EVALUATION OF ADVERSE DRUG EVENTS AMONG PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS AND THOSE CO-INFECTED WITH TUBERCULOSIS AT KENYATTA NATIONAL HOSPITAL

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A Research Dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of the University of Nairobi.

NOVEMBER, 2020

DECLARATION OF ORIGINALITY

Students Declaration

I declare that this research dissertation is my original work and has not been presented for the award of a degree in any other university.

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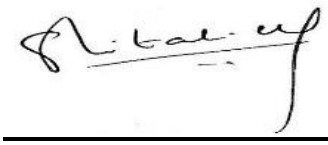
Signature:  **Date:** 28-11-2020

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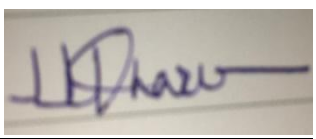
Signature:  **Date:** 28-11-2020

DEDICATION

To my lovely family and friends, thank you for the support and prayers.

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I am thankful to the Almighty God for bringing me this far and giving me the strength to accomplish this far.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ADE	Adverse drug event
ADEs	Adverse drug events
ADR	Adverse drug reaction
AIDS	Acquired immunodeficiency syndrome
Anti-TB	Anti-tuberculosis
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BMI	Body Mass Index
CCC	Comprehensive Care Centre
CrCL	Creatinine Clearance
CNS	Central Nervous System
CPT	Co-trimoxazole Preventive Therapy
d4T	Stavudine

DOTS	Directly Observed Therapy, Short-course
DTG	Dolutegravir
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed-Dose Combinations
GIT	Gastrointestinal tract
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
INH	Isoniazid
IPT	Isoniazid preventive therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
KNH	Kenyatta National Hospital
KNH-CCC	Kenyatta National Hospital- Comprehensive Care Centre
LPV/r	Lopinavir/Ritonavir
MDR-TB	Multidrug resistance tuberculosis
NASCOP	National AIDS and STI's Control Programme
NTLD-P	National Tuberculosis, Leprosy and Lung Disease Program

NVP	Nevirapine
OI	Opportunistic infections
PCP	Pneumocystis Pneumonia
PI	Protease Inhibitors
PLHIV	People Living With Human Immunodeficiency Virus
PTB	Pulmonary tuberculosis
PZA	Pyrazinamide
RIF	Rifampicin
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
WHO	World Health Organization
XDR-TB	Extensive drug resistance tuberculosis

DEFINITION OF TERMS

Adherence: It is the ability of a patient to follow medical advice or treatment regimen correctly as given by the healthcare provider.

Adverse drug event: It is an injury resulting from the use of a drug.

Adverse drug reaction: It is a response to a drug which is injurious and not intended. It occurs at normal doses used for prevention, diagnosis, or therapy of disease or the alteration of physiologic function.

Adult: An individual who is above 18 years of age.

Arthralgia: Joint pain precipitated by the use of medication.

CD4 cells: They are white blood cells that play an important role in the immune system. These are the cells that HIV usually targets and depletes.

CD4 count: It is a test that measures how many CD4 cells (lymphocytes) you have in your blood.

Continuation phase: The second phase of tuberculosis treatment. For participants on first-line TB therapy, it is four months for drug-susceptible TB.

Co-morbidity: The co-existence of two or more diseases in an individual.

Determinant: It is a factor that affects the nature or outcome of adverse drug events.

Drug-resistant TB: TB is caused by TB bacteria that are resistant to at least one first-line anti-tuberculosis drug and is determined using gene Xpert, culture, and drug susceptibility testing.

Drug susceptible TB: A type of TB that responds to first-line anti-tuberculosis drugs.

Extra-pulmonary TB: It is TB within a body organ other than the lungs.

Hepatotoxicity: An injury or damage to the liver that is caused by taking particular drugs.

HIV-infection: It is an infection caused by HIV which attacks the body's immune system hence interferes with the body's ability to fight off disease-causing organisms.

HIV/TB co-infection: It is an infection with both HIV and TB infection.

Intensive phase: The first phase of tuberculosis treatment. For participants on first-line TB therapy, it is two months for drug-susceptible TB.

Miliary TB: A form of tuberculosis that is characterized by wide dissemination by tiny *Mycobacterium tuberculosis* bacilli sized 1–5 mm via hematogenous spread into the human body.

Multidrug resistance: Tuberculosis infection resistance to at least both isoniazid and rifampicin.

Extensive drug resistance: Tuberculosis resistance to any fluoroquinolone and at least one of the three second-line injectable drugs (amikacin, capreomycin, and kanamycin), in addition to multidrug resistance.

Non-adherence: A patient is unable to follow medical advice or treatment regimen correctly as given by the healthcare provider.

Peripheral neuropathy: A condition affecting the peripheral nerves characterized by weakness, numbness, and pain usually in the hands and feet.

Pulmonary TB: It is an active TB infection of the lungs.

Smoking: Use of cigarettes before or during treatment for HIV or TB.

TB infection: It is an infection caused by Mycobacterium tuberculosis bacteria and it generally affects the lungs but it can also affect other body organs.

TB-IRIS: It is a paradoxical response that occurs when initiating ART in HIV infected patients. It results when an abnormal excessive immune response occurs against alive or dead Mycobacterium tuberculosis strain.

WHO clinical stage: It is a classification system for HIV infection and it entails four clinical stages.

ABSTRACT

Background: Adverse drug event (ADE) is an injury caused by the use of any particular drug. There is limited information available on the prevalence, types, and determinants of adverse drug events (ADEs) between patients infected with Human Immunodeficiency Virus (HIV) and those co-infected with tuberculosis**.**

Main Objective: The primary purpose of this research was to evaluate the prevalence, types and determinants of adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.

Methodology: The research was conducted at Kenyatta National Hospital, Comprehensive Care Center (KNH-CCC). The study design was an analytical cross-sectional design with two arms comprising of patients infected with HIV only and those with HIV and tuberculosis co-infection. Each arm comprised 42 participants selected using a simple random sampling approach. Data was collected using a researcher-administered questionnaire and analyzed by utilizing descriptive and inferential statistics at the level of significance of 0.05. Approval to undertake this analysis was sought from KNH-UON ERC and the Kenyatta National Hospital management.

Results: The most prevalent adverse drug event was discolored urine/tears (42, 50%), followed by skin rash/itchiness and tiredness/weakness with each having a prevalence of 30 (35.7%). The prevalence of hand numbness, tingling, feet numbness, discolored urine/tears, skin rash/itchiness, and tiredness/weakness ADEs were statistically different between HIV infected patients and those co-infected with tuberculosis. Discolored urine/tears ($p<0.001$) was the only adverse drug event with a significant p-value (adjusted OR=767.50; 95% CI=43.46, 13554.25) after a multivariate analysis was done and confounders were adjusted.

Conclusions: Adverse drug events are more likely to occur in HIV-infected adults taking anti-tuberculosis drugs than their HIV-infected counterparts not taking anti-tuberculosis drugs. Adverse drug events should be managed appropriately in the clinical settings according to the Kenyan guidelines for HIV and tuberculosis treatment. Studies to further investigate the determinants associated with adverse drug events are needed in the future. Future studies that require proper data collection are also needed to correlate the prevalence of ADEs with socio-demographic characteristics.

CHAPTER ONE: INTRODUCTION

1.1 Background

An adverse drug event (ADE) is an injury caused by the use of any particular drug. Overall, ADE comprises harm caused by the drug as well as the use of the drug". Harm resulting from the use of a drug may either be an adverse drug reaction and/or a high dose while harm caused by drug use may either be as a result of low dose and/or stopping drug therapy". Medication errors may also lead to ADEs. "Response to a drug that is injurious and not intended is defined as an adverse drug reaction. It occurs at normal doses used for prevention of disease, screening for disease, treatment of disease, or for altering a physical and biologic function" (1).

ADEs can occur either in hospitals, in-patient, and outpatient settings. The majority of these ADEs are however preventable. Minimizing these ADEs will result in safe and high-quality health care services, lower health care costs, and improved treatment outcomes (2). ADEs will most likely occur among patients infected with Human Immunodeficiency Virus (HIV) and those co-infected with tuberculosis due to the multi-drug regimens that the patients are taking and also due to the prolonged treatment periods.

According to the 2018 Global Human Immunodeficiency Virus (HIV) and Acquired immunodeficiency syndrome (AIDS) statistics, 37.9 million people are infected with HIV worldwide with 23.3 million people on antiretroviral therapy (ART) in 2018 (3). 1.6 million People in the Kenyan population are living with HIV. Among these, 69% of adults and 61% of children are on ART (4).

Tuberculosis (TB) is a communicable disease caused by the bacillus Mycobacterium tuberculosis. One of the top 10 causes of death in the world is TB infection. The World Health Organization (WHO) recommends the treatment of newly diagnosed TB patients with first-line antibiotics for 6 months. This treatment duration includes a two months intensive treatment phase followed by a four months continuation treatment phase. According to the WHO 2019 global tuberculosis report, 10 million people were estimated to be diagnosed with TB in 2018 of whom 8.6% were people living with HIV (5). A survey done by the national TB program in Kenya to determine TB prevalence in Kenya found that the prevalence of diagnosed pulmonary TB in the Kenyan adult population was 558 per 100,000 people. The survey also pointed out that the HIV/TB co-infection rate among the TB cases in Kenya was 16.7% (6).

The reason for this research was to evaluate the prevalence, types and determinants of adverse drug events between patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital. The study provided more information on these ADEs so that measures may be taken to ensure adherence and continued therapy among these patients to achieve the desired treatment outcomes.

