RETROSPECTIVE OUTCOMES AND COST ANALYSIS OF ANTIMALARIAL TREATMENT IN HIV-INFECTED PATIENTS IN A TERTIARY HOSPITAL SETTING IN SOWETO, SOUTH AFRICA

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Dissertation submitted in fulfilment of the requirements for the degree of Masters in Science (Medicine) in the Department of Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg

November 2017

DECLARATION

I, Murtala MD, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree within or at any other University.

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November 2017

DEDICATION

To my family and friends

ACKNOWLEDGEMENTS

I am grateful to my supervisors Personal Professor Robyn van Zyl, Dr Jacqui Miot, Associate Professor Colin Menezes and Adjunct Professor Alan Karstaedt.

I express my gratitude to the Faculty of Health Science Research Office for the research funding given to me. I remain thankful to the Federal University Birnin-Kebbi for the sponsorship offered to me.

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ABSTRACT

Malaria is the most lethal parasitic infection globally, with a high mortality rate in sub-Saharan Africa. Imported malaria continues to cause life-threatening illness among non-immune residents of Gauteng with an increased risk of mortality. This study followed the trends of antimalarial treatment and outcomes and performed a costs analysis among HIV-infected patients with malaria at Chris Hani Baragwanath Academic Hospital (CHBAH).

A retrospective record review was carried out of adults hospitalised with malaria at CHBAH over a 5 year period (2011-2015). Male and female patients aged 18 years and older, with or without HIV-infection were included. Pregnant women were excluded. Data collection included demographic profiles and laboratory investigations, concurrent comorbidities, as well as non-communicable comorbidities. Costing of patient's treatment and hospitalisation were recorded. Drug utilisation pathways of patients with complicated and uncomplicated malaria were compared with the South African National Guideline for Malaria Treatment.

The majority of the patient cohort (n=977) consisted of males (68%), an average age of 33 years, with most of the imported malaria cases from Mozambique (74%).The prevalence of uncomplicated malaria (69.8%) was higher than complicated malaria (30.2%), with 6.9% presenting with cerebral malaria. Quinine and doxycycline were the most frequently used antimalarial drugs with intravenous quinine administered to 9% of patients and orally to 50%. Artesunate was administered to only 13.6% of the complicated cases due to restrictive access to the medication. Of the study population, 36% were HIV-positive with the d4T+3TC+EFV regimen most frequently used. Both malaria and HIV treatment was administered in accordance with current South African Guidelines. There was a threefold difference between the number of HIV-positive patients (64.7%; 61.2%) and HIV-negative patients (35.3%; 38.8%) presenting with complicated (n=295) and cerebral (n=67) malaria. The mortality rate over the study period was 3.7%, of which 63.9% were HIV-positive patients. Acute respiratory distress was the most common clinical feature associated with death, while acute renal failure the most common laboratory complication associated with death. Low $CD4^+$ T-cell count, low platelets and low haemoglobin were some of the factors associated with an increased risk of complicated malaria; however following administration of the antimalarial agents these parameters were elevated towards normal levels. The cost of treatment was significantly higher among complicated malaria patients than uncomplicated, with the cost increasing in the HIV-positive patients with increasing immunosuppression (difference of R9700 between HIV-negative and HIV-positive malaria-infected patients). The main comorbidities were hypertension and diabetes mellitus.

As expected, the cost of managing complicated cases in HIV-positive patients was higher than uncomplicated cases, with the additional drugs for co-infections, co-morbidities and ICU admittance contributing to the extra cost. This emphasised the necessity for early diagnosis and treatment of malaria infections in HIV-negative and especially in HIV-positive patients that would reduce disease progression, outcome, and treatment cost. The current South African guidelines for the treatment of uncomplicated and complicated malaria are still highly efficacious when timeously administered; as such, these guidelines should be reinforced with all health care professionals to ensure continued efficacy of the current antimalarial agents.

ABBREVIATIONS

AKI…… Acute Kidney Injury

ALT…… Alanine Transaminase

AMFm…… Affordable Medicine Facility-malaria

AST…… Aspartate Transaminase

ARV…… Antiretroviral

ART…… Antiretroviral Therapy

ACTs…….. Artemisinin Combination Therapy

AZT…… Zidovudine

AIDS……..... Acquired Immune Deficiency Syndrome

ARDS…… Acute Respiratory Distress Syndrome

CDC…….. Centres For Disease Control

CHBAH…… Chris Hani Baragwanath Academic Hospital

DDT…….. Dichlorodiphenyltrichloroethane

DIC…… Disseminated Intravascular Coagulation

d4T…… Stavudine

DVT…… Deep Venous Thrombosis

ECG…… Electrocardiogram

EFV…… Efavirenz

E/U/Cr…… Electrolyte, Urea and Creatinine

FTC…… Emtricitabine

GCS…… Glasgow Coma Scale

HAART…….. Highly Active AntiRetroviral

Hb……Haemoglobin

HIV…… Human Immunodeficiency Virus

ICU……..Intensive Care Unit

IFN α…….. Interferon α

IL……. Interleukin

ITNs…….. Insecticide Treated Nets

IRS……. Indoor Residual Spraying

LFT……. Liver Function Test

LSDI ……..... Lubombo Spatial Development Initiative”

MI…… Myocardial Infarction

NHLS……. National Health Laboratory Services

NRTI……. Nucleoside Reverse Transcriptase Inhibitor

NNRTI…….. Non-nucleoside Reverse Transcriptase Inhibitor

PLT…… Platelet

RBS……Random Blood Sugar

RDTs…… Rapid Diagnostic Tests

SA…… South Africa

SAMA……. Signed Against Medical Advice

SADOH…… South African Department of Health

TDF…… Tenofovir

TNF……. Tumour Necrosis Factor

USD……. United States Dollar

UTI……... Urinary Tract Infection

WBC…….. White Blood Cell Count

WHO…… World Health Organisation

ZAR…….. South African Rand

Chapter One: Introduction

1.1 Malaria epidemiology

The number of malaria endemic countries reduced from 208 in 2000 to 91 countries in 2016, but a total of 15 African countries still contribute to 80% of worlds' malaria cases (WHO, 2016a). According to the World Health Organisation (WHO) malaria report, 212 million new malaria cases occurred globally in the year 2016, and the illness led to 429,000 deaths globally. The African region constituted 92% of all the malaria death cases, with children below 5 years of age accounting for 71% of the deaths in Africa, and 65% globally (WHO, 2016a). Many programs and initiatives as well as funding are aimed at malaria control; such initiatives include Roll Back Malaria, Medicine for Malaria Venture, World Bank Booster Program and Multilateral Initiative on Malaria, with the primary aim of reducing the burden of the disease (WHO, 2016b).

Malaria is endemic in most Africa countries, where it has become the number one cause of morbidity and mortality especially among pregnant mothers, people living with HIV, children less than 5 years of age and the poor (Ndong *et al*., 2014). In South Africa, transmission of malaria has seasonal variation and is epidemic. Unstable malaria is experienced in Southern Africa below a latitude of 20° S in an area comprising of Botswana, Southern Mozambique, Namibia, South Africa and Swaziland (Moonasar *et al*., 2016). The southern-most limit of malaria transmission extends to a portion of KwaZulu-Natal, with Gauteng considered a malaria-free region. The Limpopo, Mpumalanga and KwaZulu-Natal provinces of South Africa experience malaria transmission seasonally in the warm summer rainfall months, peaking from November to April (Moonasar *et al*., 2016). In 2017, following heavy rainfall experienced in some parts of Botswana, the authorities reported an outbreak and an increase in the number of malaria cases. Similarly, the Limpopo Health Department also issued a malaria warning particularly around Thabazimbi and Lephalale reporting on 46 cases (News24; 2017)

Imported malaria is now considered an increasing and significant problem in non-endemic industrialised countries. Presently malaria is endemic in 91 nations globally, which are visited by a considerable number of people and it is the main cause of fever among returning travellers reported to have contracted the disease before returning home (WHO, 2016a ; Kurth *et al*., 2017). In Gauteng, most cases of malaria occur in returning travellers. However, an average of 100 cases of Odyssean malaria was presumed to have been due to imported mosquitoes from

malarial areas transported into the province through many avenues, including suitcases, mini-buses and airplanes (Marks *et al*., 2014a; Weber *et al*., 2010). A study conducted in the Gauteng showed a considerable delay in presentation and diagnosis of Odyssean malaria cases, which resulted in a higher mortality rate (Frean *et al.*, 2014).

1.2 Malaria life cycle - *Anopheles* mosquito host

Malaria is a protozoan parasite of the genus *Plasmodium* infecting the human host following a blood meal from a feeding female *Anopheles* mosquito. Mosquitos belong to the phylum of *Arthropoda* and class of *Insecta,* order *Diptera.* The life cycle of the *Anopheles* mosquito has four distinct stages: the egg, lava, pupa, and adult (CDC, 2015). The various stages of the parasite growth and development are largely dependent on the temperature and nutritional source of food to the parasite with rapid growth under a very warm temperature (WHO, 2013). Approximately 60-70 of the 490 *Anopheles* species found worldwide can transmit malaria and of these, about 30 vectors are regarded as the most important parasitologically (Gillies & Coetzee, 1987). Some *Anopheles* bite and draw animal's blood and rarely transmit the malaria parasite to humans.

The feeding and resting pattern of mosquitoes are of great importance in vector control programs (Russell *et al.*, 2016). Most adult *Anopheles* mosquitoes bite and draw blood during the night-time, with some biting shortly after sunset, while others bite around midnight or the early morning (Van Zyl, 2016). Enophagic mosquitoes enter houses to bite and usually rest on the walls, under tables, chairs, bed or on hanging cloth (Ogama, 2010). While exophagic mosquitoes bite mostly outside houses usually rest on plants, inside holes, in trees, on the ground or in other cool dark places (Van Zyl, 2016). Some mosquitoes prefer drawing blood from humans rather than animals and these anthropophagic vectors are the most dangerous as they are able to transmit infections into the human population (Massebo *et al*., 2015).

1.2.1 Vector control

The control achieved by the South African National Malaria Control Guideline s is amongst the best in the sub-region with South Africa having a prosperous economy and good health infrastructure compared to their counterparts in the region. The threat of malaria in South Africa has been known since the early settlers in the 1800's (Blumberg and Frean, 2002). During the 1930's the indoor spraying of houses with pyrethrum was introduced and the control program covered a significant number of houses. A greater success in control was noticed after the

provision of dichlorodiphenyltrichloroethane (DDT) and new long-lasting insecticides from 1945 that later substituted pyrethrum. This resulted in an interruption of malaria transmission with the disease limited only to parts of the north-eastern region of the country, with the *Anopheles funestus* vector being totally eradicated (Blumberg and Frean, 2002). Following this, malaria transmission control was then greatly expanded during the 1960's to further reduce the number of cases of malaria transmission. Indoor residual spraying (IRS) methods with pyrethrum together with DDT were the two main chemical agents used in eliminating malaria globally in the early 1940s and late 1960s (Mabaso *et al*., 2004). In Southern Africa, IRS has been and will always be the focus of malaria control with over 13 million people currently protected by IRS in the region (WHO, 2015). Nowadays, protection with Insecticide Treated Nets (ITNs) and indoor residual spraying are commonly used methods of malaria control. Previous trial studies indicated that ITNs can reduce the frequency of complicated disease by 45% and 17% among children under the age of five (Wang *et al*., 2016). However, when both methods are used together by households they substantially cut down the level of transmission The recent reduction in the number of malaria cases in Africa may be as a result of the massive deployment of ITNs and IRS through various international organisation programs like Roll Back Malaria and the Global Malaria Action Plan introduced by the WHO, which advocate the use of IRS and ITN, which has helped in reducing malaria infections compared to when used as single entity (Hamainza *et al*., 2016). About 730 million long lasting insecticide treated nets were forecast to be distributed worldwide by 2016, through various WHO programmes, with the African sub-region expected to have the largest distribution.. In addition, the household possession of the ITNs was forecast to reach 53% by 2011, with 11% of the 'at risk population' expected to be protected by IRS in Africa (Gimnig *et al*., 2016).

1.2.2 Vector control programmes

Mozambique consistently contributes the highest number of imported cases in South Africa (Weber *et al*., 2010). An estimated 4.3 million people or 10% of the people living in endemic regions are prone to malaria infection (Blumberg and Frean, 2002; Moonasar *et al*., 2012). To address this a malaria control program was advocated as a main component of the Lubombo Spatial Development Initiative (LSDI), aimed at increasing the quality of malaria control in the highest risk malaria regions of these 3 nations (South Africa, Swaziland and Mozambique), with primary emphasis placed on extending malaria control into Southern Mozambique (Maharaja *et al*., 2016). Over the last 10 years South Africa has dramatically reduced the number of notified malaria cases, which has been attributed to a multi-disciplinary approach to

control malaria through IRS, disease treatment and rapid response to epidemics, public awareness and disease monitoring, as well as the introduction of artemisinin therapy (Hlongwana & Tsoka-Gwegweni, 2016).. Malaria was one of the important targets included in Goal 6 of the Millennium Development Goals which was to stop and reverse the disease by the year 2015 (Moonasar *et al*., 2012). South Africa has achieved and exceeded the malaria target of the Millennium Development Goals and has currently targeted malaria elimination by the year 2018. With a 50% reduction in malaria admission rate in the last 15 years and a 75% reduction in mortality rates - this goal may be achievable (WHO, 2015). New global targets for 2030 have been reported as part of the Sustainable Development Goals, where Goal 3.8 includes the eradication of 80% of deaths from malaria (UN, 2015). Global targets also aim to eliminate worldwide malaria incidences from countries where malaria is transmitted, and prevention of re-establishment of malaria in malaria-free countries (World Malaria Report, 2016).

1.2.3 Insecticide resistance

There is limited data with regards to insecticide resistance in the Southern African sub-region, except for South African, Zimbabwe and Namibia. Carbamates and pyrethroid resistance have been reported in Zimbabwe since the year 2010, but the vectors still remain sensitive to organophosphates in both Zimbabwe and Botswana (WHO, 2016). Pyrethroids are the preferred insecticides worldwide for vector control, with 81% sensitivity (Paine and Brooke, 2016). Four classes of insecticides that have public health importance include pyrethroids, organochlorines, organophosphate and carbamates, with resistance in *Anopheles* having been reported to all of them. Resistance is further potentiated by the massive deployment programmes of long lasting insecticide nets, which are dependent on pyrethroids that have been reported to further resistance to these insecticides; along with the use of sub-lethal spray doses of insecticides (Mnzava *et al*., 2015). During the 1996-2000 malaria outbreaks in South Africa, authorities placed the blame on the relative resistance to pyrethroids; whereas prior to this episode, malaria control was solely dependent on DDT, to which resistance has subsequently been reported (WHO, 2015; Brooke *et al*., 2015). In 1995, South Africa was forced to stop the use of DDT for IRS and replaced it with pyrethroids due to pressure to reduce the use of DDT. But soon a rise in the number of malaria cases was reported due to cross-border migration from neighbouring Mozambique. This increase in number of malaria cases was later attributed to pyrethroid-resistant *Anopheles funestus*. As a result, DDT was re-introduced for IRS in South Africa after the year 2000, resulting in a considerable reduction in malaria incidence with as few as 10,000 cases per year (Coetzee *et al*., 2013). Surveillance data has shown pyrethroid

resistance in at least one vector species in 53 of the 65 countries. The sudden increase in the use of organophosphates and carbamates as insecticides of choice for IRS due to pyrethroid resistance has resulted in the reported resistance to carbamates in Burkina Faso (Kleinschmidt *et al*., 2015; Edi *et al*., 2014).

Only a limited number of insecticides are available today, so while it has been reported that vector control significantly reduces disease prevalence, the impact of disease control on resistance is still not clear (Paine and Brooke, 2016). Two mechanisms of resistance have been proposed: alteration of insecticide target receptors and increased metabolism of insecticides, coupled with a lower concentration of insecticide penetrating through the thick covering of the parasite's body structure (Toé *et al*., 2015). A mutational change in the membrane sodium channel has been linked with DDT resistance, and less commonly to pyrethroids. This L1014S knock down mutation (*kdr*) has been found among *Anopheles gambiae* species in Kenya (Coetzee *et al.*, 2013; Brooke and Koekemoer, 2010).

With increasing resistance to the few available insecticides used against the malaria vector, there is a need to explore other alternative methods of vector control in South Africa. In view of the global resistance to these chemicals and even though resistance to most of them is not yet confirmed in southern Africa, their appearance could be imminent and compromise the effective vector control currently in place (Bhatt *et al*., 2015).

1.3. Malaria life cycle - Human host

The female *Anopheles* is known for its ability to feed on human blood, during which sporozoites are injected into the blood stream of the susceptible person (Figure 1.1). The four human *Plasmodium species* are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae* (WHO, 2006). However, humans occasionally become infected with *Plasmodium* species that normally infect animals, such as *P. knowlesi.* These *Plasmodium* sporozoites quickly disappear and infect the liver cells (asexual stage). The hepatic sporozoites pass through multiple asexual divisions resulting in merozoites that subsequently infect the red blood cells (SADOH, 2011; CDC, 2016).

In the *P. vivax* and *P. ovale* malaria transmission, the cycle is a little different, where a latent or exo-erythrocytic schizogony stage exists with the hypnozoites remaining dormant in the hepatic cells before replicating to produce merozoites, The resumption of the hepatic development is not fully understood, and may take months or even years after the primary

infection (Soulard *et al.*, 2015). Merozoites invade the red blood cells and undergo a second asexual multiplication, and as such multiple (16-32) new merozoites are produced in each red blood cell and the merozoites develop into the ring form (erythrocytic schizogony). The latter develop into trophozoites and then schizonts, which in turn produce more merozoites which invade erythrocytes (Figure 1.1). The cycle continues and the clinical manifestations such as fever, headache and anaemia appear (Section 1.3.1) (WHO, 2015). Some asexual parasites differentiate into sexual erythrocytic stages or gametocytes, which do not lead to any symptoms, but may persist for many weeks or even months after treatment of the acute disease (Soulard *et al*., 2015). The *Anopheles* mosquito ingests both male and female gametocytes (microgametocytes and macrogametocytes, respectively) during feeding. Multiplication of the parasite in the mosquito is called sporogony and results in sporozoites which migrate to the mosquito's digestive tract from where they are injected into another susceptible host to continue the malaria life cycle. The whole process can occur in 8-35 days (Zareen *et al*., 2016). Following a mosquito's blood meal, there is an asymptomatic incubation period of 7-30 days during which the parasites undergoes a gradual development and multiplication in the hepatic cells and in the blood system respectively. If there is no treatment, the disease condition may become acute, especially in non-immune and immunocompromised patients, pregnant mothers, and children less than 5 years (WHO, 2015).

1.3.1 Clinical presentation

The level of acquired immunity of the individual patient, which is determined by the degree of endemicity of their place of residence. A typical presentation of uncomplicated malaria includes; fever, headache, poor appetite, nausea and vomiting; while in children symptoms include irritability, poor suckling, and diarrhoea (SADOH, 2016). Severe *P. falciparum* malaria is defined as the occurrence of one or more of the following clinical sign and symptoms without an alternative cause and with *P. falciparum* as the definitive causative agent (SADPH, 2016; WHO, 2014).

1. Altered consciousness: defined as Glasgow coma scale (GCS) less than 11 in adults.
2. Prostration: loss of ability to perform a previously capable task, for example a child can walk and now he cannot walk because of the illness.
3. Convulsions: 2 or more episodes in 24 hours.
4. Acidosis: pH <7.35 or bicarbonate <15 mmol/L.
5. Hypoglycaemia: glucose <2.2 mmol/L.

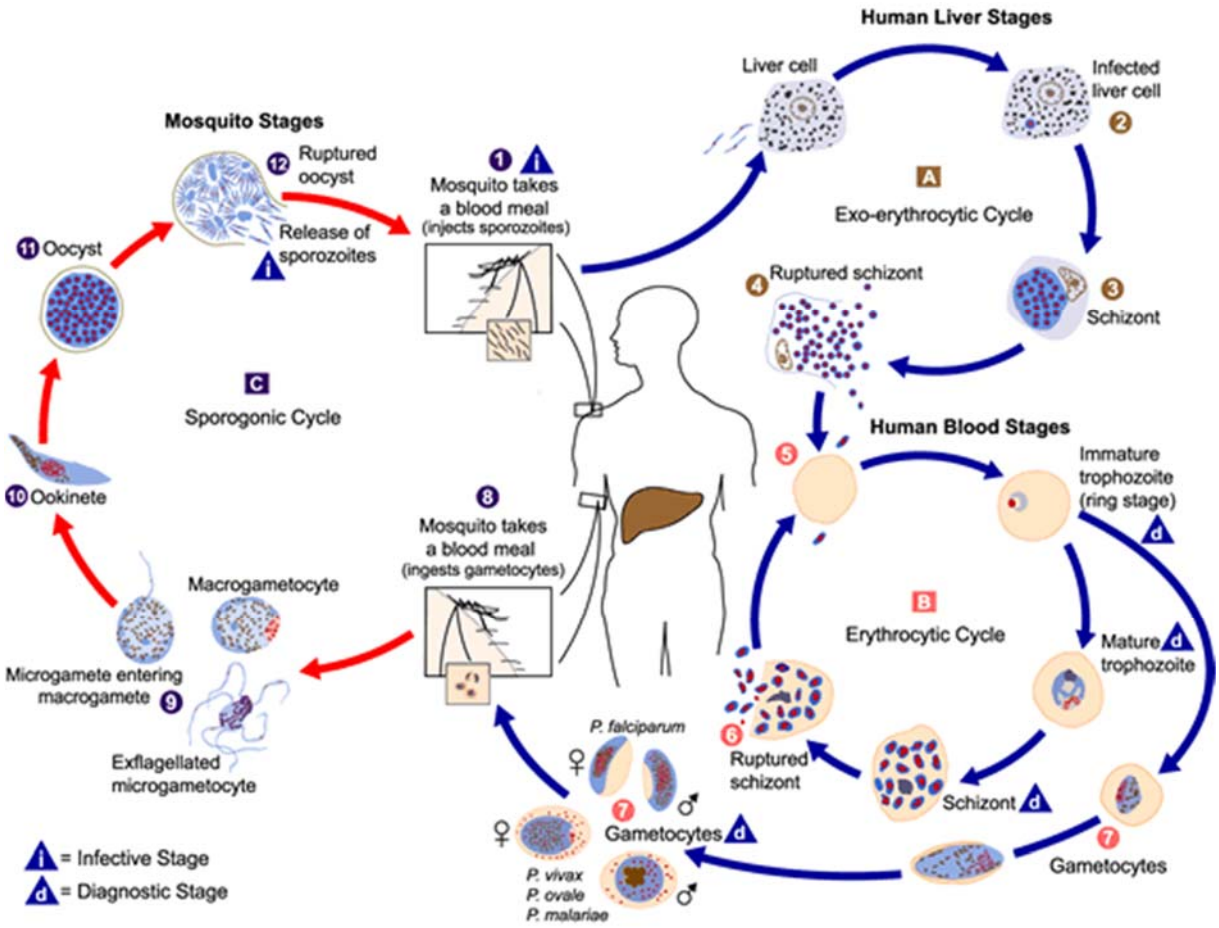


Figure 1.1: The life cycle of *Plasmodium* species in human and *Anopheles* hosts (CDC, 2016).

