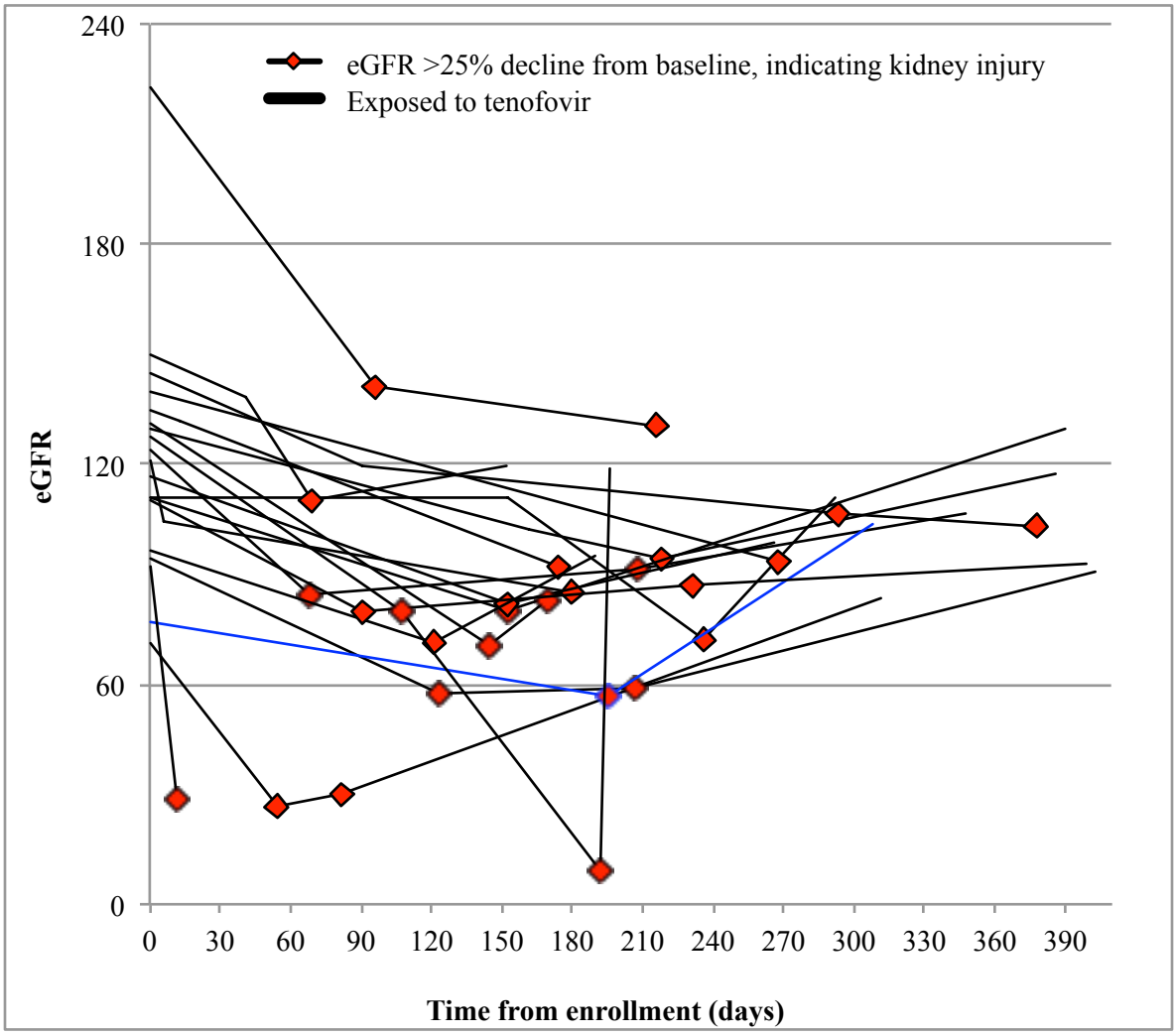

Figure 4.1: Baseline eGFR and all follow up eGFR measurements within the study period for all patients who experienced a decline in eGFR more than 25% from baseline at a minimum of one time point (n=19).

4.5 Discussion

In this study of patients beginning first-line HAART in Namibia, 11% demonstrated evidence of acute kidney injury. Of these, 68% had a subsequent increase in eGFR. After adjustment for demographics and comorbidities, nephrotoxicity was not statistically significantly associated with TDF exposure.

Table 4.3: Adjusted odds ratios for developing kidney injury during the study period (n=104).

