TITLE: A STUDY TO INVESTIGATE AN ASSOCIATION BETWEEN THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND PLASMODIUM FALCIPARUM INFECTIONS IN AN ADULT POPULATION AGED 18-60 YEARS LIVING IN A MALARIA MESO-ENDEMIC REGION IN WESTERN UGANDA

A DISSERTATION SUBMITTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF PUBLIC HEALTH (MPH) OF THE UNIVERSITY OF NAIROBI

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1990

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This work is dedicated to my Grand father Mzee L. Kanyemera, my parents, my wife Petua, my children and to all my teachers.

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LIST OF ABBREVIATIONS

BC	-	Before Christ
^{o}C	-	Degrees Celsius
CD	-	Cluster differentiation (cell surface marker molecule)
CD4-Tcell	-	A T. lymphocyte that expresses the cell surface marker CD4.
CL	-	Confidence Limits
DCH	-	Department of Community Health
ELISA	-	an acronym for "Enzyme linked Immunosorbent Assay", a test used to detect antibodies against HIV in blood samples.
G-6-PD	-	Glucose - 6 - phosphate dehydrogenase
g/l	-	grammes per litre
mg/dl	-	milligrame per decilitre
mls	-	millitres
mmHg	-	millimetres of mercury
µmol/l	-	micromoles per litre
M Med.	-	Master of Medicine
M PH.	-	Master of Public Health
OR	-	Odd's ratio
S.E.	-	Standard Error
UON	-	University of Nairobi

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SUMMARY

This study was carried out between January and May 1990 inclusive, based at Mbarara Hospital in the malaria Meso - endemic region in the West of Uganda. The study aimed at initially confirming reports of the high incidence of severe P.falciparum malaria infection in adults in the area and then investigating the possibility and nature of its association with HIV infection.

Sixty-nine adult patients aged 18-57 years with severe P.falciparum malaria infection were studied. They included patients admitted directly to the medical wards at the hospital or from the medical out patient clinics and those referred to us by other practicing Doctors in the Districts of Mbarara and Bushenyi. This number however, did not reflect the actual rate of adult patients with severe P.falciparum malaria seen and or admitted to the hospital. A number of such other cases could not be recruited into the study for one reason or another.

This group of patients was matched for age and sex with two other groups of patients viz., non-severe P.falciparum malaria cases and non-malaria controls, thus a total of 207 patients altogether were studied.

Infection with P.falciparum was ascertained on clinical signs and symptoms together with the microscopic demonstration of the asexual forms of P.falciparum parasites on a peripheral blood smear stained with Giemsa' stain. HIV serostatus was determined by ELISA. All confirmed cases of P.falciparum infection received appropriate antimalarial chemotherapy. One group received chloroquine only, another received a combination of chloroquine and Fansidar and another received quinine therapy only. Each patient's response to treatment was assessed over a 7 day period and this was then related to his/her HIV serostatus.

The high in cidence of severe adult P.falciparum malaria infection in the region was appreciated. These cases tended to present more acutely (with shorter durations) than the non-severe malaria cases. The severity of the infection did not appear to be influenced by antimalarial drugs reported to have been ingested prior to presentation. The incidence of severe P.falciparum malaria seemed to decline with advanced age, most likely in conformity with the population age structure. The infection did not show any sexual preference nor was it associated with education or place of residence.

A seroprevalence rate to HIV of 41% was found among the study participants. This was a very high rate, much higher than the one reported by ACP for the general population in the country. The discrepancy was attributed to false positive results associated with ELISA, especially as confirmatory tests on positive sera were not carried out with WESTERN BLOT because of unaffordable costs. The sex ratio was 1.1 and no association with education or place or residence was found. HIV seropositivit per se did not appear to be associated with an increased risk or severity of P.falciparum infection. However patients with ARC appeared to be at an increased risk of non-severe P.falciparum malaria infection.

P.falciparum parasite densities among the malaria symptomatic patients ranged from 1% - 13%. Mean parasite density among the severe cases was 7.15 $\pm$ S.D.) and 2.2 $\pm$ 1.1 (mean $\pm$ S.D.) among the non-severe cases. Parasite density was not associated with HIV serostatus.

Symptoms manifested by patients with severe malaria included; hyperpyrexia, hyperparasitaemia, jaundice, anaemia and cerebral malaria. Non of these symptoms was associated with HIV seropositivity.