6. Severe anaemia: haemoglobin ≤7 mg/dL
7. Renal failure: creatinine >265 µmol/L
8. Jaundice: serum bilirubin >43 µmol/L
9. Pulmonary oedema: oxygen saturation <92%, respiratory rate >30 per minutes plus crepitation on auscultation.
10. Disseminated intravascular coagulopathy (DIC).
11. Shock: systolic blood pressure <70 in the adults.
12. Hyperpyrexia: temperature >40˚C.
13. Hyperparasitaemia: >4% (laboratory), >4% (non-immune) and >10% in semi-immune.
14. Hyperlactataemia (lactate >5mmol/l)

1.3.2 Immunity to malaria

In areas of unstable malaria transmission, people of all ages suffer from acute clinical malaria with a tendency to progress to severe complicated malaria if untreated. Non-immune travellers to stable malaria areas are similarly vulnerable to malaria. Stable malaria transmission regions are areas where the population is exposed all year round to a high level of malaria infection with a parasite inoculation rate of greater than 10 per year. Some immunity is acquired in early childhood and could confer a considerable degree of protection and markedly lower the chance of acquiring complicated disease (Griffin *et al*., 2015). In areas of continuous malaria transmission, clinical immunity to mild malaria is acquired slowly over time; this slowly acquired immunity only becomes effective in early adulthood. The more severe form of the disease is seen among children below the age of 5 years; however, repeated infection confers long-term protection against the severe disease. Despite a higher exposure rate to infection among children, they commonly receive passive protection from maternal antibodies *in utero*. They exit from this period of clinical protection with considerably more malaria immunity than those who are exposed to lower transmission throughout the year (Gupta *et al.*, 1999). Previous studies indicated that immunity to complicated malaria following repeated infection with *P. falciparum* is acquired gradually, but the extent to which this immunity is acquired is still not clear (Griffin *et al*., 2015). Two components of immunity, innate and adaptive immunity are implicated; however, the primary mechanisms behind the development of clinical immunity to severe malaria still remain unknown. The gamma and delta T-cells ($V\delta2^+$ ϒδT-cells) are hypothesised to aid in controlling the primary *Plasmodium* infection by filling the gap between the innate and adaptive components of the immune system, through production of immune-mediated cells, such as interferon-ϒ (IFN-ϒ), tumour necrosis factor-α (TNF-α) and granzyme B, in addition to eliminating the blood stage merozoites directly (Kurup and Harty, 2015). The response of these cells is observed only in acute infection or the primary infection and not with subsequent infection. Jagannathan *et al.* (2014) associated the manifestation of severe clinical disease with a low gamma-delta-T-cell response. It was proposed that down-regulation of this cellular response by previous frequent exposures to plasmodia may be the main factor which allowed for better adaptation to clinical malaria. This system was based on a previous observation that gamma-delta-T-cells along with $CD4^+$ T-cell monocytes may be the main drivers for the production of cytokines and chemokines linked to complicated malaria (Jagannathan *et al*., 2014). Most South Africans do not have acquired immunity to malaria, including people living in malaria endemic provinces and are therefore at risk of developing

complicated disease. As such pharmacological and non-pharmacological preventative measures and treatment are essential.

1.3.3 Malaria vaccine

Plasmodium falciparum malaria is a serious global health problem that needs a long-term solution such as an effective vaccine. Several vaccines have been designed, with the RTS, S recombinant protein-based malaria vaccine showing the most promise with 30-65% protection against malaria. It is a hybrid protein particle, which targets the circumsporozoite protein and is formulated in a multi-component adjuvant named RTS, S/AS01 or Mosquirix (Gosling and von Seidlein, 2016). Clinical trials conducted in endemic African countries have reported a 55.8% efficacy among children in phase 3 studies with some partial protection in adults (Kazmin *et al*., 2017). However, for a global rollout a higher efficacy rate is required.

1.4 Malaria treatment in South Africa

Treatment of malaria should be done in accordance with South African National Guidelines for Malaria Control issued by the Department of Health (SADOH, 2016; Blumberg, 2015). However, only a small number of clinicians in non-malaria areas are familiar with the treatment options available (Dube *et al*., 2008). Another challenge is related to the expertise and accuracy of the laboratory technician in microscopically identifying the *P. falciparum* parasite, especially when examining the smear. Diagnosis of malaria should be based on confirmed parasitological diagnosis through microscopic confirmation rather than by clinical symptoms (Blumberg, 2015). Thick and thin blood smear microscopy is still the gold standard for malaria diagnosis. The alternative relatively inexpensive rapid diagnostic tests (RDT) have been found to be lifesaving in areas where qualified laboratory technicians are unavailable (D'Acremont *et al*., 2009). RDTs are more easily accessible than expensive microscopy, provide results immediately and are adequately sensitive for *P. falciparum* infections (Mahende *et al*., 2016). However, RDTs cannot indicate the amount of parasite and as such do not detect hyperparasitaemia that indicates severe malaria. There are RDTs for *P. falciparum* alone and for all the other *Plasmodium* species. A malaria negative microscopy test does not rule out malaria, so a repeat test should be considered within 12-24 hours. Some other diseases resemble malaria, such as typhoid fever, meningitis, viral haemorrhagic fevers and trypanosomiasis and should be excluded as part of the differential diagnosis of malaria (Blumberg, 2015).

1.4.1 Malaria prophylaxis

Protection against malaria starts with risk assessment and includes: an accurate travel plan for the travellers, possible risk behaviour of the traveller, type of accommodation and season during which the journey will be undertaken. The best option in preventing malaria is avoiding mosquito bites (D'Nothdurft and Kain, 2016). The lower extremities are the most vulnerable and preferred site for the vectors to feed on considering their feeding nature which is close to the ground. Thus, long clothing that may cover the lower extremities may go a long way in preventing mosquito bites. However, liberal application of diethyltoluamide (DEET) impregnated lotion on skin surfaces after sunset, residual indoor spraying, screened outlets, combustible mosquito coils, electrically heated treated mats, air-conditioning, as well as an electric fan are alternative sources of protection (Van Zyl, 2016). It is recommended to avoid applying both the impregnated chemicals, as well as sprays on the sensitive parts of the body.

The recommended drugs for malaria prophylaxis in South Africa include mefloquine, doxycycline or atovaquone/proguanil and are recommended based on the traveller's clinical status. Atovaquone/proguanil consistently shows protection and efficacy against *P. falciparum* malaria with good safety records during prophylaxis (Table 1.1); however, despite all these benefits, travellers may be reluctant to use it because of its high cost (Lachish *et al*., 2016).

1.4.2 Treatment of uncomplicated malaria

According to the WHO, uncomplicated malaria is defined as the presentation of malaria clinical features with a smear positive parasitological test result using RDT or microscopy, but without features suggestive of severe malaria. Prevention of the progression of uncomplicated malaria to the severe form is one of the main objectives of treatment, along with curing the patient. Uncomplicated malaria is treated with a combination of artemether and lumefantrine (Prabhu *et al*., 2016). The South African Department of Health (SADOH) has recommended various treatment alternatives for patients presenting with uncomplicated malaria (Table 1.2).

In cases of rare treatment failure with artemether-lumefantrine, a complete treatment duration of oral quinine (7-10 days) combined with 7 days of doxycycline or clindamycin can be used as an option (Table 1.2). In pregnancy, or in children up to the age of 8 years, doxycycline is replaced with clindamycin, as doxycycline is associated with adverse effects such as fetal bone growth inhibition, stained deciduous teeth and enamel hypoplasia. Other side effects of doxycycline include skin rashes, diarrhoea, vaginal candidiasis and oesophagitis (Petersen and

Regis, 2016; Rossiter, 2016). Pregnant women in the first trimester should be monitored when administered 7 day duration of oral quinine due to the increased risk of hypoglycaemia.

Table 1.1 Drugs used in malaria prophylaxis in South Africa (Blumberg, 2015; Rossiter, 2016; HDI, 2017).

Patients status	Mefloquine	Doxycycline	Atovaquone - proguanil
Pregnant mothers -avoid travel to malaria endemic areas	Recommended for first, second and third trimesters if travel is necessary. Category B.	Contraindicated. Category D.	Contraindicated due to absence of data.
Children - avoid going with children <5 years to malaria risk areas	Can be administered in children >3 months or >5 kg.	Use only in children >8 years.	Paediatric doses can be administered to children >11 kg .
Lactation – nursing infant requires own prophylaxis	Recommended for breast feeding mothers.	Contraindicated.	Contraindicated due to absence of data.
Person requiring long term prophylaxis	Can be used for up to 3 years. Risk of malaria may increase with duration.	Can be safely used for up to 2 years. Risk of malaria may increase with duration.	Can be used without caution for 1 year. Risk of malaria may increase with duration.
HIV-positive patients on ARVs	No potential interactions.	Most preferred drug. Potential risk with didanosine, efavirenz, nevirapine.	Theoretical/potential risk with indinavir, zidovudine, efavirenz.

Table 1.2: Dosing schedules of antimalarial drugs according to South African National Guidelines (Blumberg, 2015; Rossiter, 2016; MIC, 2017, SADOH, 2016).

Antimalarial	Start dose (loading)	Continues dose (maintenance)	Notes
Quinine dihydrochloride salt (IV quinine - reconstituted in 5% dextrose (5-10 ml/kg) Oral quinine (300 mg quinine sulphate)	20 mg/kg over 4 hours, then by 8 hours, subsequently maintenance dose after 8 hours -	10 mg/kg reconstituted in 5-10ml/kg of dextrose containing solution over 4-6 hours repeated every 8 hours for 7 days Oral 10 mg salt/kg body weight every 8 hours for 7 days	Used in combination with either doxycycline or clindamycin. Reduce dose after 3 doses for all patients, not only those with renal dysfunction, monitoring of blood glucose to prevent hypoglycaemia. Other side effects: arrhythmias, hypersensitivity, cinchonism and hypotension.
Add Doxycycline later	Not required	Oral 100mg twice daily for at least 7 days	Contraindicated in pregnant women and children less than 8 years.
Add Clindamycin later	Not required	Oral 10 mg/kg twice daily for 7 days	Side effect includes diarrhoea and hepatotoxicity.
IV artesunate	≥20 kg: 2.4 mg/kg intravenously at 0, 12, 24 hours	Continue daily until the patient is able to tolerate full oral course (6 doses) of artemether-lumefantrine	Side effect includes diarrhoea, vomiting/nausea, dizziness.
Oral artemether/ lumefantrine (Contains artemether 20 mg, lumefantrine 120 mg)	For ≥ 35 kg: 4 tablets stat	4 tablets after 8 hrs, then 4 tablets twice daily on each of the next two days. (total course = 24 tablets)	Administered with fatty food like milk to enhance absorption. Contra-indicated in patients with history of allergy to artemether or lumefantrine. Not considered safe in first trimester of pregnancy.

If the pregnancy is in the second or third trimester, artemether-lumefantrine can be used as it is not associated with any major adverse effects. Based on the registration of artemether-lumefantrine in South Africa, only patients weighing less than 65 kg are permitted to use the combination due to the lack of comprehensive pharmacokinetic data for patients over 65 kg (Blumberg, 2015). Since 2003, ACTs have been in use in all the malaria endemic provinces of South Africa, in accordance with the WHO recommendations (WHO, 2014). Artemisinin derivatives are rapidly acting with an acute decrease in parasite load and reduction in parasite carriage with acute patient response (WHO, 2015).).

1.4.3 Treatment of severe malaria

Severe malaria is a life-threatening infection requiring immediate parenteral drug treatment, intensive patient care, and vigorous supervision and management of complications. In sub-Saharan Africa, up to 1.24 million children under the age of five die every year due to severe malaria, along with life-threatening complications (Blumberg, 2015). Intravenous artesunate (Table 1.2) is now the treatment of choice for severe malaria in adults and children, as reflected in the WHO guidelines and has recently been registered in South Africa (WHO, 2016; MIC, 2017). When intravenous artesunate is not promptly available, intravenous quinine is initiated immediately and given 8 hourly until oral treatment is tolerated, and then followed with a complete course of artemether-lumefantrine (Table 1.2). If a patient with severe malaria is to be delayed by more than 4 – 6 hours before being transferred to a tertiary hospital, intramuscular artesunate or quinine should be administered (SADOH, 2016). The use of ACTs in clinical medicine is extended into the malaria-endemic areas of Africa and Asia, thereby replacing quinine as the main drug for severe malaria treatment (Hawkes *et al*., 2015). Some countries still continue to use quinidine or quinine because of their efficacy in treating complicated malaria, while awaiting approval of artesunate by the authorities. Artesunate is preferred not only for its superior efficacy over quinine, but also its lack of acute toxicity and ease of administration (WHO, 2016; Naidoo & Saman, 2013; Sinclair *et al*., 2011; SADOH, 2016).

1.5 Antimalarial agents

1.5.1 Artemisinin derivatives

Artemisinin derivatives like artesunate, artemether and arteether are water-soluble, semi-synthetic compounds of artemisinin, the active antimalarial component of the plant medicine *Artemisia annua* (qinqousu), discovered by Chinese researchers in 1972 (Mishra *et al*., 2016).

Artesunate requires activation by rapid transformation into dihydroartemisinin, and has been formulated into various oral, parenteral and rectal preparations. The acute effect of artesunate, easy dosing schedule and its availability in parenteral formulation makes it ideal for treatment of complicated malaria including cerebral malaria (Prabhu *et al*., 2016). Artemisinin derivatives have short plasma half-lives and variable pharmacokinetic properties with a higher recrudescence rate when used for a short treatment course, however, combining it with a long acting drug like lumefantrine helps in achieving a maximum radical cure rate of more than 90% (Prabhu *et al*., 2016). Moreover, using artemisinin as monotherapy requires multiple dosing regimens over 7 days duration, which could lead to decreased patient compliance (Mishra *et al*., 2016).

Artemisinin together with its derivatives are potent antimalarial agents against all species of human malaria, with the fast clearance of ring form parasites coinciding with an acute fall in body temperature and rapid clinical response, parasite load and reduced parasite carriage. Treating early diagnosed cases of malaria with artemisinin derivatives prevents the progression of disease to severe malaria cases and death (WHO, 2015). The artemisinin derivatives have a gametocidal effect on early developmental stages of the parasite, but not on the late fourth stage. This necessitates the need for treatment to avoid further transmission, since it does not completely eliminate post-medication infectivity (Mutabingwa, 2005). The endoperoxide bridge within the artemisinin derivatives molecule possibly interacts with haem iron of the parasite, thereby increasing the production of free radicals, which subsequently binds to the membrane protein, leading to lipid peroxidation and further damage of the parasitic food vacuole, and finally, inhibiting protein synthesis and lysing of the parasite (Tilley *et al*., 2016). Artemisinin together with its derivatives have a much lower side effect profile with relative tolerance, where the adverse effects are mild dizziness, vomiting, nausea and joint pain.

Reports on artemisinin resistance have emerged which have been linked to gene mutation, in addition to the delayed parasite clearance or partial resistance as reported in the 2016 WHO report. However, the major fear is that partial resistance may transform into full resistance over time, with possible a risk of resistance to the partner drug, thereby reducing the efficacy of the artemisinin and its derivatives (WHO, 2016). Rapid destruction and elimination of ring stage parasites is the main stay of artemisinin action, however, resistance is associated with slow clearance of this parasite with a subsequent increase in blood parasite, which may be evident 72 hours after treatment with artemisinin, and show on microscopy result (Dondorp *et al*., 2017). In 2013, an artemisinin emergency response team was launched in Greater Mekong

Subregion (GMS) by the WHO following the report of increasing resistance to the drug in the region. In order to reduce this impact of resistance in South Africa, there is a need to strictly adhere to the national guidelines for malaria treatments and control; with early diagnosis and management of cases with recommended artemisinin combination therapy and avoiding monotherapy. The registration of artesunate in South Africa for severe infections in adults and children will be of great benefit to effectively treat patients. To date there have been no reported or detected artemisinin-resistant strains of *P. falciparum* in South Africa (Dr J. Raman, personal communication, 2017). Although the occurrence of potential drug interactions is proposed to be relatively low, some have been reported. These include, artemether and/or dihydroartemisinin plasma levels increased by ketoconazole and decreased by lopinavir+ritonavir, darunavir+ritonavir, nevirapine, efavirenz, etravirine and rifampicin. The plasma levels for lumefantrine may be increased by lopinavir+ritonavir, darunavir+ritonavir, ketoconazole, possibly nevirapine, but decreased by rifampicin, efavirenz, mefloquine and etravirine (SADOH, 2016). It is also recommended to avoid concurrent administration of artemether+lumefantrine with agents that inhibit the cytochrome P450 enzyme (CYP2D6), prolong the QT interval, antidepressants, antibiotics such as the macrolides, fluoroquinolones, imidazole/triazole antifungals and non-sedating antihistamines (SADOH, 2016).

1.5.2 Lumefantrine

Lumefantrine is an antimalarial agent that resembles quinine, mefloquine, and other amyl amino alcohol groups of antimalarial drugs; sharing a similar structure, chemical properties and mechanism of action. It acts by accumulating in the parasite food vacuole blocking the polymerization of the haemoglobin product, haem into haemozoin, which in turn causes parasite toxicity and damage (Nyunt *et al*., 2016). Lumefantrine is used in combination with artemether as a fixed dose (Table 1.2) as the first recommended formulation in the management of uncomplicated *P. falciparum* infection. Lumefantrine has potent antimalarial properties with rapid reduction in parasite density (WHO, 2016). The poor bioavailability of lumefantrine is considerably enhanced by up to 16-fold when taken with or straight after fatty food, including milk. It has an elimination half-life of 4-5 days with a longer terminal half-life that helps in protecting recurrent malaria infection by clearing the remnant parasites (Prabhu *et al*., 2016). Lumefantrine is hepatically metabolised by cytochrome P450 enzymes, mainly CYP2D6, and is reduced by uridine glucoronosyl transferase enzymes (Garg *et al*., 2017).

1.5.3. Quinine

Quinine is a quinolone methanol obtained from the bark of the *Cinchona* tree, and has been a potent antimalarial drug for many decades (Roepe *et al*., 2013). After the report of chloroquine resistance on the Thai-Cambodian border and other endemic regions of Africa, quinine remained the drug of choice for treatment of chloroquine-resistant *P. falciparum*. However, with the new ACTs advocated as the first line recommended treatment for malaria, quinine has been relegated to a second line drug with some countries still retaining it as the most preferred drug for the treatment of complicated malaria in children and pregnant mothers despite the WHO recommendation of parenteral artesunate to replace it (Noubiap, 2014). Quinine is commonly combined with other antimalarial antibiotics, like doxycycline and clindamycin to improve its slow duration of action and patient adherence (Table 1.2). Quinine is a fast acting and effective schizonticide against all the human *Plasmodium* species. The drug has no effect on the gametocidal stages of *P. falciparum*, as it does for *P. vivax* and *P. ovale* (Mehta *et al*., 2015). The exact mode of action of quinine is still not fully clear, but is believed to inhibit haem detoxification within the parasite food vacuole as described for lumefantrine (Section 1.5.2). Quinine is rapidly absorbed following oral intake reaching a peak plasma level within 1-3 hours with extensive tissue distribution; however, a loading dose of quinine shortens this time. The half-life of quinine is up to 18 hours among severe malaria patients compared to 11 hours in healthy controls due to its high protein binding capacity (Achan *et al*., 2011). The metabolism of quinine takes place in the liver with reduction of the drug into a smaller number of metabolites, and ultimately excreted in the urine. The most important side effect of quinine is known as cinchonism that presents as a cluster of adverse effects such as nausea, vomiting, dizziness, tinnitus and acute blindness. These side effects can reduce patient adherence to the prescribed medications. The quinine injection is very painful with an increased risk of developing sterile abscess if standard precautions are not fully observed. However, more serious side effects of quinine result from the loading dose and rate of administration. These include hypotension, cardiac toxicity and hypoglycaemia, with the latter more common amongst children and pregnant women. Regular ECGs and blood glucose monitoring are recommended in detecting such life-threatening side effects (Noubiap, 2014).

1.5.4. Doxycycline and clindamycin

Doxycycline is a long acting derivative of tetracycline, an antibiotic antimalarial, and a prophylactic agent with potent action on erythrocytic schizonts of all the human *Plasmodium*

species, with a partial effect on the hepatic stage parasite. Doxycycline is not recommended forfor use as monotherapy, but in combination with other effective schizonticidal drugs like quinine for the management of complicated *P. falciparum* malaria (Table 1.2), thereby augmenting the action of quinine in severe malaria patients. The mode of action of doxycycline is proposed to inhibit *P. falciparum* protein synthesis by binding to and inhibiting the activity of the apicoplast that produces various proteins (Gaillard *et al*., 2015). Doxycycline, when compared to other members of the group, is more rapidly absorbed and appears in the plasma 15-30 minute following oral uptake, has rapid lipid solubility and it has a longer half-life than other cyclines. The side effects of doxycycline are mainly gastrointestinal in nature and include nausea, abdominal pain, and flatulence, although photosensitivity and vaginitis may occur (Petersen and Regis, 2016).

Clindamycin is a semi-synthetic derivative of lincomycin with a slow action against erythrocytic schizonts of *P. falciparum* and a wide range of actions on anaerobic Gram-positive bacteria. Clindamycin has the same mechanism of action as other antibiotic antimalarials. Following oral intake of the drug it reaches peak level in 45 minutes. Following conversion into three main active substances, 20% of clindamycin is eliminated through the kidneys, with the main elimination route through the bile. The half-life of clindamycin is 2-3 hours with a bioavailability of 50%. It is contraindicated in hepatic failure because the half-life is considerably prolonged and requires dose adjustment (Moole *et al*., 2015). However, the slow action of clindamycin coupled with the rapid action of quinine make their combination efficacious with considerable shortening of treatment duration to only 3 days. Clindamycin side effects are tolerable, and include diarrhoea, nausea, vomiting, heartburn, body pain, vaginal itching or discharge; however, hepatotoxicity has been linked with systemic clindamycin (Lell and Kremsner, 2002; Moole *et al*., 2015).

1.5.5 General management of malaria

Malaria patients should be fully assessed and extensively examined. When the first doses of oral antimalarial drugs are administered, the patient should be closely monitored for at least an hour to ensure no vomiting of the drugs occurs, as vomiting is common in malaria infected patients. If the patient vomits within the first hour after administration, the treatment should be repeated as this could result in inadequate absorption of the medication that could potentially lead to treatment failure (SADOH, 2016)

The laboratory and clinical responses should be carefully and frequently followed to monitor parasitaemia and disease severity to ensure a favourable outcome. Moreover, temperature, the level of consciousness, mental state, breathing pattern, presence of jaundice and urine production should be regularly monitored to identify improvement or complications (Dondorp *et al*., 2016). Healthcare professionals should also monitor the judicious administration of adequate fluids, antipyretics (such as paracetamol) to reduce fever (>39°C), administer oxygen if respiratory distress, administer diazepam to control convulsions, correct hypoglycaemia and administer ceftriaxone to treat co-existent bacterial infections if considered present (Dondorp *et al*., 2016; SADOH, 2016). Analgesics such as NSAIDs and aspirin should be judiciously used as they may increase the risk of renal failure in patients with malaria, which is dose- and duration-dependent due to their ability to inhibit prostaglandin action (Srebro and Ilic-Mostic, 2016; SADOH, 2016).

Relative clinical improvement should be expected after 2 days of active treatment. However, the parasitaemia should be re-assessed after 3 days of drug therapy, with not less than a two-third reduction of the previous parasite load count expected with recommended treatment. Additional indicators of early treatment failure could manifest as failure to show clinical improvement or no change in parasitic ring forms on microscopy by 2 days post treatment (WHO, 2015). Late treatment failure may be due to recrudescence or a new infection, which manifests as a parasitaemia after 4 weeks post-treatment, or 7 days of parasitaemia, post-treatment without dormant parasites. Treatment failure may also be due to either any of the following: antimalarial resistance, adherence to prescribed antimalarials, failure to take the artemether-lumefantrine with a fatty meal/drink (1.2g fat) resulting in inadequate absorption of the lumefantrine, a new infection and relapse due to non-*P. falciparum* species, where there was failure to identify and treat dormant parasites (WHO, 2015; SADOH, 2016). Administration of 14 days of primaquine is required to achieve a radical cure of these liver stages (SADOH, 2016; Van Zyl, 2016).

1.5.6 Primaquine and reducing transmission

Globally primaquine remains the only drug that is effective against the dormant stage of *P. vivax* hypnozoites and capable of killing mature gametocytes of *P. falciparum* with remarkable single dose efficacy. According to the WHO a radical cure with primaquine requires a recommended dose of 0.25 mg/kg, which is the daily dose administered to eradicate the hepatic stages of *P. vivax* (WHO, 2016; Greenwood and Tine, 2016; Rossiter, 2016). Despite its

effectiveness as a radical cure, this dose of primaquine is usually not administered toto glucose-6-phosphate dehydrogenase deficient (G6PD) patients due to the potential of inducing haemolysis. The haemolysis observed in G6PD patients taking primaquine is characterised by severe anaemia, intravascular haemolysis, dark urine and mild jaundice (Chu *et al*., 2017). G6PD is more prevalent in Africa (except southern and eastern Africa), where the daily dose of primaquine is reduced to 0.65 mg base/kg weekly for 8 weeks (Rossiter, 2016). The mechanism of action is proposed to be due to the production of reactive oxygen free radical species by the 5-hydroxy-metabolite, which is responsible for the haemolysis. Primaquine is reported to have a hypnozoitocidal effect on the parasite. Primaquine interacts with CYP2D6 enzymes and monoamines oxidases, with the former, as the catalyst in the pathway that lead to the production of its main metabolite, carboxyprimaquine, and 5-hydroxy-primaquine (Pybus *et al*., 2013). Primaquine undergoes rapid metabolism with a short half-life of 4 hours and reaches a peak plasma concentration 1-2 hours following oral drug uptake. However, despite the variable pharmacokinetic properties of primaquine (Marcsisin *et al.*, 2016), a WHO expert panel concluded that 0.25mg/kg as a single dose would not cause serious toxicity, even to patients with G6PD deficiency (SADOH, 2016).