1.2 Problem statement

Recent studies done in Kenya have shown that adverse drug events among HIV-infected patients on treatment occur in several cases (7). Another study done on reported adverse drug reactions (ADRs) due to antibiotics at the Pharmacy and Poisons Board revealed that anti-tuberculosis drugs accounted for the second most frequent cause of reported ADRs (8). Several studies have also been done on non-adherence to anti-tuberculosis drugs due to several factors including ADEs associated with these drugs (9).

Adverse drug events occur in patients infected with HIV receiving antiretroviral (ARV) drugs as well as in HIV patients co-infected with tuberculosis receiving both ARV and anti-tuberculosis (anti-TB) drugs (10,11). Kenya is a resource-limited country and these ADEs may lead to non-adherence. Non-adherence may lead to the development of drug-resistant TB resulting in higher cost of treatment as well as necessitating longer treatment periods (12,13). Since these patients are also on antiretroviral treatment, non-adherence due to adverse drug events may lead to poor viral suppression, increased CD4 count as well as increased opportunistic infections. Poor control of HIV infections and HIV/TB co-infection will result in higher morbidity and mortality among these patients (13).

The determinants associated with the ADEs such as type of drug regimens, age, gender, co-morbidities, alcohol, and tobacco use are an important aspect to identify and scarce data exist in this particular area. Studies have been done on ADEs among HIV infected, HIV/TB co-infected and TB infected patients (14–16). No study evaluates ADEs among patients infected with HIV and those co-infected with TB done in Kenya therefore this study contributed to the existing knowledge gap. The study findings will potentially be used in the clinical setting to better address these ADEs.

1.3 Purpose of the study

This survey sought to provide more information to health care providers on these ADEs. This will improve the management of patients with HIV as well as those with HIV/TB co-infection since the health care providers will be informed on the ADEs and their determinants and how to mitigate them**.** The health care providers will then educate the patients on potential ADEs, hence promoting adherence to achieve the desired treatment outcomes. The findings of this study may influence therapeutic approaches and inform

on the practice and treatment guidelines in Kenya regarding HIV and TB therapy. The findings may also contribute to policy change on HIV and TB therapy in the country, Kenya.

1.4 Objectives

1.4.1 Broad objective

To evaluate the prevalence, types, and determinants of adverse drug events among patients infected with Human Immunodeficiency Virus and those co-infected with tuberculosis at Kenyatta National Hospital.

1.4.2 Specific objectives

1. To identify the types of drug regimens used to treat patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.
2. To determine the prevalence and types of adverse drug events among patients infected with HIV at Kenyatta National Hospital.
3. To determine the prevalence and types of adverse drug events among patients with HIV and tuberculosis co-infection at Kenyatta National Hospital.
4. To identify the determinants of the adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.

1.5 Research questions

1. What are the types of drug regimens used to treat patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital?
2. What is the prevalence and types of adverse drug events among patients infected with HIV at Kenyatta National Hospital?

3. What is the prevalence and types of adverse drug events among patients with HIV and tuberculosis co-infection at Kenyatta National Hospital?
4. What are the determinants of the adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital?

1.6 Hypotheses

1.6.1 Null Hypothesis

There is no difference in the prevalence and types of adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.

1.6.2 Alternate Hypothesis

There is a difference in the prevalence and types of adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.

1.7 Significance

This research will be of interest to Kenyatta National hospital, specifically the Comprehensive Care Centre (CCC) which is charged with the responsibility of attending to HIV infected and those co-infected with tuberculosis. The results of this survey will add to the existing literature and may potentially be used in the clinical setting by health care practitioners to predict the ADEs. The findings will also help the KNH-CCC to come up with strategies to better manage patients on antiretroviral (ARV) and anti-tuberculosis (anti-TB) drugs and improve patient safety and adherence. These measures

may include further training the staff on ADEs and outreach programs to educate the population about the mitigation of adverse drug events.

The academic institutions concerned with the training of healthcare personnel will use the study findings in training their students and staff to enhance their skills in predicting those who might suffer from adverse drug events and devise methods of minimizing them. The study findings will also be used as resource materials for future reference in their research writings as well as form a basis for further research in this area.

Patients suffering from HIV and those co-infected with tuberculosis as well as the general public will benefit from this study in various ways. Society will be educated on the occurrence of most adverse drug reactions. The determinants associated with these ADEs will also be identified and the public notified through journal publication of the study findings to enhance monitoring, management, and prevention of these ADEs.

The study findings will inform the policymakers on any policy changes required on the ARV and anti-TB drug use in the country as well as any changes required in the standard treatment guidelines on HIV and TB therapy.

1.8 Delimitations

Kenyatta National Hospital is the area that the research will be conducted. Patients attending the Comprehensive Care Centre (CCC) will be followed up.

1.9 Limitations

The study encountered the following limitations:

a. Incomplete patient records

Patient records lacked comprehensive data mainly involving sufficient laboratory data on liver function tests and Urea, Electrolytes, and Creatinine (UECs) tests. These results were important for the study since liver and kidney damage are some of the adverse effects associated with both the ARV and anti-TB drugs. Lack of adequate patient laboratory data resulted in missing information required in the measurement of ADEs. The researcher made sure that relevant missing information was well documented as part of the study limitation when writing the final report.

b. Ineffective communication

Challenges encountered during interviews due to barriers to effective communication were physiological barriers like partial hearing difficulties.

Participants with partial hearing difficulties were assisted to fill the questionnaires by the use of written communication.

1.10 Conceptual framework

This framework illustrates the association between the independent variables and dependent variables. It shows how different variables in the study are connected with the ADEs between patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital.

The independent variables were the different types of drug regimens the patients in the comparison groups were receiving. The HIV-infected patients were on ARV drugs whereas the HIV patients co-infected with tuberculosis were on both ARV drugs and first-line anti-TB medication. Patient characteristics such as (Body Mass Index) BMI, sex, age, marital status, education level, employment status, monthly income, co-morbidities, alcohol use, and tobacco use were considered as independent variables in this study.

ADEs are dependent on several factors such as types of drug regimens and patient characteristics. ADEs were measured by assessing questionnaires administered to patients. The main body systems and organs which were assessed for these ADEs include gastrointestinal, nervous, skin, circulatory, endocrine, musculoskeletal, renal, respiratory systems as well as the liver, ears, and eyes.

Types of drug regimens and patient characteristics are closely related and therefore interact to influence the occurrence of ADEs. It has been documented that independent factors for the development of ADEs are HIV status, female gender, and advancing in age. The study also showed that the frequency of ADEs among patients on first-line anti-TB drugs was higher in HIV patients co-infected with TB as opposed to those diagnosed with TB alone (16)**.**

The age of the patient may influence the occurrence of ADEs since elderly populations are more prone to ADEs than younger populations. The female gender may be more prone to ADEs than the male gender. Lifestyle habits such as smoking and alcohol use often have negative effects on health thereby predispose patients to ADEs. The genotype

of the patient and co-morbidities of the patient may influence the severity of ADEs. Genetic predisposition to ADEs has been documented and this may occur due to the accumulation of drug metabolites due to fast metabolism in fast acetylators or due to decreased excretion in patients with kidney damage. Concurrent use of anti-TB drugs with other drugs due to co-morbidities increases the possibility of ADEs.

INDEPENDENT VARIABLES

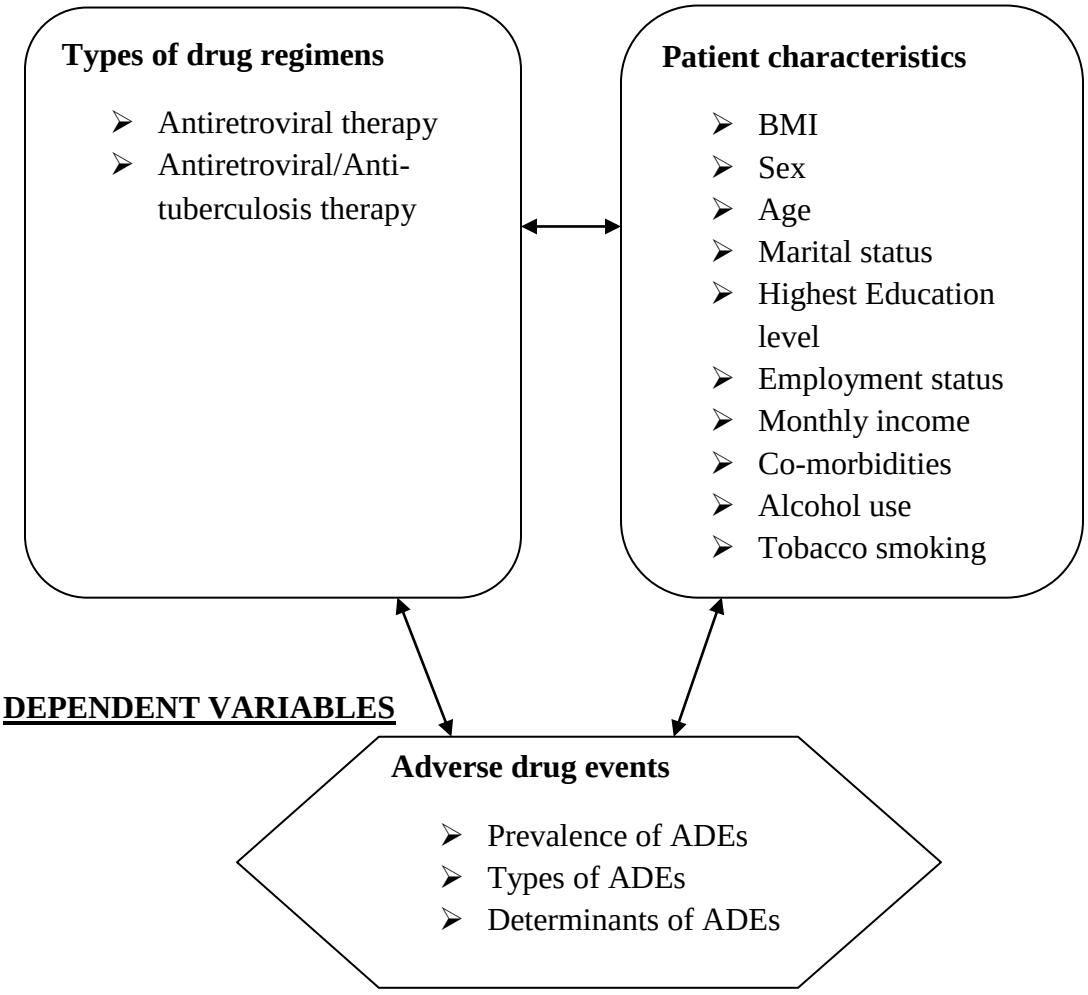

Figure 1: Conceptual framework

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter gives an overview of the findings of previous studies carried out in the area of interest. Among the aspects considered includes types of drug regimens, prevalence and types of ADEs as well as determinants associated with ADEs.