Resistance to the antimalaria drugs used was encountered. Resistance rates of 54% to chloroquine, 31% to Fansidar/chloroquin and 12% to quinine were determined. On the whole response to quinine therapy was quite satisfactory.

Response to treatment did not appear to be associated with HIV serostatus.

Finally it was concluded that the phenomenon of severe P.falciparum malaria in adults in this area is a reality. Its acute presentation could point to a relative reduction or absence of immunity to malaria. This was not necessarily due to HIV infection. The linkage of this phenomenon with malaria parasite resistance to chemotherapy and or parasite strain virulence, changes in malaria endemicity with subsequent lack of adult immunity to malaria infection were envisaged. The recommendations in light of these conclusions include the following:

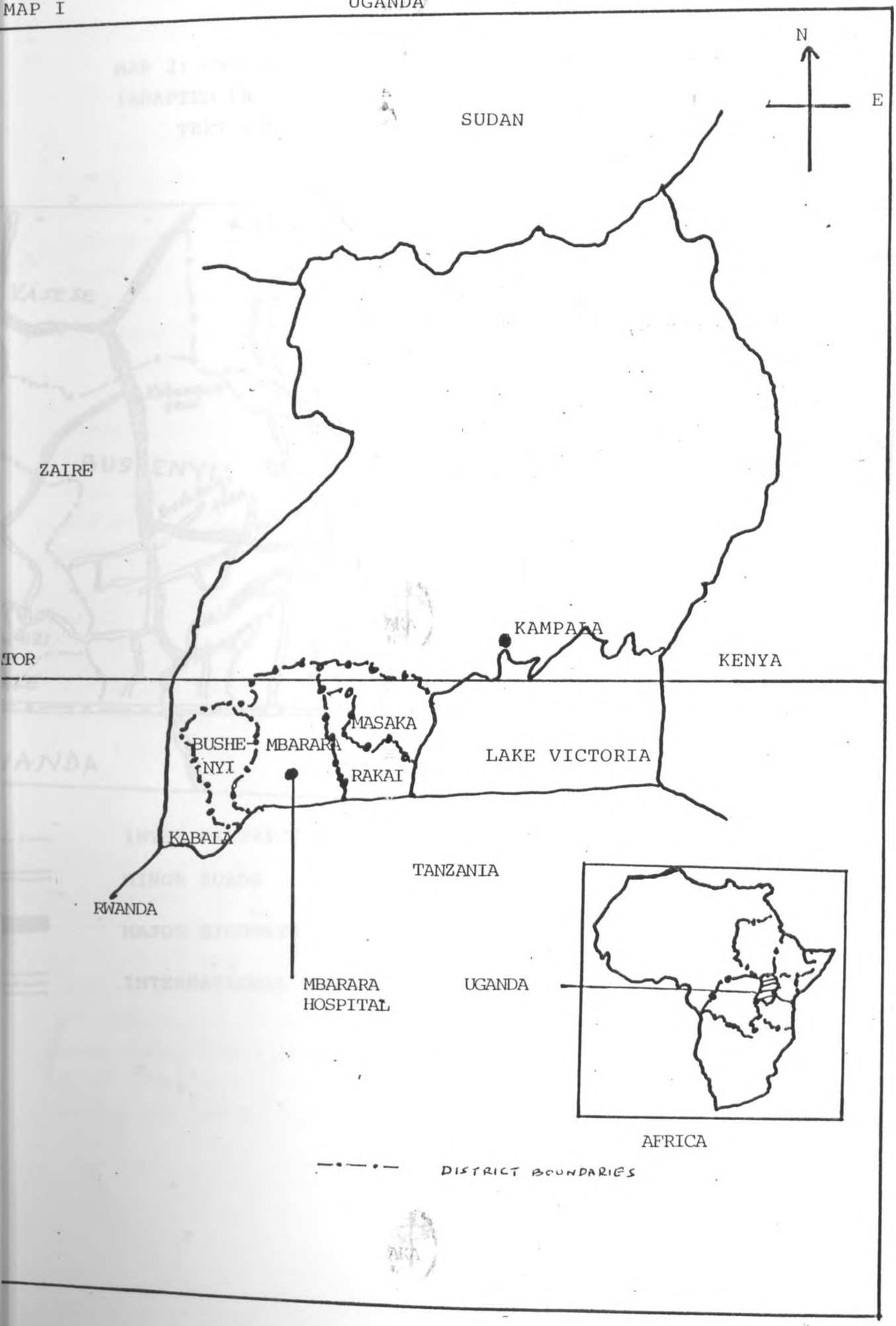
1. Further incidence and analytical research on the phenomenon of severe adult P.falciparum malaria in the region.

