THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

DEPARTMENT OF PHARMACY

SAFETY OF ATAZANAVIR-RITONAVIR FIXED DOSE COMBINATION IN HIV/AIDS PATIENTS FAILING FIRST LINE ART AT UNIVERSITY TEACHING HOSPITAL

BY

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DECLARATION

I, **Mpande Mukumbwa -Mweenechanya** hereby declare that the work on which this discussion is based is original, except where acknowledgements indicate otherwise.

This dissertation is submitted for the degree of Master of Clinical Pharmacy at the University of Zambia. Neither the whole work nor any part of it is has been submitted before for any degree or examination at this or any other university.

Signed ……on the ……..day of……

Computer Number: 531004865

CERTIFICATE OF APPROVAL

This dissertation of Mpande Mukumbwa, has been approved as fulfilling the requirements or partial fulfilment of the requirements for the award of Master's Degree in Clinical Pharmacy by the University of Zambia;

Signature for Examiner one……Date……..

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Signature for Examiner three……Date…….

DEDICATION

This Research Paper is dedicated to my late parents Rosemary and Kingston Mukumbwa, who have given me the drive and discipline to tackle any task with enthusiasm and determination. No words are sufficient to describe my parent's contribution to my life. I owe every bit of existence to them. This Paper is dedicated to their memory.

ABSTRACT

Atazanavir-ritonavir (ATV-r) has been recommended by the World Health Organization as part of second-line combination antiretroviral therapy (cART) in HIV-infected patients aged 6 years and above. In 2013, the Zambia HIV treatment program introduced ATV-r as an alternative Protease Inhibitor (PI) to lopinavir-ritonavir (LPV-r) because of its gastrointestinal tolerability, lipid profile and once-daily dosing. However, data about the safety and tolerability of ATV-r-containing regimens in sub-Saharan Africa continues to be inadequate.

A cross sectional study was undertaken which evaluated clinical and laboratory events among HIV-infected adult patients initiating ATV-r-based second-line cART at the University Teaching Hospital in Lusaka, Zambia between December 2013 and April 2014. A sample of 49 patients' medical records were selected and reviewed. SPSS version 16 was used for analysis. Association between demographic variables (age and gender) and the AEs was assessed using chi-square. Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee.

Following initiation of ATV-r, the vast majority of the study patients did not report adverse events (n=40, 81.6%). Among those with adverse events, jaundice (n=2, 4.1%) and diarrhoea (n=4, 8.2%) were the predominant complaints. Overall, hyperbilirubinaemia was the most common laboratory adverse event (n=3, 6.1%) and it was not associated with either age (p=0.755) or gender (p=0.604). The clinical adverse events reported by the patients also showed no association with the demographic characteristics. There were no treatment discontinuations of the ATV-r regimen based on these events.

ATV-r-based regimen appeared to be safe in the study population. Hyperbilirubinaemia was the most frequently observed laboratory AE though it did not prompt discontinuation of this drug. Continued safety and tolerability monitoring of ATV-based regimens is needed in resource limited settings, particularly for longer observation periods. Direct comparisons with other PI-based combinations are urgent, for the precise understanding of the efficacy and toxic effects.

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC: Lamivudine
AIDC: Adult Infectious Diseases Centre
ATV: Atazanavir
ATV-r: Atazanavir-ritonavir
ADR: Adverse Drug Reaction
AEs: Adverse Events
AIDS: Acquired Immune Deficiency syndrome
ALT: Alanine Aminotransferase
ART: Antiretroviral Therapy
ARV: Antiretroviral
AST: Aspartate Aminotransferase
BREC: Biomedical Research Ethics Committee
cART: combined Antiretroviral Therapy
CD4: Cluster of Differentiation
CNS: Central Nervous System
DRV: Darunavir
EFV: Efavirenz
FBC: Full Blood Count
FDA: Food & Drug Administration
FTC: Emtricitabine
FPV: Fosamprenavir
HAART: Highly Active Antiretroviral Therapy
HIV: Human Immunodeficiency Virus
ICF: Informed Consent Form
II: Integrase Inhibitor
LPV: Lopinavir
LPV-r: Lopinavir-ritonavir
MOH: Ministry of Health
NNRTI: Non Nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleoside Reverse Transcriptase Inhibitor
NVP: Nevirapine
PI: Protease Inhibitor

PV:	Pharmacovigilance
RTV :	Ritonavir
SAE :	Serious Adverse Event
TDF:	Tenofovir
UNAIDS:	United Nations Programme on HIV and AIDS
UNZA:	University of Zambia
UTH:	University Teaching Hospital
WHO:	World Health Organization
VL:	Viral Load
ZMRA:	Zambia Medicines Regulatory Authority

LIST OF DEFINITIONS

Acquired Immune Deficiency Syndrome: The state of profound immunosuppression which results from chronic infection with the Human Immunodeficiency Virus (HIV).

Adverse Drug Reaction: As defined by WHO, as any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy.

Adverse Events: As any untoward medical occurrence in a participant exposed to Atazanavir-r. An AE could include a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Cluster Differentiation 4: A surface antigen on T-cells that is particularly important for the immune resistance to viruses.

HAART: Combination of antiretroviral agents, usually of at least three agents and from at least two classes of Antiretroviral Drugs to improve efficacy and reduce the development of viral resistance.

Mild Adverse Drug Reaction: A reaction that does not require discontinuation of therapy or substitution, symptomatic treatment is required only when necessary.

Moderate or Severe Adverse Drug Reaction: A reaction that requires substitution of the drug from the same class of drugs but different toxicity profile or substitution of the drug with a different class ,these reactions do not require discontinuation of ART.

Prevalence of Adverse Drug Reaction: The proportion of patients experiencing ARV related to adverse drug reactions among adults.

Safety: Relative concept referring to the freedom from harm or damage resulting from adverse reactions or physical, psychological, or behavioural abnormalities that occur as a result of medicine use. Safety is usually measured with one or more of the following: physical examination (e.g., vital signs, neurological, ophthalmological, general physical), laboratory evaluations of biological samples (e.g., haematology, clinical chemistry, urinalysis, etc.), special tests and procedures (e.g., electrocardiogram, pulmonary function tests), psychiatric tests and evaluations, and determination of clinical signs and symptoms. It refers also to the long term occurrence of harm.

Serious Adverse Events: Any event which results in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity

Severe Life-threatening Adverse Drug Reaction: This is a reaction which when it occurs leads to immediate discontinuation of ART.

Tolerability: Represents the degree to which overt adverse effect can be tolerated by the subject. Tolerability is usually measured by the rate of dropouts and is much different depending on the therapeutic class.

Viral Load: The plasma level of viral RNA, which is measured to estimate the amount of circulating virus in the blood plasma.

CHAPTER ONE

1.0 BACKGROUND AND INTRODUCTION

Recent global commitments aim to provide antiretroviral therapy (ART) to about 15 million people living with HIV by 2015 however, with the current coverage at around 50% and a decline in the international funding for HIV/AIDS, there is an immense task ahead (UN General Assembly Resolution, 2011). Yet, expectations of antiretroviral (ARV) medications have never been greater than in recent times. The enormous scale up of access to ART over the last decade has demonstrated the feasibility of delivering ART as a public health intervention, with an estimated 2.5 million deaths prevented since 1995 (WHO, UNICEF, UNAIDS Progress report, 2011). Recent studies have reported plausible results supporting the need for the roll out of widespread ART use to reduce HIV transmission at the population level. These findings offer greater opportunities to reverse the epidemic. The options for ART have never been greater, there are now 27 US FDA-approved ARVs collectively targeting five different points in the HIV life cycle (US FDA, 2011).

In September 2011, Medicines Sans Frontières (MSF) , Solidarity Thérapeutique & Initiatives contre le SIDA (SOLTHIS) and Ensemble pour une solidarity Thérapeutique Hospitalière en Réseau (Esther) organised an expert consultation to provide recommendations on ARV regimens and strategies to support the further scale-up of treatment in resource-limited settings and recommended six key principles to guide ART choice. These are simplicity, tolerability and safety, durability, universal applicability, affordability and heat stability (Antiretroviral Sequencing Meeting Report, 2011). Considering these key principles, the preferred first-line regimen for adults and adolescents is the WHO-recommended combination of tenofovir, lamivudine/ emiricitabine and efavirenz available as a once-daily FDC (WHO, 2011). While the recommended first-line therapy should improve long-term adherence to treatment, some patients will develop treatment failure and will need a directed sequence of safe, independent (in terms of resistance) and convenient regimens. In the short term, the preferred regimen will likely remain the protease inhibitor-based, heat stable co-formulated atazanavir plus ritonavir low dose or darunavir-ritonavir (DRV-r), which should lower the pill burden and permit once-daily doses (Sola*s et al.,* 2008) .

Many countries including Zambia are increasingly adapting their national guidelines to start ART earlier, for both clinical and preventive benefits (Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection*, 2013*). This is due to the WHO recommendations on the implementation of the Treatment 2.0 strategy that clearly outlines the clinical guidelines across the continuum of care (Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, WHO 2013). Andrieux-Meyer et al. (2012) contended that providing people with affordable medicines, combined into effective regimens with few adverse events as possible and in a form that is practical to take and easy to adhere to remains a challenge. Improvements in the uptake and long-term adherence to treatment will likely depend on improved access to the best available ART regimens (Lynch et al, 2012). In Zambia atazanavir-r is a much less familiar drug compared to lopinavir-r and most clinicians have not had prior experience in its use.

Atazanavir, which is typically administered with low-dose ritonavir (atazanavir-r), has been an important innovation in the treatment of adult HIV infection owing to its ease of dosing, virologic potency, minimal toxicity, high genetic barrier to resistance, favourable resistance profile and lower effect on lipid and glucose metabolism. Important potential limitations to treatment with atazanavir-r are interactions with acid-reducing agents such as H2-receptor blockers and Proton Pump Inhibitors (PPIs), benign hyperbilirubinaemia with jaundice and a rare risk of nephrolithiasis. Atazanavir received US FDA approval for the treatment of adults with HIV-1 infection in 2003 and has since then been widely prescribed throughout the USA and Europe. Additionally, atazanavir-r-based cART are becoming increasingly available in resource-limited settings. Generally, cART regimens containing atazanavir-r have excellent tolerability and safety profile as evidenced by the results of various Phase II and III studies (Squires et al, 2010; Daar et al 2010; Mills et al, 2010; Soriano et al, 2009; Malan et al , 2008; Elion et al, 2008; Johnson et al, 2006; Molina et al, 2008; Smith et al, 2008; Cohen et al, 2005).The studies showed that only 1–8% of patients discontinued treatment owing to medication-related toxicity, where approximately 20–60% experienced grade 2 or higher clinical or laboratory adverse events (Division of AIDS for grading the Severity of Adult and Pediatric Adverse Events). The most common events were hyperbilirubinaemia, jaundice and nausea. Less frequently noted were scleral icterus, diarrhoea and rash. In comparison with other boosted PI regimens, atazanavir-r has better gastrointestinal tolerance with significantly less nausea and diarrhoea (Molina et al, 2008; Smith et al, 2008; Johnson et al, 2006)

In the revision of the WHO 2013 ART Guidelines atazanavir-r is highlighted as one of two preferred PI options for adults' second-line therapy along with lopinavir-r. The recommendation is based on available evidence regarding factors such as efficacy, safety, convenience and cost. In April 2011, the British HIV Association (BHIVA) in the United Kingdom revised its Treatment Guidelines and recommended starting atazanavir-r rather than any other boosted protease inhibitor for patients needing PIs for the first time. The same year in July, the Department of Health and Human Services (DHHS) in the United States issued Guidelines for the use of ARV Agents in HIV-1 Infected Adults and Adolescents that recommended atazanavir-containing regimens as one of four preferred regimens for treatment-naïve patients while lopinavir-r-containing regimens as alternative.

Mylan Pharmaceuticals have introduced the generic atazanavir and ritonavir co-formulation into the market, a combination which is attractive due to its once daily dosing thereby improving adherence and could be less expensive than lopinavir-r. It is among these reasons that the Ministry of Health has introduced atazanavir-r in its national formulary for the use as alternative PI in HIV/AIDS patients failing first line with cautions to the use of LPV-r. The study was designed to observe the safety characteristics of atazanavir-r in the Zambian population and provide data on its safety as a guide for the healthcare professionals of the adverse events to anticipate in their patients on atazanavi–r based regimens.