1.6 Malaria and HIV co-infection

In addition to the burden of malaria in Africa, most of these countries are also endemic for HIV-infections; with over 25 million people including children reported to be living with HIV/AIDS in Africa. These two important public health diseases (HIV and malaria) account for up to 4 million deaths per year worldwide (Naing *et al*., 2016). Prevalence of HIV in endemic malaria regions exposes the population to co-infection, with severe disease interactions and outcomes. Globally about 59% of new HIV infections occur in young adults aged 15-24 years, with risk factors for HIV-infection including mother to child transmission (vertical transmission), through contaminated blood products, unsafe injections (iatrogenic transmission) and sexual intercourse (horizontal transmission) (Fox and Fidler, 2010). According to the UNAIDs, South Africa has the largest number of people living with HIV/AIDS and death associated with it worldwide, with a total number of 7.1 million people and 110, 000 death in 2016 (Simbayi *et al.*, 2017; Bradshaw *et al*., 2016; Avert, 2017). *P. falciparum* has been reported to stimulate HIV viral division in lymphocytes (Whitworth *et al*., 2000). The understanding as to how HIV infection affects the severity of malaria is still limited. It is thought that the $CD4^+$ T-cell, B-cell and antigen presenting cells, which are compromised in HIV-positive patients, play a vital role

in malaria immune defence responses, so there could be a significant effect on the severity of the infection and patient's outcome. Studies indicate that increased HIV viral loads are associated with recurrent co-infections; whilst malaria increased the mortality rate of HIV-positive patients (Abu-Raddad *et al*., 2006). In malaria endemic regions, HIV-positive individuals who have some immunity to malaria may experience moderate infrequent infections, while in non-endemic region where malaria is less prevalent, HIV-infections increase the vulnerability to complicated malaria and death (Berg *et al*., 2014).

1.6.1 Association between HIV and malaria

An infection with HIV results in the suppression of the immune system with significant progressive weakening of immunity and inability to respond to infective challenges. The high impact of these associations with regards to increased viral load is seen in patients with microscopically confirmed *P. falciparum* infections and low $CD4^+$ T-cell counts, leading to a subsequent increase in complications of the disease and risk of death (Qadir *et al*., 2015). Both HIV and malaria independently can lead to complicated pathology/disease and subsequent death. However co-infection with these two infections results in an additive interaction with the potential of a poor prognosis if not optimally managed (Alemu *et al*., 2013).

1.6.2 Effect of malaria on HIV

A concurrent infection with malaria has the potential to result in a poor outcome in HIV-infected patients. Infection with malaria has been reported to activate and up-regulate the cellular cytokines thereby creating a suitable environment for the rapid replication of the HIV-1 virus (Alemu *et al.*, 2013). Malaria increases $CD4^+$ T-cell activation, which may result in further increases in target cells that allow for further HIV binding and result in new infections of activated $CD4^+$ T-cells (Qadir *et al.*, 2015).

In areas where malaria is endemic, an HIV-infection can weaken the acquired immunity resulting in a higher parasite burden from the inability to phagocytose parasitised red blood cells (Finney *et al*., 2013). In addition, an HIV-infection has been reported to interfere with the inflammatory response that is triggered in response to a malaria infection, and may take several months to be re-established even in the presence of ART (Serghides *et al*., 2015). At this juncture it is imperative to know that HIV-infected individuals are at a higher risk of experiencing frequent malaria infections compared to non-immune individuals without HIV (Qadir *et al*., 2015).

1.7 Antiretroviral Therapy in HIV-infected people

South Africa has been hit hard by the HIV epidemic, with a higher infection rate of 18.8% among the young people. According to the 2017 UNAIDs data, about 86% of the 7.1 million people living with HIV in South Africa are aware of their HIV status, 65% are on HIV-treatment, with broader access to antiretroviral treatment (Risher *et al*., 2016) and early HIV treatment reducing the infectivity rate among HIV-positive individuals (Crepaz *et al*., 2016). To achieve favourable HIV outcomes, patient compliance to the antiretroviral drug (ARV) treatment as outlined by the national ART Treatment Guidelines and retention of these patients in general care is critical (Moyo *et al*., 2016).

For those patients infected with the HIV virus, the ARV combination therapy medications may result in several adverse effects and when the patient is co-infected with malaria, there can be several drug interactions as well as additional adverse effects (Rossiter, 2016). The various ARV regimens that are recommended in South Africa include the following:

Previously, first-line ART according to the South African National Guidelines was stavudine (d4T), lamivudine (3TC) and efavirenz (EFV); while the second line regimen included zidovudine (AZT), didanosine (DDI) and lopinavir/ritonavir (LPVr) (Evans *et al*., 2013; SADOH, 2015). Subsequently, tenofovir (TDF), 3TC and EFV became first-line ART. In 2013, the fixed dose combination pill was introduced, which is made up of three drugs, TDF, emtricitabine (FTC) and EFV, and is used as the first-line regimen to increase patient adherence and reduce the number of doses patients have to take (SADOH, 2015). Patients failing the TDF-based first-line regimen are placed on AZT + 3TC + LPV/r as second line option or AZT + TDF + 3TC + LPV/r alternatively, especially in hepatitis-B co-infected patients. However, failing on d4T (stavudine) or zidovudine (AZT-based) first line regimen, TDF + 3TC (or FTC) + LPV/r is an alternative regimen according to the South African Guidelines (Meintjes *et al*., 2017). Patients failing second-line regimen are referred to a specialist for further genotypic evaluation and assessment; however, access to the third-line ART is mainly provided by the Department of Health (SADOH, 2015).

Indications for ART over the course of this study have evolved from CD4 count ≤200 cells/µl or WHO stage 4 disease to CD4 count ≤350 cells/µl or TB or WHO stage 4 disease to CD4 count ≤500 cells/µl. Currently all qualify for ART on diagnosis. Meanwhile, under the current universal test and treat paradigm WHO advocates all infected patients should be treated irrespective of CD4 count.

Co-trimoxazole prophylaxis is administered to all patients with WHO stage 2, 3 or 4 of the disease, as well as HIV/TB co-infected patients (Meintjes *et al*, 2017). Co-trimoxazole may cause serious side effects like erythema multiforme and Stevens-Johnson syndrome, which may necessitate the withdrawal of the drug (SADOH, 2015).

1.8 Malaria and HIV outcomes

HIV-infection impairs the acquired immunity to malaria in adults, with higher chances of having increased viral load and accelerated disease progression (Modjarrad *et al*., 2010). HIV-infected adults have a higher risk of quantifiable malaria, especially in non-endemic areas. Patients with CD4 count below 200 cells/µl were reported to have severe form of malaria (Qadir *et al.,* 2015). Non-immune HIV-infected patients were more prone to have repeated malaria infection than their counterpart without HIV. Recurrent hospital admission and severe anaemia due to malaria were reported to be more frequent among HIV-infected than HIV-uninfected patients (Qadir *et al*., 2015).

1.9 Cost implications of malaria

Malaria infections also significantly affect the economy of the country where the government provides the treatment and medication for the public and incurs costs whilst the patient is in hospital. Conversely, households may have to pay for the medication themselves as private patients and incur indirect costs such as through loss of salary and need for a caregiver (WHO, 2016). Little is known about the economic consequences of malaria in Africa despite its endemicity in the region. These economic effects can be either directly from the cost of prevention and treatment therapies or indirectly from morbidity and mortality; as well as low productivity, duration of time taken to seek treatment and utilisation of household resources. The direct costs of disease management can be obtained by assessing the total health care cost for each treated patient and the number of treated cases. Indirect costs of treatment can be calculated by estimating the daily income of the adult patients multiplied by the loss of work hours and days while seeking treatment (Shepard *et al.*, 1991). Household studies conducted in South Africa have indicated that a household spent between R 3.45 and R 225.00 annually on malaria preventive methods ranging from environment control, vector control and use of repellents, while spending between R 26.85 and R 375.00 (exchange rate: USD/ZAR 13.08. as of 18 October 2015) on treatment of established infections (Goodman *et al*., 2000). In 2015 the global economic burden of malaria was estimated at US$ 2.9 billion, which can significantly

affect economic and community development. Presently ACTs are the most potent of all the antimalarials and recommended by the WHO for effective treatment of uncomplicated malaria due to *P. falciparum* (WHO, 2016). Access to ACTs remains a major challenge especially among the poorer populations. Uncontrolled high prices in the private sector especially in sub-Saharan Africa, constant shortages in the public sector and a poor road network to access remote areas constitutes some of the other challenges. In 2010, various programs were organised by the WHO in over seven countries to ease the access and affordability of ACTs for people under the WHO program called Affordable Medicine Facility-malaria (AMFm). The AMFm offered public and private organisations the opportunity to acquire a large scale purchase of highly subsidised ACTs with the sole target of making the drug widely accessible at a very low price and high quality (WHO, 2015). Participating countries were also encouraged to apply intervention program measures to educate people to use the subsidised ACTs. Studies have reported that lower prices and easier accessibility to ACTs by retail suppliers has significantly increased the use of ACTs, and this has impacted on the number of people patronising the AMFm. The level of ACT use among households has also been reported to have increased, from 29% in 2010 to 80% in 2013-2015 (WHO, 2015). The cost of ACTs in the private sector is relatively expensive, with many of the suspected malaria cases purchasing their treatment from this source (Morris *et al*., 2015). In South Africa, the ACTs are relatively affordable especially in public sector hospitals, currently costing approximately R 9.38 per adult dose for three days for treatment as stated in the master price catalogue issued by the South African National Department of Health, on 28th August 2015. Considering the efficacy of the ACTs, lowering prices will go a long way to increasing use among suspected and microscopically confirmed malaria patients, where the vast majority of these patients are poor and live in remote areas without access to hospital care when needed for severe malaria and are placed at an increased risk of death. Furthermore reducing the overall drug cost to the government and hospital admission cost would be beneficial to the government and country.

1.9.1 Direct cost

Direct cost is defined as total spending on protection and personal treatment of malaria by families, and overall services provided by the health institution (Chima *et al*., 2003). Households use different types of methods to protect themselves from a malaria infection, such as coils, sprays, nets and indoor screens depending on their area and economic status. All aspects of malaria costs are determine by the type of parasite that is dominant in that

environment and endemicity of the area that will explain the immune status of the population; as well as financial status, such as income earnings and traditional belief towards the disease (Chima *et al*., 2003). Household expenditure on malaria-related treatment includes, direct out-of-pocket spending for consulting doctors, buying medicines and other miscellaneous expenses due to distance to health facilities. Direct costs of treatment have been reported to consume up to 2% of a high-income Malawian family's earnings and 28% among the very low income earners household (Ettling *et al*., 1994). Most direct cost studies reported on the notion of household spending and therefore did not show cost differences on the extent of sickness burden and financial impact throughout the year. However, reduced health care seeking behaviour among the 'at risk' patients, because of out-of-pocket spending, is shown to be high; which in return has a high impact on their basic needs like children education, food and house rent (Onwujekwe *et al*., 2013). Government spending on malaria control and treatment are considered as an aspect of direct costs, however, the exact overall public spending on malaria control and management is not well documented. In addition, estimations are inconsistent, since the majority of spending on malaria programmes is not differentiated from the cost of providing health care services (Onwujekwe *et al*., 2013).

1.9.2 Indirect costs

Indirect costs of treatment results from the inability of the malaria patients to go to work as a result of morbidity and mortality from the disease and the need for relatives to look after them. The work time lost due to the disease condition may be the key determinants of economic cost. Indirect cost also includes time taken to seek treatment, in addition to morbidity time and cost of death, with respect to the patient's loss of lifetime income (Babiker, 2016).

1.9.3 Total costs

The estimation of the total financial cost of malaria includes the sum of the direct and indirect costs of treatment, along with an estimation of the indirect disease burden costs. The majority of studies have estimated the total cost of patient's treatment from a households and government perspective including the private provider costs of management and indirect death costs, with the exception of prevention costs. However, most studies conducted in Africa found that direct costs considerably exceed the indirect morbidity costs, with both imposing a serious economic burden, especially among households (Babiker, 2016). Moreover, public hospitals owned by governments in most African countries including South Africa significantly subsidise the cost,

and cover the anticipated treatment of malaria. Generally the public sector covers direct medical costs attributable to each treatment option for complicated and uncomplicated malaria, namely the cost of antimalarial drugs, ARVs, admission and professional fees (Maka *et al*., 2016).

Finally, with the high prevalence of HIV in South Africa, malaria further escalates the potential of additional fatalities due to the increased risk in the progression of disease severity, especially in non-endemic provinces (SADOH, 2016). Against this background, we have studied adults with malaria in a tertiary hospital setting in South Africa in order to assess the impact of HIV infection on malaria severity, management, outcome and cost, However, it's imperative to mention that there is little costing information on malaria in HIV-patients.

1.10 AIM

The aim of this retrospective record review was to examine malaria-infected adult patients by HIV-serostatus with respect to malaria severity, antimalarial drug use, and mortality together with measuring direct costs of care.

1.11 STUDY OBJECTIVES

1. To describe patient outcomes in malaria-infected patients in relation to disease severity and drug use in HIV- positive versus HIV-negative patients.
2. To determine the risk factors of severe malaria among HIV-infected adults.
3. To determine if there is an association between costing of malaria treatment, disease severity and patient outcome.
4. To determine the cost of malaria treatment by malaria severity and HIV-serostatus.

Chapter Two: Methodology

2.1 Study site and population cohort

Chris Hani Baragwanath Academic Hospital (CHBAH) is the third largest public sector Hospital in the world; with a bed capacity of 3,200, serving the population of Soweto, Johannesburg, South Africa. Soweto is a malaria free zone, but many cases of imported malaria are diagnosed every year at this hospital. Patients with suspected or unsuspected clinical malaria in Soweto and environs are referred to this hospital for admission, diagnosis and management. Most patients are treated with a standard antimalarial regimen of quinine and doxycycline depending on presentation. There has previously been a high prevalence of HIV-positive patients (33%) among adults with malaria admitted to this academic hospital (Cohen *et al.,* 2005).

2.2 Study design and population

This study was a retrospective record review over a five-year period (2011-2015) using all eligible malaria positive adult patients. Men and non-pregnant women aged 18 years and above with positive malaria tests (smear and /or RDT), as reported via the National Health Laboratory Services (NHLS) Microbiology Department at the CHBAH were included. Both HIV positive and negative patients were included. The HIV status of the patients was determined either from NHLS blood results, or if, the patient declared his/her status as documented in the file or if the patient was on antiretroviral medication. Patients were excluded if found to have an inconclusive HIV result or if their HIV status could not be determined. Preliminary investigations into the viability of this study were conducted, which indicated that there were 196 patients in 2014, and as of the end of July 2015, 977 malaria positive patients (over a 5-year period) who comply with the inclusion/exclusion criteria of the study were recorded. The proportion of HIV-negative to HIV-positive patients was determined during the course of the study.

2.3 Data collection

Data collection was done by the use of a standard data collection sheet (Appendix E) It included data on demographic profiles of the patient, country of origin, length of stay in South Africa, travel history to endemic malaria areas, date of admission into the hospital, clinical features of malaria, complications of malaria, haematological, microbiological and biochemical

investigation results, admission to intensive care unit (ICU), length of hospital admission, disease outcome (discharge or death), medication prescribed, patient response to medications (improved or worsening of signs and symptoms), cost of antimalarial drug per day and per hospital stay, ARV drug cost, as well as ICU and general ward admission costs. Other therapeutic interventions given to the patient such as assisted ventilation and dialysis and number of sessions undertaken by the patient were also recorded. Comorbidities, including other infections and non-communicable diseases and their treatment were also recorded to ascertain their potential effect on the pharmacokinetics of the antimalarial drugs and patient outcome.

All the laboratory results obtained were compared to the standard laboratory reference ranges. The laboratory results were obtained from the NHLS database. Treatment charts in the clinical record were used to document. This drug utilization review provided information on antimalarial regimen used, the number of patients on a particular treatment pathway as well as dose and frequency of treatment. This information was used to measure the cost of malaria treatment. The patient records were also examined for the following information for ART and any other medications prescribed, efficacy of the antimalarial drugs in HIV positive patients, concomitant ARV drugs regimens received by the patient and any changes in drug regimen depending on changes in patient tolerability and the new drug regimens that were prescribed to the patient. Treatment pathways for patients with complicated and uncomplicated malaria were also recorded, and all the treatment was correlated to the South African Department of Health guideline for malaria treatment (SADOH, 2016; Blumberg, 2015; WHO, 2015). The information collected was then critically analysed to describe the patient's outcome in relation to drug regimen and HIV-positive status and also to explain the risk of severe malaria among HIV-infected adults.

2.4 Cost analysis

Cost analysis information of patient treatment based on the severity of the disease was obtained. This costing included antimalarial costs per day and per hospital stay (Appendix F), ARV drug costs, hospital admission, ICU and general ward length of stay costs. Pricing for the wards, ICU, antimalarial drugs as well as ARV drugs were obtained from the Chris Hani Baragwanath Administration Office, which is based on public sector pricing, using the Master Price Catalogue issued by National Department of Health (28th August 2015), pharmacy costs, and

the NHL Tariff Guide (Appendix H). The cost per patient day in a general medical ward based on 2015 costs was R 774.00 and the cost per half-day in ICU was R 3,913.00. Based on the collected clinical data, costing and various correlations were computed to determine the cost based on patient disease severity, HIV status and general management. Both individual patient and overall cost were analysed.

2.5 Ethics

Permission to conduct the retrospective study was obtained from the Medical Advisory Committee at CHBAH (Appendix A) and NHLS data-base permission was granted by the Academic Affairs and Research office of the NHLS (Appendix B). Approval to conduct the retrospective review of patient data from clinical records of CHBAH and further analysis was granted by the Faculty of Health Sciences Postgraduate Committee (Appendix D) and the University of the Witwatersrand Human Research Ethics Committee (Appendix C) - Ethics approval number: M151143 prior to the commencement of the study. Patient confidentiality was maintained at all times as it involved retrospective analysis of patient records; anonymity was upheld as patients were assigned research numbers and research codes. Patient names and numbers were kept and stored separately and were password protected. Data collected and access was limited to the researcher and supervisors and securely stored.

2.6 Statistical analysis

Data was entered into an Excel spread sheet, then imported into STATA package version 13.0 (College Station, Texas 77845 USA) for data analysis. Frequency and proportions were used to summarise categorical data. The Fisher's exact test was used to compare proportions; however, group proportions were compared by calculating odds ratio (confidence intervals). The normally distributed continuous variables were reported as means and standard deviations, however, non-uniform data was summarised as medians with interquartile ranges (IQRs). Univariate analysis was performed with baseline characteristics. Complicated malaria risk factors were analysed using logistic regression; while the Wilcoxon Rank-Sum Test was used to test the difference in patients' costing. The p-value of < 0.05 was taken as statistically significant.

Chapter Three: Results

3.1 Demographic information

Over the five-year period of the study, a total of 1000 files which met the inclusion criteria of this study were retrieved from the records department of CHBAH, Johannesburg, South Africa. A total of 23 patients were excluded due to duplication of file numbers. All 977 patients tested positive for *P. falciparum* malaria and HIV status recorded for each patient (Table 3.1; Figure 3.1). There were similar numbers of patients for each year of the study. According to WHO criteria, of the 977 patients there were 69.8% with uncomplicated malaria versus 30.2% with complicated malaria ($p < 0.05$) (Table 3.1). There were 352 HIV-positive patients (36.0%) and 625 HIV-negative patients (64.0%). Of the patients with complicated malaria, a 1.8 fold difference was observed between HIV-positive patients (19.6%) compared to 104 (10.6%) HIV-negative patients (Table 3.1).

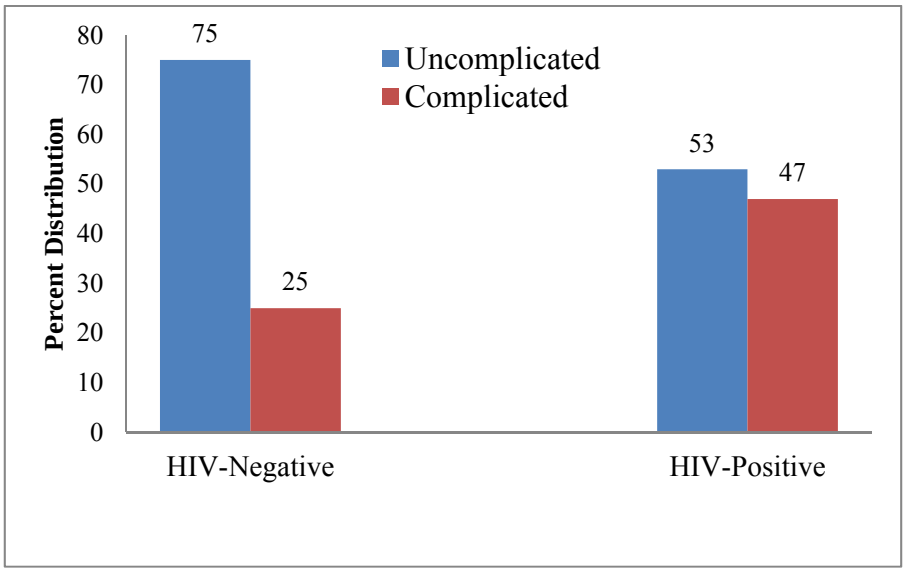


Figure 3.1 Distribution of HIV infection among malaria-infected patients.

3.1.1 Age and gender distribution

The age of the patients ranged from 25 to 45 years with no significant difference between sub-groups of patients (Table 3.2). There were 667 (68.3%) males and 310 females (31.7%) females, as such there were significantly more males than females ($p < 0.001$) (Table 3.2). There were more complicated cases amongst the HIV-positive patients (ratio uncomplicated-to-complicated - 3:1) compared to the HIV-negative patients (ratio 1.2:1) (Table 3.1), with a higher

percentage of the women testing HIV-positive than the males (ratio 1.57:1) ($p < 0.001$)(Figure 3.1).

Table 3.1: Annual distribution of malaria and HIV cases according to the severity of malaria infection.

Clinical data per year	Total (n=977)	HIV-negative (n=625)	HIV-positive (n=352)
2011 (n = 198)			
Uncomplicated malaria	142 (71.7%)	108 (54.5%)	34 (17.2%)
Complicated malaria	56 (28.3%)	14 (1.1%)	42 (21.2%)
2012 (n = 197)			
Uncomplicated malaria	127 (64.5%)	107 (54.3%)	20 (10.2%)
Complicated malaria	70 (35.5%)	22 (11.2%)	48 (24.4%)
2013 (n = 194)			
Uncomplicated malaria	148 (76.3%)	111 (57.2%)	37 (19.1%)
Complicated malaria	46 (23.7%)	15 (7.7%)	31 (16.0%)
2014 (n = 196)			
Uncomplicated malaria	131 (66.8%)	97 (49.5%)	34 (26.0%)
Complicated malaria	65 (33.2%)	23 (11.7%)	42 (21.4%)
2015 (n = 192)			
Uncomplicated malaria	134 (69.8%)	98 (51.0%)	36 (18.8%)
Complicated malaria	58 (30.2%)	30 (15.6%)	28 (14.6%)
2011-2015 (n = 977)			
Uncomplicated malaria	682 (69.8%)	521 (53.3%)	161 (16.5%)
Complicated malaria	295 (30.2%)	104 (10.6%)	191 (19.6%)

Table 3.2 Demographic characteristic of study population.

Characteristic	Overall age mean (range)	Uncomplicated malaria (n=682)	Complicated malaria (n=295)	HIV-negative (n=625)	HIV-positive (n=352)
Age mean (range)	33 (25-45)	33 (26-38)	38 (30-45)	33 (25-38)	32 (25-36)
Female (n = 310)	33 (25-34)	233 (34%)	77 (26%)	199 (32%)	188 (53%)
Male (n = 667)	35 (34-45)	449 (66%)	218 (74%)	426 (68%)	164 (47%)

3.1.2 Travel history and country of residence

The number of admitted patients who had a positive travel history recorded in their folder constituted 86% (842/977), in comparison to the rest of the patients who had no documented travel history (14% (135/977) (Figure 3.2). This was probably due to the healthcare professionals not requesting or recording this personal detail or there may not have been that history available upon presentation if the patient was confused and the doctor did not update the record upon improvement or there may have been Odyssean malaria in some. In addition, the language barrier may have been a factor. Most of the contracted infections 80% (785/977) were derived from countries bordering South Africa with Mozambique being the source of 73.69% of all cases. For cases contracted in South Africa; the Limpopo province contributed 3%, KwaZulu-Natal <1% and Mpumalanga 1% (Figure 3.2).