2. More research work on the possible association between HIV and malaria infections.

3. Promotion of enlightened awareness of the phenomenon of severe adult malaria among health care planners and providers in the country.

MAP I

UGANDA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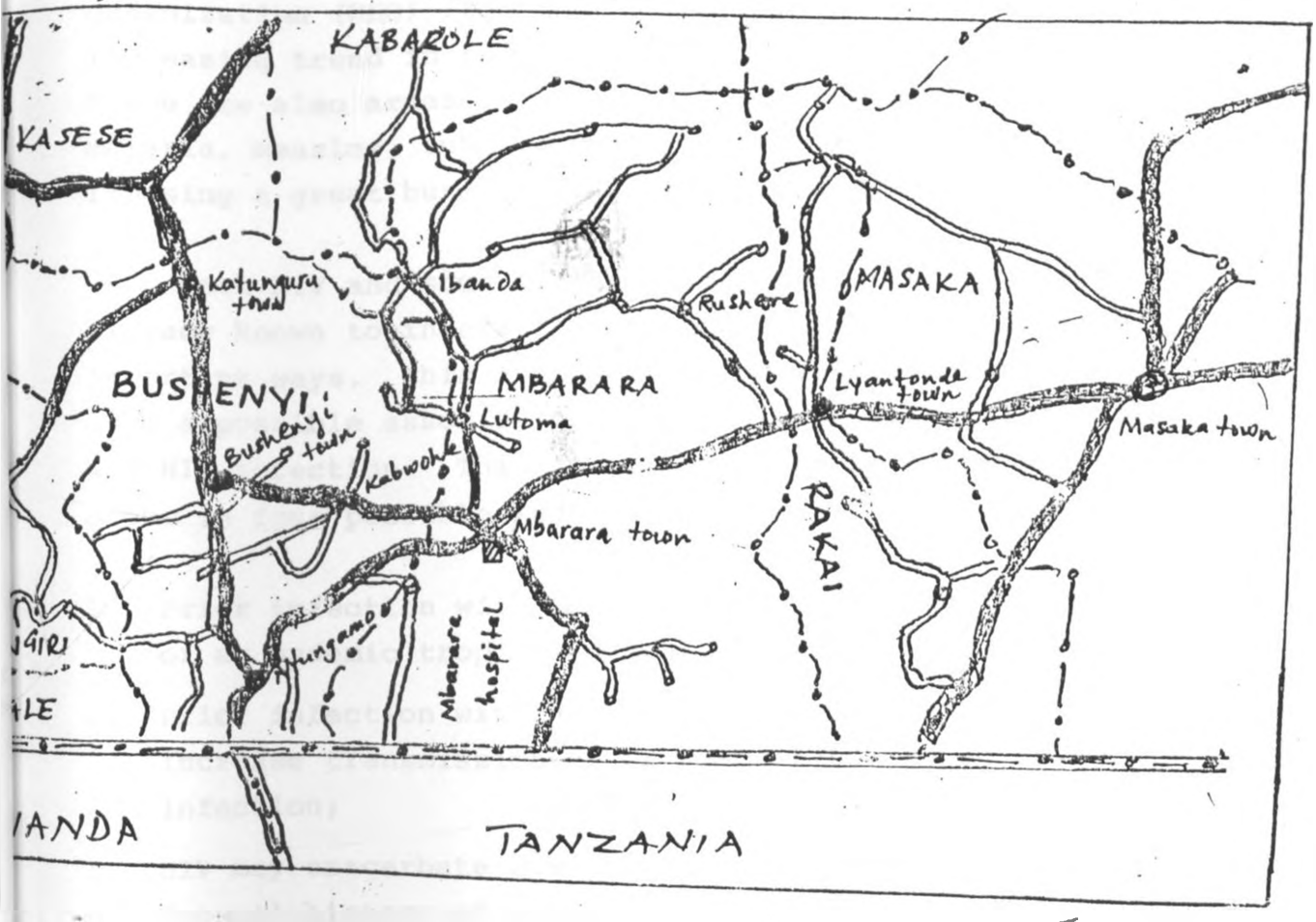
RAKAI
LAKE VICTORIA
KABALA
TANZANIA
RWANDA
MBARARA
HOSPITAL
UGANDA
AFRICA
DISTRICT BOUNDARIES