1.1 RATIONALE OF THE STUDY

With many antiretroviral agents available, clinicians need a precise understanding of the efficacy and toxic effects of the various drug combinations. Jacques *et al.*(2001) argues that when the efficacy of various drug combinations is similar, the choice of combination will be affected by the toxic effects of the drugs. Despite the remarkable benefits ARVs provide to HIV/AIDS patients the issues of drug induced toxicities have remained matters of great concern to both healthcare professionals and patients. The main adverse events associated with the use of protease inhibitors reported by several studies include hyperlipidaemia, hyperglycaemia, gastrointestinal symptoms, body-fat distribution abnormalities and insulin resistance (Barbaro, 2006; Nuesch et al, 200; Vigouroux et al, 1999). Adverse events are a major driver of poor adherence, drug substitution and treatment discontinuation, all of which undermine treatment and prevention efforts (Kranzer K et al, 2011; Mills EJ et al, 2006). Ford N et al.(2010) suggests that an ideal antiretroviral therapy regimen would be one that is safe and effective, irrespective of disease stage, usable throughout pregnancy, appropriate for infants, children and adults, and can be taken together with drugs for co-infections, notably tuberculosis and viral hepatitis. With the introduction of atazanavir-r in the Zambian formulary, there was the need to address immediate parallel information on outcomes in the Zambian population.

1.2 RESEARCH QUESTION

What is the frequency of Adverse Events observed in HIV/AIDS patients on Atazanavir-ritonavir Fixed Dose Combination (FDC) failing first line treatment from at ART Clinic, Adult Infectious Diseases Centre at the University Teaching Hospital?

1.3 STUDY JUSTIFICATION

Zambia has 17 approved ARVs with atazanavir-r registered by the Zambia Medicines Regulatory Authority (ZMRA) in December 2012 (ZMRA, 2012). The introduction in the Zambian National Formulary is to facilitate the use of ATV-r as an alternative to lopinavir-r in patients with cautions to LPV-r use, as this was recently introduced no local findings on safety profile are availble. The safety profile as noted in other settings cannot entirely be extrapolated to the Zambian population due to the variability in drug metabolic capacity among various populations which predicts variations in the gene expression of the metabolising enzymes which could be influenced by geographical/interracial differences (Pfister et al, 2003; Bertilsson 1995). Even within the same geographical locations, there is variability among individuals with respect to various metabolising isoenzymes (Stahle et al, 2004; Pfister, 2003; Bertilsson 1995). It was therefore, important that such a study was carried out in order to establish the safety profile of atazanavir-r in the Zambian population as data derived from within the country would have greater relevance and form basis for decision-making, effective patient management and follow up. The study was envisaged to assist in formulating necessary measures for prompt recognition of adverse events in these patients and to facilitate the effective planning of prevention and education programs by the Ministry of Health. This study also compared its findings with those from previously done studies in other health care settings and made appropriate recommendations to the relevant authorities. It further provided a baseline for further research.

1.4 AIM

The overall aim of this cross sectional study was to describe the safety of atazanavir-ritonavir Fixed Dose Combination (FDC) in HIV/AIDS patients failing first line treatment at ART Clinic, Adult Infectious Diseases Centre at the University Teaching Hospital.

1.5 SPECIFIC OBJECTIVES

Specifically within the context of adverse events, the objectives of the cross sectional study was to:

1.5.1 Assess the prevalence of adverse events in HIV/AIDS patients failing first line treatment.

1.5.2 Determine the association between the patient demographic variables and adverse events

CHAPTER TWO

2.0 LITERATURE REVIEW

The chaper contains review of relevant literature evaluated and analysed studies that have been conducted globally, regionally and locally on the safety profile of patients that where on atazanavir-r based regimen. This reviewed literature explored the prevalence of adverse events associated with the use of ATV-r based regimen. Details of Atazanavir-r drug properties are found in the **Appendix B**.

Adverse events associated with potent antiretroviral treatment have been recorded anecdotally and in randomised Clinical trials (Max and Sherer, 2000; Henry; Struble et al, 1997) however, little information is available on the prevalence and severity of adverse events in routine Clinical practice. Generally atazanavir-r is considered to be well-tolerated, various clinical studies conducted in other settings have reported lower toxicities for atazanavir-r as compared to other PIs. The main adverse effects associated with atazanavir-r are nausea, jaundice and diarrhoea. Jaundice is caused by elevated unconjugated bilirubin, and often causes concern to clinicians and patients however, it is important to note that this hyperbilirubinaemia is largely a cosmetic issue and not related to hepatitis or liver damage. This has been supported by results from a large prospective analysis of the Management Standardizzo di Terapia Antiretrovirale (MASTERS)cohort involving 2,404 patients in Itatly, where in most cases the atazanavir induced hyperbilirubinemia appeared to be an innocent phenomenon in as far as the risk of a subsequent increase in liver enzyme level was concerned(Torti et al, 2009).

In the U.S, Croom et al. (2005) carried a review of ATV and its management in HIV infected patients were elevated total bilirubin was also found to be the most common laboratory abnormality in clinical trials investigating atazanavir with and without ritonavir boosting. This abnormality occurred in over 80% of patients with 30–60% experiencing grade 3 or 4 elevations and 5–10% developing clinical jaundice or scleral icterus. Despite the frequent occurrence of this laboratory abnormality, study patients infrequently (<5%) discontinued atazanavir-r owing to this. Elevation in the levels of unconjugated bilirubin is a result of atazanavir-mediated inhibition of microsomal enzyme UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT 1A1). (Molina et al, 2010; Rodger et al, 2005) . In an open label non-inferiority study involving muliticentre sites in Asia, Africa, Europe , North and Molina et al. (2005) observed that reduced activity of

this enzyme has also been noted in 3–10% of the general population who have Gilbert's syndrome which is the most common inherited cause of unconjugated hyperbilirubinaemia, due to a polymorphism in the gene encoding UGT1A1.

While the physical appearance of having jaundice or scleral icterus can be distressing to some patients, atazanavir-induced Hyperbilirubinaemia has no other known adverse short or long-term consequences. In clinical studies, this phenomenon was not associated with signs, symptoms or laboratory evidence of hepatocellular injury and it should not be considered a PI-related hepatotoxicity. Grade 3 or 4 aspartate aminotransferase or alanine aminotransferase elevations occurred in less than 10% of patients on atazanavir-r and there has been no evidence of acute or progressive liver disease, even among those with viral hepatitis co-infection (Guaraldi et al, 2008; Bentue-Ferrer et al, 2009;Malan et al, 2008; Johnson et al 2006; Molina et al 2010; Perez-Elliaz et al,2009; Torti et al, 2009; Sulkowski, 2004; Rodríguez-Nóvoa et al, 2008; Guilleni et al, 2010; Rodríguez-Nóvoa et al, 2008; Anderson et al, 2007;Chan–Track et al, 2007; Izzedine H et al ,2007;Pacanoswski et al, 2006; Gavazzi et al, 2000; Murphy et al 2010; Stanley et al, 2009). 118 HIV-infected individuals receiving ATV 300 mg daily plus ritonavir 100 mg daily at one clinic in Spain were examined by Rodríguez-Nóvoa et al. (2008) and they reported a greater frequency of bilirubin elevation and jaundice during PEGylated-interferon and ribavirin treatment in patients co-infected with HIV and HCV receiving atazanavir-based cART of HCV compared with those on cART regimens without atazanavir.

Malan et al.(2008) in Sydney Austrailia conducted the only head-to-head randomized clinical trial that compared frequency of the occurrence of adverse events in patients on atazanavir-r- and unboosted atazanavir-based regimens. It was observed that pharmacologic boosting with ritonavir increased the frequency of total bilirubin elevation (greater than 2.5 times the normal upper limit in 60 vs 20%, respectively) and clinical jaundice (3 vs <1%, respectively). An equal number of participants in each arm experienced grade 3 or 4 total bilirubin and alanine amino-transferase or aspartate aminotransferase elevation (3 vs 3%, respectively). Discontinuation of therapy owing to hyperbilirubinaemia was numerically higher in those on atazanavir-r (4 vs <1%), but this difference did not reach statistical significance ($P > 0.1$).

A rare side effect reported in patients receiving atazanavir that healthcare providers should be aware of is nephrolithiasis (Anderson et at, 2007; Chan –Track et al, 2007; Izzedine et al ,2007;Pacanoswski et al, 2006). Several case reports (Anderson et al, 2007; Izzedine et al ,2007;Pacanoswski et al, 2006) and a review of the FDA's adverse event reporting system (*Noor et al, 2006*) identified this problem several years ago. In the FDA report, from December 2002 to January 2007, there were 30 cases of nephrolithiasis in HIV-infected patients taking atazanavir-based cART. Among the 20 cases reporting complete cART information, 13 patients were receiving concomitant tenofovir and 17 patients were receiving atazanavir boosted with low-dose ritonavir. Atazanavir was detected, by infrared spectrophotometry, in kidney stones of 12 of 14 cases undergoing stone analysis. There was considerable morbidity, with 18 (60%) patients requiring hospitalization, seven (23%) patients receiving outpatient care and eight (27%) patients requiring interventions of lithotripsy, ureteral stent insertion, endoscopic stone extraction or nephrostomy study placement. A total of five patients (17%) developed elevation in serum creatinine, suggestive of acute renal insufficiency. Renal function normalized after stone removal and atazanavir discontinuation in all patients except one with baseline chronic renal disease. Owing to the small number of cases, risk factors for atazanavir-induced nephrolithiasis are not known. Therefore, there is uncertainty as to whether or not increased atazanavir drug levels or prolonged use are associated with this adverse condition. Gavazzi et al, (2000) explains that nephrolithiasis is a well-known adverse effect associated with indinavir therapy, with a reported frequency of approximately 12%. Like indinavir, atazanavir has pH-dependent solubility (optimal pH: 1.9), and may crystallise in a basic environment. It is unclear if strategies to maintain high urinary output or achieve urine acidification are safe or effective in preventing atazanavir-associated nephrolithiasis. Healthcare professionals who prescribe cART with atazanavir-r should be aware of the possibility of nephrolithiasis and if signs or symptoms of this problem occur, one should consider discontinuation of Atazanavir and substitution with an appropriate alternative agent.

Over the past several years, one of the major issues in HIV management has been the development of metabolic disturbances, including hyperlipidaemia, and the potential for increasing cardiovascular disease risk. Nearly all HIV-infected patients experience increases in lipid levels on cART, but this increase in serum lipids has been most pronounced among patients treated with PIs until the introduction of atazanavir.

There have been various clinical trials of atazanavir-r and its effects on lipids in comparison with other medications. These studies have reported increases in all serum lipids after 48 weeks of atazanavir-r-based cART. Generally, the total cholesterol levels increased from 15 to 31 mg/l, LDL increased from 4 to 22 mg/dl, HDL increased from 4 to 11 mg/dl and triglycerides increased from 7 to 34 mg/dl (Malan et al, 2008; Smith et al, 2008; Squires et al, 2010; Daar et al 2010; Soriano et al, 2009; Molina et al, 2010; Squires et al, 2010).

Comparative studies involving three boosted PIs (fosamprenavir/r, lopinavir-r and atazanavir-r) revealed that ATV-r had consistently lower elevations in nearly all lipid levels by week 48 of therapy (Johnson et al, 2006; Molina et al, 2008; Smith et al, 2008; Squires et al, 2010). The greatest differences were observed in the serum levels of triglycerides and total cholesterol.

The Adult Clinical Trial Group (ACTG) 5202 study undertaken by Daar et al (2010) in 59 sites in the U.S and Peurto Rico reported that at 96 weeks of therapy, patients treated with atazanavir-r had significantly lower increases in fasting total cholesterol, LDL and HDL compared with efavirenz, regardless of the NRTI backbone used. Several other studies have switched patients with suppressed HIV RNA from other PI-based cART regimens to atazanavir-r, with subsequent improvements observed in lipids (Murphy et al, 2010; Stanley et al, 2009; Soriano et al, 2008; Calza et al, 2009). Using this strategy, the total cholesterol decreased from 12 to 25 mg/dl, LDL decreased from 4 to 6 mg/dl and triglycerides decreased from 38 to 182 mg/dl, depending on the population studied. In the Switch to atazanavir and Brachial Artery (SABAR) a randimised open label study in U.S, Argentina and Italy , lipids improved, but there was no observed change in brachial artery reactivity among those who switched to atazanavir-r compared with those who stayed on a different boosted PI. After 48 weeks of simplification of atazanavir-r to unboosted atazanavir in the Atazanavir ,Ritonavir Induction with Epzicom Study (ARIES), the median increases of total cholesterol, LDL and triglycerides were 16, 7 and 30 mg/dl lower, respectively compared with patients remaining on atazanavir-r in the U.S, Canada and Peurto Rico (Squires et al, 2010). This suggests that low-dose ritonavir or its pharmacologic boosting effect on atazanavir results in a smaller lipid increase over time, and that simplification to atazanavir, if viremia is suppressed, might be a viable strategy for patients with elevated lipids or high cardiovascular risk on atazanavir-r-based regimens (Squires et al, 2010; Sension et al, 2009).