Patients from Mozambique contributed the greatest portion of the admissions among the individual countries, followed by all the endemic provinces of South Africa (Limpopo, KwaZulu-Natal, Mpumalanga) and Zimbabwe. While other countries such as Malawi, Ethiopia, Congo, Bangladesh, Nigeria, Tanzania, Sudan, Ghana, Burundi, Angola, Lesotho, Swaziland, and Zambia altogether contributed 6.14% (60/977), probably due to lack of documentation of country of residence.

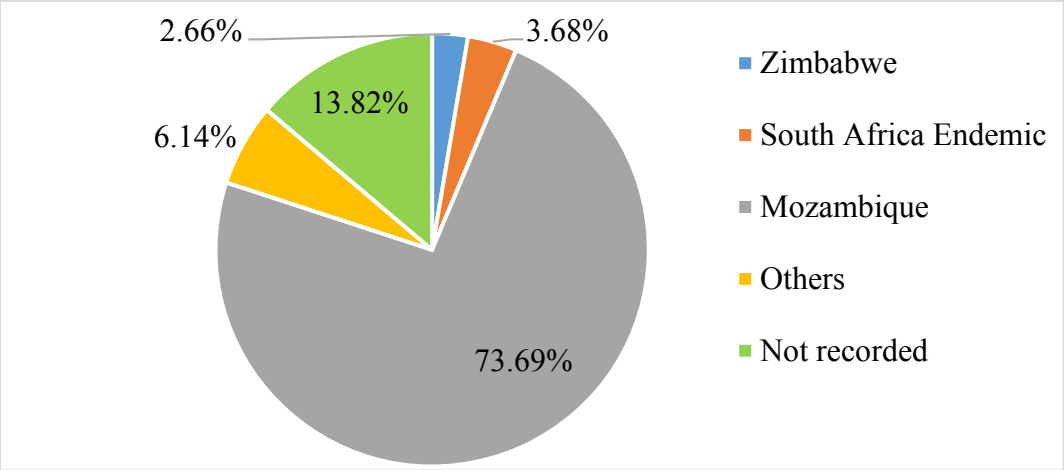


Figure 3.2: Percentage distribution of imported malaria cases admitted to CHBAH according to the country of origin.

3.1.3 Seasonal transmission

Fifteen to 20 cases of malaria were diagnosed monthly (mean, 17.2). Despite all year round diagnosis of malaria, seasonal transmission started from November to May each year (summer months), commonly among those provinces bordering Mozambique. Transmission in southern Africa decreases from June to November (Dube *et al*., 2008).

3.2 Laboratory findings

3.2.1 Haematological and biochemical test results

Of the 977 patients admitted, not all had every investigations performed so the denominators varied accordingly (Table 3.3).

Table 3.3 Laboratory findings of patients admitted with malaria (SADOH, 2016; WHO, 2011).

Laboratory Findings	Reported
Disseminated intravascular coagulopathy	10/977 (1%)
Jaundice (Serum bilirubin >43 µmol/L)	17/977 (2%)
Hypoglycaemia (Blood sugar < 2.2 mmol/L)	36/977 (4%)
Metabolic acidosis (pH <7.35/Bicarbonate <15 mmol/L)	76/977 (8%)
Severe anaemia (Hb <7 g/dL)	98/976 (10%)
Thrombocytopenia (Platelet <137 x 10^9/L)	107/977 (11%)
Hyperparasitaemia (≥4%)	215/882 (24%)
Renal impairment/failure (Creatinine >265 µmol/L)	249/977 (26%)
HIV-positive	352/977 (36%)

A review of the WHO criteria for severe malaria enabled the physician to categorise patients as having complicated or uncomplicated malaria (WHO, 2014). Table 3.4 below shows the different criteria in number and percentage used to diagnose complicated malaria; as well as differences in gender and outcomes using Pearson's chi-square test. Laboratory investigations were commonly performed immediately after patients were admitted (date 1); repeated after 2-3 days following initiation of medication (date 2) and before patients were finally discharged. Tests were performed more regularly for patients in ICU.

Table 3.4: Percentage distribution of malaria criteria for complicated malaria according to gender.

	Totals	Males	Females
Total malaria cases	977/977 (100%)	667/977 (68%)	310/977 (32%)
Complicated malaria	295/295 (100%)	218/295 (74%)	77/295 (26%)*
Renal failure	249/977(26%)	188/667 (28%)	61/310 (20%)*
Acidosis	76/977 (8%)	57/667 (9%)	19/310 (6%)
Hypoglycaemia	36/977 (4%)	29/667 (4%)	7/310 (2%)
Severe anaemia	98/977 (10%)	58/667 (9%)	40/310 (13%)*
Hyperparasitaemia	215/882 (22%)	148/608 (24%)	67/274 (24%)
Impaired consciousness	67/977 (7%)	52/667 (8%)	15/310 (5%)*
Jaundice	17/977 (2%)	14/667 (2%)	3/310 (1%)*
ICU admission	112/977 (12%)	90/667 (13%)	22/310 (7%)*
Mortality	36/977 (4%)	25/667 (4%)	11/310 (4%)
HIV-positive	352/352 (100%)	164/352 (47%)	188/352 (53%) **

*P < 0.05, **P < 0.001

Renal failure was defined as a serum creatinine level of >265 μmol/L and was found to be present in 26% of the patients (WHO, 2014). The mean difference between creatinine levels in complicated and uncomplicated malaria patients was 18.2 μmol/L. Although not one of the criteria for complicated malaria, thrombocytopenia was documented in 11% of the patients with a platelet count of less than 137 $x10^9$/L as defined by the WHO criteria (Table 3.3) (Perovic *et al*., 2000; WHO, 2011). Severe anaemia was the second most predominant clinical feature (Hb <7 g/dL) found in 10% of patients. Disseminated intravascular coagulopathy (DIC) was least common among patients, constituting 1% of patients. Impaired level of consciousness that is

common among cerebral malaria patients was found in 7% of the patients. Patients with acidosis constituted 8% in which the majority had renal failure. There were 2% of patients who had jaundice (serum bilirubin >43 μmol/L). The patients with hypoglycaemia (<2.2 mmol/L)(4%) (Table 3.3) presented with complicated malaria and were initially treated with quinine/doxycycline before being discharged on oral artemether/lumefantrine.

3.2.2 Outcomes

Of the 977 patients that were analysed in this study, Table 3.5a and Table 3.5b report on the clinical outcomes of malaria cases; where the number of cases per year, percentage distribution and mortality among complicated and uncomplicated malaria patients were recorded.

3.2.3 Malaria tests

All 977 patients in this study had RDT and thick and thin smears for *Plasmodium falciparum* done (Table 3.5a; 3.5b). Of these, 90% (883/977) had positive smears for *P. falciparum*, but 10% (94/977) had no record for percentage parasitaemia. Hyperparasitaemia was evident in 22% of patient; whereas the parasite densities ranged from <1% to 46%; with a mean of 4.3% on date one and 1.0% on date two, respectively (Table 3.5b). However, the mean parasitaemia among HIV-positive and HIV-negative patients was 6.0% and 3.0%, respectively (Figure 3.3). Percentage parasitaemia reduced as treatment progressed. Investigations done immediately before discharge had undetectable parasitaemia indicating full recovery in all patients

3.2.4 Inpatients management

All the patients in this study were managed as inpatients. All admissions were in the male and female medical wards. Most of the patients were first admitted into the emergency ward before onward transfer to various other wards.

Table 3.5a Clinical outcomes of malaria cases at CHBAH over a five year period.

Clinical data (n=977)	2011 (n=198)			2012 (n=197)			2013 (n=194)			2014 (n=196)			2015 (n=192)		
	Total	HIV-	HIV+	Total	HIV-	HIV+	Total	HIV-	HIV+	Total	HIV-	HIV+	Total	HIV-	HIV+
Uncomplicated malaria	142 (72%)	108 (55%)	34 (17%)	127 (64%)	107 (54%)	20 (10%)	148 (76%)	111 (57%)	37 (19%)	131 (67%)	97 (49%)	34 (17%)	134 (70%)	98 (51%)	36 (19%)
Complicated malaria	56 (28%)	14 (7%)	42 (21%)	70 (36%)	22 (11%)	48 (24%)	46 (24%)	15 (8%)	31 (16%)	65 (33%)	23 (12%)	42 (21%)	58 (30%)	30 (16%)	28 (14%)
Cerebral malaria	14 (7%)	6 (3%)	8 (4%)	17 (9%)	6 (3%)	11 (6%)	6 (3%)	2 (1%)	4 (2%)	13 (7%)	5 (3%)	8 (4%)	17 (9%)	7 (4%)	10 (5%)
Complicated malaria & AKI	39 (20%)	17 (9%)	22 (11%)	47 (24%)	19 (9%)	28 (14%)	34 (18%)	13 (7%)	21 (11%)	40 (20%)	17 (9%)	23 (12%)	27 (14%)	11 (6%)	16 (8%)
Complicated malaria & heart failure	2 (1%)	2 (1%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	3 (1.5%)	3 (0%)	0 (0%)	7 (4%)	7 (4%)	0 (0%)	4 (2%)	4 (2%)	0 (0%)
Parasitaemia, ≥ 4%	53 (27%)	14 (7%)	39 (20%)	51 (26%)	16 (8%)	35 (18%)	30 (15%)	5 (3%)	25(12 %)	41 (21%)	14 (7%)	27 (14%)	40 (21%)	11 (6%)	29 (15%)
Discharge	180 (91%)	155 (78%)	25 (13%)	176 (89%)	166 (84%)	10 (5%)	183 (94%)	176 (91%)	7 (4%)	178 (91%)	164 (84%)	14 (7%)	180 (94%)	169 (88%)	11 (6%)
Mortality	10 (5%)	4 (2%)	6 (3%)	11 (6%)	3 (2%)	8 (4%)	2 (1%)	0 (0%)	2 (1%)	11 (6%)	5 (3%)	6 (3%)	2 (1%)	1 (1%)	1 (1%)
Readmission	7 (4%)	6 (3%)	1 (1%)	7 (4%)	7 (4%)	0 (0%)	9 (5%)	7 (4%)	2 (1%)	2 (1%)	2 (1%)	0 (0%)	8 (4%)	5 (3%)	3 (2%)
Sign against medical advice	1 (1%)	0 (0%)	1 (1%)	3 (2%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (3%)	4 (2%)	1 (1%)	2 (1%)	2 (1%)	0 (0%)

Table 3.5b Total number of clinical outcomes of malaria cases in HIV-positive and HIV-negative patients at CHBAH. (Percentages calculated from total number of cases)

Clinical data	Total (n=977)	HIV-negative (n=625)	HIV-positive (n=352)
Uncomplicated malaria	682 (69.8%)	521 (76.4%)	161 (23.6%)
Complicated malaria	295 (30.2%)	104 (35.3%)	191 (64.7%)
Cerebral malaria	67 (6.9%)	26 (38.8%)	41 (61.2%)
Complicated malaria & AKI	187 (19.1%)	77 (41.2%)	110 (58.8%)
Complicated malaria & heart failure	17 (1.7%)	17 (100%)	0 (0.0%)
Parasitaemia, ≥ 4%	215 (22.0%)	60 (27.9%)	155 (72.1%)
Discharge	897 (91.8%)	830 (92.5%)	67 (7.5%)
Mortality	36 (3.7%)	13 (36.1%)	23 (63.9%)
Readmission	33 (3.4%)	27 (81.8%)	6 (18.2%)
Sign against medical advice	11 (1.1%)	9 (81.8%)	2 (18.2%)

3.3 Patients response: Biochemical and haematological results

As expected, hyperparasitaemia patients on antimalarial drugs had a significant parasite load reduction after a few days of commencement of medication, compared to the level obtained on the first date measurement with a mean parasitaemia of 4.31% compared to the next measurement (date 2) mean parasitaemia with a 1.06% ($p < 0.001$)(Figure 3.3). Mean haemoglobin among malaria patients was 11.63 g/dL, on date 1 compared to mean of 12.64 g/dL, on the second measurement (date 2) ($p = 0.166$). Other investigations such as platelet count, white blood cell counts showed significant changes between date one and date two (Figure 3.3).

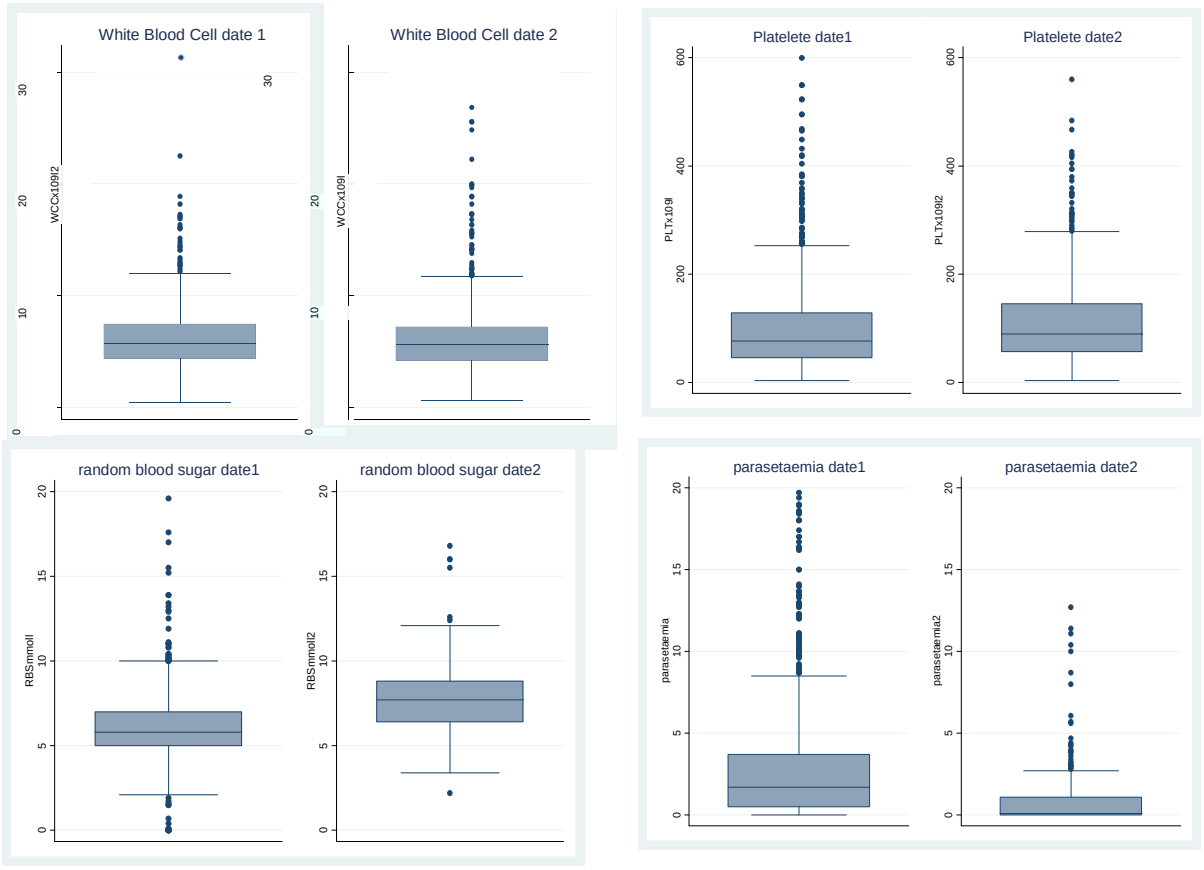


Figure 3.3 Patient investigations on day one (referred to as Date one) and the subsequent test date recorded (date two) (WBC, platelets, random blood sugar (RBS) and parasitaemia.

There were significant increases in blood sugar on date 2 of investigations compared to date 1 in median random blood sugar, range, 5.86-6.25 mmol/L date 1 versus date 2 RBS range, 7.53-54 mmol/L, respectively ($p < 0.001$)(Figure 3.3). Complications of complicated malaria such as hypoglycaemia were reversed by the slow administration of 50% dextrose water (1 ml/kg) and continued with 10% dextrose infusion (2 ml/kg) per hour for prevention. Patients with bleeding diathesis were transfused with appropriate coagulation factors.

For the 98 patients with severe anaemia (haemoglobin <7 mg/dL) (Table 3.4), blood was cross matched and transfused. Diuretics like intravenous furosemide were commonly administered before and after blood transfusion to avoid volume overload. Acute renal failure patients were first assessed for dehydration and reduced urine output, and if found to be dehydrated were hydrated with intravenous fluid where patients could not tolerate oral replacement.

The haematological and biochemical laboratory results indicated that most of the parameters were significantly different for patients who were discharged/SAMA compared to those who died; except for serum potassium and serum sodium (Table 3.6).

Table 3.6 Laboratory investigations between patients that survived and died.

Investigations	Standard range	Survivors		Patients that died		p. value
		Median	IQR	Median	IQR	
Albumin	35-52 g/L	31.00	24.0-36.0	28.50	23.5-29.6	0.0063
Total Bilirubin	0-21 μmol/L	16.00	8.0-28.	24.50	15-47	0.0073
WCC	4.0-10.0 $x10^9$/L	5.64	4.2-7.08	8.05	4.2-11.7	0.0045
Platelet count	137-373 $x10^9$/L	77.00	47.0-130.	53.50	23-115	0.0184
Haemoglobin	Male, 14.3-18.3 g/dL, Female, 12.1-16.3 g/dL	12.10	9.8-13.60	9.30	6-13	0.0030
RBS	Up to 11.1 mmol/L	5.80	5.0-7.0	5.05	4.3-6.5	0.0122
ALT	5-40 U/L	28.00	21.0-44.0	57.0	19.5-82	0.0299
AST	5-40 U/L	32.00	23.0-55.0	102.5	43-165	0.0000
Urea	2.6-7.0 mmol/L	5.80	4.3-9.4	17.0	7.1-27.3	0.0000
Creatinine	47-90 μmol/L	86.00	65.0-117.0	197.0	98-332	0.0000
Serum potassium	3.30-5.30 mmol/L	3.80	3.4-4.3	3.70	3.2-4.6	0.7912
Serum sodium	135-147 mmol/L	134.0	130.0-137.0	133.0	129-136	0.2118

3.4 Comorbidities

Of the 977 malaria-infected patients, 50 patients had comorbidities (5%). Comorbidities were defined as the presence of one or more additional diseases/disorders co-occurring with the primary disease/disorder. As such the comorbidities documented along with the malaria infection included hypertension (34 patients), diabetes mellitus (14 patients), myocardial infection and cerebrovascular disease (stroke) (2 patients each) (Figure 3.4). Renal failure was difficult to ascertain whether arising from diabetes mellitus or as a result of complicated malaria. Three patients had chronic renal failure and one patient required a liver transplant. A total of 3% (34 patients) patients had hypertension, 11 were females and 23 were males. The median blood pressure among hypertensive patients was 160/100mmHg (range: 145/90-190/110 mmHg). The two patients who had a myocardial infarction during their admission and they were both hypertensive. Both strokes were diagnosed as haemorrhagic stroke. The two

patients who developed a stroke while on admission were known diabetic and hypertensive patients. Only one diabetic patient developed diabetic ketoacidosis and was placed on subcutaneous insulin and later changed to oral hypoglycaemic drugs.

The maximum random blood sugar level recorded among diabetic patients was 54 mmol/ L. One patient had glycosuria up to 3+ (glucose in the urine). The median creatinine among diabetic patients with malaria was 165.2 mmol/L; range: 138.42-196.21 mmol/L compared to non-diabetic with malaria with a median value of 111.54 mmol/ L (range, 111.4-121.6 mmol/L). The blood pressures of hypertensive patients were checked regularly to monitor for a drop in pressure. Blood investigations such as electrolytes, urea and creatinine (E/U/Cr) were done to monitor kidney function, since renal impairment is a common complication of long standing hypertension. Hyperglycaemia in diabetic patients was monitored by performing a RBS (normal, up to 11.1 mmol/L) or fasting blood sugar (FBS, range, 3.9-5.6) and haemoglobin A1c to monitor glucose control (range: 4.0-5.6%), Echocardiograms and electro-cardiograms (ECG) were carried out to monitor cardiac function among hypertensive and stroke patients.

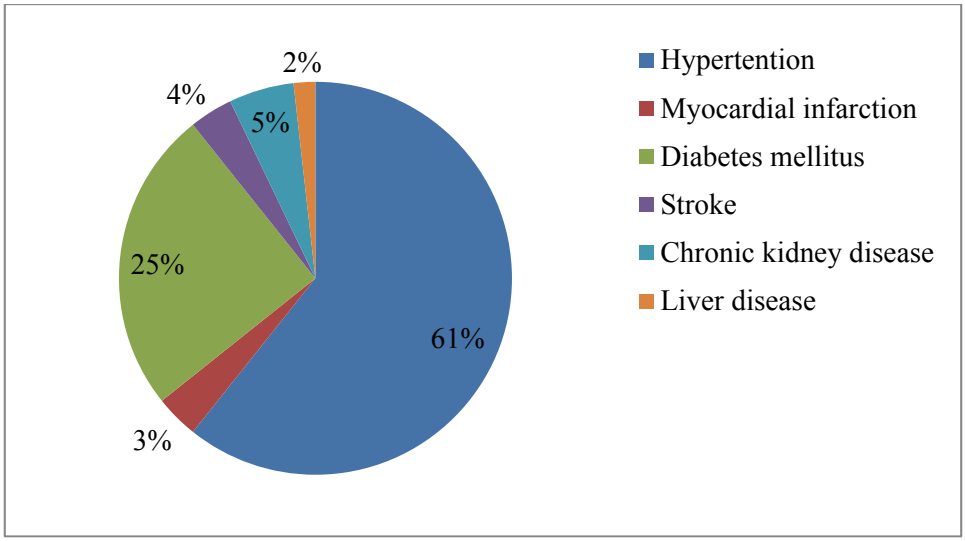


Figure 3.4 Percentage distributions of comorbidities.

3.5 Treatment options

3.5.1 Antimalarial treatment

Of the 977 patient files retrieved, all the patients had malaria treatment documented (Table 3.7). Severity of the malaria always determined the route and antimalarial drug to be used. Uncomplicated malaria is a symptomatic infection with no sign of underlying organ

dysfunction. For simple uncomplicated malaria, oral artemether-lumefantrine was commonly prescribed for the patients. IV quinine plus oral doxycycline were commonly prescribed drugs for treatment of patients with complicated malaria. Table 1.2 (Section 1.8.2) shows the dosing schedules of antimalarial medications used which were in accordance with the South African National Guidelines (SADOH, 2016). Only 5% of the total number of malaria-infected patients were treated with IV artesunate, that was made up of 13.6% of the complicated malaria patients (40/295), of which there were 28 HIV-negative and 12 HIV-positive patients (Table 3.7).

Table 3.7: Percentage distribution of antimalarial drugs used in malaria treatment, ART and antibiotics.

DRUGS ADMINISTERED	PERCENTAGE OF PATIENTS (n = 977)
ANTIMALARIAL DRUGS	
Intravenous quinine (loading dose)*	9%
Oral quinine	50%
Clindamycin	9%
Artemether-lumefantrine	50%
Intravenous artesunate	4.1%, 13.6% (of complicated cases)
Chloroquine	Only one patient
ANTIRETROVIRAL DRUGS**	
D4T + 3TC + EFV	17%
TDF + 3TC + EFV	3%
AZT + 3TC + ALV	< 1%
ANTIBIOTICS	
Cotrimoxazole	9%
Intravenous amoxicillin-clavulanic acid	27%
Oral amoxicillin-clavulanic acid	18%
Intravenous ceftriaxone	46%

* Plus oral doxycycline.
** For newly diagnosed HIV-positive patients or did not bring ARVs with them.

Side effects due to malaria treatment were not commonly documented among the study patients. According to the patient files, only one malaria-positive patient admitted to the emergency ward was initially treated with oral chloroquine as she was thought to be pregnant. However, the patient experienced severe side effects. The chloroquine therapy was terminated due to the sudden onset of acute blindness, which later resolved. Further detailed examinations revealed

that the patient was not pregnant, and she was then appropriately treated. History of antimalarial prophylaxis and malaria notification to the relevant health authority was poorly documented in the patient's files.