2.2 Types of drug regimens

Patients diagnosed with HIV infection only receive ARV drugs while those diagnosed with HIV/TB co-infection receive both ARV and anti-TB drugs.

2.2.1 Antiretroviral drug regimen

According to the Kenyan guidelines on the treatment of HIV, ART should be started as soon as possible, that is, within two weeks from the time of HIV diagnosis. However, there is an exception for patients with TB or cryptococcal meningitis. ART is eligible to all People Living with HIV (PLHIV) irrespective of CD4 cell count, WHO clinical stage, age, pregnancy condition, or co-morbidities. The preferred first-line ART for adult patients whose age is 18 years and above is TDF/3TC/DTG or TDF/3TC/EFV in women of childbearing age or those who cannot tolerate DTG. ABC is used in place of TDF in impaired renal function of CrCL less than/equal to 50ml/min. The preferred second-line treatment is the use of protease inhibitors (PI) based regimens.

HIV infected patients should also be screened for any opportunistic infections and prevention measures put into place. Lifelong co-trimoxazole preventive therapy (CPT) is usually used. Patients with sulfa allergy or who develop toxicity due to CPT may use another substitute drug. Dapsone is a substitute drug that can be used instead of co-

trimoxazole for Pneumocystis Pneumonia (PCP) prophylaxis. It is prescribed for patients who have an absolute CD4 count of ≤ 200 cells/mm^3 and/or patients in WHO clinical stage 4. It is discontinued when a patient is virally suppressed and has a stable CD4 count of > 200 cell/mm^3 (10).

2.2.2 Anti-tuberculosis drug regimen

TB treatment entails the use of drugs in the form of Fixed Dose Combinations (FDCs). Anti-TB drugs used as first-line for the treatment of drug-sensitive TB include four drugs, namely, Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB). Treatment for TB consists of two phases, namely, an intensive phase and a continuation phase. The first two months of therapy uses four drugs and this intensive phase is used to rapidly reduce the bacillary load in the body. The continuation phase takes place after the intensive phase whereby two drugs, Rifampicin (RIF) and Isoniazid (INH), are used for 4 or 10 months. Steroid therapy is given to some TB patients in particular situations such as Pulmonary TB (PTB) with respiratory distress, TB meningitis, PTB with airway obstruction due to hilar lymph nodes, pericardial effusion, or severe miliary TB. Pyridoxine supplementation is also recommended for some TB patients on isoniazid. This is for either TB prophylaxis or minimizing the risk of developing peripheral neuropathy with the use of isoniazid (11).

Drug resistance TB occurs when the *Mycobacterium tuberculosis* bacilli mutate enabling it to resist effective first-line anti-TB drugs. Treatment for multidrug-resistant TB (MDR-TB) and extensive drug-resistant TB (XDR-TB) requires second-line or third-line anti-TB drugs. Second-line anti-TB drugs include group A fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin), group B injectable aminoglycosides (amikacin, capreomycin,

kanamycin), group C other core agents (prothionamide, cycloserine, clofazimine, linezolid). Third-line anti-TB drugs include group D add-on agents such as group D1 (pyrazinamide, ethambutol, high dose isoniazid), group D2 (delamanid, bedaquiline), and group D3 (p-aminosalicylic acid, meropenem, amoxicillin/clavulanate). The anti-TB regimen for drug-resistant TB is individualized based on the drug susceptibility testing results and treatment is for a longer period ranging from 9 to 15 months (11). Bedaquiline and delamanid combination have shown to be effective and safe in the treatment of MDR-TB and XDR-TB (17).

HIV patients confirmed with TB infection are started on CPT, which is a part of their comprehensive treatment care. Anti-TB treatment should also be started immediately and as soon as the anti-TB medications are well tolerated, ART is initiated, preferably within 2 weeks. If the patients are already on ART, they should start anti-TB treatment at once and ART continued. Changes to the ART regimen can be made based on known drug-drug interactions (10,11).

2.3 Prevalence and types of ADEs among HIV infected patients

ART has been proved efficacious in reducing morbidity and mortality due to HIV infection. However, ART is also associated with ADEs. A prospective observational study conducted in India monitored patients receiving AZT/3TC/NVP and AZT/3TC/EFV. GIT side effects, CNS side effects, and anemia were among the common ADEs among these patients. The study showed that TDF-containing regimens were safer than AZT-containing regimens. The study concluded that the type of ARV regimen and time since initiation of ART was associated with the causality of related ADEs (18).

A retrospective study analysis of a cohort of HIV-infected patients who were given an integrase strand transfer inhibitor (INSTI) in two large German out-patient clinics was carried out between 2007 and 2016. The study was to determine the rate of discontinuation of dolutegravir because of neuropsychiatric adverse events and it concluded that the rate was significantly higher than for other INSTIs, at almost 6% within 12 months (19).

A cohort study done in South Africa involved adult patients receiving second-line ARV drugs. The primary outcome measured was ADE occurrence during the first 24 months of initiating the second-line ART. The study concluded that ADEs rates were reduced among patients on a TDF-containing regimen compared to patients on the ABC-containing regimen. Deteriorated health at the time of ART switch was a risk factor for developing ADEs (20).

The literature on ADEs due to ART is limited in the sub-Saharan African countries. A prospective study done in Mali showed that the prevalence of ADRs by organ system was 45.9% for neurological, 29.4% for metabolic, and 15.4% for the hematological system. The study concluded that peripheral neuropathy and anemia were the most frequent ADRs and these were linked to AZT and d4T use among these patients (21). A hospital-based retrospective study done in Ethiopia in 2014 concurred with the findings found in the study done in Mali. The study concluded that lipodystrophy and peripheral neuropathy were significantly associated with D4T-based regimens while anemia was significantly associated with AZT-based regimens (22).

ADRs are highly prevalent among HIV patients on ART. A four-year prospective cohort study done in Ethiopia revealed that ADEs occurred early after ART initiation with about

87% of reported toxicities limited to the skin, nervous, and blood organ system. The study also revealed that ART related toxicities in the developing world are more prevalent because the regimens contain older and more toxic agents like d4t, AZT, and NVP. In addition to these, a patient's late presentation with advanced disease states, the occurrence of opportunistic infections, and co-morbidities have contributed to the development of ADEs. Concomitant anti-TB treatment was the strongest independent predictor of toxicity (23). A similar four-year prospective study done in Nigeria also revealed that 96% of ADRs that were reported occurred between the third to the eighteenth months of ART treatment with the commonest ADRs being peripheral neuropathy, itching, anemia, dyspepsia, skin rashes, and various forms of dermatitis (24).

A high prevalence of ADRs due to ART was reported in a cross-sectional survey done in Kenya in 2008. 65.2% of the patients enrolled in the study experienced ADRs. The most common ADR was peripheral neuropathy with the least common one being hepatotoxicity. The study also found an association that was important to the development and reporting of ADRs and age, weight, occupation, marital status, education level, and religious participation (14).

A four-year retrospective study done at KNH between 2003- 2006, revealed that ADRs were associated with the use of didanosine and d4T-containing regimens. In resource-limited countries, these were the current standard regimens and were associated with a high risk of ADEs development (25). A two-year prospective cohort study carried out in Kenya from 2003 to 2005 also showed ADEs occurring with the previously recommended standard regimens. Single drug substitutions were made due to drug

toxicities including changing NVP to EFV due to rash and d4T to AZT due to neuropathy or lipodystrophy (26).

2.4 Prevalence and types of ADEs among HIV/TB co-infected patients

HIV debilitates the patient's immune system. This enhances the likelihood of TB infection among HIV infected patients. TB is curable however the drugs used have several ADEs that increase morbidity and mortality. India accounts for one-fifth of the TB burden globally. A prospective observational study was conducted in two DOTS (Directly Observed Treatment Short Course Therapy) centres in 2014. The two DOTS centres were selected randomly. The patients were followed up during the intensive treatment phase and the incidence of ADRs was observed in 20.4% of the 102 patients recruited for the study. The most common ADEs were associated with the GIT system followed by the skin (27).

An 8-year retrospective cohort study was carried out in Thailand in the year 2008-2015. The study revealed that cutaneous ADRs are prevalent in HIV/TB co-infected patients with maculopapular rash being the most prevalent type. The study also showed that ART use during TB treatment was associated with a lower risk of cutaneous ADRs. There was no difference in the development of cutaneous ADRs between patients with low or high CD4 cell count (28).

The association between anti-TB drug blood levels and drug-induced hepatotoxicity (DIH) is not well known. A retrospective cohort study carried out in Korea revealed that basal serum drug levels of the patients on the prescribed doses of the first-line anti-TB

drugs were not related to the chance of developing anti-TB DIH. RIF, INH, and mostly PZA were the drugs implicated (29).