Several studies have evaluated the effects of atazanavir-r on fat and glucose metabolism. The phase IV randomised open label in 30 centres in 10 countries in North and South America, Africa and Europe compared with unboosted atazanavir, after 96 weeks of treatment, patients treated with atazanavir-r-based cART had no significant difference in increases in total or subcutaneous adipose tissue measured by computed tomography and dual-energy X-ray absorptiometry (Mccomsey et al 2009). In a randimised non blinded comparison on continuing therapy with LPV-r vs switching to ATV-r conducted in Massachesettes in the U.S showed that patients who switched from lopinavir-r to atazanavir-r, 6 months after this change, there was a significant increase in glucose uptake by muscle, decreased visceral adipose tissue and decreased fasting glucose (Stanley TL et al, 2009). A randimised cross over study in North Carolina U.S comparing HIV-negative healthy volunteers on lopinavir-r and atazanavir-r found that those on atazanavir-r had less glucose uptake inhibition in vitro and lopinavir-r led to detectable insulin resistance in vivo (Noor et al, 2006). These results suggest that patients treated with Atazanavir-r may have less long-term metabolic toxicity with decreased incidence of metabolic syndrome and diabetes compared with those treated with other PIs.

There is limited information available within the sub region Zambia included, concerning the safety of atazanavr/r in HIV /AIDS patients. The dearth of information therefore highlighted the need for study which aimed at filling the gap in the lack of data.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

A cross sectional study using patient file review was conducted over 7 months from the time of UNZABREC approval.

The study design was selected as it was the cheapest and easiest method to provide useful information over a short period of time on the safety outcomes of patients on atazanavir-r based regimen. A cross sectional study was the appropriate research strategy to determine the prevalence of adverse events and identify associations between the patient demographic variables and the occurrence of adverse events that could then be more rigorously studied using relatively expensive research strategies such as a ohort study or randomised controlled clinical trial.

3.2 Study Site

This cross sectional study was conducted in the ART Clinic at the Adult Infectious Diseases Centre (AIDC) located at the University Teaching Hospital. AIDC is a centre of excellence where complicated infectious diseases are managed. It has the country's only Advanced HIV Treatment Clinic offering third line therapy and the only HIV Clinic offering atazanavir-r based regimen. It is run by Infectious diseases specialists, Physicians, Pharmacists', Nurse Counsellors and other supportive staff

3.3 Target Population

The target population in this study comprised patients attending the ART Clinic at AIDC

3.4 Study Population

Adult patients failing first line ART at AIDC -University Teaching Hospital who met the eligibility criteria

3.5 Eligibility

Ages eligible for study; patients aged bove 18 years

Genders eligible for study; both male and female patients

3.6 Inclusion Criteria:

ART-experienced patients with history of NNRTI use, that failed first line ART and switched to Atazanavir-r based regimen.

3.7 Exclusion Criteria:

ART-experienced patients with history of NNRTI use, that failed first line ART and switched to LPV-r

ART-experienced patients on second line therapy failing to tolerate LPV-r and switched to Atazanavir-r

ART - experienced patients on third line therapy with Atazanavir-r based regimen

3.8 Sample Size

The sample size was determined using statistical calculation Epi Info Version 7

A review of the medical records indicated that a mean of **150** patients (sample population) satisfying the inclusion criteria are switched to an atazanavir-r based regimen in six (6) months (An average of **25** patients fail first line monthly.)

Using Epi Info version 7 (CDC, Atlanta, GA,USA)

- at **95%** confidence interval
- expected frequency of **5%** as revealed by the findings of the CASTLE Study (Molina et al, 2010) which was a multicenter, open-label, 96-week noninferiority randomized trial of Atazanavir-r (300/100 mg) once daily vs. Lopinavir-r (400/100 mg) twice daily, each in combination with fixed-dose TDF/FTC 300/200 mg once daily, in antiretroviral-naive, HIV-1-infected patients. The average Grade 2-4 prevalence of AEs (diarrhea, nausea and vomiting) in patients exposed to ATV-r based regimen was 5%)
- **5 %** confidence limit
- a sample size of **49** was determined and included in the study. Therefore, 49 patients files of eligible study patients were examined.

Subject Selection

Study patients were selected using simple random sampling of all ART experienced patient with a history of NNRTI use that failed first line ART and subsequently switched to atazanavir-r based regimen from December 2013.

Each individual was chosen randomly and entirely by chance where;

- The 150 patients (sampling frame) were allocated with numbers 1, 2, 3…..150
- Generated random numbers from the computer to obtain a simple random sample of size (**49**) from the population of the intergers 1,2,3……150
- The simple random sample of patients selected for the study consisted of the patients in the list that correspened to the numbers in the simple random sample of numbers

Each member of the population had an equal chance of being included in the sample

3.9 Outcome Measures

The primary outcome measure of the study was observation of the safety of atazanavir-ritonavir in HIV/AIDS patients. Safety was assessed by changes from baseline of laboratory tests (including clinical, chemistry and haematology), vital signs, clinical serious adverse events/adverse events (diseases, signs and symptoms) that where reported and recorded in the patient files by physicians during the scheduled visits.

Serious adverse events (SAE) were defined as any event which resulted in death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity. AEs were defined as any untoward medical occurrence in a patient on the atazanavir-r based regimen. An AE included a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs were classified as per the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 1.0 (DAIDS, 2004)

3.10 Variables

Table 1: Variables with their associated definitions and scales of measurements

Variable	Definition	Scale of Measurement
Gender	Male or Female	Nominal Female =1 Male =2
Age	Age was grouped as less than 21 (18-20), 21- 30 years, 31-40 years and 41 years and above	Categorical 18-20 =1 21-30=2 31-40=3 41 and above = 4
Previous HAART regimen	Was grouped according to the first line regimens available in Zambia	Categorical TDF/FTC/EFZ (1) TDF/FTC/NVP (2) AZT /3TC/NVP (3) AZT/3TC/EFZ (4) ABC/3TC/NVP (5) ABC/3TC/EFZ (6) D4T/3TC/NVP (7) D4T/3TC/EFZ (8)
Duration on previous	Was grouped as less than 1 year, 1-2	Categorical

HAART regimen	years, greater than 2- less than 3 years, greater than 3-less than 4 years, greater than 4 – less than 5 years and greater than 5 years	less than 1 year =1 1-2 years =2 greater than 2, less than 3 years, =3 greater than 3 less, than 4 years =4 greater than 4,less than 5 years =5 greater than 5 years =6
Symptoms of patients at baseline and whilst on ATV-r base regimen	AEs were grouped according to the most prevalent according to the CASTLE study	Categorical No Symptoms =1 Nausea =2 Fever =3 Diarrhea =4 Abdominal pain =5 Rash =6 Jaundice =7 Depression =8 Vomiting =9 Headache =10 Insomnia=11 Drowsiness =12 Muscle and Joint aches =13 Malaise =14

Baseline tests of patients	Routine Tests conducted at baseline	Continuous Bilirubin- Number- Scale
Routine tests of patients		Bilirubin- Number- Scale
Baseline and routine Bilirubin		Categorical 0-1=1 2-3=2 4-5=3 6-7=4 Above 7=5

3.11 Data Collection

Data was collected from study patient files of eligible patients on atazanavir-r based regimen.

The data collection tool (**Appendix A**) captured information such as

- Date of initiation of ATV-r based regimen
- Patient demographics (age and gender)
- Previous HAART regimen
- Duration on previous HAART regimen
- Physician notes on patient general condition , complaints and experiences during the medical visits at 0 weeks prior initiation of atazanavir-r and weeks 4, 8 and 12 after initiation of atazanavir-r
- Laboratory results of Bilirubin at baseline.
- Routine Laboratory results of Bilirubin after initiation of atazanavir-r based regimen.

Data were collected by the investigator over a period of seven months and then coded and entered on Microsoft Excel spread sheets.

3.4 Data Analysis

Data was analysed using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA)

The Categorical variables for categorical data such as **age, gender, length of time on previous regimen, AEs and bilirubin** were expressed as frequencies and percentages and presented using simple bar charts.

Laboratory results being continuous variables were analysed using descriptive statistics and expressed as mean, median, range, interquartile range(IQR) and standard deviation (SD).

Association between the categorical variables (demographic variables and the AEs) were studied using the chi square tests (odds ratios) using a **95%** confidence interval estimation

3.13 Ethical Considerations

The study focused on review of patient files of eligible study patients and did not involve direct contact of interview of study patients. Study patients continued to receive their routine clinical care from the healthcare providers without any interruption from the Principal investigator or the study assistant. Patient confidentiality was maintained as only anonymised data were analysed. Data collected were not disclosed to any third party at all times. Only the Principal investigator had access to the pass word to the computer on which data were entered and stored.

Permission to undertake the cross sectional study in the ART clinic at AIDC was given by the University Teaching Hospital Management. (**APPENDIX B**) The University of Zambia Biomedical Research Ethics Committee (UNZABREC) granted formal ethical approval for the conduct of the study (**APPENDIX C).**

CHAPTER FOUR

4.0 RESULTS

4.1 Sample Description

4.1.1 Demographics of study patients

A total of 49 patients had their medical records reviewed. Out of these patients, 29 (59.2%) were females while 20 (40.8%) were males. The age of the study patients was in categorised, study patients with ages within 18-20 years were 3 (6.1%), 21-30 years were 4 (8.2%), 31-40 years were 18(36.7%), and those above 40 years were 24 (49%)

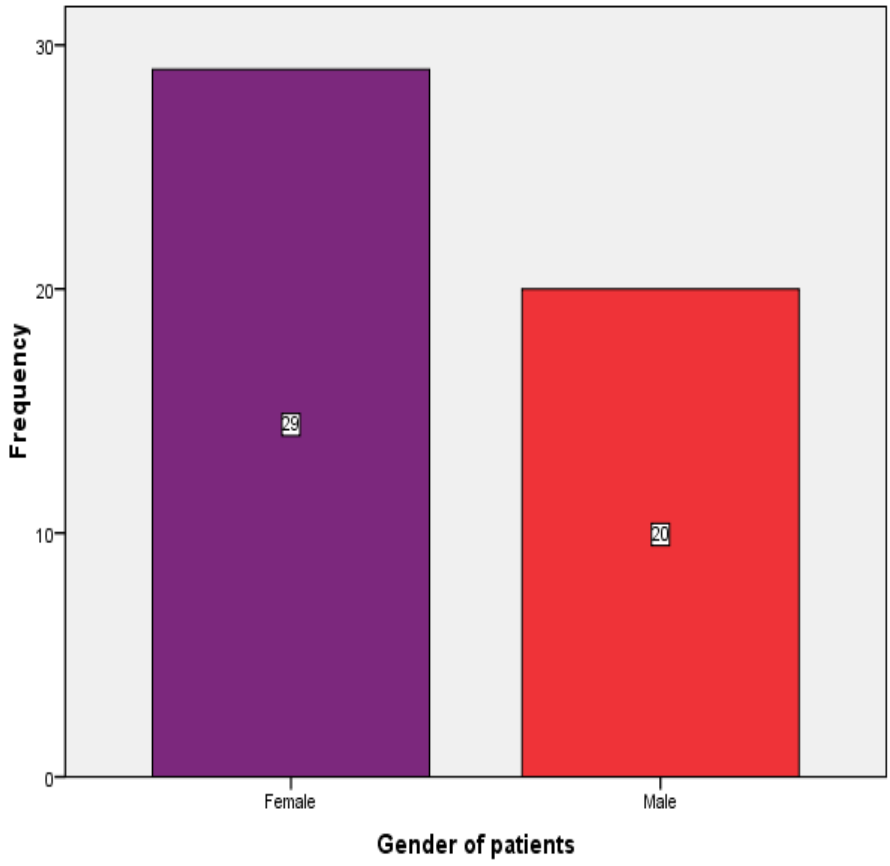

Figure 1: A bar chart showing the gender of the study patients

Table 2: Age groups of study patients

Age of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	18-20 years	3	6.1	6.1	6.1
	21-30 years	4	8.2	8.2	14.3
	31-40 years	18	36.7	36.7	51.0
	Above 41 years	24	49.0	49.0	100.0
	Total	49	100.0	100.0	

From **table 2**, the study patients were mainly from the age group above 41 years with a frequency of 24 out of 49 study patients. The age group with the least number of patients was 18-20years with a frequency of 3 out of 49 patients.