3.5.1.1 Effect of antimalarial treatment on clinical parameters

The various antimalarial drugs used in the treatment of malaria patients in this study are shown in Table 3.7. Haematological parameters such as the platelet count and red blood cell counts showed a statistically significant association on date 1 and date 2 ($p<0.05$) for patients treated with intravenous artesunate and oral artemether-lumefantrine; however, similar outcomes were obtained with oral and intravenous quinine among a different patient groups (Table 3.8). The average haemoglobin concentration on date 2 of treatment was increased across both categories, but low haemoglobin concentrations were more prevalent among the complicated malaria patients with an HIV-positive status.

3.5.2 Anti-retroviral treatment

Of the HIV-positive patients admitted into this study all were on ART, including those diagnosed prior to admission. Those who knew their HIV status were admitted with their ART medication such that the 21% of patients prescribed ART were documented in Table 3.7. A total of 17% of the patients were given a combination of stavudine, lamivudine and efavirenz (d4T + 3TC + EFV) compared to 3% that used tenoforvir, lamivudine and efavirenz (TDF + 3TC + EFV). Less than 1% was prescribed a combination of zidovudine, lamivudine, tenoforvir and emtricitabine (AZT + 3TC + TDF/FTC/) (Table 3.7).

All HIV patients were on first line regimens. Rapid HIV tests were commonly done among high risk patients to determine their HIV status (all patients with a positive rapid test had an ELISA done automatically to confirm the result; ELISA tests were occasionally used to confirm a discordant result). Informed consent was obtained from the patients by the health care workers before carrying out the HIV tests in addition to counselling. When tested positive for HIV, some patients were started on ART if they fulfilled the criteria of the $CD4^+$ T-cell $\leq$ 500 cells/μL, HIV / Tuberculosis co-infection. However, the majority of the patients came with their medications. Newly diagnosed HIV patients were commenced on ARV drugs and prescribed aa month supply, before being subsequently referred to a local hospital for further ARV collection after discharge. The mean parasitaemia was found to be increased among HIV-infected patients (11.1%) compared to HIV-negative patients (0.97%) (Figure 3.5).

Table 3.8: Effect of antimalarial agents on clinical parameters of uncomplicated and complicated malaria in HIV-positive and HIV-negative patients. [Q-D: Quinine-Doxycycline; AL: Artemether-Lumefantrine].

DRUGS	UNCOMPLICATED MALARIA				COMPLICATED MALARIA			
	HIV –VE		HIV + VE		HIV –VE		HIV + VE	
	% parasitaemia (date 1)	% parasitaemia (date 2)	% parasitaemia (date 1)	% parasitaemia (date 2)	% parasitaemia (date 1)	% parasitaemia (date 2)	% parasitaemia (date 1)	% parasitaemia (date 2)
Q-D	-	-	-	-	6.9% (3.5-10.5)	2.8% (2.3-5.1)	7.2% (4.0-11.1)	3.2% (3.0-5.3)
AL	4.3% (2.2-6.8)	1.0% (0.0-1.3)	5.3% (2.6-7.1)	0.5% (0.0-1.6)	-	-	-	-
Artesunate	-	-	-	-	8.2% (6.9-13.2)	0.9% (1.0-2.1)	8.8% (7.5-15.4)	0.5% (0.3-2.0)
	Platelet count (date 1) 150-450x10^9 mmol/l	**Platelet count (date 2)**	**Platelet count (date 1)**	**Platelet count (date 2)**	**Platelet count (date 1)**	**Platelet count (date 2)**	**Platelet count (date 1)**	**Platelet count (date 2)**
Q-D	-	-	-	-	96x10^9 (80-162)	154x10^9 (132-299)	62x10^9 (55-103)	145x10^9 (110-244)
AL	60x10^9 (56-121)	148x10^9 (134-401)	74x10^9 (63-136)	160x10^9 (150-239)				
Artesunate	-	-	-	-	74x10^9 (69-122)	210x10^9 (197-344)	88x10^9 (79-291)	194x10^9 (131-230)
	White blood cell count (date 1) 4-11x10^9 mmol/l	**White blood cell count (date 2)**	**White blood cell count (date 1)**	**White blood cell count (date 2)**	**White blood cell count (date 1)**	**White blood cell count (date 2)**	**White blood cell count (date 1)**	**White blood cell count (date 2)**
Q-D	-	-	-	-	20x10^9 (13-29)	12x10^9 (10.1-17.5)	28x10^9 (21-37)	18x10^9 (14-27)
AL	5x10^9 (3.8-14)	4.2x10^9 (2.3-12)	5.8x10^9 (4.1-13.3)	4x10^9 (3.8-12.7)	-	-	-	-
Artesunate	-	-	-	-	21x10^9 (18-29)	10.3x10^9 (8.2-16.7)	22x10^9 (17-34)	11x10^9 (9.7-15.8)
	Haemoglobin (date 1) g/dl	**Haemoglobin (date 2)**	**Haemoglobin (date 1)**	**Haemoglobin (date 2)**	**Haemoglobin (date 1)**	**Haemoglobin (date 2)**	**Haemoglobin (date 1)**	**Haemoglobin (date 2)**
Q-D	-	-	-	-	9.8 (6.0-10.1)	10.0 (8.1-10.1)	8.9 (6.8-9.2)	9.2 (7.3-9.4)
AL	10.5 (7.6-10.9)	10.7 (6.9-9.3)	9.8 (7.6-10.3)	10.2 (9.4-10.5)	-	-	-	-
Artesunate	-	-	-	-	7.7 (6.3-9.4)	8.1 (6.8-10.1)	6.9 (5.5-8.9)	7.2 (6.4-10.0)

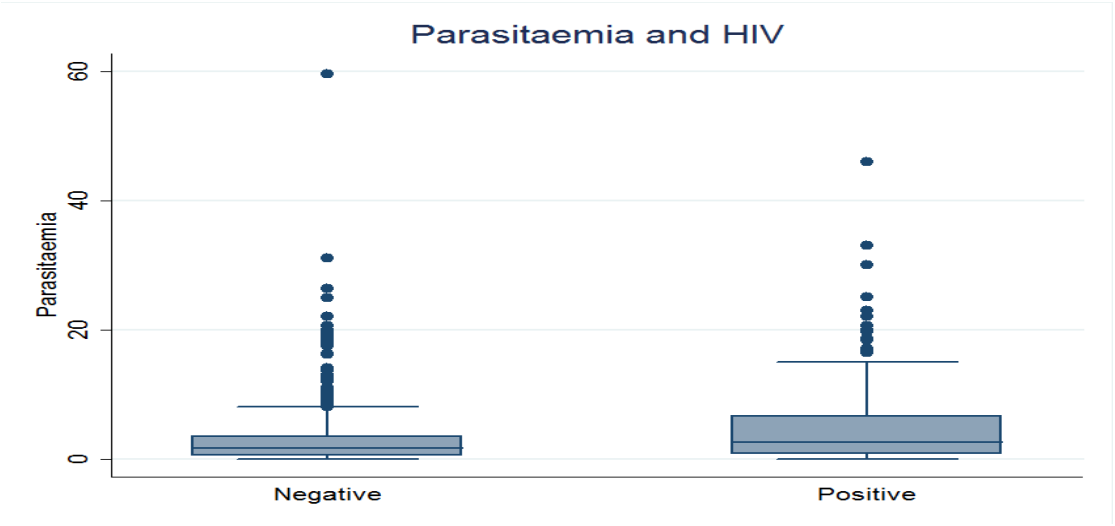


Figure 3.5: Increase in percentage parasitaemia (HIV-positive versus HIV-negative).

3.5.3 Treatment of opportunistic infections

Treatment of opportunistic infections was part of HIV treatment; however, patients with a $CD4^+$ T-cell count less than 200 cells/µL were more prone to opportunistic infections (Table 3.6). Acyclovir and cotrimoxazole were the most commonly prescribed drugs for prophylaxis of opportunistic infections at a dose of 200 mg five times daily for acyclovir, and a maximum daily dose of 320 mg/1600 mg for co-trimoxazole (Table 3.7). The opportunistic infections most commonly diagnosed included Kaposi's sarcoma (4 cases), pneumonia (26 cases), oesophageal candidiasis (5 cases) and crypto

coccal meningitis (2 cases). For cryptococcal meningitis, amphotericin-B was prescribed with the dosage determined by the indication (0.3-0.7-1.0 mg/kg) and for oesophageal candidiasis, fluconazole 100-200 mg/day was given or 14 days.

The majority of patients with opportunistic infections presented with bacterial infections, like Gram-negative septicaemia, aspiration pneumonia (26 cases) and urinary tract infection (UTI) and were appropriately treated with broad spectrum antibiotics (Table 3.7 and 3.8) after blood culture results were obtained. A total of 269 patients were administered various antibiotics, of which 9% were prophylactically administered oral cotrimoxazole (Table 3.9), while 27% of patients were administered intravenous amoxicillin-clavulanic acid (625 mg) and 18% of patients had oral amoxicillin-clavulanic acid (Table 3.7). Intravenous ceftriaxone was administered to 46% of patients either as a stat dose of 2 g and subsequently 1 g every 12 hours.

The dose of oral amoxicillin-clavulanic acidic acid prescribed included 625 mg and 375 mg 8 hourly, while the intravenous dose was 1.2 g 8 hourly.

Table 3.9: Summary of other drugs used in HIV-positive and HIV-negative patients with uncomplicated or complicated malaria.

Administered/ Prescribed drugs	Total	HIV-negative (n=654)	HIV-positive (n=233)	Uncomplicated malaria (n=682)	Complicated malaria (n=295)
Analgesic/ antipyretic	499/977 (51%)	284 (43%)	215 (92%)	219 (32%)	280 (94%)
Antihypertensive	11/977 (1%)	10 (1.5%)	1 (0.4%)	8 (1%)	3 (1%)
Antibiotics	269/977 (28%)	98 (15%)	171 (73%)	115 (17%)	154 (52%)

3.5.4 Other drug treatment

Anticonvulsants such as sodium valproate (n=11), diazepam (n=19), carbamazepine (n=14) and prochlorperazine (n=6) were the most common drugs administered for patients presenting with convulsion, restlessness or bizarre behaviours (67/977, 6.86%), which was a common symptom among cerebral malaria patients. Sodium valproate was prescribed in a dose of 200 mg twice a day for 2 or 3 days depending on the physician decision. Diazepam 5 mg at night was the most commonly prescribed drug among the cerebral malaria patients with irrational behaviour, although diazepam could also be administered to control seizures (WHO, 2012). Carbamazepine was administered at 100 mg twice a day and prochlorperazine prescribed at a dose of 5 mg daily (Table 3.7).

Due to the long hospital admission period for those patients with complicated malaria in ICU, enoxaparin sodium (n=15) was administered subcutaneously to prevent deep vein thrombosis (DVT) (n=91) in a dose of 40 mg daily. Occasionally other anti-coagulant drugs such as heparin and warfarin were administered to prevent DVTs among the malaria patients with chronic cardiovascular disease. The dose for heparin (n=45) was 5000 units intravenous (bolus dose) followed by 1300 units per hour by continuous intravenous infusion. Warfarin (n=31) was prescribed in a dose of 2-5 mg or 10 mg daily.

Among the 98 patients that had severe anaemia (Hb <7 g/dl), 50% were transfused with packed cells, while the remaining patients recovered and were discharged on haematinics and counselled on a balanced diet. Haematinics were also administered to patients with mild to moderate anaemia. Fersolate (ferrous fumarate/folic acid) in a dose of 200 mg three times daily

was commonly prescribed and folic acid was co-administered together with fersolate. Folic acid was prescribed in a dose of 5 mg daily (n=254).

Several other medications were administered to the patients:

- Metoclopramide 10 mg orally three times a day was administered to treat patients with nausea with or without vomiting or epigastric discomfort (n=132).
- Patients with acute peptic ulcer disease or at risk for it were treated with intravenous pantoprazole 20 mg twice daily (n=25) and occasionally ranitidine 150 mg twice daily was used.
- Patient with complaints of a sore throat were commonly prescribed benzydamine hydrochloride.
- Oral potassium chloride was commonly administered for correction of low serum potassium in a dose of 2 tablets daily or 600 mg (n=36).
- Analgesics and anti-pyretic agents (n=499) such as paracetamol (2 tablets or 1 g 3-4 times a day) were commonly used to decrease body temperature and for relief of pain in malaria-infected patients, especially to those presenting with complicated malaria (94%) (Table 3.9). Other stronger analgesics such as tramadol (50 mg) was administered three times a day were to patients with moderate to severe pain.

Antihypertensives (n=34), oral hypoglycaemic agents (n=14), as well as anti-lipidaemic drugs (n=6) were prescribed to treat hypertension, diabetes and hyperlipidaemia among chronic co-morbidity patients.

- Nifedipine (n=15) was the commonest antihypertensive prescribed in a dose of 20 mg once daily with more antihypertensives prescribed to HIV-negative patients and the uncomplicated malaria group of patients (Table 3.9).
- Insulin was used in one patient with high blood glucose (54 mmol/ L) to control their blood sugar. An oral hypoglycaemic agent, metformin (500 mg twice daily) was administered to diabetic patients (n = 14) to control blood sugar.
- Simvastatin 20 mg daily was commonly prescribed for the treatment of patients with hyperlipidaemia (n=28).
- Diuretics like furosemide (n=22) were used in the management of patients with renal dysfunction and cardiac disease; which helps in restoring renal function by increasing the urine output from the patients thereby restoring the normal renal function. Patients were

initiated on an intravenous formulation and then as the patients improved it was switched to the oral route.

- Intravenous fluids such as normal saline (n=22) were administered to patients during resuscitation especially among hypovolemic-shock patients.
- To compensate for the hypoglycaemia caused by intravenous quinine causes hypoglycaemia, 50% dextrose (n=36) was administered.

3.6 Ventilation

Based on clinical, biochemical and haematological criteria 112 (38%) of the patients with complicated malaria were admitted to the ICU or high care (WHO, 2014). A total of 93 patients out of 977 (9%) required mechanical ventilation, secondary to acute respiratory distress syndrome (ARDS). Of the patients ventilated, 37% (34/93) were HIV-positive on ARVs. One of the ICU male patients died of a heart attack, while on mechanical ventilation. Of the 93 patients, 25% (23/93) were females and 75% (69/93) were males. A total of 112 patients were admitted into the ICU (Table 3.4), 68% (76/112) required ventilation compared to 2% (16/977) of the whole study group who did not ($p < 0.001$). Patients with complicated malaria and acute kidney injury that required ventilation constituted 66% (74/112)($p < 0.001$); acidotic patients that required ventilation accounted for 47% (53/112)($p < 0.001$).

3.7 Haemodialysis

Of the 977 patients, 109 (11%) required haemodialysis of which 22% (24/109) were females ($p = 0.726$). Patients were categorised based on the number of sessions they had (Figure 3.8). There were 16 females and 51 males that had one session, while only two male patients had four sessions, while one male each had five or seven session. Renal failure accounted for most of the indications for haemodialysis (26%).

3.8 Discharge versus death

Among the 977 patients, 91.8% (897/977) were treated and successfully discharged from the hospital. The total mortality rate during the study period was 3.7% (36/977) out of which 33% (12/36) were HIV-positive, comprising of five females and seven males (Table 3.4; 3.5b). Discharged patients were given appointments to report back to the hospital for follow up.

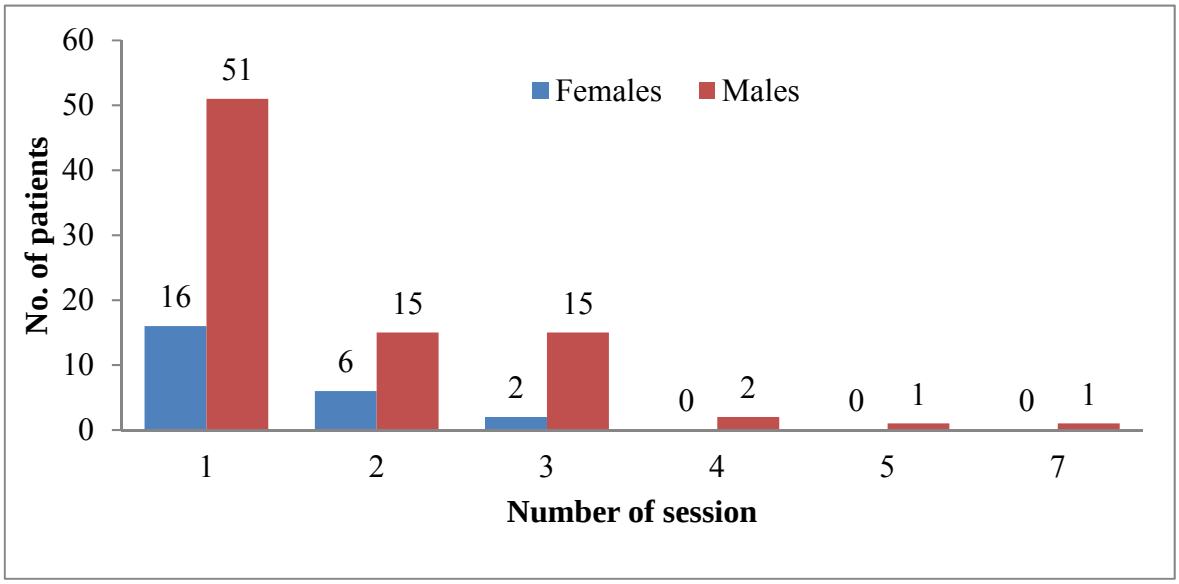


Figure 3.6 Distribution of dialysed patients based on the number of recorded sessions per patient.

3.9 Readmission versus sign against medical advice

There were 3.4% (33/977) patients readmitted over the five year study period, of whom 11 were HIV-positive ($p = 0.189$). However there was no documented history of any previous admission at CHBAH due to a malaria infection, which indicated that these were new infections rather than readmissions due to relapses. Alternatively, this could have been incorrectly interpreted due to missing files or being admitted at another hospital for prior treatment. Despite rigorous counselling, a total of 11 patients discharged themselves against medical advice (SAMA) with two patients being HIV-positive.

3.10 Malaria-related deaths

A total of 36 patients died (11 females and 25 males), during the course of the study period directly due to complications arising from the infection, with all 36 patients fulfilling the WHO criteria for complicated malaria (Table 3.4; Table 3.6). There were no significant age differences between those that died and survived. The criteria that was significantly associated with fatalities included renal failure (75%) and ventilation (67%).

One male patient had a DIC and 10 patients had shock (5 females and 5 males), and 21 patients (10 males and 11 females) had hyperparasitaemia. Laboratory investigations among the patients that died showed minimum white cell count levels were as low as 0.9×10^9 /L in the demised

group compared to those that did not die ($p < 0.001$) (Table 3.6). The mean creatinine was higher in the patients who died compared to the survivor group (197 μmol/l compared to 86 μmol/L). The mean haemoglobin was lower among the patients who died (9.3 g/dL) compared to the survivors, 12.1 g/dL. Total bilirubin was also higher among the patients who died compared to the survivor group (25 μmol/L and16 μmol/L, respectively) ($p = 0.001$) (Table 3.6). The mean alanine transaminase among the patients who died was 57 U/L compared to 28 U/L of the survivor group ($p < 0.001$). All the patients who died were given mechanical ventilation. Cardio-pulmonary resuscitation was also performed on all the patients before they died.

3.11 Malaria and HIV

Of the 977 patients tested for HIV, 36.0% tested positive (Table 3.1) with an average $CD4^+$ T-cell count was 658 x 10^6 cells/μL (range, 22-948 cells/μL). A comparison between the HIV-positive and -negative group showed that 31.3% (110/352) of HIV-positive patients had renal impairment compared to 12.3% (77/625) among HIV-negative patients ($p = 0.05$). There were 12.5% (44/352) of HIV-positive patients with severe anaemia compared to 8.6% (54/625) that were HIV-negative ($p = 0.05$) (Figure 3.7). The hyperparasitaemia was significantly more prevalent in HIV-infected patients compared to the HIV-negative group (44%, 155/352 compared to 9.6%, 60/625) ($p < 0.001$). Acidosis was more prevalent among the HIV-positive group compared to the HIV-negative group (8%, 27/352 versus 7.6%, 48/625) ($p = 0.0162$). A total of 9.7% (34/352) of the HIV-positive patients received mechanical ventilation, while on admission in the ICU compared to 8.9% (56/625) of the HIV-negative group who did not require ventilation ($p = 0.002$).

3.12 ICU Admissions

There were 112 patients admitted to the ICU, among which 41.3% (90/218) were males and 28.5% (22/77) were females ($p = 0.003$). Severe renal impairment was more prevalent among the ICU group (89/112) compared to the non-ICU group (144/865) ($p = 0.005$). There was a significant association between acidotic group (53/112) patients with tacompared to the non-acidotic group (23/865) ($p = 0.05$) with renal impairment.

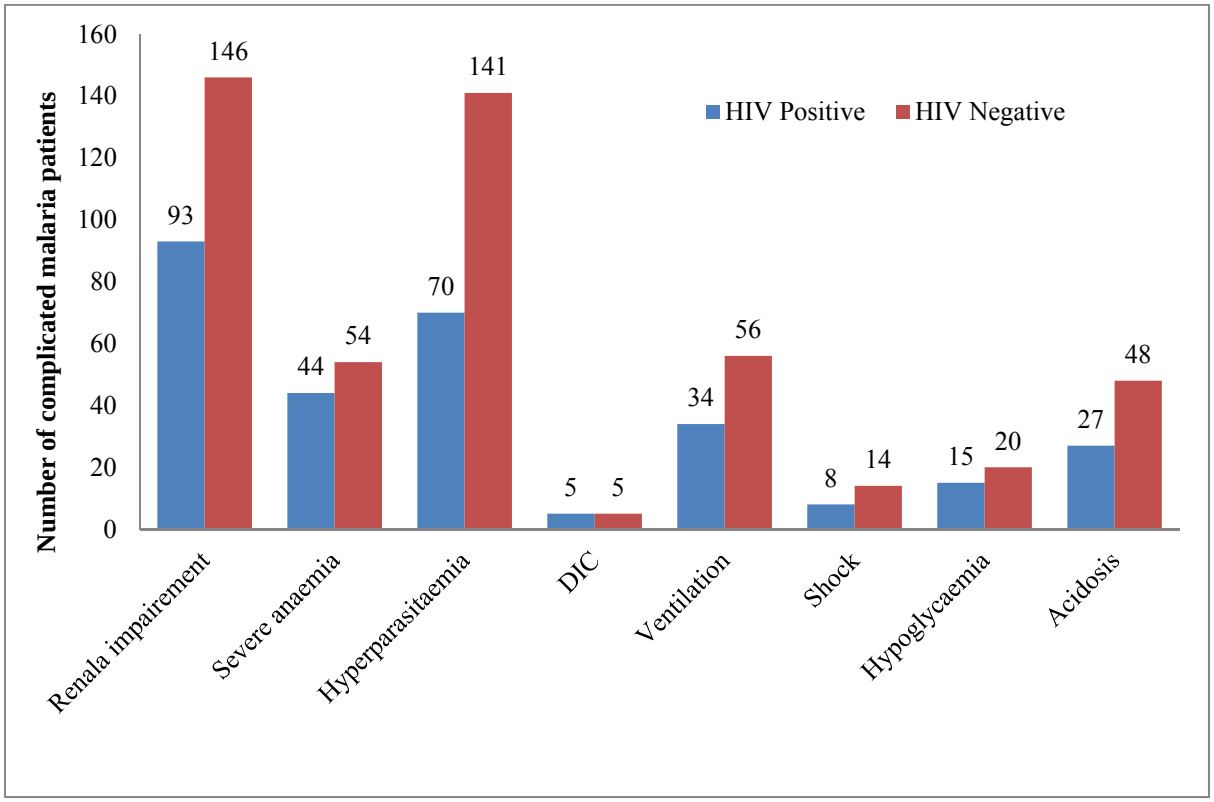


Figure 3.7: Distribution of WHO criteria among complicated malaria patients with HIV.

Hypoglycaemia among complicated malaria patients also had a significant association (25/112) compared to the non-complicated malaria patients (11/865) ($p = 0.05$). Shock, severe anaemia, DIC, ventilation and hyperparasitaemia among ICU patients had a strong association (Table 3.10) compared to the non-ICU group ($p = 0.05$). All ICU patients were infected with *Plasmodium falciparum* species with 107 of 112 ICU patients diagnosed with complicated malaria ($p = 0.003$) and 30 with cerebral malaria (Figure 3.7). Of the remaining five patients with uncomplicated malaria, one patient with a known history of hypertension, had a cardiac arrest and was taken straight to the ICU, another had diabetic complications and the remaining 3 patients had co-morbidity which required ICU admission (Section 3.4). Out of the 108 patients tested for HIV in ICU, 44 were found to be positive ($p < 0.001$).