MAP 2: CATCHMENT AREA FOR MBARARA HOSPITAL
(ADAPTED FROM "ROAD MAP OF EAST AFRICA" 1979
TEXT BOOK CENTRE LTD., NAIROBI)



INTER DISTRICT BOUNDARIES

MINOR ROADS

MAJOR HIGHWAYS

INTERNATIONAL BOUNDARIES

CHAPTER I.

1. INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

At the moment HIV infection is the world's most threatening epidemic with reports to the World Health Organization (WHO) from most African countries showing an increasing trend in the incidences of this infection (1). These are also areas in which tropical diseases such as malaria, measles, tuberculosis etc. are endemic and already imposing a great burden of illness and death.

Both HIV and some of these tropical infections are already known to interact with the immune system in some important ways. This is the basis of a growing anxiety over a possible association between these tropical diseases and HIV infection. This association can be conceived to occur in four possible ways (1):

1. Prior infection with HIV may facilitate acquisition of an endemic tropical disease;
2. Prior infection with a tropical disease may increase transmission of or susceptibility to HIV infection;
3. HIV may exacerbate a latent infection or worsen the natural history of a tropical disease;
4. Acquisition of a tropical disease in an HIV infected person may worsen the natural history of HIV infection.

It is now confirmed that HIV infection predisposes an individual to multiple opportunistic infections particularly of endogenous viruses, facultative intracellular micro-organisms, fungi, protozoa and certain bacteria, and that most of the clinical syndromes of HIV infection that we now encounter are as a result of this predisposition. (2).

Studies by Pitchenik (3) and Mann (4) for instance, have shown an increased risk of tuberculosis among individuals infected with HIV. Beyley et al [5] have associated the sudden rise in the incidences of an aggressive form of Kaposi sarcoma in some parts of Africa with HIV infection.

If indeed there exists a positive association between HIV infection and these endemic tropical diseases, will the overall impact of HIV infection in Africa not be worse than has been anticipated, based upon studies of the natural history of HIV infection in developed countries?

Studies of such associations are needed and very important in that for most of these endemic diseases effective interventions are available. Such studies would help in the determination of the potential impact of such associations on these interventions. Evidence of adverse association would call for a more efficient employment of these interventions and stimulate the need to establish new surveillance programmes on these diseases or strengthen existing ones.

1.2 LITERATURE REVIEW

1.2.1 Malaria Infection

Malaria is one of the world's most serious infections with transmission rising globally. Global estimates of new clinical cases run to over 300 million per year; during the same period, three million people die of the disease. Sixty million of these new cases of malaria are found in Africa with an estimated one million children under five years dying [6].

This is a disheartening truth when more than 30 countries have either eliminated malaria or dramatically reduced the number of cases. Now more than half of the world's population live in malaria danger zones covering Africa, areas of the Middle East, India, Pakistan, part of Asia and Central South America. The disease is certainly a major public health problem with malaria parasites being resurgent in more than 90 countries around the globe. (6).

1.2.2. The Agent

The causative agent of the human malaria fever is a blood parasite of microscopic size beloning to the genus Plasmodium, of which there are four species known to infect humans; P. falciparum, P. malaria, P. ovale and P. vivax.

The P. falciparum, occuring for more than eighty five per cent of reported malaria cases in Africa is the most virulent and morbid of the four and often produces a fulminating infection in the non-immune patient. The other three species although widespread also, the incidence of the malaria they cause in Africa is relatively small. Although malaria parasites also infect other animals, humans are the only reservoirs of these four species of Plasmodia. (7,8).

1.2.3. Historical Outline

Malaria is quite an old disease dating back into antiquity. This is confirmed by the fact that about 100 parasitic species similar to those of man are found in a wide range of vertebrates from reptiles or birds to higher apes. None of these parasites, except for those found in some monkeys can be transmitted to man. This high host specificity indicates a long association between the human species and the four particular species of Plasmodia that infect man.

It is probable that the disease has its origin in Africa which is believed to be the cradle of the human race. From here malaria followed in the wake of human migrations to the Mediterranean shores, to Mesopotamia, Indian Peninsula and South East Asia.