4.2 Previous HAART Regimen and duration of treatment

Of the 49 patient medical records evaluated, the majority of the study patients (n= 25,) had previously been on tenofovir/emitricitabine based regimen with either efavirenz or nevirapine while only patient had been on a stavudine based regimen. More than half of the study population had been on these various first line treatment for a durations greater than three years as shown in **figure 2:**

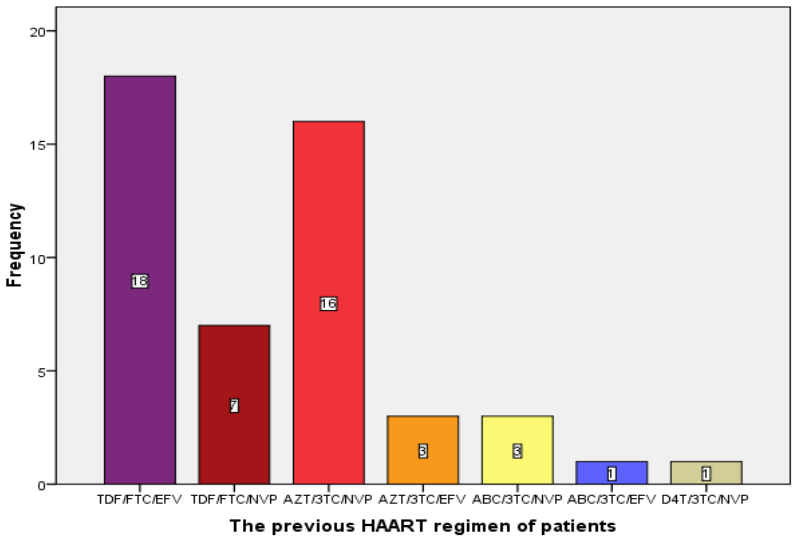

Figure 2: A bar chart showing the previous HAART regimen of patients

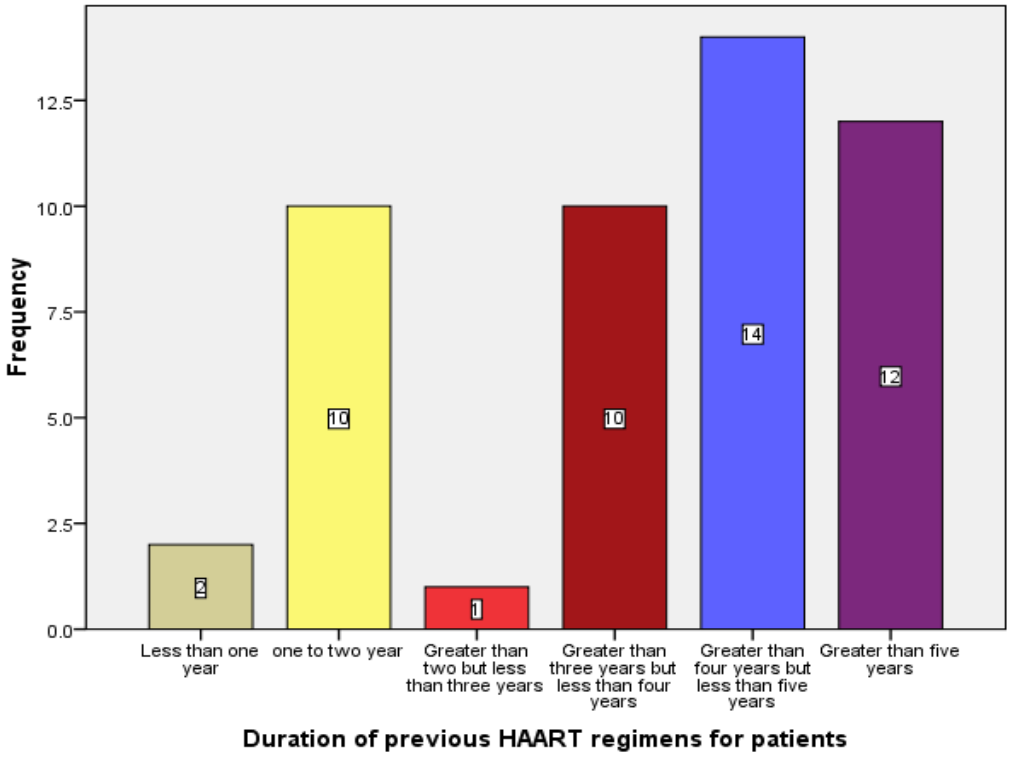

Figure 3: A bar chart showing the duration of treatment on previous HAART regimens for patients

4.3 Patient symptoms

4.3.1 Symptoms of Patients at baseline

Figure 4 shows the symptoms of study patients at baseline. The majority of patients 28(57.1%) did not report experiencing any symptoms, whist 14(28.6%) patients reported to be experiencing gastrointestinal tract (GIT) related symptoms such as diarrhoea, and abdominal pains, nausea and vomiting. Most of these patients 7 accounting for 50% of all the patients with GIT symptoms experienced diarrhoea.

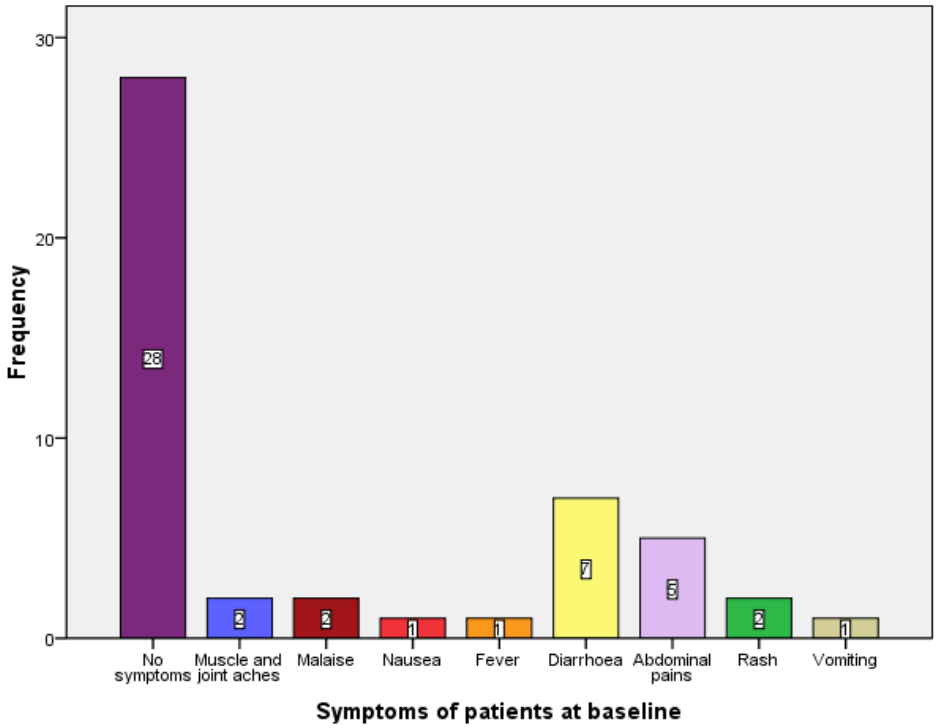

Figure 4: A bar chart showing symptoms of patients at baseline

4.3.2 Symptoms of Patients whilst on ATV-r based regimen

Table 3 shows all the symptoms experienced by the study patients on the ATV-r based regimen through week 12 of therapy. There were no clinical abnormalities recorded in 81.6 % (40/49) of the study patients as most of them did not report any occurrence of adverse events to the Physicians.

Generally the most prevalent adverse event reported was diarrhoea which occurred in 8.2% (4 of 49). The second predominant adverse event was jaundice reported as 'yellow eyes' (which occurred in 4.1 %(2 of 49).

Table 3: Symptoms of patients whilst on ATV-r based regimen

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No symptoms	40	81.6	81.6	81.6
	Headache	1	2.0	2.0	83.7
	Muscle and joint aches	1	2.0	2.0	85.7
	Diarrhoea	4	8.2	8.2	93.9
	Rash	1	2.0	2.0	95.9
	Jaundice	2	4.1	4.1	100.0
	Total	49	100.0	100.0	

4.4 Laboratory Characteristics

Table 4 shows the laboratory characteristics in the patients at baseline. All of the patients did not show any noteworthy baseline laboratory tests as no abnormalities were detected in the parameters reviewed.

Table 4: Baseline Laboratory Characteristics

		Baseline CD4 count of patients	Baseline viral load of patients	Baseline bilirubin of patients	Baseline ALT of patients	Routine body weight of patients
N	Valid	49	49	49	49	49
	Missing	0	0	0	0	0
Mean		260.39	337378.04	3.097	21.647	66.331
Median		212.00	32155.00	2.800	19.200	67.000
Mode		43[a]	40	1.0[a]	16.0[a]	75.0
Std. Deviation		198.957	1215376.473	1.6719	10.8841	12.7546
Variance		39584.076	1.477E12	2.795	118.463	162.679
Range		956	6860760	6.8	57.1	58.3
Percentiles	25	69.00	6035.00	1.850	13.800	56.250
	50	212.00	32155.00	2.800	19.200	67.000
	75	401.50	89198.00	4.000	26.000	75.000

Table 5 shows the laboratory characteristics through the study period, laboratory abnormalities were recorded for 6.1 % (3 of 49) with Hyperbilirubinaemia noted as the commonest adverse event.

Table 5: Laboratory characteristics of patients on ATV-r based regimen

		Routine ALT of patients	Routine bilirubin of patients
N	Valid	3	48
	Missing	46	1
Mean		38.033	4.123
Median		30.000	3.500
Mode		19.1[a]	3.0[a]
Std. Deviation		23.9813	3.4409
Variance		575.103	11.840
Range		45.9	19.0
Percentiles	25	19.100	2.250
	50	30.000	3.500
	75	65.000	4.300

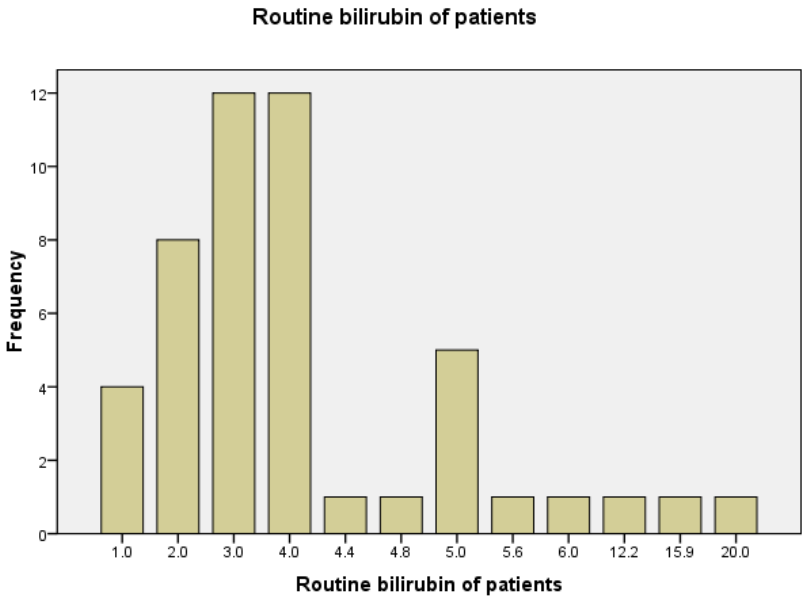

Figure 5: A bar chart showing routine bilirubin of patients

4.5 Association of AEs and the demographic characteristics

The **tables (6 and 7)** show the chi square tests for demographic characteristics of the patients' with the association to the various AEs reported whilst on ATV-r based regimen. The study demonstrated that there was no statistically significant association between demographic variables (age and gender) and patient symptoms whist on ATV-r. The p values for age and gender and the association with the hyperbilirubinemia did not demonstrate statistical significance (p=0.755 and p=0.604) respectively.