Limited data exist on the burden of serious ADRs in sub-Saharan Africa and yet HIV and TB prevalence is high within this region. A cross-sectional survey was carried out in South Africa whereby admitted patients were followed up over sequential 30-day periods in 2013. An assessment done on the ADRs found out that 164 of 1951 patients admitted were ADR-related with renal impairment due to TDF and liver injury due to rifampicin being among the most commonly implicated ADRs (30). A parallel cross-sectional study was conducted in South Africa in 2013 to assess ADR related deaths. The study showed that ADRs contributed to 2.9% of deaths of medical admissions. Rifampicin, TDF, and co-trimoxazole were the drugs mostly implicated with 43% of ADRs being known as preventable (31).

A comparative study of ADRs profile was conducted in Zimbabwe by analyzing individual case safety reports. The study was carried out among 3 groups of patients. The first group consisted of patients on highly active antiretroviral therapy (HAART). The second group was of patients on HAART and isoniazid preventive therapy (HHAART). The third group consisted of patients on HAART and anti-TB treatment (ATTHAART). The study concluded that ART was related to a higher rate of gynecomastia, lipodystrophy, and Stevens-Johnson syndrome. ART and anti-TB drugs co-administration was related to a higher number of peripheral neuropathy and drug-induced liver injury cases. Finally, psychosis development was associated with concurrent use of ART and isoniazid preventive therapy (IPT) (32).

Tuberculosis (TB) is crucial in causing morbidity and mortality in patients infected with HIV, with Kenya being among the countries with a high TB burden. A cross-sectional study carried out in Kenya in 2017 to determine the prevalence of ADEs of first-line anti-TB medication revealed that the most common ADEs were neurological, immunological, and GIT disturbances. The study also compared ADEs between patients infected with HIV and non-HIV co-infected TB patients. Even though HIV-infected participants were on ART, the prevalence of these ADEs between patients infected with HIV and those not infected with HIV was not statistically different (33). A retrospective cohort study done at KNH between 2006-2007 comparing ADEs among HIV infected and uninfected adults on anti-TB concluded that GIT disturbances and peripheral neuropathy were the most common ADRs in both groups (15).

A review was done in Kenya on compiled data from various sources on multiple ADEs due to concomitant use of ART and anti-TB drugs. The review concluded on some ADEs such as d4T and INH-induced peripheral neuropathy, NVP, and RIF associated hypersensitivity rash, and AZT induced myelosuppression among others. Overlapping toxicities was also a concern with associated clinical implications (34).

2.5 Determinants of ADEs

ADEs are among the leading causes of morbidity and hospitalization. Some studies have been conducted to find some factors associated with ADEs due to ARV and anti-TB drugs. A cohort study was carried out in Brazil between the years 2009-2011 to estimate the incidence of GIT symptoms and associated factors in patients infected with HIV. The study revealed that a high incidence of GIT symptoms was found among HIV-infected patients and it was significantly associated with female sex and tobacco use. Nausea,

vomiting, dyspepsia, heartburn, diarrhea, constipation, and flatulence were the GIT symptoms that were evaluated in the study (35).

Neuropsychiatric ADEs have been reported with the use of EFV over the years. Patients of black ethnicity are genetically at greater risk of developing EFV-associated nervous system toxicity. A prospective longitudinal observational study was carried out on HIV infected adult patients on EFV 600 mg. The patients were assessed for factors associated with EFV neuropsychiatric disturbances. Age, weight, CD4 count, WHO clinical stage, gender, and ARV agents (TDF/3TC/EFV or AZT/3TC/EFV) were not significantly associated with the risk of ADEs (36).

A similar retrospective cohort study involving HIV infected was carried out in Nigeria between the years 2004-2012. The patients were aged 15 years and above. The study assessed the neuropsychiatric ADEs associated with EFV-based ART. The study concluded that neuropsychiatric symptoms were more common in females than males though the percentage of reported neuropsychiatric ADRs declined with increasing age. A higher proportion of neuropsychiatric ADRs was reported among those with advanced HIV disease initiated on EFV-based ART. In addition to this, the risk of neuropsychiatric ADRs increased in patients on AZT and d4T-based regimens as opposed to those on TDF-based ARV drug combination (37).

A retrospective study was conducted in Ethiopia in the year 2011-2016 on ADEs and factors associated with ADEs among HIV infected patients on treatment. The study concluded that most of the ADRs developed within the first year of ART initiation. Occupation, educational status, advanced clinical stage, and opportunistic infections (OI)

prevention therapy were among the factors associated with ADRs development. Patients who were working in a non-governmental organization were at an increased risk of developing ADRs as opposed to those working in governmental organizations. Patients with no formal education and who had completed primary education at the time HAART was initiated had an increased risk of developing ADRs as opposed to those with higher educational levels. The risks of ADRs in the WHO clinical stage I was lower than in WHO clinical stage II, III, and IV. Patients not on OI prophylaxis were more at risk of ADRs compared to those who were on OI prophylaxis (38). Another cross-sectional study carried out in Ethiopia in 2014 to assess the occurrence of ADRs and associated factors with ADRs revealed that low CD4 cell count at treatment initiation and concomitant use of co-trimoxazole with ARVs was a major risk factor for ADRs (39).

A cross-sectional survey conducted in Kenya in the year 2008 involved 354 patients on ARVs. A significant correlation between occurrence and reporting of ADRs was found out with weight, age, marital status, education level, occupation, and religious participation. However, the duration of ARVs and gender did not significantly affect the incidence and the reporting of ADRs. The study also did not reveal any association between diet and ADRs occurrence (14).

A systematic review of published studies during the 1965-2012 periods was done in Brazil. The studies indexed in the MEDLINE and LILACS databases were reviewed. The review identified the risk factors associated with ADRs due to anti-TB drugs. Treatment regimens, age above 60 years, alcoholism, anemia, and HIV co-infection were among the identified risk factors. Nutritional deficiencies of sodium, iron, and albumin were also among the identified risk factors. The review also identified that male gender and

rapid/intermediate N-acetyltransferase 2 acetylator phenotype were among the factors protecting against hepatic ADEs of anti-TB drugs (40).

An Indian prospective observational study carried out in 2014 revealed that pulmonary TB (PTB), a history of alcoholism, and associated co-morbidities were significantly associated with the incidence of ADRs. There were more occurrences of ADRs in PTB than extra-pulmonary TB (EPTB) (27). This is a different finding from a study done in Rwanda which concluded that EPTB was related to an increased risk of serious ADEs (41).

A retrospective cohort study conducted in Thai between 2008-2015 showed that there was no correlation between CD4 count, total T-lymphocyte count, and cutaneous ADR incidence due to anti-TB drugs. However, concomitant ART use in HIV/TB co-infected patients was an independent factor associated with a lower risk of cutaneous ADRs. The study also revealed that a history of drug sensitivity, co-trimoxazole use, decreased GFR, and ART naïve patients were more at risk of developing cutaneous ADRs due to anti-TB drugs (28).

Tuberculosis (TB) and HIV/TB co-infection is a significant population health concern in resource-limited settings like Rwanda. A prospective observational study of a cohort of patients treated for TB was done from 2008-2009. The study assessed the risk factors of ADEs during anti-TB treatment. Concurrent infection, drug-induced hepatitis, and tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS) were among the common factors associated with ADEs. In addition to this, HIV infection and EPTB were related to an increased risk of serious ADEs. EPTB and CD4 cell count of 100 cells/ mm^3

in that period TB was confirmed were independent predictors for HIV patients co-infected with TB. (41).

2.6 Summary and Research gap

Adverse drug events are among the leading causes of morbidity and hospitalization. There is a notable gap in the literature on the ADEs between patients infected with HIV and those co-infected with tuberculosis. Limited recent research has been done locally in this particular area involving these two groups, especially among the patients infected with both HIV and TB infections. Treatment guidelines have been changing often especially on the ART regimen and yet studies available are not giving recent findings on these new recommended regimens. This gap is what this research aimed to address. As a result, the study findings will contribute to the existing literature and will also help in finding ways in which to address these ADEs hence improving ART and anti-TB treatment safety and effectiveness.

CHAPTER THREE: MATERIALS AND METHODS

3.1 Introduction

This chapter contains an overview of how the study was carried out. It describes the research design, study location, study population, sampling size, and techniques as well as data collection tools. It also describes how data was collected and analyzed. Logical and ethical considerations are also included in this chapter.

3.2 Research design

An analytical cross-sectional design was used to evaluate the adverse drug events among patients infected with HIV and those co-infected with tuberculosis at Kenyatta National Hospital. A cross-sectional design was less time consuming and less expensive. This design was effective in collecting data at a given point in time from a sample population that represents a larger population. Cross-sectional studies can reveal associations between dependent and independent variables.

3.3 Location of the study

Kenyatta National Hospital, Comprehensive Care Center (KNH-CCC) is the area of study. It is a national referral and teaching hospital located in the capital city of Kenya, Nairobi. It can accommodate 1800 beds though it hosts patient numbers as high as 3000. The hospital is located 3.5 kilometers west of Nairobi City, the capital city of Kenya. The hospital offers a variety of health services including holistic care and management for patients with HIV/AIDS at the CCC. The clinic days for ART therapy run through-out the weekdays. The hospital plays a role in the College of Health Sciences at the

University of Nairobi by benefiting the students with teaching opportunities. The study focused on HIV infected adult patients attending the CCC.

3.4 Target and study population

The target population included patients attending KNH for the provision of health services. The study population involved HIV infected patients and those co-infected with HIV and tuberculosis attending the CCC for follow-up care. The average number of patients infected with HIV and TB infection attending the CCC for follow-up was approximately 70 patients. Only the patients who satisfy the inclusion criteria were allowed to take part in the research.