Its establishment in the New World is still a subject of speculation. Reference to seasonal and intermittent fevers exist in the ancient Assyrian, Chinese and Indian religious and medical texts but their true identity with malaria is uncertain.

These afflictions, usually ascribed to punishment of gods or vengeance by evil spirits, were met only by incantations or sacrificial offerings. It was only in 400 BC that Hippocrates, a Greek physician rightly linked it to seasons of the year and the environment, it being endemic only in swampy and marshy areas. In consequence . . the disease in the 18th century received the name "malaria" or "Roman fever", Italian for "bad air"(i.e. foul air) commonly found in marshy areas. In 1880 malaria parasites were first isolated and described in human red blood cells by a certain French Army Surgeon in Algeria, Alphonse Laveran.

Soon after that Romanowsky in Russia developed a new method of staining the malaria parasites in blood films and this made further studies of Plasmodia very much easier. Patric Manson, a Scotish doctor while practicing medicine in China in 1880's theorised that malaria transmission from person to person was aided by mosquitoes as the carrier. Following this line of thinking, Ronald Ross, a surgeon in the British Army whose further studies lent credance to this theory when in 1897, he found these parasites in the body of a mosquito that had previously bitten a patient with Plasmodia in his blood. The Italians, Amico Battista Grassi and their colleagues are to be congratulated for their study in 1898-99 which made clear the whole complex picture of the developmental cycle of malaria parasites in man and in the female Anopheles mosquito. The story on malaria transmission was concluded by other studies carried out by Patric Manson and his colleagues near Rome and in London in 1990. They successfully proved that protection from the bites of Anopheles mosquitoes prevents the occurrence of the infection. By the middle of the twentieth century Shortt and Gamnham had discovererd the exo-erythrocytic stage of malaria in man. This helped to explain what happens to the parasite during the incubation period, how the relapses of malaria infection occur, and gave a new impetus to the chemotherepeutic research which was soon to develop new and powerful drugs (7).

1.2.4. Transmission

The tiny, live malaria organism is transmitted to humans by the bite of an infected female Anopheles mosquito. The insect requires blood to produce her eggs and she obtains this nutrient by breaking the skin of her victim and regurgitating enzymes from her salivary glands which help breakdown living tissues.

The important species of the Anopheles mosquito in Africa include A. gambiae, A. funestus, A. moucheti, A. pharoensis, A. hancocki.

The parasites may also be transmitted accidentally by transfusion with infected blood and transplacentally[10].

1.2.5. Pathogenesis and Life cycle

The malaria parasites complete part of their life cycle (EXOGENOUS SEXUAL/SPOROGONIC PHASE) in the mosquito. A sexual cycle of reproduction takes place in the gut of the mosquito. The result is an ameboid form of the parasite, capable of migrating into the insect's gut epithelium. Here a form of cyst is developed which, when raptured, releases nasses of flagellated sporozoite cells, each having a whip-like form that provides mobility to the organism. These sporozoites reach the salivary glands and inoculated into the human host when the mosquito to take a blood meal.

The parasites then begin the second part of their life cycles (THE ENDOGENOUS ASEXUAL PHASE). After a brief period the sporozoites disappear from the blood circulation. Some may be destroyed by phagocytosis but others travel to the liver and find their way into its great mass of cells where they grow and segment (THE TISSUE PHASE). The nuclei of the resulting schizonts (large multinucleate, cyst like structures) form into new, small elongated cells called merozoites. These are then released into the blood circulation and invade the red blood cells.

Here they undergo further asexual multiplication into more merozoites (ERYTHROCYTIC PHASE). It is worth noting that a merozoite bears a characteristic new set of antigens on its surface different from those of the sporozoite. The merozoite stage also shows considerable variation between strains of the parasite. This means that malaria parasites isolated from different patients can bear variable antigens on their surface.(8)

In all but P.falciparum and P.malarial infections, a proportion of the sporozoites become dormant forms called hypnozoites; when these later become reactivated they initiate schizogony in the hepatocytes and cuase a relapse of the disease in the patient P.falciparum species invade all erythrocytes, young and old, thus causing relatively higher parasite densities.