Table 6: Chi Square Tests for association of age and patient symptoms

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	17.099[a]	15	.313
Likelihood Ratio	15.725	15	.401
N of Valid Cases	49		

Table 7: Chi Square Tests for association of gender and patient symptoms

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.050[a]	5	.692
Likelihood Ratio	4.107	5	.534
N of Valid Cases	49		

Table 8: Chi Square Tests for association of age and bilirubin

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.848[a]	9	.755
Likelihood Ratio	6.515	9	.687
N of Valid Cases	49		

Table 9: Chi Square Tests for association of gender and bilirubin

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.850[a]	3	.604
Likelihood Ratio	2.294	3	.514
N of Valid Cases	49		

5.0 DISCUSSION

5.1 Demographic Characteristics

The study had slightly more females (29) than males (20), with the majority of the study patients from the age group above 41 years (24) followed by age group 31-40 years (18) and the remaining (7) from below 30 years.

5.2 Previous cART and duration of treatment

The patients' previous cART regimen was grouped into the first line cART regimens available in Zambia. Most of the patients included in the study had previously been on TDF/FTC based regimen as the NRTI backbone (n=25). These results indicate that the majority of the study patients had been initiated on ART as per national guidelines, with the recommended first line treatment of TDF/FTC/ with either EFV or NVP unless indicated otherwise. In the study before initiation of the ATV-r based regimen 18 of these patients were on TDF/FTC/EFV while 7 patients were on TDF/FTC/NVP.

The second most common NRTI backbone was AZT/3TC based regimen accounting for 22(44.9%) patients. 16/22 (72.7%) of these patients were on AZT/3TC/NVP whereas 6/22(27.3%) of the patients were on AZT/3TC/EFV.6/49 (12.2%) of all study patients were on ABC/3TC/NVP. With the phasing out of D4T based regimen from the national formulary due its' safety and tolerability profile , only 1 patient accounting for 2% of all patients was on D4T based regimen before the commencement of the ATV-r based regimen.

Most of the patients 39 (73.5%) had been on the previous cART regimen for a period greater than three years. Out of these 39 study patients, 38.9% had been on HAART regimen greater than four years but less than five years, while 33.3% greater than 5 years and the remaining 27.8% patients' had been on previous cART regimen greater than three years but less than four years.

This study showed that 13/49 (26.5%) had been on the previous cART for a period of less than three years, further investigation was required as to why the patients had failed treatment early. Studies have shown that majority of patients are usually maintained on first line treatment for longer than 3 years as is evidenced by a large prospective study conducted by Orrel C et al (2007) were more than 95% of the patients were retained on a

first line treatment over 3 years. 2 /13 (15%) in the study had been on the previous cART regimen for a duration of less than a year with both patients experiencing a fall of CD4 count to below the baseline after 6 months on Cart and therefore required change in therapy.

5.3 Patient Symptoms

The adverse events in this study were grouped according to the most prevalent as shown in the CASTEL STUDY conducted by Molina et al. (2010).

At baseline most patients 14/49 reported experiencing GIT related symptoms such as nausea (1/14) vomiting (1/14), abdominal pains (5/14) and diarrhoea (7/14). Of these GIT related symptoms diarrhoea was the most predominant complaint and accounted for 50% of the patients that reported GIT related symptoms with diarrhoea. Most of the patients 28 (57.1%) did not report experiencing any symptoms.

After ATV–r initiation, the number of study patients that did not report experiencing adverse events improved from the baseline of 57.1 % (28/49) to 81.6% (4/49) through week 12 on ATV-r based regimen with most of the patients not reporting the occurrence of adverse events to the Physicians. From the 14/49 (28.6%) study patients that had reported GIT related adverse events at baseline, after the ATV-r based regimen initiation 12/49 (24.5%) patients reported the GIT related symptoms to have resolved and no adverse events experienced however, 2/49 (4.1%) of the patients that had reported the occurrence of diarrhoea at baseline reported persistent diarrhoea through the 12 week therapy. The implication was the two patients' required further investigation to the cause of the diarrhoea as is was most likely not associated to ATV-r use.

The most prevalent clinical adverse events reported in this study were jaundice 2/49 (4.1%) with both patients experiencing mild jaundice (Grade I) and diarrhoea 4/49 (8.2%) which was graded as being mild to moderate (Grade I or 11) these findings are consistent with various studies that have reported lower toxicities for ATV-r compared with other PIs where the main adverse events associated with ATVr were nausea, jaundice and diarrhoea (Malan et al , 2008; Elion et al, 2008; Johnson et al, 2006; Molina et al, 2008; Smith et al, 2008; Squires et al, 2010; Daar et al 2010; Soriano et al, 2009; Mills et al, 2010; Cohen et al, 2005).

Jaundice was reported by the 2/49 patients as 'yellow eyes'. This cross sectional study involved patient file review and therefore, could not explore the impact of the 'yellow eyes' on the study patients.

Adherence remains the single most important strategy for long term success and sustainability of patients on cART. According to Conway (2007) inadequate adherence to HAART may be due to many factors such as, tolerability of therapy, pill burden, dosing frequency, food requirements and safety concerns. It is not surprising therefore that Carr and Amin (2008) share this view and have suggested that treatment related diarrhoea has emerged as a risk factor for treatment failure.

Despite the views held by Conway (2007) and Carr and Amin (2008), this study showed that ATV-r based regimen was safe with no overall treatment discontinuation and there were no unexpected safety events noted. The adverse events experienced by the patients were not treatment limiting as all of the reported adverse events were graded as mild to moderate (Grade I-II). According to the Zambia HIV consolidated guidelines (2014) adverse events Grade I-II (mild to moderate) do not require change in therapy and symptomatic treatment may be given. Should adverse events continue and no improvement is experienced in the patients, substitution with a drug in the same ARV class but with a different toxicity profile is then recommended.

5.4 Laboratory Characteristics

At baseline, patients had a median of 9.2 U/L ALT A and 2.8 umol/L Bilirubin, there were no patients with abnormal levels of both ALTs and Bilirubin. After the initiation of ATV-r based regimen through week 12 on therapy the prevalence of abnormal bilirubin was predictable in 3/49 (6.1%) study patients. All the three events were graded as being moderate (Grade II) however, out of the 2/49 (4.1%) that reported jaundice only 1/49 (2%) had abnormal bilirubin levels whilst the other patient had levels with the normal range.

The study findings are consistent with various studies previously conducted where the prevalence of hyperbilirubinaemia was highlighted as the most common laboratory abnormality in studies investigating atazanavir with and without ritonavir boosting (Molina et al 2010; Croom et al, 2009; Rodger et al 2005).

Although hyperbilirubinaemia and jaundice maybe of concern to patients and the health care providers because of their potential effect on the patient's quality of life, none of the 3

(6.1%) patients in the study had their ATV-r based cART discontinued due to jaundice in the 12 weeks therapy. It is clear from these results that the occurrence of hyperbilirubinaemia does not have a significant effect on ATV-r tolerability. Croom et al (2009) also observed that despite the frequent occurrence of the bilirubin abnormality, study patients infrequently (< 5%) discontinued the atazanavir-r owing to this. The findings of this study are similar to those reported by a large prospective analysis involving 2,404 patients of the Management Standardizzo di Terapia Antiretrovirale (MASTERS) cohort. The MASTERS cohort revealed that 90% of the patients had a total bilirubin higher than normal at any time were the percentage of hyperbilirubinaemia Grade 3 or higher was 63.6%. In most cases, atazanavir induced hyperbilirubinaemia appeared to be an innocent phenomenon as far as the risk of a subsequent increase in liver enzyme level was concerned and even when the bilirubin values were equal or higher than Grade III, or even when the jaundice was noticed, none of the patients chose to stop ATV (Torti et al, 2009).

The other tests conducted at baseline such as ALT were not routinely conducted through week 12 at the Centre as result most of the patient files did not have these records. This did not conform to the standard on the frequency of monitoring which according to the Zambia consolidated treatment guidelines testing is recommended every 6 months

5.5 Association of AEs reported and demographic characteristics

The hyperbilirubinaemia and AEs reported by the study patients exposed to ATV-r showed no evidence of statistically significant association with age (p=0.755) and gender (p=0.604).

This meant that the AEs experienced by the study patients were independent of both their gender and the age. The study supported the findings in the MASTERS cohort by Torti et al. (2009) were the cohort study revealed that was no association for developing Grade III of higher hyperbilirubinaemia with either age (p=0.18) and gender (p=0.97)

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Limitations

The study had several limitations and the following were identified

The observational cross sectional design made it difficult to exclude biases. Study evaluated patient medical records, as a result the impact of adverse events on the patients could not be explored. Cormobidities such as HBV or HCV may not have been investigated or let alone documented. Some studies have shown that patients coinfected with HIV and HCV receiving ATVr based cART had greater frequency of bilirubin elevation (Roddriguez-Novoa et al, 2008). Study design also limited the capacity to check for nephroliathias.

The number of patients included in the study was relatively low and thus the power of the findings smaller.

Other laboratory tests conducted at baseline (ALTS, Viral Load, Serum creatinine) were not done at through the 12 weeks of therapy therefore did not study the impact of atazanavir-r on transaminases and creatinie .

Medical notes in the patient clinical records were not well documented and were sometimes illegible therefore, not all the relevant information was collected. Important information such as concomitant medication the patient was taking which was a possible cofounding factor with respect to some of the AEs experienced by the study patients

6.2 Conclusion

The study demonstrates that short term (12 weeks) with ATV-r based regimen is safe. Hyperbilirubinaemia was the most prevalent observed laboratory adverse event 3/49 (6.1%). Diarrhoea (8.4%) and jaundice (4.1%) were the most prevalent reported clinical AEs. The AEs experienced by the patients did not lead to the discontinuation of ATV-r based regimen.

In view of the high prevalence of cART related AEs the information provided by this study is essential for the appropriate management of patients. Various cART treatment regimens have comparable efficacy in managing HIV infection therefore, cost, previous medication history, AEs, drug interactions, pill number and size are factors that may drive

the choice of treatment when patient suffer from comorbidity or from previous treatment induced AEs (Jacques et al, 2001). Clarke et al. (2000) asserts that more than two thirds of patients might have complaints if precisely questioned and that AEs have an effect on adherence and the consequent development of viral resistance which may lead to treatment discontinuation or failure.

A longer study would give a more precise understanding of adverse events that were experienced in this short term therefore, future studies involving long term observation are needed to determine the incidence and the impact of AEs particularly the hyperbilirubinaemia in the Zambia patients receiving ATV-r.

6.3 Recommendations

In view of the findings of this cross sectional study, the following recommendations are made

1. Education of patients and healthcare professionals on cART associated AEs/ADRs. It also important for the healthcare professionals to advise the patients who are about to start ATV about the occurrence of hyperbilirubinaemia and jaundice, and reassure them since it has not been associated with liver damage, is only of cosmetic importance, and might be improved with certain measures.