3.4.1 Inclusion and exclusion criteria

Participants included in the study had the following characteristics;

a. Eighteen years of age and above.
b. Patients who were HIV-infected without TB infection.
c. Patients who were HIV-infected with confirmed TB infection.
d. Patients on first-line drugs for tuberculosis infection.
e. Patients who were able to communicate effectively in either Kiswahili or English.
f. Those who gave their consent to take part in the study.

Patients who did not meet the above criteria were not included in the study.

3.5 Sampling

3.5.1 Sample size calculation

The sample size was calculated following the sample size determination formula for two independent groups. The formula applied to estimate equal sample sizes in the two study groups is as shown (42):

$$n = \frac{[(a + b)^2 (p_1 q_1 + p_2 q_2)]}{x^2}$$

Where:

n = sample size per group.

p_1 = proportion of HIV infected participants with ADEs in Group 1.

q_1 = proportion of HIV infected participants without ADEs in Group 1 ($1 - p_1$).

p_2 = proportion of HIV infected participants co-infected with tuberculosis with ADEs in Group 2.

q_2 = proportion of HIV infected participants co-infected with tuberculosis without ADEs in Group 2 ($1 - p_2$).

x = the difference between the two proportions ($p_1 - p_2$).

a = conventional multiplier for alpha. In this study, the level of significance used is 0.05. Therefore the value of a=1.96.

b = conventional multiplier for beta. In this study, the power used is 0.80 which is adequate to give reliable results. The value of b=0.842.

Using two studies done in Kenya, the prevalence of ADEs among patients infected with HIV is 65.2% in group 1 (14) and the prevalence of ADEs among HIV-infected patients co-infected with tuberculosis on first-line anti-TB drugs is 44.6% in group 2 (15).

The difference between the two proportions (x) = 0.652-0.446= 0.206

$$\mathbf{n = \frac{[(1.96+0.842)^2 (0.652\times0.348 + 0.446\times0.554)]}{0.206^2} = 87}$$

There are approximately 70 HIV/TB co-infected patients followed up at KNH-CCC. This constitutes a finite study population of which the formula for finite population correction was adopted for this study as shown (43):

$$\mathbf{\text{Corrected sample size} = \frac{(n \times N)}{(n + N - 1)} = \frac{87\times70}{87+70-1} = 39.}$$

Where n is the estimated sample size and N is the source population and the corrected sample size is the desired sample size.

Therefore the corrected sample size with an additional contingency for non-responses yielded a sample of 42 patients for each arm of the study when adjusted by 10%. The total number of participants to be recruited was 84 patients.

3.5.2 Sampling technique

Simple random sampling is the approach that was utilized to obtain a representative sample. The researcher visited the KNH-CCC clinic and introduced themselves to the personnel working in the clinic to seek permission to select study participants. As the HIV-infected patients streamed into the CCC for follow-up for ART, the researcher flipped a coin and the patient who scored the head was approached and requested to

volunteer to take part in the study. The patients who agreed to enter the study were taken through the voluntary consenting process as guided in **Appendix 1**. Only those who consented were allowed to participate in the study. The sampling procedure was done again until the desired sample was attained. HIV/TB co-infected patients were recruited similarly as the HIV-infected patients from among the patients visiting the CCC for follow-up for ART and anti-TB treatment. A total of 84 participants were recruited equally with each arm having 42 HIV-infected patients and 42 HIV/TB co-infected participants.

3.6 Research instruments

Data collection tools that were used to obtain and record information from the patients were self-administered structured questionnaires by the principal investigator **(Appendix 2).** The questionnaire had four main sections. The first part contained information on the socio-demographic characteristics of the participant. The second part contained information on the types of drug regimens the participants were using. The third part contained information on the phase of TB treatment the HIV-infected patients co-infected with TB were currently on. Finally, the fourth part contained information on the adverse drug events among participants infected with HIV and those co-infected with tuberculosis.

3.7 Pre-testing

Pre-testing the questionnaires for validity and reliability was done using a small set of respondents at the KNH-CCC. The questionnaires were tested for face validity by giving it to an expert in the given area to critically evaluate it. The questionnaire was then pre-

tested using a subset of the intended target population. Finally, internal consistency was analyzed to check whether the individual questions had good validity and reliability.

3.8 Validity

In addition to face validity being assessed, context, content, and construct validity was evaluated using approximately 10 patients at the KNH-CCC. The questionnaires administered were evaluated for any problems so as find possible solutions. This ensured that the research instrument estimated what it was intended to measure.

External validity ensured that the results could be generalized to the wider population. This was achieved by ensuring that a representative sample was selected for both arms of the study using a random sampling technique which was a type of probability sampling. This technique prevented selection bias from occurring during the recruitment process. The correct sample size was also used for both arms of the study to ensure that the precision of the study was adequate. The estimated sample size was computed using the sample size determination formula for two independent groups.

Internal validity refers to how well the study was conducted by eliminating systematic errors, bias, or confounders. This was achieved by ensuring that every process carried out in the study was done appropriately. The researcher ensured that the data collected was accurate and complete and maintained integrity during the data collection process. The researcher also guaranteed that the participants comprehended the questions in the data collection tool and gained rapport with the participants to minimize non-response bias that would occur due to non-participation. The environment where the researcher

collected the data was conducive for the participant by ensuring privacy and avoiding distractions such as noise.

The research instrument was well structured and standardized to ensure that the participants understood the questions and the printing was done well so that the questions were legible. A good questionnaire design minimized information bias that would arise due to participants recalling the past events inaccurately or responding to questions incorrectly to please the researcher. Data management ensured the confidentiality of participants' information by using private passwords to secure the stored information and the data was also backed up regularly. Confounders such as age, gender, alcohol, smoking, the socioeconomic status were identified before the study commenced. These confounders were controlled during data analysis by logistic regression modeling.

3.9 Reliability

Reliability refers to the degree to which the research method yields consistent results. A study is reliable when the same research method is conducted under the same conditions and it generates the same results. Reliability shows that the study fulfills its forecasted aims and hypothesis. It also shows that the research findings are due to the study carried out and not due to any possible external variables. Research with good reliability shows that the research findings can be used as scientific evidence.

Reliability was tested using the test-retest method, also known as absolute reliability, which focused on within-subjects' results. Five of the ten respondents from the CCC at KNH were given the same research instrument twice after two weeks’ time-lapse. The correlation for the test-retest method was then evaluated between the two sets of scores.

This was carried out by graphing the data in a scatter plot and then the Pearson's *r* was computed. A test-retest correlation of +0.80 or more indicated that the research had good reliability.

3.10 Data collection techniques

Data collection was done using researcher assisted administered questionnaires to participants who voluntarily consented to be included in the study. They were invited individually for a face to face interview and assisted to complete the questionnaire. This was done at the KNH-CCC in a secluded room to ensure privacy and confidentiality. The data which was not obtained directly from the participants was abstracted from the clinic records and entered into the questionnaire. Participants were requested to give verbal consent for the researcher to access their clinical records. Authority to access the patients' records was sought out from the respective administrators. The questionnaire had four main sections, namely, socio-demographic characteristics, types of drug regimens, phase of TB treatment, and the adverse drug events among HIV-infected participants and those co-infected with tuberculosis participants. Different types of drug regimens and patient characteristics were the independent variables and the dependent variables were the adverse drug events.

Socio-demographic characteristics that were assessed included BMI, sex, age, marital status, highest education level, employment status, monthly income, co-morbidities, alcohol use, and tobacco smoking. The type of drug regimens that were assessed were ARV drugs the HIV infected patients were receiving and both ARV drugs and first-line anti-TB drugs the HIV infected patients co-infected with tuberculosis were on. The phase of TB treatment for the HIV/TB co-infected patients was also assessed to determine if the

patient was in the intensive or continuous phase. The aspects of ADEs included prevalence, types, and determinants of ADEs which were measured by assessing questionnaires administered to patients. Assessment for these ADEs was done according to the main body systems and organs and included the gastrointestinal, nervous, skin, circulatory, endocrine, musculoskeletal, renal, respiratory systems as well as the liver, ears, and eyes. The different signs and symptoms were shown in the questionnaire.

The data collected was saved in a computer and secured with a unique password to ensure the privacy and confidentiality of the patient's data. Data stored was backed up regularly and in a separate location from the primary data. The researcher then analyzed the data with the assistance of a statistician.

3.11 Data analysis

The quantitative data generated from the questionnaires were coded and keyed into a password-protected Microsoft Excel spreadsheet. The frequency of each ADEs was computed and tabulated as an absolute number and as a percentage. Stata version 13 data analysis software was used to analyze data collected in this study. Fisher's exact test and chi-square test were performed to compare the prevalence of ADEs across socio-demographic characteristics and the type of drug regimens. Bi-variable and multivariable analysis was used to assess the strength of the relationship between ADEs and socio-demographic characteristics and types of drug regimens. Determinants were identified as those variables with an odds ratio greater than one and a p-value of less than or equal to 0.05 in a logistic regression model.

Inferential statistics was carried out by testing the hypothesis to determine whether to reject or not reject the null hypothesis using the p-value computed from the chi-square test of homogeneity. This test was applied to a single categorical variable (ADEs) derived from two separate populations (participants infected with HIV and those co-infected with tuberculosis). A p-value of less than or equal to 0.05 was treated as significant.

3.12 Logistical and ethical considerations

3.12.1 Approval

Approval to carry out the study was obtained from the Kenyatta National Hospital-University of Nairobi Ethics and Research Review Committee, approved through the reference number KNH-ERC/A/170) before the commencement of the study. The study was registered by the KNH Department of Research and Programs reference number CCC/104/2020 as well after approval from the ethical review board. All other protocols, including seeking authority to carry out the research from the study sites were also observed before the study commenced.