As the erythrocytes burst to release the parasites, pyrogens are released and these are responsible for the fever that characterises the infection. The infected erythrocytes adhere (sequestration) to the endothelium of the blood capillaries and in this way virtually all organs in the body may be affected through disturbance of their blood supply. Some of the new malaria parasites formed in the red blood cells are capable of sexual reproduction (Gametocytes). When the patient is bitten by another mosquito the blood meal infects the insect and a sexual cycle of reproduction starts in its gut.(7)

.2.6. Immunity and Susceptibility

Nearly all humans are susceptible to malaria infections although the degree of severity of the infection differs depending on the immune status of the individuals to the infection. Recurrent exposure to malaria parasites gradually confers partial immunity to the individual. This partial immunity does not however, preclude the development of malaria, as frequent reinfection is necessary to maintain the acquired immunity or it will decline.

The immunity limits the parasitaemia and enhances physiological tolerance such that low parasitaemia produces no fever.

Passive immunity can also occur transplacentally in utero. Similarly those with inherited disorders like sickle cell trait and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency are relatively protected because there occurs a genetical interference with the development of the parasites in their red blood cells. Immunity acquired through contact with particular malaria parasite/antigen can however be suppressed by pregnancy, major surgery, severe illness of any type and immunosuppressive drugs.

There is now sufficient evidence to suggest that immunity in malaria is both cell-mediated and humoral, all being T-cell dependent, requiring a sufficient number of T4-lymphocyte and B.lymphocyte cells. The important antibody is IgG.

However, the malaria parasite have developed a series of highly refined strategies for evading the human immune system. The highly complex lifecycle of the parasite with its various forms (sporozoites, merozoites, gametocytes) ensures that it can evade the attack of the antibodies and immune lymphocytes. These parasites are even able to alter the surface antigen which they display at various times during their life cycles.

A further mechanism of confounding the immune system is their capacity to synthesise large amounts of antigenic material which are released into the blood stream of the infected humans and which stimulate the immune system to synthesise large amounts of antibodies. In many cases these antibodies are however useless being directed against soluble antigens.

This is in effect a smoke-screen which the parasite uses to divert the immune attack away from itself. This constant change of costume and masks confuses the immune system and makes its job of mounting an effective attack on the parasites extremely difficult. Thus it is still not yet possible for one to develop a lasting active immunity against malaria infections. These are also issues related to failure to develop a vaccine against malaria.(11,12,13).

1.2.7. Symptoms and case definition

Malaria infection manifests with a wide range of symptoms. The first manisfestations can be vague bouts of fever, body aches, slight dizzines and a general feeling of malaise, shaking chills followed by a rapid rise of temperature. The symptoms then advance to pounding headache, high fever and profuse sweating. Other common indications include such gastrointestinal symptoms like frequent blood stained stools, mucous or pus, water diarrhoea and muscle cramps. The sequel from this stage depends on the immunity of the individual to malaria infection. In the majority of semi-immune individuals, the symptoms may not become worse and if untreated the disease become chronic, characterised mainly by general chronic illhealth due to anaemia and splenic enlargement. The parasitaemia is depressed and usually limited to not more than five percent of parasitised erythrocytes.

In the non-immune individuals P.falciparum infection, if untreated will almost invariably present in severe or complicated form. The WHO has reviewed this subject and defined severe P.falciparum infection as the demonstration of asexual form of P.falciparum in the peripheral blood of a patient with potentially fatal manifestations or complication of malaria when other causes have been excluded (14). The diagnosis of this severe malaria is made when the patient has one or more of the following:

a) Hyperparisitaemia:- a density of asexual form of P.FALCIPARUM in the peripheral blood smear equal to or exceeding 5% of erythrocytes parasitised.

b) Cerebral malaria - diagnosed if the patient has the following three features:

(i) Unarousable coma - defined as motor response to noxious stimulus is non-localising or absent.