2. Improvement of laboratory monitoring of safety and efficacy of patients on cART.

3. Strengthening of the post marketIing surveillance and the reporting AEs/ADRs by healthcare professionals.

4. Need for further well designed research to assess the safety and tolerability effects of ATV-r compared with other PIs in the Zambian population

CHAPTER SEVEN: RFEERENCE LIST

7.0: REFERENCE LIST

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CHAPTER SEVEN: APENDICES

APPENDIX A:DATA COLLECTION TOOL

- Gender

Female =1

Male =2

- Age

18-20 =1

21-30 =2

31-4 =3

41 and above =4

- Previous HAART regimen

TDF/FTC/EFZ =1

TDF/FTC/NVP =2

AZT /3TC/NVP =3

AZT/3TC/EFZ =4

ABC/3TC/NVP=5

ABC/3TC/EFZ =6

D4T/3TC/NVP =7

D4T/3TC/EFZ =8

- Duration on previous HAART regimen

less than 1 year =1

1-2 years =2

greater than 2, less than 3 years =3

greater than 3 less, than 4 years =4

greater than 4,less than 5 years =5

greater than 5 years =6

- Symptoms of patients at baseline and whilst on ATV-r base regimen

No Symptoms =1

Nausea =2

Fever =3

Diarrhea =4

Abdominal pain =5

Rash =6

Jaundice =7

Depression =8

Vomiting =9

Headache =10

Insomnia =11

Drowsiness =12

Muscle and Joint aches =13

Malaise =14

- Baseline tests of patients

CD4 –Number- Scale

Viral Load –Number- Scale

Body Weight- Number –Scale

ALT -Number –Scale

Bilirubin- Number- Scale

- Routine tests of patients

ALT -Number –Scale

Bilirubin- Number- Scale

Body Weight -Number –Scale

- Baseline and routine Bilirubin

0-1=1

2-3 =2

4-5 =3

6-7 =4

Above 7=5

APPENDIX B: ATAZANAVIR DRUG PROPERTIES

Pharmacology/ Mechanism of Action	Atazanavir is an azapeptide HIV–1 protease inhibitor. The compound selectively inhibits the virus-specific processing ofviral Gag and Gag-Pol polyproteins in HIV–1 infected cells, thus preventing formation of mature virions.
Activity	Atazanavir exhibits anti-HIV–1 activity with a mean 50% effective concentration (EC50) in the absence of human serum of 2-5 nM against a variety of laboratory and clinical HIV–1 isolates. Atazanavir has additive in vitro antiviral activity with the protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) and NRTIs (didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine) without enhanced cytotoxicity.
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: I50L, I84V#, N88S Minor: L10I/F/V#, G16E#, K20R/M/I, L24I, V32I, L33I/F/V# , M36I/L/V, M46I/L#, G48V, I54L/V/M/T, D60E# , I62V, A71V/I/T/L, G73C/S/T/A, V82A/T, I85V# , L90M, I93L as major & minor mutations accumulate, susceptibility to PIs decreases presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M is present
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSenseTM (http://hivdb.stanford.edu/): I50L: 6-fold _ (intermediate-to-high level resistance) I84V + L90M: 10-fold _ (high level resistance)
Cross-Resistance	Baseline phenotypic and genotypic analyses of clinical isolates from atazanavir clinical trials of protease Inhibitor-experienced subjects indicate: • the I50L and I50V substitutions yield selective resistance to atazanavir and amprenavir, respectively, and do not appear to confer cross-resistance. • other atazanavir-resistant isolates are highly crossresistant (51%-100%) to other protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). • a clear trend toward decreased atazanavir susceptibility as isolates exhibited resistance to multiple protease inhibitors.
Oral Bioavailability	Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir if antacids, buffered medications, H2-receptor antagonists, and proton-pump inhibitors are administrated with atazanavir. Avoid concomitant use (kinetic study showed significantly reduced atazanavir exposure when coadministered with omeprazole; atazanavir absorption did not improve when given either boosted with ritonavir or with 8 oz cola).
Effect of Food	Administration of atazanavir and atazanavir/ritonavir with food enhances bioavailability (35-70% _ AUC) and reduces pharmacokinetic variability by 50%.(Giguere et al. 2010).

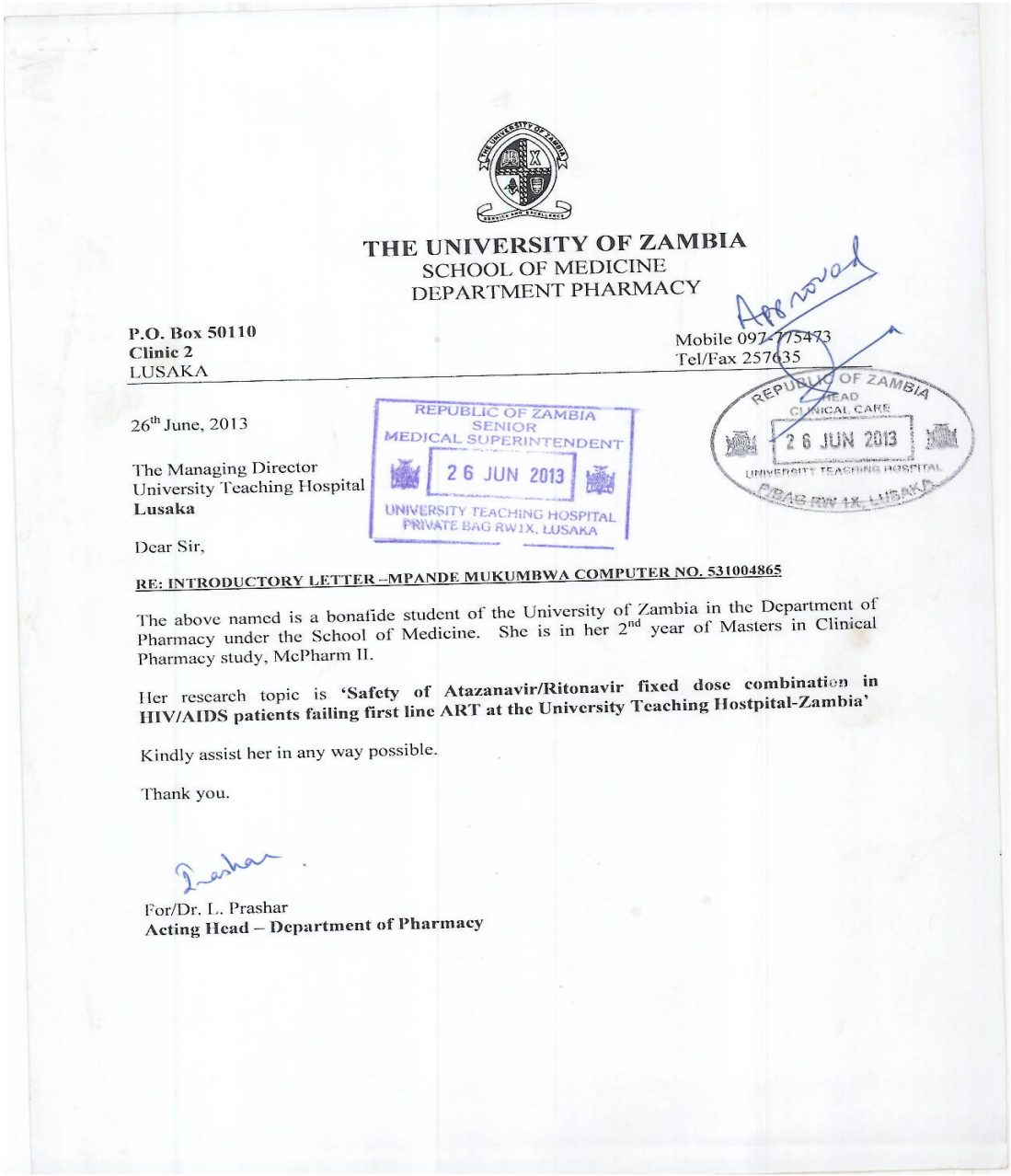
Protein Binding	86%, binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively).
Tmax	2-2.5 hours
serum T 1/2	Approximately 7 hours
Drug Concentrations	Steady-state atazanavir concentrations in HIV-positive subjects after 400 mg QD administration with food: Cmax 3152 ng/mL, Cmin 273 ng/mL, AUC 22262 ng.h/mL Atazanavir plasma concentrations after 300/100 mg ritonavir QD : Cmax 5233 ng/mL, Cmin 862 ng/mL, AUC 53761 ng.h/mL Atazanavir administered in a fixed-dose tablet (300 mg atazanavir/150 mg cobicistat) demonstrated bioequivalence to coadministration of the individual components when given with a light meal in healthy adult subjects.[Tao et al. 2014] 10 HIV positive patients on ATV 400mg daily switched to ATV 200mg BID, atazanavir kinetics assessed at baseline and after 10 days of BID regimen. Atazanavir 200mg BID led to higher plasma Ctrough, lower Cmax and similar AUC compared to standard ATV 400mg daily dose.(Bonora et al. 2008; Gonzalezde Requena, 2010.) Increased bilirubin levels with BID regimen not clinically important. Atazanavir accumulates within the cell to a slightly greater extent versus plasma. Open label, prospective, single center study to investigate kinetics of lower dose ATV/r. 22 Thai HIV infected adult patients suppressed on ATV/r 300mg/100mg daily were changed to 200mg/100mg daily (7 pts were also on TDF). No patients had subtherapeutic levels (<0.15mg/L). (Gorowara M et al. 2008). Results of ATV/r 200/100mg daily in Thai subjects comparable to Caucasian population on standard dose (Burger et al AAC, 2006). In 29 HIV-infected patients receiving atazanavir-based therapy (14 unboosted, 15 boosted), median intracellular atazanavir Ctrough concentrations were higher for boosted vs. unboosted atazanavir, and intracellular concentrations were higher than median plasma Ctrough: In 416 HIV-positive subjects on atazanavir-based regimens, routine atazanavir Ctrough was not significantly different between smokers (n=246) and non-/ex-smokers (n=170) .[Guillemi et al. 2010]. In healthy subjects taking either atazanavir or atazanavir/ritonavir, moderate tobacco use (up to 10 cigarettes per day) was not associated with a significant difference in atazanavir pharmacokinetics.[Blonk et al. 2011] In 18 HIV-infected women on J 6 months of cART (tenofovir, emtricitabine, atazanavir, and ritonovir) with plasma viral loads < 50 copies/mL, blood and cervicovaginal samples were collected twice weekly for three weeks following menses. The ratio of cervicovaginal to plasma drug concentrations (geometric mean) was 11.6 for emtricitabine (CI 8.1-16.6), 3.18 for tenofovir (CI 1.94-5.21), 2.59 for atazanavir (CI 1.81-3.71), and 1.52 for ritonavir (CI 1.04-2.23). HIV-1 RNA was detected in 14 cervicovaginal samples (13.7%, CI 7.7%-24.1%) from 8 (44%)

	women; all virus-positive samples had virus loads < 500 copies/10 mL CVL.[Sheth et al. IAS 2011] Atazanavir total and unbound concentrations were measured in HIV-positive subjects with compensated cirrhosis (n=8, median MELD 11, Child score A, n=7 or B n=1) and HIV-positive subjects without hepatic disease (n=3). In patients with compensated cirrhosis, total and unbound atazanavir concentrations were similar to controls and historical data.[Curran et al. 2013] A case report of a 37 year old HIV/HCV coinfected male (60 kg) who ingested 8700 mg atazanavir without ritonavir; last Ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48 hours post-overdose; values returned to baseline at one-month followup. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012]
Minimum target trough concentrations (for wildtype virus)	Median wild-type EC90 = 14 ng/mL Suggested minimum trough: 150 ng/mL.
CSF (% of serum)	In 4 HIV-positive subjects dosed with atazanavir 400 mg QD for 12 weeks, the cerebrospinal fluid/plasma ratio ranged between 0.0021 and 0.0226. In 26 participants receiving atazanavir 300/ritonavir 100 mg QD, ATV concentrations in the CSF were highly variable, and were 100-fold lower than plasma concentrations. 17 (65%) CSF samples were >11 ng/mL (ATV IC50 for WT) [Best et al. CROI 2006]. 2010 CNS Penetration Effectiveness (CPE) Score: 2 (boosted and unboosted atazanavir) [Letendre S et al. 2010]
Metabolism	Extensively metabolized by CYP3A4. Atazanavir inhibits CYP3A and UGT1A1 at clinically relevant concentrations. Atazanavir is a weak inhibitor of CYP2C8. Caution when unboosted atazanavir is coadministered with drugs that are 2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir. Atazanavir does not inhibit CYP2C19 or CYP2E1 at clinically relevant concentrations.
Excretion	Approximately 7% excreted unchanged in the urine. 47 HIV-positive patients treated with ATV containing regimens were tested to determine if ABCB1 and CYP3A5 polymorphisms are associated with ATV concentrations and/or immunological responses. • ABCB1 haplotype (3435CT-2677GT) was significantly associated with faster ATV oral clearance than 3435CC-2677GG (mean 12.79 VS 7.3L/hr, p=0.018). Trend for O clearance observed in C3435T and G2677T variant carriers