All the 112 ICU patients had a range of 3 to 6 criteria for complicated malaria. The most common causes of admission to ICU included acute kidney injury (Figure 3.7) with worsening serum creatinine, declining level of consciousness, hepatic dysfunction with worsening jaundice and dyspnoea secondary to acute respiratory distress syndrome. There were 74 ICU patients that required ventilation due to respiratory distress and 16 who did not ($p < 0.001$). Among the admitted ICU patients, 19 died (almost 17% mortality rate) ($p < 0.001$).

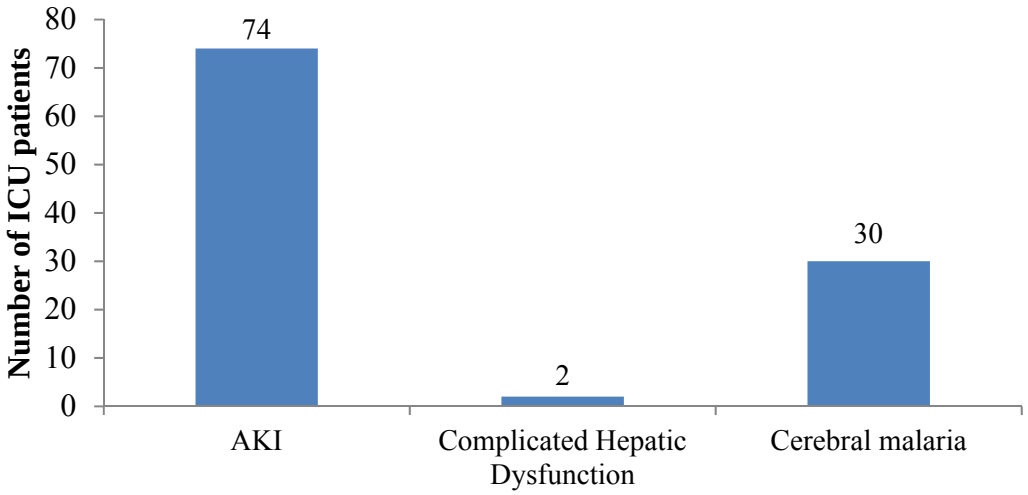


Figure 3.8: Distribution of ICU patients with complicated malaria. (AKI: acute kidney injury).

3.13 Risk factors of complicated malaria among HIV patients

There were six risk factors found to be strongly associated with complicated malaria among HIV-positive patients as shown in Table 3.10.

Table 3.10: Risk factors associated with complicated malaria among HIV patients.

Risk factors	Odd ratio (OR)	p. value	Confidence interval (CI)
Age (>50 years)	1.10	P = 0.02	1.02-1.19
$CD4^+$ <T-cell200 cells/µL	0.46	P = 0.03	0.23-0.91
Platelets (<137 x 10^9/L)	0.99	P = 0.002	0.98-0.99
Haemoglobin (<7 g/dL)	0.62	P < 0.05	0.48-0.80
Creatinine (>265 µmol/L)	1.02	P < 0.05	1.01-1.03
Total bilirubin (>43 mmol/L)	1.04	P = 0.002	1.01-1.06

Logistic regression model analysis indicated that the following factors were found to be associated with an increased risk of complicated malaria among HIV-patients, namely: increased age (greater than 50 years) (p = 0.02), low $CD4^+$ T-cell count (less than 200 cells/µL) (p = 0.03), low platelets (less than 137 x 10^9/L)((p < 0.001), low haemoglobin (less than 7 g/dL) (p < 0.001) and high creatinine level (greater than 265 µmol/L)(p < 0.001), as well as high bilirubin (greater than 43 mmol/L)(p = 0.002)(Table 3.10). The median cell count in the HIV infected patients was 658 x 10^6 cells/µL. According to the logistic model, among the HIV

patients, the older patients had a higher risk of complicated malaria. For a one year increase in age, the risk of complicated malaria increased by 5%. Among the patients who were HIV-positive, a decrease in $CD4^+$ T-cell count by 200 cells/μL is associated with increased risk of complicated malaria. For a unit increase in haemoglobin, the odds of having complicated malaria among HIV-positive patients were reduced by more than 20% and vice versa. A reduction in platelet count among HIV patients increased the risk of developing DIC and complicated malaria. Increased creatinine levels in HIV-positive patients increased the risk of renal dysfunction and having complicated malaria. High levels of total bilirubin among HIV patients increased the risk of having complicated malaria. Even though place of residence is a risk factor for malaria and HIV; it was not included in this analysis because some patients declared themselves to be South African citizens on the demographic record. However, it was found that there were language barriers and these patients spoke a foreign (non-South African) language. Hence this is probably an under estimated number of foreign residents, making it difficult to be included as a risk factor.

3.14 Cost of patient treatment and disease severity

The Table 3.11 below shows the median costs, and ranges of antimalarial, ARV, ICU, general ward and other drug costs among complicated and uncomplicated malaria-infected patients. The total cost of the other administered drugs included the analgesics, antibiotics and antidepressants (Appendix G).

Table 3.11: General costing of patient treatment in South African rands.

Disease severity	Cost item	Median	25th percentile	75th percentile
Uncomplicated malaria	Antimalarial cost	270.39	9.37	378.55
	ARV cost	68.11	68.11	68.11
	ICU cost	1,304.00	1,141.00	4,565.00
	General ward cost	2,322.00	1,548.00	3,870.00
	Other drug costs	5.29	2.27	41.20
Complicated malaria	Antimalarial cost	303.95	196.41	378.55
	ARV cost	68.11	68.11	68.11
	ICU cost	7,826.00	3,913.00	15,652.00
	General ward cost	5,418.00	3,096.00	8,514.00
	Other drug costs	53.90	25.87	161.10

Patient costings were based on public sector prices using the Master Price Catalogue issued by the National Department of Health (28th August 2015). Pricing was adjusted to reflect 2015

cost. Costing was not normally distributed; so the Wilcoxon sum rank test was used to test the differences. There was a significant difference in costing between complicated and uncomplicated malaria ($p < 0.001$). The average total cost per admission with uncomplicated malaria and HIV was R 3,969.79 (range: R 2,768.74-R 8,922.86) compared to R 13,669.96 (range: R 7,299.39-R 24,773.76) of the complicated group with HIV. In comparison, the average total cost per admission of uncomplicated malaria without HIV was R 3,901.68 (range, R 2,700.64-R 8,854.55). The average total cost per admission of complicated malaria without HIV was R 13,601.85 (range: R 7,231.28-R 24,705.55) (Table 3.11). Meanwhile, the average total cost per year for the uncomplicated malaria with HIV over the five year period of the study was R 541,479.39 compared to R 806,527.64 of the complicated group with HIV. Moreover, the average total cost per year for uncomplicated malaria without HIV was R 532,189.16 compared to R 802,509.16 of the complicated group. However, there was a difference between antimalarial costs per person among uncomplicated group (median cost: R 270.39; range: R 9.37-R 378.55) compared to complicated group (median cost: R 303.95; range: R 196.41-R 378.55) ($p < 0.001$).

There was no difference in ARV cost per person among the two groups.. However, the costing of an ICU admission per person with complicated malaria was R 7,826.00 (median cost) with a range of R 3,913.00-R 15,652.00 ($p < 0.001$). The median cost for the general ward per person among uncomplicated malaria patients was R 2,322.00 with a range of R 1,548.00- R 3,870.00; compared to R 5,418.00 median cost among the complicated malaria patients with a range of R 3,096.00-R 8,514.00 ($p < 0.001$). The cost of other drugs administered per person (Table 3.11). General ward admission and ICU cost per person (including maximum and minimum amounts) for the complicated and uncomplicated malaria patients are compared in Table 3.12.

Table 3.12: Cost distribution of other drugs administered (median cost), general and ICU ward per individuals.

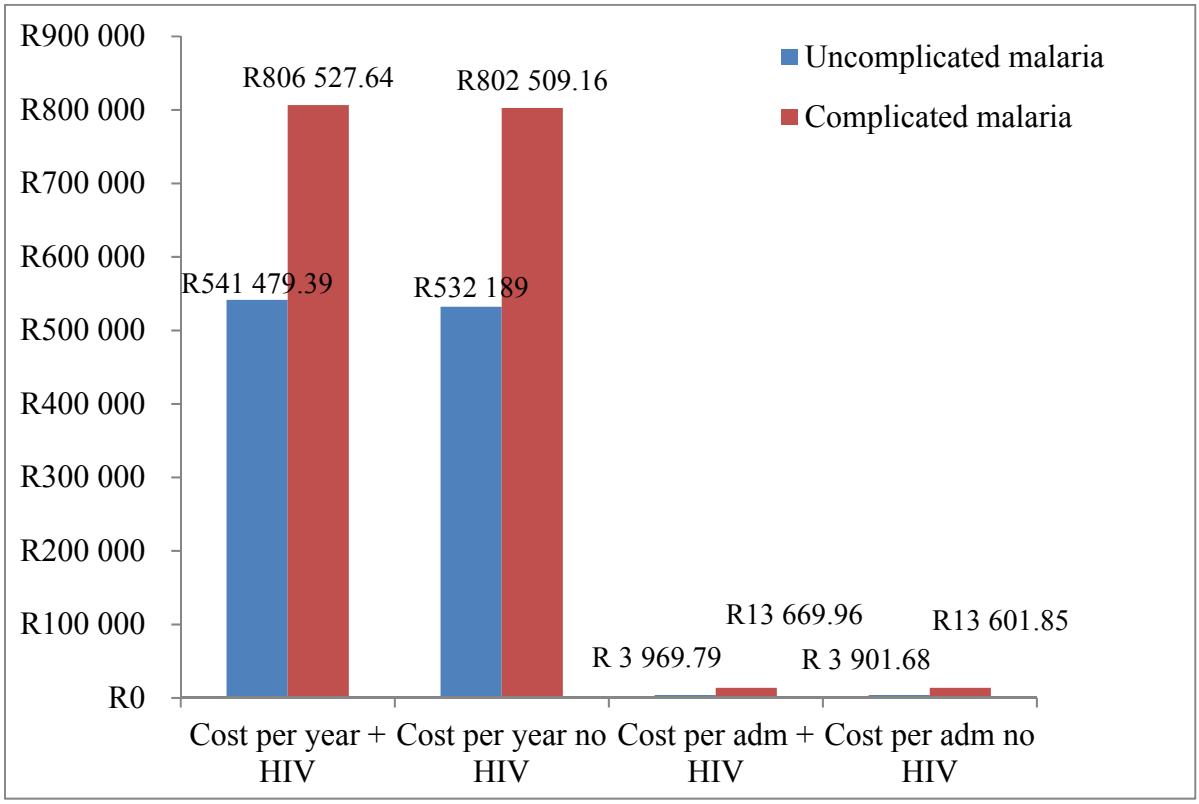
Cost item	Other drugs cost/person (median cost)	General ward admission cost/ person (Max/ Min)	ICU cost/ person (Max/ Min)
Uncomplicated malaria	R 5.29 (range: R 2.27- R 41.20)	R 23,220.00/ R 233.00	N/A
Complicated malaria	R 53.9 (range: R 25.87- R 161.1)	R 53,406.00/ R 233.00	R 39,120.00/ R 652.00
Duration / person	14 days / 3 days	3 month/ one day	120 hours/ 2 hours

N/A: not applicable

The ICU admission was measured based on the number of hour's each patient spent on admission (Table 3.11); where a total of 5,948 hours were spent on admission by all the ICU patients. Patients in ICU were charged based on the hours spent in the unit (per 12 hours). A total of R 3,913.00 was charged per 12 hours.

The ARV costing for the complicated and uncomplicated malaria were virtually the same since the regimens were in a fixed dose and were given for same duration over one month; however, a median cost of ARV for one month per person was R 68.11 with a maximum cost of R 117.24 and were the same for those patients with complicated or uncomplicated malaria. Comparisons between costing of patients' treatment and outcomes using Students T-test showed only General Ward costs to be relative significant between patients that died and those discharged ($p = 0.0339$); however, there was no association among readmitted and SAMA patients. Figure 3.9 and 3.10 illustrates cost distribution of malaria and HIV treatment per year and per admission, as well as drugs and admission cost per person respectively in South African rands (ZAR).

Costing of antihypertensive, oral hypoglycaemic, and anti-lipidaemic drugs among chronic co-morbidity patients before hospital admission were not included in the other drug cost. Patients with comorbidities were commonly on a long-term medication prior to hospital admission, which was likely to continue during admission and subject to dose adjustment depending on the patient's clinical condition.



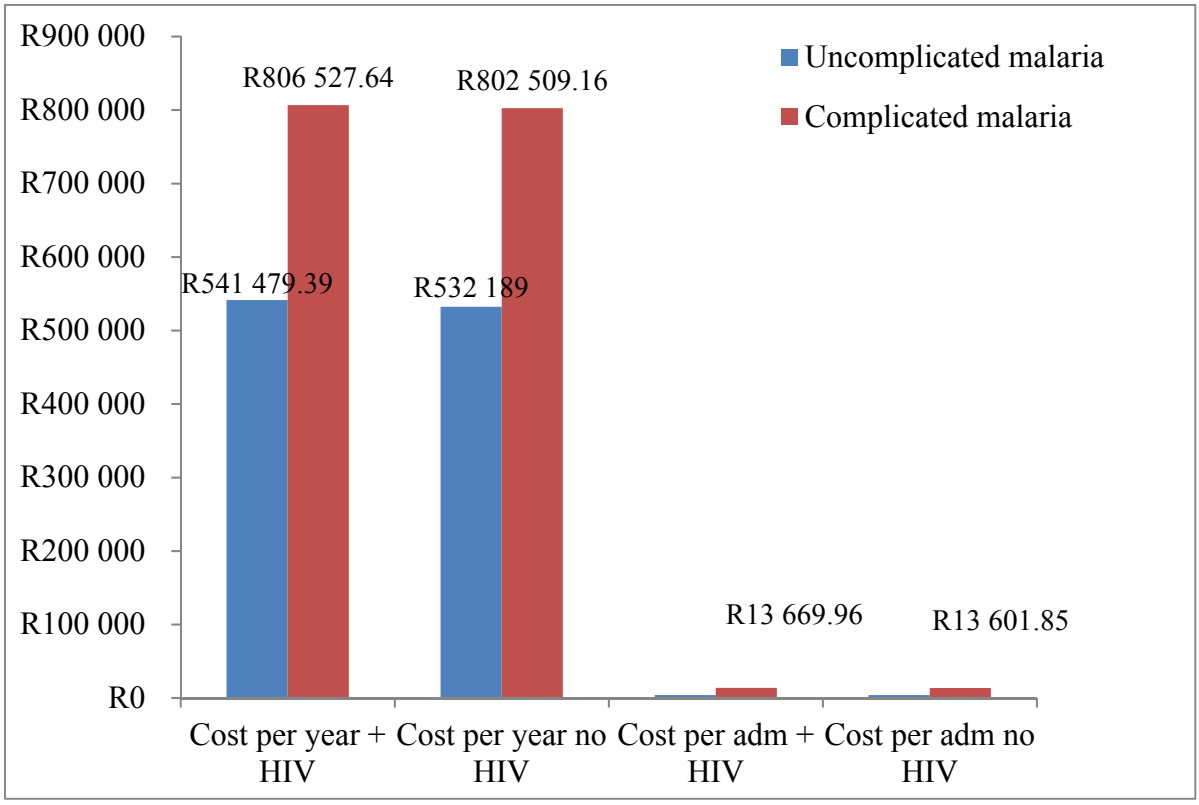


Figure 3.9: Cost distribution of malaria and HIV treatment per year (ZAR) and per admission.

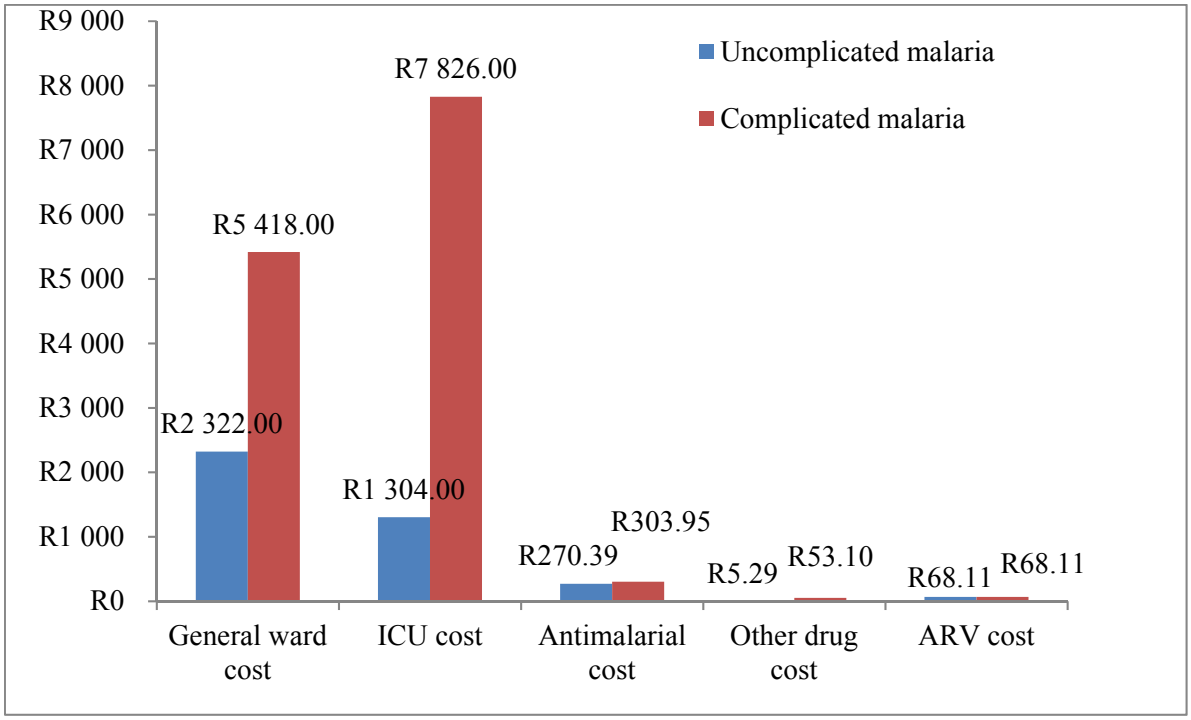


Figure 3.10 Distribution admission and drug cost (ZAR) among individuals with malaria.

Chapter Four: Discussion

4.1 Malaria incidences in South Africa

The number of malaria cases reported at CHBAH from 2011 to 2015 were relatively consistent at 195.8 per year (total number of cases: 977) (Table 3.1), even though the overall incidence of malaria in South Africa has been reported to be on the decrease since 2000 (Perovic *et al*., 2000). A retrospective survey of malaria cases diagnosed in CHBAH showed a significant escalation in the number of malaria cases over the six-year period of the study with 207 cases in 1993 to 508 cases in 1998, with a total number of 2044 cases over the six year period (Perovic *et al*., 2000). Meanwhile, another retrospective study conducted in a non-endemic area of South Africa, namely, Pretoria and Johannesburg showed an increasing number of malaria cases in South Africa (Reddy *et al*., 2016; Dube *et al*., 2008). Some of the factors that may increase the number of reported malaria cases in South Africa could probably be explained by the changes in weather patterns of South Africa; proximity to neighbours where no malaria control systems in place and migration of people from such areas; development of resistance by the malaria parasite and/or the possible effect of HIV on Southern African population (Maharaj *et al*., 2016). Recently, Johannesburg witnessed an increase in number of imported malaria cases despite being in a non-malaria endemic region. Similarly, a study conducted in Pretoria showed a considerable increase in the number of imported malaria cases into this non-endemic area (Dube *et al*., 2008). The mean age of the patients in the current study was 33 years (range: 25-45 years) (Table 3.2). This was consistent with a study conducted in CHBAH, Johannesburg in 2004 where the age range was 15-49 years and mean age was 30 years (Cohen *et al*., 2005). A total of 68% of the study population was male, which is comparable to the Limpopo and Mpumalanga study where men were predominately infected with malaria; as reported in the current study (Table 3.2). Reasons for this increase amongst men may include: determined nature of men to search for a job in neighbouring countries, high social activities among males or sleeping outdoors which have also been reported in other studies (Cotter *et al*., 2013). However, a small percentage of malaria cases were locally transmitted from endemic provinces (Figure 3.2).

4.1.1 Imported malaria

A total of 86% of the cases in this study had a positive travel history to endemic neighbouring countries, from endemic provinces of South Africa (Figure 3.2). About 80% of the malaria

infections were acquired and imported from neighbouring countries; with the highest number of imported cases from Mozambique, Zimbabwe and Malawi (Figure 3.2). Endemic provinces of South Africa contributed to only 4% of the cases reported on in this study. This is comparable with a study conducted in Gauteng where 84% of malaria was acquired from Mozambique (Reddy, 2016; Perovic *et al*., 2000); whilst nationals from Somalia and Bangladesh dominated the number of imported malaria cases in Cape Town (Opie *et al*., 2014). Gauteng, a non-malaria province, the economic capital of the South Africa, and home to international travel, continues to receive migrant labourers looking for a job and bringing with them imported malaria. This would eventually exact pressure on the health care system of the province and nation at large. The Gauteng province contributes 20% of South Africa's malaria cases, mainly in the form of imported cases (Frean *et al*., 2014). A total of 14% of the patients had no travel history documented, nor a history of mechanical transmission, such as a blood transfusion; and as such some of these patients could have been cases of Odyssean malaria. Where Odyssean malaria is defined as malaria acquired in a non-malarious/non-endemic area from the bite of an imported mosquito. Poor understanding of this type of malaria among health care workers may lead to delayed diagnosis and treatment, where many diagnoses of malaria are made at autopsy (Frean *et al*., 2014). Gauteng is home to an international airport and a large number of road travellers from neighbouring endemic countries and provinces; where mosquitoes can be transported in suitcases, taxis, minibuses and hand luggage to various parts of the province, thereby increasing the burden (Frean *et al*., 2014; Dlamini, 2014). A total of 46 cases of Odyssean malaria were diagnosed from 1996-2004 in Gauteng; with another study reporting 14 laboratory confirmed cases and seven probable cases of Odyssean malaria with two deaths (Dlamini, 2014; Frean *et al*., 2014). Currently there have been several news reports of malaria cases being diagnosed in non-malaria areas in South Africa and have been attributed to be cases of Odyssean malaria (News24, 2017).

4.1.2 Seasonal variation

Seasonal transmission has been found to increase during January and February, with summer and autumn being the peak seasons; however, there were decreased malaria infections rates between June to November. These latter months coincide with the winter period, which is not favourable for the mosquitoes to thrive (SADOH, 2016). This trend was observed over the five year study period. The two seasons were probably related to both favourable climate conditions and the festive period during which people travelled more to visit relatives/friends. Studies

show that people from stable malaria areas who travel across the borders into the endemic countries as well as endemic provinces to visit relatives were more prone to malaria infection than those who travelled for an unrelated reason. Marks *et al*. (2014b) proposed that the potentially low risk of developing complicated malaria was due to partial immunity that these travellers had acquired over the years of commuting. But this needs further verification for the population group being admitted to CHBAH. It would appear as if the majority of the population in this study neither took prophylaxis for malaria nor sought medical advice prior to the journey as evidenced from the patients' history profile record. This was in keeping with a South African study which showed poor adherence and improper use of prophylactic antimalarial drugs (Leggat *et al*., 2002). Previous studies have shown that these patient are at risk of contracting malaria (Dube *et al*., 2008, Dlamini, 2014). Studies have shown that more than 10,000 international travellers who visit malaria endemic areas acquire malaria every year and in most of these cases, malaria prophylaxis either was not prescribed, incorrectly prescribed or the patient did not adhere to prophylaxis (Pavli *et al.*, 2017). Moreover, it was noticed that in the cohort of this study, there was poor documentation in the patients' history profile of taking malaria prophylaxis. It is unclear whether in fact this omission is due to the patients not being asked by the health care staff or just not recorded. For a complete history of the patients, it could be recommended that this question be added to the standard patient history sheet to be obtained on admission.

Delay in the diagnosis of malaria among newly diagnosed HIV-positive patients was observed but not recorded in this study. A delay of 1-2 days is known to worsen the patient outcome and prognosis (Trampuz *et al*., 2003). Two studies done in CHBAH have shown a mean delay of less than one day for HIV-positive and HIV-negative patients with malaria, and found no association with increased risk of complicated malaria (Perovic *et al*., 2000, Cohen *et al.*, 2005).