3.12.2 Informed consent and confidentiality

An informed consent affirmed that the participant was aware of the study, understood the risks/discomfort involved, and accepted to be part of the research without any form of intimidation. The decision to take part in the study was voluntary and those who declined to consent were not discriminated against. All willing participants signed informed consent.

The confidentiality of the participants was observed in the study. The filling of the questionnaires and interviews was conducted in private and quiet rooms by the principal

investigator. The participant's information was kept confidential through re-identification since the actual names or file charts were not used at data entry. Access to the data entered was also restricted by a unique password to prevent access to unauthorized users.

3.12.3 Dissemination plan

The study findings were shared through a PowerPoint presentation and dissertation documents submitted to the School of Pharmacy at UON and KNH department. The health care providers would be sensitized to the findings through continuous medical education and outreach programs. The patients would be educated by the health care providers during patient counseling sessions. Finally, the findings would be published in a relevant medical journal for a wider audience such as treatment guidelines and policymakers such as the National AIDS and STI's Control Programme (NASCOP) and National Tuberculosis, Leprosy and Lung Disease Program (NTLD-P) who are under the Ministry of Health, the general public, and the society.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter focuses on the findings of this study. The data is summarized in frequency tables and charts.

4.2 Socio-demographic characteristics of the participants

Forty (47.6%) participants had a normal BMI of between 18.6-25 kg/m^2 as shown in **Table 1**. Six (7.1%) of the participants had a low BMI of less than 18.5 kg/m^2. The majority (54, 64.3%) of the respondents were female and 49 (58.3%) of them were above 40 years. Forty-six (54.8%) of them were single and 34 (40.5%) had attained a primary level of education. More than half (59, 70.2%) of the participants were in non-formal employment with the majority of the participants (41, 48.8%) earning a monthly income of 10,000 Kenyan shillings and below.

Hypertension was the most prevalent co-morbidity (10, 11.9%) and eight (9.5%) took alcohol.

Table 1: Participants socio-demographic characteristics

Variable	Frequency (n)	Percentage (%)
BMI (kg/m^2)		
Below 18.5	6	7.1
Between 18.6 to 25	40	47.6
Between 25 to 30	23	27.4
Above 30	15	17.9
Sex		
Male	30	35.7
Female	54	64.3
Age (years)		
18-30	15	17.9
31-40	20	23.8
Above 40	49	58.3
Marital Status		
Married	37	44.0
Single	46	54.8
Education Level		
Primary level	34	40.5
Secondary level	27	32.1
Tertiary	23	27.4
Employment Status		
Formal	25	29.8
Non-formal	59	70.2
Monthly Income (Ksh)		
10,000 and below	41	48.8
Between 10,000 to 20,000	25	29.8
Between 20,000 to 30,000	7	8.3
Above 30,000	10	11.9
Malnutrition	6	7.1
Diabetes mellitus	2	4
Hypertension	10	11.9
Alcohol use	8	9.5
Tobacco smoking	3	3.6

4.3 Types of drug regimens and Tuberculosis treatment phase

The regimens which were used for HIV treatment at the time of the study included TDF/3TC/DTG, TDF/3TC/EFV, and ABC/3TC/DTG as first-line drugs while protease inhibitors (PI) based regimens such as AZT/3TC/LPV/r and AZT/3TC/ATV/r were used as second-line agents among the participants. Lifelong co-trimoxazole preventive therapy was also used among the participants for Pneumocystis Pneumonia (PCP) prophylaxis.

The majority (35, 83.3%) of the HIV/TB co-infected participants were in the continuation phase of TB treatment. In the intensive phase, the participants were on a combination of four drugs, namely, Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB). In the continuation phase, the participants were on two drugs, Rifampicin (RIF) and Isoniazid (INH). Pyridoxine supplementation was recommended for all HIV/TB patients in both the intensive and continuation phase to prevent or minimize the risk of developing isoniazid-induced peripheral neuropathy.

4.4 Prevalence of Adverse Drug Events

The prevalence of ADEs among the 84 recruited participants are summarized below (**Table 2**). The most frequently reported ADE was discolored urine/tears (42, 50%), followed by skin rash/itchiness and tiredness/weakness with each having a prevalence of 30 (35.7%).

Table 2: Prevalence of ADEs among the study participants

Types of ADEs	n	%
Discolored urine or tears	42	50
Skin rash/ itchiness	30	35.7
Tiredness/weakness	30	35.7
Increased thirst/hunger	28	33.3
Loss of appetite	23	27.4
Numbness of feet	23	27.4
Numbness of hands	21	25.0
Tingling	20	23.8
Flatulence	19	22.6
Somnolence/insomnia	19	22.6
Nausea, Vomiting	18	21.4
Arthralgia	18	21.4
Headache/dizziness	16	19.0
Mental depression	16	19.0
Diarrhea, constipation	14	16.7
Psychosis/confusion	13	15.5
Abdominal cramps	9	10.7
Clumsiness/unsteadiness	9	10.7
Pain and swelling of joints especially the big toe/knee and hot skin over affected joints	9	10.7
Sore throat	8	9.5
Muscle twitching	6	7.1
Increased or decreased amount of urine/ frequency of urination	6	7.1
Rapid breathing	4	4.8
Taste disturbance	3	3.6
Seizures	2	2.4
Unusual bleeding and bruising	2	2.4
Jaundice	2	2.4
Blurred vision	2	2.4
Loss of vision	2	2.4
Eye pain	2	2.4

4.5 Comparison of adverse drug events between patients infected with HIV and those co-infected with tuberculosis

The comparison of different types of ADEs among patients infected with HIV and those co-infected with tuberculosis are summarized in **Table 3**. The fisher's exact test and chi-square test performed found that the ADEs which were statistically significant across the two arms of the study were hand numbness ($p<0.001$), tingling ($p<0.001$), feet numbness ($p=0.002$), discolored urine/tears ($p<0.001$), skin rash/itchiness ($p=0.009$), and tiredness/weakness ($p=0.009$). The prevalence of the mentioned ADEs was statistically different among HIV infected patients and those co-infected with tuberculosis.

Table 3: Comparison of ADEs among HIV infected patients and those co-infected with tuberculosis

Types of ADEs	HIV infected (n=42)	HIV/TB Co-infected (n=42)	
	FREQUENCY (n, %)	FREQUENCY (n, %)	P-Value
Gastrointestinal disturbances			
Loss of appetite	8 (34.8%)	15 (65.2%)	0.091
Nausea, Vomiting	8 (44.4%)	10 (55.6%)	0.440
Diarrhea, constipation	7 (50%)	7 (50%)	0.576
Abdominal cramps	3 (33.3%)	6 (66.7%)	0.266
Flatulence	8 (42.1%)	11 (57.9%)	0.344
Taste disturbance	1 (33.3%)	2 (66.7%)	0.518
Sore throat	2 (25%)	6 (75%)	0.148
Neurological disturbances			
Numbness of hands	3 (14.3%)	18 (85.7%)	**<0.001**
Tingling	2 (10%)	18 (90%)	**<0.001**
Numbness of feet	5 (21.7%)	18 (78.3%)	**0.002**
Headache/dizziness	9 (56.3%)	7 (43.8%)	0.351
Clumsiness/unsteadiness	6 (66.7%)	3 (33.3%)	0.218
Seizures	-	2 (100%)	0.259
Mental depression	5 (31.3%)	11 (68.8%)	0.099
Psychosis/confusion	8 (61.5%)	5 (38.5%)	0.243
Somnolence/insomnia	7 (36.8%)	12 (63.2%)	0.192

Musculoskeletal disturbances			
Muscle twitching	5 (83.3%)	1 (16.7%)	0.090
Arthralgia	8 (44.4%)	10 (55.6%)	0.440
Pain and swelling of joints especially the big toe/knee and hot skin over affected joints	6 (66.7%)	3 (33.3%)	0.218
Visual disturbances			
Blurred vision	-	2 (100%)	0.259
Loss of vision	-	2 (100%)	0.259
Eye pain	-	2 (100%)	0.259
Renal disturbances			
Increased or decreased amount of urine/ frequency of urination	2 (33.3%)	4 (66.7%)	0.361
Discolored urine or tears	1 (2.4%)	41 (97.6%)	**<0.001**
Others			
Skin rash/ itchiness	9 (30.0%)	21 (70.0%)	**0.009**
Unusual bleeding and bruising	1 (50.0%)	1 (50.0%)	0.741
Tiredness/ weakness	9 (30.0%)	21 (70.0%)	**0.009**
Increased thirst/hunger	11 (39.3%)	17 (60. 7%)	0.158
Jaundice	-	2 (100%)	0.259
Rapid breathing	1 (25.0%)	3 (75.0%)	0.326

The comparison of different types of ADEs among patients co-infected with HIV and tuberculosis during the intensive and continuous phase of TB therapy is summarized in **Table 4**. The ADEs which were statistically significant across the two phases of TB treatment were abdominal cramps (p=0.048) and taste disturbance (p=0.024).