	• Mean CD4 counts were 375 for ABCB1 2677GG and 547 for 2677GT (p=0.036) • No relationships were identified with CYP 3A5 Authors state these pilot data provide rationale for the development of individualized ATV regimens [Ma et al. ICAAC
Adjust in Liver Dysfunction	In adults with moderate to severe hepatic impairment (Child-Pugh B and C), mean atazanavir AUC after a single 400 mg dose was 42% greater than in healthy volunteers, while the mean half-life was 12.1 hours compared to 6.4 hours. The following dosage adjustments are recommended: Child-Pugh Score 7-9: 300 mg QD Child-Pugh score >9: not recommended In a cohort of HIV/HCV coinfected patients on stable atazanavir 400 mg QD, median atazanavir Ctrough was 0.60 ug/mL vs. 0.24 ug/mL in HIV+/HCV- patients, p<0.001. Median atazanavir Ctrough with ATV 300/rtv 100 mg QD was not statistically different between the groups (0.70 vs. 0.73 ug/mL, respectively).[Regazzi et al. 2009]
Adjust in Renal Failure/Dialysis	In an open-label study in HIV-negative participants, steady-state kinetics of atazanavir 400 mg QD were compared between renally impaired (Clcr<30 mL/min) and non-renally impaired (Clcr>80 mL/min) subjects. Compared to controls, atazanavir AUC _ 19% and Cmin _ 96% in the renally impaired group. No dosage adjustment of atazanavir is necessary in renal impairment not managed with hemodialysis.[Agarwala et al. 2007] In subjects on hemodialysis, atazanavir exposures were _ 25-40% compared to non-renally impaired controls; atazanavir exposures were decreased independent of time of administration in relation to dialysis. Atazanavir dialysis clearance was low, with 2.1% of the administered dose eliminated over a 4 hour dialysis period. May wish to consider boosted atazanavir (300 mg/ritonavir 100 mg QD) in hemodialysis patients.[Agarwala et al. 2007] Atazanavir (Reyataz) Monograph: For patients with renal impairment, including those with severe renal impairment who are not managed with hemodialysis, no dose adjustment is required for atazanavir. Treatment-naive patients with end stage renal disease managed with hemodialysis should receive atazanavir 300 mg with ritonavir 100 mg. Atazanavir should not be administered to HIV-treatment experienced patients with end stage renal disease managed with hemodialysis
Toxicity	Skin rash (21%), < 1% severe rash; asymptomatic indirect hyperbilirubinaemia (30%), jaundice (10%), headache, fever, arthralgias, depression, insomnia, dizziness, nausea/vomiting/diarrhea, paresthesias, prolongation of PR interval of EKG. Protease class effects include: hyperlipidemia & hypertriglyceridemia (except atazanavir), hyperglycemia, fat

	maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. Kidney Stones (uncommon) • American Reports: 30 cases ATV associated nephrolithiasis recorded between Dec 2002 to Jan 2007 in the US FDA Adverse Event Reporting System Database (Voluntary reporting) • French Case Series: 11/1134 patients developed ATV nephrolithiasis (Mar 2004 – Feb 2007). 4 pts had history of kidney stones before ATV exposure. Mean onset for ADR ~ 23 months. 1/6 patients that were kept on ATV developed recurrent kidney stones despite instructions to drink more fluids, including acidic beverages such as cola. • Reports suggest kidney stones composed of 60-100% ATV crystals • Exact mechanism for ADR is unknown. • 7% of the ATV dose is excreted unchanged in the urine. Like IDV, the solubility of ATV is increased in acid fluids Risk Factors: not drinking enough fluid, having urine that is not acidic, having a history of kidney stones. A case report of a 37 year old HIV/HCV coinfected male (60 kg) who ingested 8700 mg atazanavir without ritonavir; last ritonavir 100 mg dose was taken ~24 hours prior to overdose. Transient elevation in total bilirubin and Scr and asymptomatic increases in PR and QTc intervals were observed at 24-48 hours postoverdose; values returned to baseline at one-month follow-up. Atazanavir plasma concentrations were 5400 ng/mL and 594 ng/mL at 22 and 62 hours post-overdose.[Toy et al. 2012]
Drug Interactions	Avoid concomitant administration with antacids, proton-pump inhibitors, or H2-blockers, as atazanavir absorption is significantly compromised. Atazanavir is an inhibitor of CYP3A and UGT1A1. Atazanavir is a weak inhibitor of CYP2C8. With boosted atazanavir, ritonavir appears to induce CYP2C8 and offset inhibition by ATV.(Sevinsky et al. 2008)
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease (less with ATV), osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.

APPENDIX C: CLEARANCE LETTER FROM UTH MANAGEMENT



THE UNIVERSITY OF ZAMBIA
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REPUBLIC OF ZAMBIA
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MEDICAL SUPERINTENDENT
26 JUN 2013
UNIVERSITY TEACHING HOSPITAL
PRIVATE BAG RW1X, LUSAKA

REPUBLIC OF ZAMBIA
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CLINICAL CARE
26 JUN 2013
UNIVERSITY TEACHING HOSPITAL
P/BAG RW 1X, LUSAKA

26th June, 2013

The Managing Director
University Teaching Hospital
Lusaka

Dear Sir,

RE: INTRODUCTORY LETTER –MPANDE MUKUMBWA COMPUTER NO. 531004865

The above named is a bonafide student of the University of Zambia in the Department of Pharmacy under the School of Medicine. She is in her 2nd year of Masters in Clinical Pharmacy study, McPharm II.

Her research topic is **'Safety of Atazanavir/Ritonavir fixed dose combination in HIV/AIDS patients failing first line ART at the University Teaching Hostpital-Zambia'**

Kindly assist her in any way possible.

Thank you.

Prashar

For/Dr. L. Prashar
Acting Head – Department of Pharmacy

APPENDIX D:ETHICAL APPROVAL

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
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IRB00001131 of IORG0000774

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

10th December, 2013.

Your Ref: 002-10-13.

Ms. Mpande Mukumbwa,
University Teaching Hospital,
Department of Pharmacy,
P/Bag RW 1X,
Lusaka.

Dear Ms. Mukumbwa,

RE: RE-SUBMITTED RESEARCH PROPOSAL: **"SAFETY OF ATAZANAVIR/RITONAVIR FIXED DOSED COMBINATION IN HIV/AIDS PATIENTS FAILING FIRST LINE TREATMENT AT THE UNIVERSITY TEACHING HOSPITAL IN LUSAKA, ZAMBIA" (REF. No. 002-10-13)**

The above mentioned research proposal was re-submitted to the Biomedical Research Ethics Committee with recommended changes on 21st October, 2013. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

Dr. J.C Munthali
CHAIRPERSON

Date of approval: 10th December, 2013. **Date of expiry:** 9th December, 2014.

APPENDIX E: SPSS EXTRACTS

DEMOGRAPHICS OF STUDY PATIENT

Frequencies

		Gender of patients	Age of patients	The previous HAART regimen of patients	Duration of previous HAART regimens for patients	Symptoms of patients at baseline	Symptoms of patients whilst on ATV-r based regimen	Baseline bilirubin of patients
N	Valid	49	49	49	49	49	49	49
	Missing	0	0	0	0	0	0	0

Frequency Table

Gender of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	29	59.2	59.2	59.2
	Male	20	40.8	40.8	100.0
	Total	49	100.0	100.0	

Age of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	18-20 years	3	6.1	6.1	6.1
	21-30 years	4	8.2	8.2	14.3
	31-40 years	18	36.7	36.7	51.0
	Above 41 years	24	49.0	49.0	100.0
	Total	49	100.0	100.0	

The previous HAART regimen of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	TDF/FTC/EFV	18	36.7	36.7	36.7
	TDF/FTC/NVP	7	14.3	14.3	51.0
	AZT/3TC/NVP	16	32.7	32.7	83.7
	AZT/3TC/EFV	3	6.1	6.1	89.8
	ABC/3TC/NVP	3	6.1	6.1	95.9
	ABC/3TC/EFV	1	2.0	2.0	98.0
	D4T/3TC/NVP	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Duration of previous HAART regimens for patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Less than one year	2	4.1	4.1	4.1
	one to two year	10	20.4	20.4	24.5
	Greater than two but less than three years	1	2.0	2.0	26.5
	Greater than three years but less than four years	10	20.4	20.4	46.9
	Greater than four years but less than five years	14	28.6	28.6	75.5
	Greater than five years	12	24.5	24.5	100.0
	Total	49	100.0	100.0	

Symptoms of patients at baseline

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No symptoms	28	57.1	57.1	57.1
	Muscle and joint aches	2	4.1	4.1	61.2
	Malaise	2	4.1	4.1	65.3
	Nausea	1	2.0	2.0	67.3
	Fever	1	2.0	2.0	69.4
	Diarrhoea	7	14.3	14.3	83.7
	Abdominal pains	5	10.2	10.2	93.9
	Rash	2	4.1	4.1	98.0
	Vomiting	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Symptoms of patients whilst on ATV-r based regimen

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No symptoms	40	81.6	81.6	81.6
	Headache	1	2.0	2.0	83.7
	Muscle and joint aches	1	2.0	2.0	85.7
	Diarrhoea	4	8.2	8.2	93.9
	Rash	1	2.0	2.0	95.9
	Jaundice	2	4.1	4.1	100.0
	Total	49	100.0	100.0	

Baseline bilirubin of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0-1	13	26.5	26.5	26.5
	2-3	30	61.2	61.2	87.8
	4-5	6	12.2	12.2	100.0

Baseline bilirubin of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0-1	13	26.5	26.5	26.5
	2-3	30	61.2	61.2	87.8
	4-5	6	12.2	12.2	100.0
	Total	49	100.0	100.0	

Routine bilirubin of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		1	2.0	2.0	2.0
	0-1	4	8.2	8.2	10.2
	2-3	39	79.6	79.6	89.8
	4-5	5	10.2	10.2	100.0
	Total	49	100.0	100.0	

PATIENT SYMPTOMS

		Baseline CD4 count of patients	Baseline viral load of patients	Baseline bilirubin of patients	Baseline body weight of patients	Routine bilirubin of patients
N	Valid	49	49	49	49	48
	Missing	0	0	0	0	1
Mean		260.39	337378.04	3.097	63.573	4.123
Median		212.00	32155.00	2.800	62.000	3.500
Mode		43[a]	40	1.0[a]	50.0[a]	3.0[a]
Std. Deviation		198.957	1215376.473	1.6719	13.0999	3.4409
Variance		39584.076	1.477E12	2.795	171.607	11.840
Range		956	6860760	6.8	61.5	19.0
Percentiles	25	69.00	6035.00	1.850	54.700	2.250
	50	212.00	32155.00	2.800	62.000	3.500
	75	401.50	89198.00	4.000	72.100	4.300

		Baseline CD4 count of patients	Baseline viral load of patients	Baseline bilirubin of patients	Baseline body weight of patients	Routine bilirubin of patients
N	Valid	49	49	49	49	48
	Missing	0	0	0	0	1
Mean		260.39	337378.04	3.097	63.573	4.123
Median		212.00	32155.00	2.800	62.000	3.500
Mode		43[a]	40	1.0[a]	50.0[a]	3.0[a]
Std. Deviation		198.957	1215376.473	1.6719	13.0999	3.4409
Variance		39584.076	1.477E12	2.795	171.607	11.840
Range		956	6860760	6.8	61.5	19.0
Percentiles	25	69.00	6035.00	1.850	54.700	2.250
	50	212.00	32155.00	2.800	62.000	3.500
	75	401.50	89198.00	4.000	72.100	4.300

a. Multiple modes exist. The smallest value is shown

Frequency Table

Baseline CD4 count of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	2.0	2.0	2.0
	31	1	2.0	2.0	4.1
	37	1	2.0	2.0	6.1
	43	2	4.1	4.1	10.2
	52	1	2.0	2.0	12.2
	53	1	2.0	2.0	14.3
	54	1	2.0	2.0	16.3
	60	2	4.1	4.1	20.4

61	1	2.0	2.0	22.4
69	2	4.1	4.1	26.5
74	1	2.0	2.0	28.6
110	1	2.0	2.0	30.6
126	1	2.0	2.0	32.7
152	1	2.0	2.0	34.7
164	1	2.0	2.0	36.7
180	1	2.0	2.0	38.8
182	1	2.0	2.0	40.8
183	1	2.0	2.0	42.9
188	1	2.0	2.0	44.9
210	2	4.1	4.1	49.0
212	1	2.0	2.0	51.0
225	1	2.0	2.0	53.1
259	1	2.0	2.0	55.1
280	1	2.0	2.0	57.1
287	1	2.0	2.0	59.2
298	1	2.0	2.0	61.2
312	1	2.0	2.0	63.3
319	1	2.0	2.0	65.3
335	1	2.0	2.0	67.3
337	1	2.0	2.0	69.4
340	1	2.0	2.0	71.4
373	1	2.0	2.0	73.5
379	1	2.0	2.0	75.5
424	1	2.0	2.0	77.6
429	1	2.0	2.0	79.6
432	1	2.0	2.0	81.6
440	1	2.0	2.0	83.7
465	1	2.0	2.0	85.7
474	1	2.0	2.0	87.8
481	1	2.0	2.0	89.8
547	1	2.0	2.0	91.8