4.1.3 Laboratory results

Thrombocytopenia was recorded in 11% of our study population (Table 3.3), which is in contrast with other studies in which thrombocytopenia was the most common laboratory abnormality in patients with malaria (Santos *et al*., 2012; Perovic *et al*., 2000). Thrombocytopenia should raise a high index of suspicion when co-incidentally found in a patient with or without travel history to malaria endemic areas (Frean *et al*., 2014). The mechanism of thrombocytopenia is partially immune-mediated during malaria infection,

platelet aggregation and low activity of platelet leading to intravascular lysis and platelet consumption (Akhtar *et al*., 2016). Another study has shown that thrombocytopenia is not associated with adverse outcomes, because the platelet count tends to increase 3-4 days after admission; however, the correlation between thrombocytopenia and malaria is more pronounced with *P. falciparum* (Singh *et al*., 2016).

In this study, 26% of patients had severe renal failure with a significant association between those that died and survivors (Table 3.6). Other studies reported an increased incidence of renal failure in patients admitted with imported malaria to be as high as 53%, with a range of 23-75% in prior studies (Liese *et al*., 2015; Saravu *et al*., 2014) and as low as 1-5% in endemic areas (Marks *et al*., 2014b). There are several reasons for the reduced incidence of renal failure in the study cohort, such as quality of care or dialysis facilities. A large number of patients could ot be classified as having renal failure in line with the WHO guidelines (moderate renal failure); however, patients with renal failure in this study tended to improve after antimalarial therapy and fluid resuscitation alone. The series of events that lead to AKI includes: cell adherence of parasitised red blood cells to glomerular blood vessels, cytokine release, immune complex deposition, hypovolaemia and haemolysis (Marks *et al*., 2014b). A total of 11% of the patients required haemodialysis (Figure 3.6) and all of them were admitted to the ICU. Renal failure accounted for one-quarter of the complications of patients admitted to ICU (Figure 3.8). Renal failure patients had very high levels of creatinine which was associated with a high risk of mortality (Table 3.6); however, dialysis was able to reduce the risk of mortality. A study conducted in Vietnam showed two-thirds of the mortality among non-dialysed patients with renal failure and one-third mortality among dialysed, meanwhile rapid initiation of haemodialysis proved useful in the restoration of renal function (Bruneel *et al*., 2003, Boushab *et al*., 2016). Moreover, the same study showed the superiority of haemodialysis over peritoneal dialysis. Meanwhile, venovenous haemodialysis has also been shown to be effective in malaria patients (SADOH, 2016), which is consistent with the findings in this study (Figure 3.6).

Severe anaemia is defined as haemoglobin level less than 7 g/dl according to the South African Department of Health (SADOH, 2016).) Severe anaemia causes serious morbidity and mortality and develops rapidly among malaria patients. Anaemia may result from a combination of either of the following or both: haemolysis, dyserythropoeisis, and subsequent elimination of the parasitised red blood cells from the system by the spleen (Marks *et al*., 2013). Severe anaemia occurred in 10% of the study population (Table 3.3), where the majority of the patients

presenting with mild (n= 671) to moderate (n= 208) anaemia responded well to haematinics and conservative management. Pre-haemoglobin levels of 8.7 g/dl improved to 11.7 g/dl post treatment. Where mild anaemia was defined as a haemoglobin level between 9.5-13 g/dl, moderate anaemia as 8.0-9.5 g/dl and severe as <7.0 g/dl. About half of the patients with severe anaemia (n= 98) in this study had a blood transfusion. Exchange blood transfusions were not performed in any of the patients in our study. This technique has been around for over four decades and has been used as part of the treatment protocol in complicated malaria patients with high levels of parasitaemia; thereby reducing parasite load, parasite-mediated antigen volume, as well as immune mediated cytokines (Riddle *et al*., 2002, Marks *et al.*, 2014b). The efficacy of this exchange blood transfusion technique remains controversial. A meta-analysis conducted by Riddle *et al*. (2002) found that there was no survival benefit among patients treated with an exchange blood transfusion. However, a single-centred study found that there was no mortality among 25 individuals who were managed on exchange blood transfusion (Marks *et al*., 2014b). Due to the surrounding controversies, exchange blood transfusion has not yet been advocated to be used in national guidelines or the WHO.

The pathogenesis of hypoglycaemia in complicated malaria patients is thought to result from utilization of blood glucose by the parasite and interference with the patient's gluconeogenesis rather than increased blood insulin or malnutrition; however, low blood glucose or hypoglycaemia can be exaggerated by intravenous quinine therapy (Barennes *et al*., 2016).

Expectedly, *P. falciparum* was the only species detected in this cohort, with 90% of the laboratory reports indicating *P. falciparum;* with the remainder of the patient files reporting a "malaria" infection. The latter were confirmed *P. falciparum* infections since the RDT used at CHBAH only detects this species. This implied that the cross-border migration was solely within sub-Saharan Africa, where it has been reported that more than 90% of malaria infections were caused by this species (Dube *et al*., 2008). Other species such as *P. vivax,* and *P. ovale* were less likely to cause severe infection, but have been shown in other regions like Asia, Central America and North Africa (Saravu *et al*., 2014; Roe and Pasvol, 2009).

4.1.4 Risk factors of complicated malaria among HIV-infected patients

Following multivariate regression analysis, the risk of complicated malaria among HIV-positive patients was found to be associated with: increased age (greater than 50 years), low $CD4^+$ T-cell count (<200 cells/μL), low platelets (<137 x 10^9/L), low haemoglobin (<7 g/dL)

and high creatinine level (>265 μmol/L), as well as high bilirubin (>43 mmol/L) (Table 3.3). Low level haemoglobin or anaemia may be primarily due to malaria or HIV or both leading to an additive effect, where co-infection leads to lower mean haemoglobin levels among HIV-positive than HIV-negative patient, which is in keeping with other studies (Shah *et al*., 2006).

The $CD4^+$ T-cell count below 200 cells/μL were associated with increased risk of complicated malaria among HIV patients; this scenario has been observed in areas of low unstable transmission, however, strong reliable data reports in endemic areas are still lacking (González *et al*., 2012). A small Ugandan study reported that multiple *P. falciparum* infections were associated with an acute reduction in $CD4^+$ T-cell counts possibly due to loss of immune responsiveness to the malaria antigen (Mermin *et al*., 2006). While in Zambia, it was reported that a higher risk of recurrent parasitaemia among co-infected patients with low $CD4^+$ T-cell less than 300 cells/μL compared to uninfected patients was obtained (Shah *et al*., 2006).

Repeated infections with *P. falciparum* lead to a reduction in the $CD4^+$ T-cell count that allowed for a shorter recovery time, and were correlated with a high burden of opportunistic infection and sepsis as reported in sub-Saharan Africa (González *et al*., 2012). It has also been shown that systemic anti-coagulant pathways were significantly impaired in sepsis and malaria with subsequent consumption of anti-coagulants, as shown by reduced plasma levels of anti-thrombin, protein C and free protein S among co-infected patients (Huson *et al*., 2016).

The diagnosis and treatment of patients with a co-infection were observed to be delayed among newly diagnosed co-infected patients in this study, since not all HIV-patients were routinely diagnosed. A cross-sectional study conducted in central Ethiopia reported that fear of stigmatisation in addition to auto-medication and delay in diagnosis by doctors, as a possible reason for delayed hospital presentation and ultimately delayed diagnosis and treatment (Tadesse *et al*., 2016; Cohen *et al*., 2005; Marks *et al*., 2013). Despite being conducted in a tertiary hospital where specialist and modern equipment were expected to be available, mortality among the malaria and HIV co-infected was 12/352 (Table 3.5b). A large study conducted in endemic rural areas of South Africa reported mortality of 50-60% among co-infected patients, where no such facilities and expertise existed (Mee *et al*., 2016). However, provision of adequate training and treatment facilities would avert such mortalities (Nimmo and Clapham, 2016). The median $CD4^+$ T-cell counts among this study's' population group were relatively low, which may explain the increased prevalence of complicated malaria among the co-infected group (Table 3.6). However, this study group may exhibit clinical features that

resemble both clinical malaria and opportunistic infections. A Kenyan study reported that immunosuppressed HIV-infected adults suffer from recurrent malaria-like symptoms that may be wrongly diagnosed as malaria and treated as such, thereby placing huge pressure on antimalarial drugs (Sanders *et al*., 2011). This latter study forecasted higher prevalence of resistant parasites in endemic areas.

4.1.5 ICU patients

ICU admission is prioritised in patients with complicated malaria because of possible rapid deterioration of patient's condition within the first 24 hours; however, a high standard of care will go a long way in reducing mortality especially during the acute stage (Santos *et al*., 2012). In developed countries, the presence of at least a life-threatening organ dysfunction among malaria patients warrants ICU admission, however this is not the case in sub-Saharan Africa due to limited financial resources (Bruneel *et al*., 2010). Admission into the ICU is determined by the availability of the bed space irrespective of the patient's clinical condition; with other patients having to be delayed in a general ward before being transferred to the ICU. All the 112 patients with complicated malaria that required ICU admission in this study were eventually admitted (Figure 3.8), and closely monitored, and had treatment support according to the dysfunction presented. The presence of cerebral malaria, respiratory distress, acute renal failure, worsening jaundice, hyperparasitaemia, metabolic acidosis, hypoglycaemia, shock, DIC and co-infection were significantly associated parameters that predicted ICU care being required ($p< 0.001$) (Table 3.3) – an expected correlation. Hence indicating a strong association between ICU admission and complicated malaria. Admitted ICU patients in this study had an average of 4 WHO criteria (range, 3-6), whilst according to a study conducted in Portugal, the presence of at least one WHO criteria warranted ICU admission. However, the presence of more than three criteria carried an 80% higher chance of being admitted into the ICU due to clinical deterioration of patient's condition (Sagaki *et al*., 2013, Santos *et al.,* 2012). In this study, it was recorded that there was a mortality rate of 17% among the ICU patients with complicated malaria (Section 3.12). However, no mortality was recorded among patients on intravenous artesunate, all 36 patients that died were on quinine treatment. In two Asian studies comparing artemisinin and quinine therapy in adults with complicated malaria in stable regions, it was found that there was a mortality rate of 15%/13% in patients on artemisinin compared to 22%/17% in patients on quinine in the respective studies (Dondorp *et al*., 2005; Hien *et al*., 1996). A lower mortality rate of 10.5% and 10-25% were respectively reported in two additional

studies conducted in London and Portugal (Santos *et al.*, 2012; Marks *et al*., 2013). The low percentage of patients who received artesunate over this five year period, can be attributed to the procedures at CHBAH to access artesunate. The drug is managed and its distribution controlled by the ICU staff and after hours the drug was not easily accessible resulting in quinine/doxycycline being administered as an alternative (Prof C. Menezes, personal communication). The overall profile of patient outcomes should dramatically improve with the 2017 registration of the drug in South Africa (MIC, 2017).

Predictors of mortality among this study's cohort included acute renal failure and requiring mechanical ventilation (respiratory distress and ARDS) (Table 3.6; Section3.6). The latter arose from endothelial dysfunction and changes in capillary permeability due to cell adherence and sequestration of parasitised red blood cells; as well as exaggerated inflammatory and immune responses of the host, particularly interleukin-1 (IL-1), IL-6, IL-8 and TNF-α (Marks *et al*., 2013). Contrary to other studies, the current study did not find a strong association between mortality and the following criteria: hypoglycaemia, severe anaemia, hyperparasitaemia and shock, even though the latter were more frequent among patients who died (Table 3.3). However, prognostic values of the latter criteria were more pronounced among children than adults and the commonest cause of death among complicated malaria patients particularly in the ICU (Marks *et al*., 2013). Other reasons reported for not observing any correlation could include the small sample size of the study done over a long period of time (Bruneel *et al*., 2003). In addition, research done in an industrialised non-endemic country among severe imported malaria patients, no variable was found to be significantly associated with the risk of death (Marks *et al*., 2014a). Community-acquired Gram-negative bacterial infections like pneumonia were more frequent especially among the co-infected patients with complicated malaria (Section 3.5.4), moreover, data on the frequency of bacteraemia among adults were very few, as previously reported (Marks *et al*., 2014a), where malaria-induced immunosuppression and impaired splanchnic perfusion, were the main aetiology behind the pathology. However, some studies reported on the prevalence of confirmed community-acquired bacterial infections among patients requiring ICU admission with malaria reaching 5-10% (Marks *et al*., 2014b). Gram-negative bacteria with non-typhoidal salmonella infections have been more commonly reported among children with malaria than adults (Berkley *et al*., 1999). The bacterial infections among the patients in this study were sensitive to amoxicillin-clavulanic acid and intravenous ceftriaxone was administered to 46% of the patients following bacterial confirmation from

blood culture, with a rapid clinical response after 48-72 hours of starting treatment (Table 3.7; Table 3.9).

4.1.6 Malaria treatment

Malaria treatment in terms of dosage and duration of treatment in the vast majority of cases was in accordance with South African guidelines for malaria treatment, issued by the South African Department of Health (Table 1.2). Quinine was the most frequent drug used in the treatment of complicated malaria in our cohort either as monotherapy or in combination with other drugs (Table 3.7). The loading dose of quinine improved clinical response, but failed to prevent the death of 36 patients in this study (Table 3.5a,b). Intravenous quinine was previously the most effective treatment for complicated malaria before the emergence of chloroquine resistance in the 1970s (Lin *et al*., 2010). Even though quinine is still effective against *P. falciparum* malaria, resistance to it has been detected in South-East Asian countries like Cambodia and less frequently in sub-Saharan Africa (Amaratunga *et al*., 2012). However, malaria resistance to quinine is a relative term in context rather than an absolute term, meaning some malaria parasites remain sensitive to quinine despite evidence of resistance to quinine (resistance to quinine does not mean zero sensitivity to the drug). Quinine is a known secretagogous drug, and as such hypoglycaemia and QT-prolongation monitoring is the rule when treating patients being administered a quinine regimen (Noubiap, 2014).

A total of 50% of the patients were treated with oral artemether-lumefantrine with a remarkable clinical response (Table 3.7), which along with its convenient dosing schedule and better-tolerated side effects are reasons why it has been recommended by WHO as first-line treatment for uncomplicated malaria (WHO, 2016). Artemether-lumefantrine remains efficacious in South Africa with no reported cases of resistance to date (Dr J. Raman; SA-NICD, 2017 personal communication). Intravenous artesunate was administered in less than 5% of the complicated malaria patients in this study (Table 3.7), and as expected, with remarkable patient recovery and death prevention in all the patients that were treated with it (Table 3.7). According to the South African guidelines for malaria treatment, parenteral artesunate prevents malaria-related death in 32% of patients receiving it, in addition to better survival rate (SADOH, 2016; Dr J. Raman, SA-NICD, 2017 personal communication). Recently, a large randomised clinical trial showed that artemisinin derivatives like artesunate were superior to quinine for the treatment of complicated malaria (Dondorp *et al*., 2010). Based on all the clinical data available, artesunate is now licenced in South Africa, as in many other European countries (MIC, 2017;

Lalloo *et al*., 2016; SADOH, 2016; Sinclair *et al*., 2011). The advantage of artemisinin derivatives over quinine is that monitoring of hypoglycaemia and QT-prolongation is not necessary. However, monotherapy of artemisinin derivatives is associated with a high rate of recrudescence and as such should be combined with lumefantrine as recommended for the South African population (SADOH, 2016). Despite its effectiveness, partial artemisinin resistance has been reported along the Thai-Cambodian border, with the delayed clearance associated single nucleotide polymorphisms in the parasite as the main pathology, however, K13 mutations have also been implicated (Putaporntip *et al*., 2016). Meanwhile, in South Africa two single nucleotide polymorphisms on chromosome 10 and 13 were identified as useful markers of delayed parasite clearance during a surveillance study for artemisinin resistance (Lin *et al*., 2010). Treatment failure in South Africa has yet to be reported with ACT, but concerns about resistance spreading to sub-Saharan Africa is a major fear (WHO, 2016). Since the year 2012, post artemisinin delayed haemolysis complicated by AKI was reported among 38 non-immune patients with malaria after a few weeks of drug administration. The proposed mechanism included damaging of ring stage parasitised red blood cells followed by subsequent destruction by spleen, however, this phenomenon was not observed in this study, and has not been reported in non-endemic areas yet (Plewes *et al*., 2015).

When comparing the clinical outcomes, the quinine-doxycycline regimen was found to be less efficacious compared to artemether-lumefantrine; as well as artesunate (Table 3.8). The rate at which artemether-lumefantrine and artesunate reduced the parasitaemia within one day of commencement of treatment was remarkably faster when compared to quinine-doxycycline among the complicated and uncomplicated malaria patients with or without HIV (Table 3.8). The case fatality rate increased among the complicated malaria patients with increased parasitaemia, especially among HIV-positive patients (Table 3.5a; 3.5b). The efficacy of ACT was significantly more superior compared to quinine with other clinical outcomes also showing a significant improvement with the initiation of treatment. This contrasts to some other studies which indicated no significant difference with these outcomes (Gupta *et al*., 2017). Moreover, patients treated with either quinine or artemisinin-based antimalarials, all showed a considerable rise in platelet count within 24 hours of treatment in both complicated and uncomplicated malaria patients with or without HIV (Table 3.8). This improvement has also been previously reported (Santos *et al.*, 2012). In the current study thrombocytopenia among complicated malaria patients (n=107) on day 1 of admission did not completely correlate with an increase in disease severity (Figure 3.3; Table 3.8); but demonstrated good prognostic values

(Gupta *et al*., 2017). Despite marked thrombocytopenia among the patients in this study, there was a small number of patients presenting with bleeding (n=3) as reported in the study by Das and Ganguly (2017). Unexplained recoveries of platelet count noticed among these patients require further explanation by researchers. Leucocytosis (increased white blood cell count) was slightly higher among the complicated malaria patients (commonly due to sepsis), but improved relatively faster with intravenous artesunate than quinine-doxycycline regimen in both HIV-positive and HIV-negative patients (Table 3.8). The average white blood cell count on date 1 of admission was significantly higher among patients treated with both antimalarials (Figure 3.3; Table 3.8). Haemoglobin counts showed a slight increase among patients receiving both antimalarial drugs (HIV-positive and HIV-negative patients)(Table 3.8). Accordingly, most patients were anaemic, mild anaemia (Hb < 9.5-13.5 g/dL, n= 671), to moderate anaemia (Hb < 8.0-9 g/dL.5n= 208) but severe anaemia (Hb < 7.0 g/dL, n= 98) was relatively infrequent. This is indicative of the fact that the current study was performed exclusively in adult patients, with some studies suggesting that the prognostic value of the haemoglobin concentration and platelet count may have little impact in the adult population (D'Souza *et al*., 2017). However, low levels of haemoglobin and platelets can be used to predict disease progression and these haematological changes enable clinicians to establish an effective and early therapeutic intervention in order to prevent the occurrence of severe complications. A comparative study on haematological changes in infections due to *P. vivax* and *P. falciparum* indicated that characteristic haematological changes could be an important prognostic indicator in the diagnosis of malaria and the type of malaria. For instance, patients with *P. vivax* and *P. falciparum* malaria experience a high degree of thrombocytopenia as demonstrated by this study (D'Souza *et al*., 2017), which is in keeping with the findings in the current *P. falciparum* infected patients (Table 3.3; 3.8).

Significant increases in the activity of liver enzymes, such as the transaminases (AST, ALT) were also demonstrated in this present study (Table 3.6). A sudden rise in the level of these enzymes were more pronounced among the patients who died (Table 3.6). These enzymes are biomarkers of liver disorders and a sudden increase in the level of these enzymes correlate with the liver disease as reported by Al-Salahy *et al*. (2016). Jaundice is one of the common manifestations of complicated malaria and more common in adults than children. High levels of jaundice is significantly associated with mortality in reported in the current study and directly associated with increased levels of AST and ALT (Table 3.6) (Goyal *et al*., 2016). Among the patients that died, the median serum bilirubin reached as high as 47 μmol/L (normal range, 0-

21 μmol/L), compared to the survivors with 28 μmol/L. The decrease in sodium and potassium levels among both group of patients were not statistically significant (Table 3.6). However, a slightly lower sodium level (Na^+, 134 mmol/l and 133 mmol/l) observed in both group of patients may likely have resulted from vomiting and on-going haemolysis seen in patients with complicated malaria and conditions that increase plasma potassium levels, thereby moving sodium back into the cell to maintain electrolyte neutrality. The normal potassium level reported in the current study among both groups of patients is not in keeping with a study that reported a correlation between serum potassium and haemolysis of red blood cell in patients infected with malaria (Udoh *et al*., 2017). Blood glucose levels (median RBS, 5.8 mmol/ L, 5.05 mmol/ L) among the current study population was not elevated, including those patients that died (Table 3.3; Figure 3.3). This may be due to strict compliance with the protocol during administration of antimalarial drugs that required co-administration with intravenous dextrose to correct the potential hypoglycaemic side effect of the antimalarials. This is in contrast to the study by Udoh *et al*. (2017) in which the glucose levels of malaria-infected subjects were found to be lower than that of control group.

4.1.7 Malaria and HIV

A total of 9% of patients with co-infection/s were on primary prophylaxis of cotrimoxazole, however, early commencement of treatment with it may have prevented death in 67% (24/36) of this studies co-infected patients that had low $CD4^+$ T-cells count at admission (Table 3.7). A large study conducted in South Africa reported a significant 36% reduction in mortality when co-trimoxazole preventive therapy was used at the initiation of antiretroviral therapy irrespective of the patients' $CD4^+$ T-cells count (Hoffmann *et al*., 2010). Cotrimoxazole, an antifolate antibiotic is known to possess antimalarial property, and is currently recommended by the WHO for all HIV-positive patients including pregnant women to receive a daily dose in order to prevent opportunistic infections (Gutman and Slutsker, 2017). The tremendous benefit of co-trimoxazole prophylaxis has been shown to prevent death, recurrent episode of illness and hospitalisation in adults with early and advanced HIV disease, with a relative risk of 0.69, 0.76 and 0.66, respectively (Grimwade and Swingler, 2016). Both studies agreed that early commencement of cotrimoxazole with ARVs helped in reducing mortality at every stratum of $CD4^+$ T-cell count irrespective of the advanced WHO stage. It was speculated that bacterial infections either independently or as co-infection were a major risk factor for death, but the use of cotrimoxazole significantly reduced mortality among these patients (Grimwade and

Swingler, 2016; Gutman and Slutsker, 2017). A study in 2007 at CHBAH reported an increased resistance to cotrimoxazole, whilst use of cotrimoxazole in areas where sulfadoxine-pyrimethamine resistance already exists in South Africa, it may select for a mutation in the genes for dihydropteroate synthase and dihydrofolate reductase, respectively (Khoo *et al*., 2005). As such this combination is no longer used in South Africa (SADOH, 2016).

Antiretroviral treatments in this study were in accordance with South African Department of Health Guidelines for the treatment of HIV (Section 3.6). The stavudine regimen was the most frequent regimen, accounting for up to 17% (Table 3.7). In this study, no patients were reported to suffer from adverse drug effect that may warrant withdrawing patient from a particular ART regimen. Studies have reported that two of the most important clinical interactions with ARVs include protease inhibitors that induce P450 enzymes (CYP 3A4, CYP 2B6, 2D6) and less often Non-nucleosides reverse transcriptase inhibitors (NNRTI) that cause inhibition or induction of P450 enzymes, and some of the antimalarial drugs are metabolised by the same P450 enzyme pathway which metabolize protease inhibitors (Wilby *et al*., 2016), where protease inhibitors are known to also induce their own metabolism. In contrast the NRTIs interact less often at a cellular level with some of the antimalarial drugs (Smart, 2016).

A Ugandan study on the pharmacokinetic interactions between artemether-lumefantrine and EFV among co-infected patients, reported that the co-administration of artemether-lumefantrine and EFV-based ARVs resulted in a decreased concentration of artemether-lumefantrine or dihydroartemisinin with a higher risk of treatment failure (SADOH, 2016; Byakika-Kibwika *et al*., 2012. An extension of the duration of artemether-lumefantrine treatment to five days has been proposed by the SA Department of Health (SADOH, 2017).