Table 4: Comparison of ADEs among HIV/TB co-infected patients during the intensive and continuous phase of TB therapy

ADEs	Intensive Phase n (%)	Continuous Phase n (%)	P-value
Loss of appetite	4 (26.7%)	11 (73.3%)	0.225
Nausea, vomiting	2 (20%)	8 (80%)	1.000
Diarrhea, constipation	3 (42.9%)	4 (57.1%)	0.077
Abdominal cramps	3 (50%)	3 (50%)	**0.048**
Flatulence	3 (27.3%)	8 (72.7%)	0.353
Taste disturbance	2 (100%)	-	**0.024**
Sore throat	-	6 (100%)	0.567
Numbness of hands	4 (22.2%)	14 (77.8%)	0.438
Tingling	5 (27.8%)	13 (72.2%)	0.118
Numbness of feet	4 (22.2%)	14 (77.8)	0.438
Headache/dizziness	-	7 (100%)	0.326
Clumsiness/unsteadiness	1 (33.3%)	2 (66.7%)	0.430
Seizures	-	2 (100%)	1.000
Mental depression	1 (9.1%)	10 (90.9%)	0.654
Psychosis/confusion	-	5 (100%)	0.569
Somnolence/insomnia	3 (25%)	9 (75%)	0.387
Skin rash/ itchiness	3 (15%)	17 (85%)	1.000
Bleeding and bruising	-	1 (100%)	0.833
Tiredness/weakness	4 (20%)	16 (80%)	0.691
Increased thirst/hunger	2 (12.5%)	14 (87.5%)	0.690
Jaundice	-	2 (100%)	0.691
Muscle twitching	-	1 (100%)	1.000
Arthralgia	2 (20%)	8 (80%)	1.000
Arthritis	1 (33.3%)	2 (66.7%)	0.430
Increased or decreased amount of urine/ frequency of urination	-	4 (100%)	1.000
Discolored urine or tears	7 (17.1%)	34 (89.9%)	1.000
Blurred vision	-	2 (100%)	1.000
Loss of vision	-	2 (100%)	1.000
Eye pain	-	2 (100%)	1.000
Rapid breathing	1 (50%)	1 (50%)	0.309

4.6 Predictor factors for HIV and HIV/TB co-infection drug regimens

Hand numbness was 9.12 times more likely to occur among patients with HIV/ HIV-TB co-infection on ART and anti-TB drug regimens compared to those without HIV/ HIV-TB co-infection and not on the ART/anti-TB regimens, and the difference was statistically significant (p=0.001). The tingling sensation was 14.04 times more likely to occur among patients on ART and anti-TB drug regimens compared to those, not on the ART/anti-TB regimens and the difference was statistically significant (p=0.001). Feet numbness was 5.18 times more likely to occur among patients on ART and anti-TB drug regimens compared to those, not on the ART/anti-TB regimens and the difference was statistically significant (p=0.004). Skin rash/itching and tiredness/weakness were both 3.39 times more likely to occur among patients on ART and anti-TB drug regimens compared to those, not on the ART/anti-TB regimens and the difference was statistically significant (p=0.012). Discolored urine/tears were 0.82 times more likely to occur among patients on ART and anti-TB drug regimens compared to those, not on the ART/anti-TB regimens, however, this was the most statistically significant ADE (p<0.001) as shown in **table 5**.

After adjusting for confounders, discolored urine/tears (p<0.001) was the only ADE with a significant p-value (adjusted OR=767.50; 95% CI=43.46, 13554.25). Discolored urine/tears were 767.50 times more likely to occur among patients with HIV/ HIV-TB co-infection on ART and anti-TB drug regimens compared to those without HIV/ HIV-TB co-infection.

Table 5: Logistic regression on ADEs for HIV and HIV-TB co-infected participants

Variable	Bivariate analysis Crude OR (95% CI)	P-Value	Multivariate analysis Adjusted OR (95%CI)	P-Value
Appetite loss	2.21 (0.82, 5.98)	0.118	0.98 (0.05, 21.37)	0.988
Numbness of hands	9.12 (2.43, 34.22)	**0.001**	602211 (-)	0.996
Tingling	14.04 (3.00, 65.80)	**0.001**	1.82 (0, 40503.34)	0.907
Numbness of feet	5.18 (1.70, 15.80)	**0.004**	5.35e-06 (-)	0.997
Depression	2.48 (0.78, 7.89)	0.126	0.66 (0.02, 21.39)	0.814
Muscle twitching	0.17 (0.02 1.54)	0.115	0.21 (0, 53.11)	0.584
Discolored urine or tears	0.82 (71.50, 9404.65)	**<0.001**	767.50 (43.46, 13554.25**)**	**<0.001**
Skin rash/ itchiness	3.39 (1.31, 8.79)	**0.012**	4.17 (0.26, 67.83)	0.316
Tiredness/ weakness	3.39 (1.31, 8.79)	**0.012**	3.96 (0.24, 65.04)	0.335

CHAPTER FIVE: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses the findings of this study. The conclusions and recommendations based on the findings are also included.

5.2 Discussion

The majority of the participants had a normal BMI which is similar to studies carried out in Africa (20,44). The minority of the participants were underweight which is contrary to a previous study done in Nairobi in which the minority of the participants were overweight or obese (44). This variation in BMI could be due to some factors which the individual has no control over like sex, age, ethnicity, and other factors that can be controlled like diet, physical activity, environmental and social factors (45).

The majority of the respondents were female which is similar to several studies done in South Africa, Mali, Ethiopia, Kenya (14,20–23,26,38,46) which focused on adverse events of antiretroviral drugs. This shows that in the African setting more females are on treatment for HIV as opposed to males since most studies recruited most females. The prevalence of HIV in women is higher than in men in Kenya according to the Kenya Population-based HIV Impact Assessment (KENPHIA) survey, also explaining the reason why the majority of the recruited participants were female (47). This was contrary to some studies carried out in Kenya in which the majority of the participants were males (16,41,44,48) and this may be because males are more predisposed to developing tuberculosis as these studies focused on adverse events of anti-tuberculosis drugs. Possible reasons why men were more predisposed to tuberculosis than women include

differences in health-seeking behavior, differences in immunity, and more frequent outside contacts for men than women (44).

Majority of the participants were single, had attained the primary level of education, and were in non-formal employment. This was similar to studies carried out in Ethiopia and Kenya with the single category of marital status including the widowed and separated participants in this study (14,23). The non-formal employment may explain the reason why the majority of the participants were earning a meagre monthly income. This may be explained by the fact Kenya is a developing country and a substantial proportion of the population is poor.

Most participants were aged above 40 years in this study. This was contrary to a study done in India and Ethiopia in which most participants were aged between 18-30 years and 30-39 years respectively (18,22). A possible reason for this variation in age could be due to differences in population composition whereby a larger proportion of the population could be in the younger age groups.

The most prevalent co-morbidity reported in this study was hypertension. Alcohol intake came in second as the second most reported factor that may be associated with the development of ADEs. This is contrary to two studies carried out in Rwanda and Kenya whereby alcohol intake was the most prevalent factor associated with the development of ADEs though these studies only looked at alcohol intake and tobacco smoking (41,48) while this study included malnutrition, hypertension, and diabetes mellitus among the co-morbidities studied. This finding also contradicts a study carried out in India which

included co-morbidities as factors associated with the development of ADEs and alcoholism was the most frequently reported factor (27).

The regimens which were used for HIV treatment at the time of the study as first-line and second-line agents, as well as co-trimoxazole preventive therapy among the participants, were following the Kenyan ART guidelines (10). This was similar to a study carried out in India (18). Studies carried out in Kenya and South Africa contradict this study in terms of ART as stavudine and didanosine were agents used previously in the treatment of HIV (14,20,48) but were phased out over the years due to their related toxicities (49). First-line anti-tuberculosis drugs used for TB treatment as well as pyridoxine supplementation for all the HIV/TB patients in both the intensive and continuation phase were following the Kenya TB guidelines (11). This mirrors similar studies, in which participants on anti-TB drugs were on the same regimen in both the TB treatment phases (15,16,28,29).

The majority of the HIV/TB co-infected participants were in the continuation phase of TB treatment. These findings are consistent with findings of a similar study (16) in which the majority of the participants with TB were in the continuation phase of treatment as opposed to the intensive phase since it is usually of a shorter duration.

Discolored urine/tears were the most prevalent ADEs reported followed by skin rash/itchiness and tiredness/weakness. Rifampicin was the drug responsible for urine/tears orange-red discoloration. Skin rash/itchiness could be due to overlapping toxicities caused by various drugs such as ARV drugs like nevirapine, efavirenz, abacavir, atazanavir, and/or all anti-TB drugs. Co-trimoxazole or dapsone for PCP prophylaxis may also be responsible for these cutaneous reactions. Tiredness /weakness

may be a sign of anemia caused by zidovudine and/or co-trimoxazole or a sign of peripheral neuropathy caused by isoniazid and/or ethambutol (10,11,34,50). These findings were contrary to two studies carried out in Kenya and Nigeria in which peripheral neuropathy was the most frequent in ADE with cutaneous reactions being the second most prevalent ADE (14,16). Three other studies carried out in India and Kenya also contradicts this study since gastrointestinal disturbances were the most frequent ADEs followed by neurological disturbances (15,18,48). A study done in Mali and Ethiopia contradicts these findings as peripheral neuropathy and metabolic disturbances/lipodystrophy were the most frequently reported ADEs in these studies (21,22). These variations in the different studies may be caused by the fact that stavudine and didanosine were previously used in the management of HIV and these two drugs were associated with peripheral neuropathy and lipodystrophy ADEs (14,21,22,48). Discolored urine or tears attributable to rifampicin was also not considered as an adverse drug event for participants on anti-TB drugs explaining why it was not among the most frequently reported ADE (16).