	557	1	2.0	2.0	93.9
	564	1	2.0	2.0	95.9
	623	1	2.0	2.0	98.0
	956	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Baseline viral load of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	40	4	8.2	8.2	8.2
	45	1	2.0	2.0	10.2
	50	1	2.0	2.0	12.2
	2670	1	2.0	2.0	14.3
	3600	1	2.0	2.0	16.3
	4709	1	2.0	2.0	18.4
	5200	1	2.0	2.0	20.4
	5654	1	2.0	2.0	22.4
	5670	1	2.0	2.0	24.5
	6400	1	2.0	2.0	26.5
	6480	1	2.0	2.0	28.6
	8861	1	2.0	2.0	30.6
	11309	1	2.0	2.0	32.7
	12376	1	2.0	2.0	34.7
	14800	1	2.0	2.0	36.7
	19784	2	4.1	4.1	40.8
	20095	1	2.0	2.0	42.9
	21300	1	2.0	2.0	44.9
	23780	1	2.0	2.0	46.9
	27790	1	2.0	2.0	49.0
	32155	1	2.0	2.0	51.0
	34987	1	2.0	2.0	53.1
	35200	1	2.0	2.0	55.1

	41436	1	2.0	2.0	57.1
	41821	1	2.0	2.0	59.2
	43220	1	2.0	2.0	61.2
	45000	1	2.0	2.0	63.3
	64390	1	2.0	2.0	65.3
	65200	1	2.0	2.0	67.3
	68484	1	2.0	2.0	69.4
	84760	1	2.0	2.0	71.4
	86239	1	2.0	2.0	73.5
	88631	1	2.0	2.0	75.5
	89765	1	2.0	2.0	77.6
	94301	1	2.0	2.0	79.6
	95200	1	2.0	2.0	81.6
	104200	1	2.0	2.0	83.7
	253780	1	2.0	2.0	85.7
	380653	1	2.0	2.0	87.8
	402350	1	2.0	2.0	89.8
	476890	1	2.0	2.0	91.8
	670420	1	2.0	2.0	93.9
	912670	1	2.0	2.0	95.9
	5238455	1	2.0	2.0	98.0
	6860800	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Baseline bilirubin of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	6	12.2	12.2	12.2
	1.3	2	4.1	4.1	16.3
	1.5	1	2.0	2.0	18.4
	1.6	1	2.0	2.0	20.4
	1.7	1	2.0	2.0	22.4

	1.8	1	2.0	2.0	24.5
	1.9	1	2.0	2.0	26.5
	2	6	12.2	12.2	38.8
	2.2	1	2.0	2.0	40.8
	2.6	2	4.1	4.1	44.9
	2.7	1	2.0	2.0	46.9
	2.76	1	2.0	2.0	49.0
	2.8	1	2.0	2.0	51.0
	3	4	8.2	8.2	59.2
	3.2	1	2.0	2.0	61.2
	3.3	1	2.0	2.0	63.3
	3.4	1	2.0	2.0	65.3
	3.6	1	2.0	2.0	67.3
	4	5	10.2	10.2	77.6
	4.2	1	2.0	2.0	79.6
	4.8	1	2.0	2.0	81.6
	5	3	6.1	6.1	87.8
	5.3	1	2.0	2.0	89.8
	6	2	4.1	4.1	93.9
	6.1	1	2.0	2.0	95.9
	6.3	1	2.0	2.0	98.0
	7.8	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Baseline body weight of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	33.5	1	2.0	2.0	2.0
	41.5	1	2.0	2.0	4.1
	44	1	2.0	2.0	6.1
	45	1	2.0	2.0	8.2
	48.9	1	2.0	2.0	10.2

50	2	4.1	4.1	14.3
51	1	2.0	2.0	16.3
52	1	2.0	2.0	18.4
53	1	2.0	2.0	20.4
53.5	1	2.0	2.0	22.4
54.4	1	2.0	2.0	24.5
55	1	2.0	2.0	26.5
55.8	1	2.0	2.0	28.6
56	1	2.0	2.0	30.6
56.3	1	2.0	2.0	32.7
56.4	1	2.0	2.0	34.7
57	2	4.1	4.1	38.8
58	1	2.0	2.0	40.8
60	1	2.0	2.0	42.9
60.9	1	2.0	2.0	44.9
61	1	2.0	2.0	46.9
61.6	1	2.0	2.0	49.0
62	1	2.0	2.0	51.0
63	2	4.1	4.1	55.1
63.4	1	2.0	2.0	57.1
66	1	2.0	2.0	59.2
66.6	1	2.0	2.0	61.2
67.4	1	2.0	2.0	63.3
68	1	2.0	2.0	65.3
68.3	1	2.0	2.0	67.3
70	1	2.0	2.0	69.4
71	1	2.0	2.0	71.4
71.1	1	2.0	2.0	73.5
71.4	1	2.0	2.0	75.5
72.8	1	2.0	2.0	77.6
73	1	2.0	2.0	79.6
75	1	2.0	2.0	81.6
76	1	2.0	2.0	83.7

	77	1	2.0	2.0	85.7
	78	1	2.0	2.0	87.8
	82	2	4.1	4.1	91.8
	84	1	2.0	2.0	93.9
	85.3	1	2.0	2.0	95.9
	92	1	2.0	2.0	98.0
	95	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Baseline ALT of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	7.9	1	2.0	2.0	2.0
	8.9	1	2.0	2.0	4.1
	9	1	2.0	2.0	6.1
	10.3	2	4.1	4.1	10.2
	11.2	1	2.0	2.0	12.2
	11.8	1	2.0	2.0	14.3
	12	1	2.0	2.0	16.3
	12.5	1	2.0	2.0	18.4
	13	2	4.1	4.1	22.4
	13.6	1	2.0	2.0	24.5
	14	2	4.1	4.1	28.6
	15	2	4.1	4.1	32.7
	16	3	6.1	6.1	38.8
	17	1	2.0	2.0	40.8
	18	2	4.1	4.1	44.9
	19	2	4.1	4.1	49.0
	19.2	1	2.0	2.0	51.0
	20	1	2.0	2.0	53.1
	21.7	1	2.0	2.0	55.1
	22.9	1	2.0	2.0	57.1

	23	2	4.1	4.1	61.2
	23.4	1	2.0	2.0	63.3
	24	1	2.0	2.0	65.3
	24.8	2	4.1	4.1	69.4
	25	1	2.0	2.0	71.4
	26	3	6.1	6.1	77.6
	28	1	2.0	2.0	79.6
	28.2	1	2.0	2.0	81.6
	30	1	2.0	2.0	83.7
	31	3	6.1	6.1	89.8
	33	1	2.0	2.0	91.8
	34	1	2.0	2.0	93.9
	34.2	1	2.0	2.0	95.9
	55	1	2.0	2.0	98.0
	65	1	2.0	2.0	100.0
	Total	49	100.0	100.0	

Routine body weight of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	36	1	2.0	2.0	2.0
	40	1	2.0	2.0	4.1
	44.5	1	2.0	2.0	6.1
	52	1	2.0	2.0	8.2
	52.2	1	2.0	2.0	10.2
	53	1	2.0	2.0	12.2
	53.7	1	2.0	2.0	14.3
	54	1	2.0	2.0	16.3
	54.2	1	2.0	2.0	18.4
	55	2	4.1	4.1	22.4

55.5	1	2.0	2.0	24.5
57	1	2.0	2.0	26.5
58.3	1	2.0	2.0	28.6
59	1	2.0	2.0	30.6
60	1	2.0	2.0	32.7
61	3	6.1	6.1	38.8
62	1	2.0	2.0	40.8
63	1	2.0	2.0	42.9
65	2	4.1	4.1	46.9
66	1	2.0	2.0	49.0
67	3	6.1	6.1	55.1
68	1	2.0	2.0	57.1
70	2	4.1	4.1	61.2
71	2	4.1	4.1	65.3
72	1	2.0	2.0	67.3
73	2	4.1	4.1	71.4
73.7	1	2.0	2.0	73.5
75	4	8.2	8.2	81.6
77	1	2.0	2.0	83.7
78	1	2.0	2.0	85.7
80	1	2.0	2.0	87.8
83.2	1	2.0	2.0	89.8
85	1	2.0	2.0	91.8
86	1	2.0	2.0	93.9
90	1	2.0	2.0	95.9
90.6	1	2.0	2.0	98.0
94.3	1	2.0	2.0	100.0
Total	49	100.0	100.0	

Routine ALT of patients

	Frequency	Percent	Valid Percent	Cumulative Percent

Valid	19.1	1	2.0	33.3	33.3
	30	1	2.0	33.3	66.7
	65	1	2.0	33.3	100.0
	Total	3	6.1	100.0	
Missing	System	46	93.9		
Total		49	100.0		

Routine bilirubin of patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	4	8.2	8.3	8.3
	2	8	16.3	16.7	25.0
	3	12	24.5	25.0	50.0
	4	12	24.5	25.0	75.0
	4.4	1	2.0	2.1	77.1
	4.8	1	2.0	2.1	79.2
	5	5	10.2	10.4	89.6
	5.6	1	2.0	2.1	91.7
	6	1	2.0	2.1	93.8
	12.2	1	2.0	2.1	95.8
	15.9	1	2.0	2.1	97.9
	20	1	2.0	2.1	100.0
	Total	48	98.0	100.0	
Missing	System	1	2.0		
Total		49	100.0		

ASSOCIATIONS OF AES AND DEMOGRAPHIC CHARACTERISTICS

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent

Age of patients * Symptoms of patients at baseline	49	100.0%	0	.0%	49	100.0%
Age of patients * Symptoms of patients whilst on ATV-r based regimen	49	100.0%	0	.0%	49	100.0%

Age of patients * Symptoms of patients at baseline

Count									
		Symptoms of patients at baseline							
		No symptoms	Muscle and joint aches	Malaise	Nausea	Fever	Diarrhoea	Abdominal pains	Vomiting
Age of patients	18 - 20 years	1	0	0	0	0	1	1	0
	21 - 30 years	3	0	0	0	0	1	0	0

	31 - 40 years	11	0	2	1	0	1	1	1
	Above 41 years	13	2	0	0	1	4	3	0
Total		28	2	2	1	1	7	5	1

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	15.628[a]	24	.901
Likelihood Ratio	18.119	24	.797
N of Valid Cases	49		

a. 34 cells (94.4%) have expected count less than 5. The minimum expected count is .06.

Symmetric Measures[a]

	Value
N of Valid Cases	49

a. Correlation statistics are available for numeric data only.

Age of patients * Symptoms of patients whilst on ATV-r based regimen

Crosstab

Count								

		Symptoms of patients whilst on ATV-r based regimen						
		No symptoms	Headache	Muscle and joint aches	Diarrhoea	Rash	Jaundice	Total
Age of patients	18-20 years	1	0	0	1	0	1	3
	21-30 years	3	0	0	1	0	0	4
	31-40 years	17	0	0	0	0	1	18
	Above 41 years	19	1	1	2	1	0	24
Total		40	1	1	4	1	2	49

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	17.099[a]	15	.313
Likelihood Ratio	15.725	15	.401
N of Valid Cases	49		

a. 22 cells (91.7%) have expected count less than 5. The minimum expected count is .06.

Symmetric Measures[a]

	Value
N of Valid Cases	49

a. Correlation statistics are available for numeric data only.

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Gender of patients * Baseline bilirubin of patients	49	100.0%	0	.0%	49	100.0%

Symmetric Measures[a]

	Value						
N of Valid Cases	49						
Gender of patients * Routine bilirubin of patients		49	100.0%	0	.0%	49	100.0%

Gender of patients * Baseline bilirubin of patients

Crosstab

Count					
		Baseline bilirubin of patients			
		0-1	2-3	4-5	Total
Gender of patients	Female	9	18	2	29
	Male	4	12	4	20
Total		13	30	6	49

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.211[a]	2	.331
Likelihood Ratio	2.199	2	.333
N of Valid Cases	49		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.45.

Symmetric Measures[a]

	Value
N of Valid Cases	49

a. Correlation statistics are available for numeric data only.

Gender of patients * Routine bilirubin of patients

Crosstab

Count						
		Routine bilirubin of patients				
			0-1	2-3	4-5	Total
Gender of patients	Female	1	2	22	4	29
	Male	0	2	17	1	20

Crosstab

Count						
		Routine bilirubin of patients				
			0-1	2-3	4-5	Total
Gender of patients	Female	1	2	22	4	29
	Male	0	2	17	1	20
Total		1	4	39	5	49

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.850[a]	3	.604
Likelihood Ratio	2.294	3	.514
N of Valid Cases	49		

a. 6 cells (75.0%) have expected count less than 5. The minimum expected count is .41.

Symmetric Measures[a]

	Value
N of Valid Cases	49

a. Correlation statistics are available for numeric data only.