	OR[6]	Std. Err.	p-value	95% CI
TDF exposure	1.89	2.72	0.66	(0.1 - 32)
Age	1.09	0.05	0.05	(1.0 - 1.2)
Female	2.25	1.85	0.33	(0.5 - 11)
Weight	0.98	0.04	0.67	(0.9 - 1.1)
WHO stage				
1	Reference			
2	1.18	1.15	0.87	(0.2 - 8)
3	0.40	0.45	0.41	(0.1 - 4)
4	0.03	0.07	0.13	(0.0 - 3)
CD4	1.00	0.00	0.44	(1.0 - 1.0)
Diabetes	26.4	58.2	0.14	(0.4 - 1980)
Hypertension	1.01	1.70	0.99	(0.0 - 27)
Cancer	17.1	32.5	0.13	(0.4 - 701)

The results presented here differ from previously published results in that no significant association between TDF use and nephrotoxicity was found. Several studies, including many taking place in low- and middle-income countries, did find a significant association [29,68–70]. The study presented here has a small sample size, therefore limiting power for statistical significance. However, our study did find a high incidence of nephrotoxicity compared to non-HIV patients, HIV-patients in the pre-HAART era, or even other studies of patients on HAART[69,78,79]. Some of the observed changes in eGFR in the study population may have been due to fluctuations in weight, which can occur frequently in HIV-positive populations.

This study had several limitations. Data were limited to those with complete creatinine testing data, defined as at least two creatinine measurements (a baseline and follow-up) during the study period. Though recommended in the Namibian treatment guidelines [58], creatinine is not consistently tested in all patients, therefore limiting our sample size. Additionally, the study sample was likely subject to selection bias. TDF containing regimens are recommended in Namibia; therefore the majority of patients were exposed to TDF, limiting

our statistical power to detect differences in those not exposed to TDF. Finally, follow-up time was limited to the study period; therefore longer-term outcomes could not be evaluated.

This study found high incidence of nephrotoxicity among patients beginning first-line HAART in Namibia, the majority of whom were exposed to TDF. Our results indicate a need for consistent, reliable, and accurate creatinine testing in countries where TDF use is prevalent. Consistent creatinine testing and correct interpretation and use of test results by health care providers could lead to earlier detection of kidney injury, which could improve health outcomes and population health.

[6]Abbreviations: TDF – tenofovir disoproxil fumarate, OR – odds ratio, Std. Err. – standard error, CI – confidence interval, WHO – World Health Organization

Chapter 5

SUMMARY

This sentinel site active surveillance program aimed to enroll all eligible patients beginning first-line antiretroviral therapy at two ART sites in Windhoek, Namibia. Completeness of AE recording on the active surveillance forms was high, while completeness of demographic characteristics varied widely. The incidence of experiencing at least one adverse event was 33 per 100 person-years among the patients included in this active surveillance pharmacovigilance activity. The most common adverse event was rash, followed by abdominal pain. The risk of experiencing an adverse event was higher for those with an atypical ART regimen or with WHO stage 2 disease. Age, gender, and CD4 count did not alter risk of experiencing an AE.

In terms of data quality, AEs were recorded consistently on the active surveillance forms. While demographic variables such as age were reasonably complete on the active surveillance data collection forms, concomitant illnesses or conditions had missing data almost a third of the time. Moreover, for the follow-up Part B of the form, there were missing data for each of the variables assessed ranging from 2% to 42%. While 82% of patients had at least one follow-up visits recorded, 34% of total visits were missed. This demonstrates that physicians were likely recording more visits soon after the patients began ART, and fewer in later months. These results indicate the need for consistent training and follow-up with the doctors by pharmacovigilance staff. Incorporating the active surveillance form into the PCB would likely increase use on follow-up visits. Additionally, physicians would be more likely to continue recording visits in a longer-term program with additional training.

The results on data quality indicate a high level of quality for recording AEs, and opportunity for improvement in the completeness of the paper-based forms for the active surveillance.

It is important to note that much of the data on the first page of the active surveillance data collection form is duplicative with the PCB. Integrating the form into the PCB, which has been proposed as a potential next step if the program is continued, would likely eliminate many missing data issues, as the baseline information would be filled in the PCB itself, and therefore the physician or nurse would not have to fill it in twice. Additionally, practitioners would likely record more follow-up visits as it became standard practice with longer-term use. This is indicated by the continuity of recording after TIPC staff ended weekly visits to encourage recording.