There was a statistical difference in the prevalence of peripheral neuropathy (hand numbness, tingling, and feet numbness), discolored urine/tears, skin rash/itchiness, and tiredness/weakness among patients infected with HIV and those co-infected with tuberculosis. Peripheral neuropathy which was mainly reported among the HIV/TB co-infected participants may have been caused by isoniazid or ethambutol anti-TB drugs. These ADEs were statistically significant since ARV drugs that might have caused peripheral neuropathy were withdrawn. Discolored urine/tears were also mainly observed among HIV/TB co-infected participants because rifampicin was the drug responsible for

this ADE. Skin rash/itchiness may have been caused by overlapping toxicities from both the ARVs and anti-TB drugs. Cutaneous reactions were mainly reported by HIV/TB co-infected participants as they were taking more drugs compared to their HIV-infected counterparts. HIV/TB co-infected patients with concomitant co-trimoxazole use would have an increased risk of cutaneous ADEs. Tiredness/weakness, a sign of either anemia or peripheral neuropathy, was mainly reported among the TB co-infected participants because of the possibility of anemia caused by zidovudine and/or co-trimoxazole and peripheral neuropathy caused by isoniazid and/or ethambutol (10,11,34,50,51). A study done in London echoes these findings since peripheral neuropathy was among the significant ADE among HIV-infected and HIV uninfected individuals on anti-TB treatment. On the contrary, this same study contradicts the findings as persistent vomiting was the other ADE which was significant across the two groups of study (52). The persistent vomiting could be attributed to the fact that the study involved TB patients who started treatment hence follow-up was from the intensive phase of TB treatment as opposed to this study whereby the majority of the HIV/TB co-infected participants were in the continuation phase of treatment. Vomiting is a common ADE associated with the use of anti-TB drugs in the early weeks of therapy and usually becomes less intense with time on treatment (11).

The ADEs which were statistically significant across the intensive and continuation phase of TB treatment were abdominal cramps and taste disturbance. These findings are echoed by similar studies done in Kenya in which gastrointestinal disturbances were the most prevalent ADEs among patients on anti-TB drugs (15,48). The prevalence of the mentioned ADEs is statistically different between the intensive and continuous phase of

TB therapy. This may be because gastrointestinal disturbances are observed more commonly in the intensive phase but usually lessens with time on treatment and supportive therapy (11,53).

This study revealed that some variables were predictors of ADEs. Hand numbness, tingling, feet numbness, discolored urine/tears, skin rash/itchiness, and tiredness/weakness were the ADEs more likely to occur among patients on ART and anti-TB drug regimens compared to those not on the ART/anti-TB regimens. These findings mirror similar studies done in Nigeria and Kenya in which after multivariate analysis concluded that HIV positive status was associated with an increased risk of developing ADEs to TB regimens compared to HIV negative patients (15,16,48). The study done in Kenya is further similar to these study findings in that peripheral neuropathy was an ADE more likely to occur in HIV infected than HIV uninfected patients. On the contrary, the study revealed that gastrointestinal disturbances were the other significant ADEs more likely to occur in HIV infected than HIV uninfected patients (15).

After adjusting for confounders, only discolored urine/tears ADE was found to be a significant predictor of HIV and HIV/TB drug regimens causing this particular ADE. This is explained by the fact that rifampicin causes an orange-red discoloration of the urine and tears which is not a harmful side effect (11). The stools, saliva, lung secretions, and sweat may also get this orange-red discoloration (54).

5.3 Conclusions

Foremost the most prevalent ADE was discolored urine/tears followed by skin rash/itchiness and tiredness/weakness coming in as the second most prevalent ADEs. Secondly, there was a statistical difference among HIV-infected patients and those co-infected with tuberculosis patients with regards to the prevalence of hand numbness, tingling, feet numbness, discolored urine/tears, skin rash/itchiness, and tiredness/weakness. Thirdly, hypertension was the most prevalent co-morbidity reported in this study. Fourthly, hand numbness, tingling, feet numbness, discolored urine/tears, skin rash/itchiness, and tiredness/weakness were the ADEs more likely to occur among patients on ART and anti-TB drug regimens compared to those, not on ART/anti-TB regimens. Finally, discolored urine/tears were the only ADEs found to be significant among HIV and HIV/TB drug regimens after adjusting for confounders.

5.4 Recommendations

5.5.1 Recommendations for policy and practice

Peripheral neuropathy, skin rash/itchiness and, tiredness/weakness are adverse drug events that draw concern in the clinical settings and their management should be re-enforced according to the Kenyan guidelines for HIV and tuberculosis treatment.

The underlying cause of tiredness/weakness ADE among HIV-infected patients and those co-infected with tuberculosis should be investigated in the clinical settings and the cause managed appropriately.

5.5.2 Recommendations for further research

Studies to further investigate the association between malnutrition, diabetes mellitus, hypertension, alcohol use, and tobacco smoking with the prevalence of adverse drug events should be carried out in the future.

Studies that require proper data collection to further investigate the correlation between the prevalence of ADEs with socio-demographic characteristics are needed in the future.

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APPENDICES

Appendix 1: Consent Form

Title

Evaluation of adverse drug events among patients infected with Human Immunodeficiency Virus and those co-infected with tuberculosis at Kenyatta National Hospital.

Principal Investigator

Dr. Margaret W. Mburu, Department of Pharmaceutics and Pharmacy Practice, UON, Tel: 0729569361

Introduction

I am Dr. Margaret W. Mburu, a student at the University of Nairobi, pursuing Master of Pharmacy in Clinical Pharmacy. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. The main objective of this study is to evaluate the adverse drug events associated with drugs used to treat HIV and tuberculosis. I am therefore requesting you to allow me to ask you questions and examine the body to assess the adverse drug events on different systems and also peruse through your medical records to assess the relevant laboratory test results. I will request you to sign your name on this form once you agree to take part in the study. We will give you a copy of this form for your records. Kindly, I request you to oblige.

Voluntary participation

Your participation in the study is voluntary. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal. Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities.

Risks and/or discomfort

There is no major risk involved. There will be no financial obligation on your side. During the assessment, precautions will be taken to ensure your privacy and comfort.

Benefits

The results obtained will be shared with your clinician and may be used effectively to manage your condition. Any information concerning the disease will be offered at no financial cost. Therapy may be altered to ensure that adverse drug events are minimized. The results may be used by the government to predict the incidence of adverse drug events associated with ARVs and TB drugs.

Confidentiality

The effort will be made to keep personal information confidential. The information will be kept under lock and key and electronic information will be under a password. The information will only be used to facilitate your treatment and for academic purposes.

Justice

You will be given the same treatment as other participants regardless of the outcome. Your social status, gender, culture, or lifestyle will not negatively affect the treatment. There will be no discrimination.

Veracity

I will be truthful with all the information given. The importance of each question will be explained if requested.

Problems or questions

If you have further questions or concerns about participating in this study, please call or send a text to Dr. Margaret W.M. on Telephone number 0729569361.

For more information about your rights as a research participant, you may contact the Secretary, Kenyatta National Hospital-University of Nairobi-Ethics, and Research Committee on Telephone number 2726300 Ext. 44102.

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that all efforts will be made to keep information regarding my identity confidential. By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

Participant name: _____Participant signature/Thumb print: _____

Date: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: _____**Researcher's signature: _____**

Date: _____

Appendix 2: Questionnaire

Title: Evaluation of adverse drug events among patients infected with Human Immunodeficiency Virus and those co-infected with tuberculosis at Kenyatta National Hospital.

Date: _____

Code number: _____

Instructions

1. Answer by ticking appropriately on the spaces provided.
2. For the open-ended questions, please write your response on the spaces provided.
3. Feel free to ask for clarification whenever in need.

a. Socio-demographic characteristics

1. Weight_____ Height_____

BMI

Category of BMI	Code	
Below 18.5	1	☐
Between 18.6 to 25	2	☐
Between 25 to 30	3	☐
Above 30	4	☐

2. Sex

Male	1	☐
Female	0	☐

3. Age _____

4. Age category

Age category (Years)	Code	
18-30	1	☐
31-40	2	☐
Above 40	3	☐

5. Marital status

Category	Code	
Married	0	☐
Single	1	☐

6. Highest education level

Category	Code
No formal education	1 ☐
Primary level	2 ☐
Secondary level	3 ☐
Tertiary	4 ☐

7. Employment status
    1. Formal ( )
    2. Non-formal ( )

8. Income per month

Income (KSH)	Code
10,000 and below	1 ☐
Between 10,000 to 20,000	2 ☐
Between 20,000 to 30,000	3 ☐
Above 30,000	4 ☐

Co-morbidities/social habits

S/No	Factor	Present(1)	Absent (0)
9	Malnutrition		
10	Diabetes mellitus		
11	Hypertension		
12	Alcohol use		
13	Tobacco smoking		

b) Types of drug regimens

Category	Code
ART	0 ☐
ART/ANTI-TB	1 ☐

c) The phase of Tuberculosis treatment

No of drugs	Code
Intensive phase	1 ☐
Continuation phase	2 ☐

d) Adverse drug events

S/No	Adverse drug events	Present (1)	Absent (0)
16	Loss of appetite		
17	Nausea, vomiting		
18	Diarrhea, constipation		
19	Abdominal cramps		
20	Flatulence		
21	Taste disturbance		
22	Sore throat		
23	Numbness of hands		
24	Tingling		
25	Numbness of feet		
26	Headache/dizziness		
27	Clumsiness/unsteadiness		
28	Seizures		
29	Mental depression		
30	Psychosis/confusion		
31	Somnolence/insomnia		
32	Skin rash/ itchiness		
33	Unusual bleeding and bruising		
34	Tiredness/weakness		
35	Increased thirst/hunger		
36	Jaundice		
37	Muscle twitching		
38	Arthralgia		
39	Pain and/or swelling of joints especially the big toe/knee and hot skin over affected joints		
40	Increased or decreased amount of urine/ frequency of urination		
41	Discolored urine or tears		
42	Blurred vision		
43	Loss of vision		
44	Inability to distinguish green and yellow		
45	Eye pain		
46	Rapid breathing		

LABORATORY RESULTS

S/No	Variable	Low (1)	Normal (2)	High (3)
47	AST level (10- 40 IU/L)			
48	ALT level (7-56 IU/L)			
49	BUN level (5-20 mg/dl)			
50	Creatinine level (0.6-1.2mg/dl)			
51	Sodium level (135-145 mmol/L)			
52	Potassium level (3.5- 5 mmol/L)			

Thank you for participating in the study.