Co-administration of artemether-lumefantrine with nevirapine among HIV-infected volunteers in South Africa showed a remarkable reduction in artemether, dihydroartemisinin and a surprising elevation in lumefantrine exposure (Byakika-Kibwika *et al*., 2012). In contrast to the latter, two studies found that there was a minimal risk of having recurrent malaria when artemether-lumefantrine was co-administered with lopinavir/ritonavir in comparison to NNRTIs-based ART (Kasirye *et al*., 2016). As such protease-based ART regimens may have both clinical and public health relevance, with the possibility of a poor treatment outcome for uncomplicated malaria infected patients (Parikh *et al*., 2016; Maganda *et al*., 2014). Additional studies that would explain the pharmacokinetic and pharmacodynamic benefits/disadvantages

of these interactions would go a long way in contributing to a wider understanding and knowledge of these interactions between these drugs.

4.1.8 Mortality rate

A total of 36 patients (4%) died during the course of this study during 2011 to 2015 (Table 3.5a,b). The WHO criteria for malaria severity among patients that died were relatively higher than those that did not die (a minimum of 3 criteria, range, 3-6) (Section 3.10). Respiratory distress/ARD was the most common clinical feature associated with death (Table 3.6), thereby causing irreversible and untreatable respiratory failure among the ICU patients who died. While acute renal failure was the most common laboratory complication associated with death and a major reason for ICU admission (Section 3.12). Hyperparasitaemia was also frequently elevated in the patients that died (range, 3.6-5.0%)(Table 3.3-3.5; Section 3.2.3), but was not strongly correlated to death. These findings are in keeping with another study (Bruneel *et al*., 2003). The case fatality in this study was 4% higher than the national target of 0.5% (Frean *et al*., 2014). Some of the possible reasons for this increase may have included: delayed patient presentation to the hospital, self-medication by the patients to suppress fever, delay by doctors at arriving at a diagnosis and poor financial status of the patient to seek medical assistance (Romay-Barja *et al.*, 2016). However, it should be noted that in this study, there was a high number of complicated malaria cases admitted and treated at the study centre (CHBAH) following referral from peripheral centres. As such, the higher number of fatal cases was expected as observed in the study by Sagaki *et al*. (2013). A study conducted in non-endemic industrialised areas suggested that adults with complicated malaria admitted in the ICU of specialist centres responded well to treatment, while those treated by a non-specialist carried a higher risk of complicated malaria with poor response (Seringe, 2011). Supportive management in ICU has been shown to significantly improve the patient's outcome and is achievable through a multidisciplinary team approach, the introduction of new protocols of mechanical ventilation, the correct and effective use of antimalarial, haemodialysis, fluid administration and infection control (Shingadia, 2016). Despite all of these developments and interventions, the mortality rate of imported malaria remains significant, and a 20% case fatality in non-immune travellers requiring ICU admission has been reported in some studies (Trampuz *et al*., 2003).

4.1.9 Cost outcomes

This study has demonstrated that the cost of antimalarial treatment in HIV-infected adults at a tertiary hospital in Soweto was higher among complicated malaria patients than uncomplicated malaria patients (Table 3.11; Table 3.12), with the cost increasing with increasing immunosuppression (Section 3.14). This was an expected find, but the difference in expenditure was important to determine for budgetary considerations of the hospitals and Department of Health. The reason for the increased cost for co-infected patients with immunosuppression compared to those with no co-infection was primarily due to the fact that the former group of patients were admitted for longer period and utilized more resources that contributed to the overall cost of treatment. A South African study in urban and semi-urban areas reported on the high cost of ART provision in HIV-positive patients with low $CD4^+$ T-cell count (Rosen and Long, 2010). The average inpatient cost for a period of one year for complicated and uncomplicated malaria patients without co-infection with HIV was R 802,509.16 and R 532,189.16, respectively (Section 3.14). While for those with complicated and uncomplicated malaria with a HIV co-infection, the average cost per year was R 806,527.64 and R 541,479.39, respectively (Figure 3.9). However, when comparing HIV-infected patients who presented with complicated malaria compared to uncomplicated malaria, the average total cost per admission was significantly higher for the former group of patients and amount to R 13,601.85, compared to R 3,969.79 in the latter HIV infected group. Similarly, an increase in cost differences was noted for the complicated and uncomplicated group without an HIV co-infection (Section 3.14). Immunosuppression and prolonged hospital admission (non-drug cost and diagnostic cost) were observed to considerably increase the patient's cost of treatment in this study. The high in-patient cost was more pronounced just before and during treatment when the disease condition was severe and several laboratory tests were being done to confirm infection and the patient vitals. This was consistent with the study done by Long *et al*., (2016. It was noted that co-infected patients with acute kidney injury did increase the overall cost due to specialised treatment and increased hospital admission.

This current study also showed a significant difference between the antimalarial cost for uncomplicated and complicated malaria (Table 3.10), in keeping with an Indian study (Modi *et al*., 2016). The median cost of the antimalarial drugs for uncomplicated malaria treatment was R 270.39 compared to R 303.95 for complicated malaria group. The current study found no difference in antiretroviral drug cost among the complicated and uncomplicated malaria groups, where it only accounted for less than 1% of the total cost of treatment (Table 3.10). The reason

for this was that the antiretroviral medications were in a fixed dose formulation administered over the same duration of one month; secondly, the majority of patients were on the same regimen (Section 3.14). A study in the United States of America reported that the cost of antiretroviral medication accounted for up to 71-84% of the total cost of treatment, based on private sector supply (Gebo *et al*., 2010). However, in South Africa, antiretroviral drug costs are lower in absolute and relative terms than those reported in higher income developed countries like the United States. It is important to mention that diagnostic cost, radiology, transfusions and drips were not included in the total costing of treatment in this study, since the management of complicated malaria is solely in the hospital. The bed-day cost included capital, personnel and infrastructures cost The study mainly focused on the cost from the first day of admission to the final day of discharge. On average, complicated malaria patients spent significantly more time admitted in ICU than those patients treated in General Ward, with a mean cost of the intensive care admission of R 7,826.00 compared to R 5,418.00 for complicated malaria patients admitted in the General Ward (Figure 3.10; Table 3.12). This difference in cost (R 2,408.00) was firstly, due to the ICU patients receiving additional medications and oxygen therapy, along with other adjuvant treatment and procedures compared to their counterparts in the general ward. Secondly, maintenance and professional fees in the ICU were considerably higher than that of the general ward (Appendix H). However, other drug costs considerably increased the cost for managing complicated malaria and contributed a significant percentage to total cost. This was in keeping with a Cameroonian study which reported that adjuvant treatment cost increased the overall cost of treatment by 34.1% (Maka *et al*., 2016). Antibiotics, antipyretics, antidepressant and other adjuvant therapies were more likely to be administered to complicated malaria patients than uncomplicated malaria patients, hence increasing the overall cost of treatment for the complicated malaria patients (Section 3.5.5). Treatment of complicated malaria remains relatively expensive in this tertiary hospital and hospital finances are further challenged due to the high number of low-income patients that patronise its services. Despite government subsidies of the patient's treatment, the patients still need to pay a considerable sum for their treatment. ICU admission, other drug costs or adjuvant treatments considerably add to the overall cost of treatment among complicated malaria patients. Although all the costs are covered by the South African Government for South Africans, the majority of the cases admitted to the CHBAH over this study period, were from foreign nationals (Figure 3.2), who are required to pay their account in full. This places a financial burden on South African Department of Health if these are accounts are not paid. The South African government should ensure strong collaboration with it's neighbouring countries

such that, malaria and *Anopheles* are better controlled in those countries; moreover, provision of better treatment in their own countries to avoid travelling to South Africa to obtain better and cheaper treatment will further reduce the number of imported or Odyssean malaria cases in patients (Moonasar *et al*., 2016).

4.10 Outcomes of comorbidities

In addition to the morbidity and mortality associated with malaria infections, the inclusion of comorbidities caused an even higher economic burden on the patients and hospital. This study identified three major non-communicable comorbidities namely, hypertension, diabetes mellitus and stroke (Figure 3.4). Two patients developed myocardial infarction secondary to long standing hypertension. The mean random blood sugar among type-2 diabetic patients with malaria was higher compared to non-diabetic patients with malaria (median RBS: 32.95 mmol/L; range: 11.9-54 mmol/L); which would make them prone to a *P. falciparum* malaria infection (Raghunath, 2016; Izah, 2016). This increased risk of malaria infection may be due to a compromised immune system, as well as a favourable environment for the parasite to thrive. It was also observed that the mean parasitaemia among Type-2 diabetic patients with malaria was relatively higher compared to non-diabetic malaria patients, in keeping with a Ghanian case-control study, which reported that out of 1,466 adults with Type-2 diabetes, 46% had an increased risk of having a higher parasite density and risk of severe *P. falciparum* malaria compared to non-diabetic patients. This was supported by a second Nigerian study (Danquah, 2010).

4.11 Limitations

The retrospective nature of the study coupled with the shortage of staff in the Record Department of CHBAH made retrieving folders a very difficult task, with the absence of vital laboratory investigation and clinical history in the folders further complicating the study. Multiple duplications in the patient files and absence of files in the records were also encountered. Retrospective studies are difficult to cost all services and expenses, as such not all items could be costed.

Chapter Five: Conclusions

This study demonstrated that the majority of malaria infected adult patients admitted to the CHBAH during the period of 2011 to 2015 were imported malaria cases mainly from the countries sharing a border with South Africa (Figure 3.2); with Mozambique accounting up to 80% of cases (Moonasar *et al*., 2013). Male, migrant workers continue to be predominantly infected with *P. falciparum* while searching for better employment and living conditions (Frean *et al*., 2014). Considering the number of people seeking refuge in this country every year, South Africa continues to witness a huge number of such visitors, bringing along with them imported cases of malaria, thereby increasing the pressure on the healthcare systems of the provinces and the country at large. There is a need on the part of the regional governments to set up a tighter border control aimed at reducing the risk of imported malaria which would assist in decreasing the possibility of those living in the non-endemic cities like Johannesburg from being infected. One should also bear in mind that South Africans travel to other endemic areas, thereby contributing to this statistic. To date a tremendous achievement has been made in South Africa, including neighbouring countries, in terms of malaria prevention and control, by targeting the poorer populations who are often more prone to the disease and its burden, with the sole aim of elimination being targeted (Moonasar *et al*., 2016). However, more financial allocations by these countries are required to sustain this success to prevent, control and eliminate the disease from the region (Liu *et al.*, 2017). The non-endemic nature of the majority of South Africa, including Gauteng, necessitates that all healthcare practitioners familiarise themselves with the disease and its differentials in order to avoid unnecessary delays and inappropriate treatment. A failure to do so could have dire consequences for the patients. The absence of travel history should not rule out malaria diagnosis; especially with the increased number of reports of Odyssean malaria in South Africa. Odyssean malaria should be considered when taking a clinical history from patients presenting with the classical symptoms of malaria (SADOH, 2016), as this would delay patient's management and increase disease burden (Dlamini, 2014). Imported malaria carries a higher risk of morbidity, and mortality of more than 50% among male adults, especially in unstable malaria areas (Lüthi and Schlagenhauf, 2015). Although many patients are observed to present late to the hospital, rapid commencement of the appropriate management can significantly reduce the potential of a poor outcome. Integrated management of complicated malaria, including fluid administration, dialysis and ventilation should be readily available and these protocols should be familiar to all levels of healthcare personnel who provide emergency care, so as to minimise morbidity and mortality. Moreover,

additional staff, treatment facilities and equipment in ICU may go a long way in reducing delayed admission into such important lifesaving facilities. Routine staff training to improve their skills may also add to the quality of care. It should be considered that the majority of the migrants are most probably not taking antimalarial chemoprophylaxis before embarking on the journey to South Africa, and as such regional malaria programmes should focus more on public enlightenment on the dangers of malaria infection with more emphasis on the importance of prevention. The lack of information regarding any prophylactic agents being taken by the patients should be addressed if preventative programmes are being implemented, as an indicator of the success of these programmes. HIV-infected patients with malaria as a co-morbidity should be assessed to avoid any delay in the onset of treatment that may result in a poor outcome. Ensuring the implementation and familiarisation of the management protocols as issued by the South African Department of Health for these patients will also help.

Studies have provided insight into the understanding of the interaction between malaria and HIV with the potential of a poor outcome if all clinical parameters such as a low $CD4^+$ T-cell count among complicated malaria patients are not considered when managing a HIV-infected patient (Qadir *et al*., 2015). An HIV and malaria co-infection can accelerate the progression of both diseases if appropriate interventions are not timeously implemented. It has been noted that not all malaria-infected patients are routinely screened for an HIV-infection before the initiation of antimalarial treatment. It is therefore recommended that, based on the outcomes of this study, the procedures followed at the CHBAH be mirrored at other healthcare facilities, whereby routine HIV screening among malaria-infected patients, especially the returning migrants, be offered still highly efficacious when to significantly reduce the delay in the diagnosis of HIV.

At this point, it is important to mention that all the patients over the five years of this study period received treatment (malaria and HIV treatment) in line with South African guidelines issued by the Department of Health. Although i.v. artesunate was the preferred treatment for severe complicated malaria-infected patients, the limited availability of the medication restricted its use. The rapid response exhibited by the majority of patients receiving intravenous artesunate is indicative of why it is now registered in South Africa and readily available from the hospital pharmacy to have a greater impact on patient outcomes (MIC, 2017). Furthermore, the concept of pharmacovigilance should be given higher priority which allows for detection, assessment, understanding and prevention of the adverse drug reactions among admitted patients receiving different drug regimens.

This study was also able to demonstrate that the cost of patient treatment was significantly more expensive for the complicated malaria-infected patients than the uncomplicated malaria-infected patients. Moreover, the cost increased with a progressive decrease in immunosuppression. However, the addition of adjuvant treatment further compounded the cost. The cost of ARVs was relatively affordable and free which may explain the voluntary declaration of the status by the patients and adherence to medications and follow-up.

Comorbidities add more burdens to the existing disease condition, however, they should be well assessed and treated appropriately from the time of admission, during the malaria treatment and referred to a specialist immediately after discharge for follow-up. This practice would assist in reducing morbidity and mortality. Comorbidities such as diabetes mellitus worsen malaria outcomes by increasing the risk of having the severe form of the disease (Danquah, 2010). However, routine glucose tests and blood pressure check-ups will assist in better managing this disease. In addition to the burden of the disease that may increase the risk of morbidity and mortality, comorbidities also increase patient's overall cost of treatment, by increasing the patient's length of hospital stay and other drug costs, and might even result in loss of life in the long term.

Finally, the current South African guidelines for the treatment of uncomplicated and complicated malaria are still highly efficacious when timelessly administered; as such these guidelines should be re-enforced with all health care professionals to ensure continued efficacy of the current antimalarial agents. The management protocols issued by the South African Department of Health should be implemented for optimal treatment of patients co-infected with malaria and HIV to prevent disease progression and ensure a favourable outcome. However, in addition to the various programmes carried out to target malaria; political good will, collaboration and commitment from the side of the government, neighbouring countries, health care professional and the public are required..

Chapter Six: References

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Appendix A – Approval to conduct the study at CHBAH.

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 19 Jan 2016

TITLE OF PROJECT: Retrospective review on the outcomes and cost analysis of antimalarial treatment in HIV-infected patients in a tertiary care setting in Soweto, South Africa

UNIVERSITY: Witwatersrand

Principal Investigator: MD Muhammed

Department: Pharmacology

Supervisor (If relevant): RL van Zyl, C Menezes, A Karstaedt

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Jan 2016
Date of completion of data collection: Jan 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 19 January 2016

.....
Approved/Not Approved
Hospital Management
Date: 19/01/16

Appendix B - Approval from NHLS to conduct study and use the laboratory data.

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

29 March 2016

Applicant: Dr Murtala Muhammad Dandare
Institution: University of the Witwatersrand
Faculty: Health Science
Department: Pharmacy and Pharmacology
Tel: 060 316 2880
Email: 1332308@students.wits.ac.za

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**Retrospective Review on the Outcomes and Cost Analysis of Antimalarial Treatment in HIV-Infected Patients in a Tertiary Care setting in Soweto, South Africa**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you to conduct the proposed study as outlined in the submitted application.

Please note that the approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Ethics approval is obtained from a recognised SA Health Research Ethics Committee.
- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research. Once all requirements have been met, please complete and sign the attached data request form. This should be submitted to Academic.research@nhls.ac.za for processing by the Corporate Data Warehouse. Any data related queries may be directed to Sue Candy, manager NHLS Corporate Data Warehouse, Tel: (011) 386 6036. Email: sue.candy@nhls.ac.za.

Yours sincerely,

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Appendix C - Human Ethics Clearance from WITS Human to conduct study.

R14/49 Dr Muhammad Dandare Murtala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151143

NAME: (Principal Investigator)	Dr Muhammad Dandare Murtala
DEPARTMENT:	Pharmacy and Pharmacology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Retrospective Review on the Outcomes and Cost Analysis of Antimalarial Treatment in HIV-Infected Patient in a Tertiary Hospital Setting in Soweto, South Africa
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Colin Menezes, Prof Robyn van Zyl and Dr Jacqui Miot
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/04/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in November and will therefore be due in the month of November each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10004, 10th floor.
Medical School Secretariat: Phillip Tobias Building, 2nd Floor
Private Bag 3, Wits 2050, www.wits.ac.za

Tel +27 (0)11-717-1252
Tel +27 (0)11-717-2700
Fax +27 (0)11-717-1265

30 November 2015

To Whom It May Concern

SUBJECT: **CONFIRMATION OF STUDY APPROVAL**

Protocol Ref No: M151143

Protocol Title: Retrospective outcomes and Cost Analysis of Antimalarial treatment in HIV infected Patients in a Tertiary Academic setting in Soweto, South Africa

Principal Investigator: Dr. Murtala Muhammad Dandare

Department: Pharmacy and Pharmacology

This letter serves to confirm that the Human Research Ethics Committee (Medical) has received an ethics application for the abovementioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this study cannot commence without your approval and receipt of the Clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1252/1234/2700 or by email Rhulani.Mkansi@wits.ac.za

Yours Faithfully,

.....

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
30 NOV 2015
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Appendix-D - Protocol approval letteral

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

07 March 2016
Person No: 1332308
PAG

Mr MD Murtala
Federal University
Birnin Kebbi
Pmb 1157
0000
Nigeria

Dear Mr Murtala

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Retrospective outcomes and cost analysis of antimalarial treatment in HIV-infected patients in a tertiary hospital setting in Soweto, South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix-E – Data collection sheet (demographic & laboratory)

DATA COLLECTION SHEET

Patient Study No.	

1. Demographic characterization

- Age
- Sex/ gender

M	F

- Residence

SA	other:

- Duration of stay in S.A

Entry into SA

- Travel history

endemic area	
non-immune	semi-immune

- Ward No
- Date of admission
- Date of discharge

General	ICU	Duration

2. Features of severe Malaria

Cerebral Malaria
Severe Anaemia
Renal Impairment
Shock
Acidosis
Hypoglycemia
Hepatic dysfunction
DIC

3. Lab Finding		**date**	**date**	**date**
Microbiology				
Malaria blood slides	+ / ++ / +++			
Malaria Species	F / O / V / M			
Haematology				
FBC	values (units)			
WBC	values (units)			
Platelet	values (units)			
PCV/HB	values (units)			
Random blood sugar (RBS)	values (units)			
E/U/Cr	values (units)			
Na+	values (units)			
K+	values (units)			
Creatinine	values (units)			
Urea	values (units)			
HIV Infection	+VE -VE			
HIV Infection- CD4+ T-cell count	values (units)			

• Viral load	values (units)			
• **Chemical Pathology**				
• **LFT**				
• ALT	values (units)			
• AST	values (units)			
• Total Albumin	values (units)			
• Total bilirubin	values (units)			
• **Urinalysis**				
• Glucose	+ / ++ / +++			
• Ketones	+ / ++ / +++			

4. Therapeutic Intervention		**date**	**date**	**date**
• Quinine	I.V.: dose			
•	oral: dose			
• Clindamycin	oral: dose			
• Doxycycline	oral: dose			
• Artemether-lumefantrine	I.M.: dose			
	I.V.: dose			
• Dialysis specify session	yes/no			
• Ventilation	duration			
		date	**date**	**date**
• Antiretroviral	drug regimen:			
• Others:				
1	oral/IV/IM: dose			
2	oral/IV/IM: dose			
3	oral/IV/IM: dose			
4	oral/IV/IM: dose			
5	oral/IV/IM: dose			

5. Outcomes				
• Death	date:			
• Discharge				
• Date				
• Medication				

Appendix-F – Cost analysis data collection sheets

Cost analysis	**Patient Study No.**	

Hospital stay	duration	cost/day	amount
• ICU cost			
• General Ward cost			

Therapeutic Intervention		**duration**	**cost/unit**	**amount**
• Quinine	I.V.: dose			
•	oral: dose			
• Clindamycin	oral: dose			
• Doxycycline	oral: dose			
• Artemether-lumefantrine	I.M.: dose			
	I.V.: dose			
• Dialysis specify session	cost/session:			
• Ventilation	duration			
• Antiretroviral	drug regimen:			
• Others:				
1	oral/IV/IM: dose			
2	oral/IV/IM: dose			
3	oral/IV/IM: dose			
4	oral/IV/IM: dose			
5	oral/IV/IM: dose			

Appendix-G – List of drugs and prices

Drugs	Number of tablet/capsule	Price (ZAR)
Amoxicillin 500 mg	15	6,64
Amoxicillin-clavulanic acid acid 875/625 mg	10	18,14
Artemether-lumefantrine 20/120 mg	24	37,50
Azithromycin 500 mg	100	90,00
Ceftriaxone 1 g	1	5,40
Chloroquine 68 mg/ml	100 ml	25,44
Chlorpromazine 100 mg	28	13,44
Ciprofloxacin 500 mg	10	7,25
Co-trimoxazole480 mg	28	5,40
Diazepam 5 mg	100	9,04
Doxycycline 100 mg	14	4,78
Efavirenz 600 mg	28	29,94
Enoxaprim 100 mg/ml		42,80
Fluconazole 50 mg	14	7,71
Folic acid 5 mg	100	4,82
Furosemide 10 mg/2ml		1,67
Furosemide 40 mg	28	2,40
Glibenclimide 5 mg	28	1,98
Hyocine butyl bromide 10 mg	10	5,84
Insulin soluble 1000/ml	3	30,22
Lamivudine 150 mg	56	15,16
Metformin 500 mg	28	5,84
Metoclopramide 10 mg	10	1,64
Metronidazole 400 mg	14	3,24
Paracetamol 500 mg	20	1,90
Phenytoin 100 mg	84	48,90
Quinine 300 mg/ml		8,39
Ranitidine 100 mg	30	10,05
Sodium valproate 100 mg	100	75,00
Stavudine 300 mg	56	15,76
Tenofovir + Emtricitabine 300/200 mg	28	60,70
Tramadol 50 mg	20	6,35
Vitamin B complex	28	0,89
Zidovudine 300 mg	56	65,84

Appendix-H – In-patient admission price list.

DESCRIPTION	BASIS	Professional Fee (ZAR)	FACILITY FEE		
			LEVEL 1	LEVEL 2	LEVEL 3
			ZAR	ZAR	ZAR
Dialysis					
Haemo – Facility Fee	Day		1254	1254	1436
Haemo-dialysis – General medical practitioner	Day	238			
Haemo-dialysis – Specialist medical practitioner	Day	299			
Peritoneal Dialysis – Facility Fee	Session		193	193	220
Peritoneal Dialysis – General medical practitioner	Session	39			
Peritoneal Dialysis – Specialist medical practitioner	Session	46			
Inpatients					
Inpatient High care – Facility Fee	12 hours		997	1245	1785
Inpatient High Care – General medical practitioner	12 hours	69			
Inpatient High Care – Specialist medical practitioner	12 hours	132			
Inpatient Intensive care – Facility Fee	12 hours		3274	3274	3913
Inpatient Intensive Care – General medical practitioner	12 hours	77			
Inpatient Intensive Care– Specialist medical practitioner	12 hours	147			
Day patient – Facility Fee	Day		535	675	989
Day patient – General medical practitioner	Day	133			
Day patient – Specialist medical practitioner	Day	233			
Day patient – Nursing practitioner	Day	77			
Inpatient Boarder – Facility Fee	12 hours		154	154	154
Inpatient Boarder/Patient Companion – Nursing practitioner	12 hours	13			
Inpatient General ward – Facility Fee	12 hours		322	411	774
Inpatient General Ward – General medical practitioner	12 hours	67			
Inpatient General Ward – Specialist medical practitioner	12 hours	115			
Inpatient General Ward – Nursing medical practitioner (MOU)	12 hours	43			
Inpatient Chronic care – Facility Fee	12 hours		189	189	189
Inpatient Chronic care – General medical practitioner	12 hours	21			
Inpatient Chronic care – Specialist medical practitioner	12 hours	48			
Inpatient Chronic care – Nursing practitioner	12 hours	16			