The MoHSS is considering expanding active surveillance pharmacovigilance to the national level. The data quality analysis can aid in determining applicability of this pilot program to larger-scale programs. A TIPC coordinator completed periodic site visits throughout the sentinel site program, which likely increased physician engagement and therefore data completeness. In order to scale up the program, the number staff would likely have to be increased to maintain this data quality. Such an analysis could assess the feasibility of ART active surveillance on a larger scale in Namibia, active surveillance for other medicines in Namibia, or active surveillance in other countries. Future work could explore linking active surveillance pharmacovigilance to eHealth initiatives, expand active surveillance pharmacovigilance to the tuberculosis program, or expand active surveillance pharmacovigilance to pregnant women receiving ARVs.

This study was limited by the relatively small sample size as well as relatively short follow-up time. Many adverse events occur in the weeks following initiation of HAART[31,32], therefore, the likely key relevant time points would have been captured in this study. Those AEs with longer exposure or detection time frames would not have been captured. To capture these events would require a combination of longer active surveillance augmented with targeted spontaneous reporting methods. Additionally, sentinel sites may not represent the general population or the incidence of disease; therefore, there are some limitations in generalizing for national disease patterns and trends. The study population is generally representative of the population of people with HIV in Namibia[46]. As TDF/3TC/NVP is

the WHO and Namibia's recommended first-line regimen, this is likely the most commonly prescribed regimen.

The ICER for a single cohort of 9,413 patients over their lifetime for active surveillance PV compared to spontaneous reporting PV was of $3,017 per QALY, which would be considered highly cost-effective based on the current GDP of $9,736 per capita in Namibia. For the entire population of 94,130 patients beginning HAART in Namibia over 10 years, an active surveillance PV system was cost saving compared to a spontaneous reporting PV system. Although the cost of active surveillance PV system was projected to be higher than that of spontaneous reporting for a single cohort of patients, active surveillance would save more lives and improve patient quality of life over time, resulting in a cost-effective program. When costs were distributed more realistically over an entire population, active surveillance was projected to save both costs and QALYs.

The population analysis results presented here represent a program analysis over a 10-year time horizon. We chose this approach in order to provide useful population level information about potential program implementation in Namibia. Under the assumptions discussed above, we conclude that an active surveillance PV system would be projected to be cost saving in Namibia. This is one of the first studies of cost-effectiveness of an active surveillance PV system. The analytic methods used here may also be applied to other health systems or other settings to assess potential cost-effectiveness of these health system improvements.

There are potential benefits to active surveillance PV system that, though they cannot be incorporated in a model, would likely be important for improving health. Active surveillance PV may improve treatment guidelines and policies to include improve health by including medicines with a lower incidence or severity of AEs [58]. Active surveillance PV could also lead to identification of incidence rates of and risk factors for adverse events, which improves knowledge of medicine safety. Additionally, data from active surveillance PV could be used to guide high quality studies of risks associated with HAART and other treatments in Namibia.

We demonstrated a potential use of active surveillance data by examining the association between tenofovir use and incidence of nephrotoxicity in the active surveillance sentinel

site activity population. This study found high incidence of nephrotoxicity among patients beginning first-line HAART in Namibia, the majority of whom were exposed to TDF. In this patient population, after adjustment for demographics and comorbidities, nephrotoxicity was not statistically significantly associated with tenofovir exposure. Our results indicate a need for consistent, reliable, and accurate creatinine testing in countries where TDF use is prevalent. Consistent creatinine testing and correct interpretation and use of test results by health care providers could lead to earlier detection of kidney injury, which could improve health outcomes and population health.

The quality of data collected through active surveillance demonstrated potential for high quality pharmacovigilance. With improved logistical considerations such as implementing active surveillance into the medical record, a sustainable national active surveillance program could be successful. The results of the pilot program as well as potential for a national program will provide valuable information for assessing the feasibility of active surveillance and pharmacovigilance health program improvement for low- and middle-income countries worldwide. Active surveillance pharmacovigilance was projected to be a highly cost-effective or even cost saving system to improve safety of HIV treatment in Namibia. Knowledge of costs and benefits of a health program prior to implementation is of particular importance when resources are limited. Using the results presented here, along with the motivation and government support to improve health systems in Namibia, it may be feasible to improve medicine safety for HIV patients and more efficiently allocate resources for pharmacovigilance in Namibia.

Appendix A

ACTIVE SURVEILLANCE DATA COLLECTION FORM

ACTIVE SURVEILLANCE FORM FOR ART NAIVE ADULT PATIENTS PART A (Baseline)

Patient Unique Identification Number:	0	0	0	-	0	0	0	0	-	0	0	0	0	0	0	
Assigned Case Identification Number:									Date of enrolment into the cohort:	D	D	M	M	Y	Y	

Date of Birth	D	D	M	M	Y	Y	Age if DOB unknown	________years	Sex	M	F
Date of HIVDiagnosis	D	D	M	M	Y	Y	Enrolment date for HIV care	D D M M Y Y			

PATIENT STATUS AT START OF ART:

Weight:	Height:	Functional Stage:			WHO Clinical Stage:				Smoking			Alcohol Abuse			Other Subs. Abuse		
Kg	cm	W	A	B	1	2	3	4	*N*	*Y*	*U*	*N*	*Y*	*U*	*N*	*Y*	*U*

BASELINE LABORATORYVALUES closest to start of ART:

CD4	Serum Creatinine level	ALT	Random Blood Sugar	HB	WBC	RPR	HepB	Urine Protein

OTHER CLINICAL CONDITION AT START OF ART (Concurrent illness)

Diabetes			Hypertension			Renal			Chronic Liver Disease			Active Liver Disease			Anaemia			TB			Cancer			Pregnancy		
N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U	N	Y	U

ART TREATMENT:

1st LINE ART regimen ***(enter code)***	**DOSE** ***(e.g. 300/150/200 twice daily)***	**START DATE**						
		D	D	M	M	Y	Y	

Figure A.1: Active Surveillance Form Page 1 of 2

ACTIVE SURVEILLANCE FORM FOR ART NAIVE ADULT PATIENTS PART B (Follow-up)

Patient Unique Identification Number: **Case Identification NO:**

PATIENT ENCOUNTERS FROM START-UP OF ART THROUGH FOLLOW-UP

DATE OF VISIT ___/___/___	ART REGIMEN (code)	OTHER MED (code)	ADVERSE MED EVENTS (code)	OTHER ADVERSE EVENTS (code)	CHANGES IN MED REGIMEN (code)	OUTCOME OF ADVERSE EVENTS (code)	LABORATORY FINDINGS					OTHER NOTABLE CONDITIONS (code)	COMMENTS
							VL	CD4	S Cr	ALT	HB		
DD/MM/YY													
DD/MM/YY													
DD/MM/YY													
DD/MM/YY													
DD/MM/YY													
DD/MM/YY													

CODES

ART REGIMEN	OTHER MEDICINES	ADVERSE MEDICINE EVENTS		OTHER ADVERSE EVENTS	CHANGES IN MEDICINE REGIMEN	OUTCOMES OF ADVERSE EVENTS	OTHER NOTABLE CONDITIONS
0 = TDF/3TC/NVP 1 = AZT/3TC/NVP 2 = AZT/3TC/EFV 3 = TDF/3TC/EFV 4 = Other:	0= None 1= Cotrimoxazole 2= Iron suppl. 3= SP antimalarials 4= Artemisinin Combinations 5= Aspirin and other NSAIDS 6= Paracetamol 7= Antibiotics-Ciprofloxacin 8=Antibiotics-penicillin 9= Multivit 10= INH 11= Other (specify)	0= None 1=Abdominal pain/discomfort 2= Anaemia 3=Peripheral Neuropathies 4= CNS 5= Diarrhea 6=Fat changes 7=Fatigue 8=Headache 9= Jaundice 10= elevated LFT 11= Hepatitis 12=Lactic acidosis exposure	13= Lipodistrophy 14= Nausea 15= Rash 16= Hyperpigmentation 17= Serious skin reaction 18= Gynecomastia 19= Pancreatitis 20= Congenital anomaly in pregnancy 21 = Elevated Cr 22= Renal failure 23 =Other (specify)	0 = None 1 = Hospitalized 2 = Dead 3 = Suspected treatment failure 4=Lost to follow up 5 = other (specify)	0 = None 1 = TDF Dose reduced 2 = TDF substituted 3 = AZT substituted 4 = NVP substituted 5 = EFV substituted 6= All ART stopped 7= Other medicines stopped 8=Switched to 2nd line 9= Other (specify)	0 = None 1 = Resolved 2 = Resolving 3 = Resolved with sequelae 4 = Not resolved 5 = Worse 6 = Death 7 = Unknown	0= None 1= Pneumonia 2= Kaposi's sarcoma 3= Hookworm 4= Malaria 5= GI bleeds 6= liver cirrhosis 7= Blood disorders 8 = malnutrition 9 = Pregnancy 10= other (specify)

Figure A.2: Active Surveillance Form Page 2 of 2

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