(ii) No other cause of coma

(iii) Confirmation of P.falciparum infection by demonstration of asexual forms in the peripheral blood.

c) Severe anaemia - defined as a hematocrit less than 20% or hemoglobin less than 7 g/dl.

d) Jaundice - detected clinically or defined by a serum bilirubin concentration more than 50Umol/l.

e) Renal failure - defined as urine output of less than 400mls/24hrs and a serum creatinine more than 265Umol/l (3.0mg/dl) failing to improve after rehydration.

f) Hyperthermia - defined as a rectal or axillary body temperature above 39^{0}c.

g) Circulatory collapse - shock and hypotension.

h) Bleeding and blood clotting disturbances including retinal haemorrhage.

i) Haemglobinuria.

j) Hypoglycaemia

1.2.8. Malaria Control

The war against malaria dates back to the earliest times. The Chinese for two thousand years used Chiang Shan (Dickroa febrifugal) roots and Quinghaosu (Artemisia annua) for therapeutic purposes. The first real treatment was discovered in the 17th century when the "peruvian back" was used for the treatment of fevers. Later in 1735 Linnaeus gave the scientific name Cinchona to the tree producing the "peruvian bark" found in the peruvian forests. Pellefier and Caventon later in France in 1820 isolated Quinine the active principle in Cichona against malaria. Its use grew from the South American natives to Spain spreading to Europe, where it was used in the form of powder extracts.

At the onset of World War 1, German chemists began serious search for quinine alternatives. By 1928 the first synthetic antimalarial drug PAMAQUINE was discovered. MEPACRINE (OR QUINACRINE) successful as routine treatment and prophylaxis was synthesised three years later as an improvement on Pamaquine. At the same time German, French and American scientists in collaboration developed derivatives of four-aminoquinolines. This led to the introduction of chloroquine and amodiaquine both of which remained very popular as antimalarials for years. At the moment there is not a single drug effective against all the developmental stages of the malaria parasite. A variety of drugs are available effective against sporozoites (sporontocidal), blood schizonts (schizontocidal), tissue schizonts (tissue schizontocidal).

In the treatment of malaria, however, the primary aim is to rapidly eliminate the erythrocytic forms of the plasmodia by means of schizontocidal agents like quinine, chloroquine and Fansidar.

In early 1930's Paul Muller discovered in Switzerland the high insecticidal action of DDT. Later on other more effective residual insecticides including hexachlocyclohexane (HCH) and Dieldrin were introduced. The availability of these residual insecticides together with synthetic antimalarials and the apparent success in their use against mosquitoes in Venezuela led to the adoption of the malaria eradication concept by the World Health Assembly in 1955. In 1957 the WHO launched the global campaign for malaria eradication.

It's results over the next fifteen years were excellent helping to protect millions of people living in hitherto malaria regions from infection.[7,15,16]

1.2.9. Resistance in Malaria

Since 1966 the scenario in malaria control has dramatically changed with malaria cases rising daily owing to, among other things, vector resistance to insecticides, socio economic factors and increased human population movements (15, 16, 17, 19) The concept of eradication of malaria has since given way to control of malaria. Since 1978, the emphasis is on integrating malaria control with primary health care systems and on integrating health with development (20).

One of the serious current problems is the emergence and spread of Plasmodium falciparum resistant to antimalarials especially the time-honoured chloroquine. Resistance in malaria (and in other parasites) has been defined as "ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommend but within the limits of tolerance of the subject"(21) This resistance in essence covers a spectrum of responses to the chemotherapy, from a mere survival with subsequent recruduscence in the blood to active multiplication during the course of treatment.

Prior to 1961 resistance by human plasmodia, was known only to pyrimethamine and proguanil in many parts of the world with the first drug resistance having been reported in 1910 (22). The first real description of chloroquine resistant Plasmodium falciparum was reported in Columbia in 1961 by Moore and Linier (23). The report came almost simultaneously with reports from Thailand in 1962 by Harinasuta et al, and from Venezuela by Morbeti et al in 1960 (22,23,24). Since then chloroquine resistant Plasmodium falciparum has been spreading in South-East Asia, South America and Tropical Africa (19, 25)

Sporadic cases of chloroquine resistant malaria had been reported in Africa since 1974 but were not confirmed. (26,27,28). Jepsen and Efforsoe in 1979 reported a case of chloroquine resistant. P. falciparum malaria in a Dane who had come to tour Kenya (29). Spencer reported the first case of chloroquine resistant p. falciparum in an indigenous Kenyan infant in 1983 (30). Weniger reported another case of an American tourist who returned to U.S.A. from Kenya and developed chloroquine resistant P.falciparum malaria of the RIII type (31) The first case of resistant p. falciparum malaria in an adult in East Africa was reported by Bhatt et al in 1984. This was a local Kenyan who got the infection from Mombasa (32)

At the moment p. falciparum is the only species of plasmodia that has developed resistance to chloroquine (21,33). Resistance is theorised to develop because parasites multiply rapidly and can spontaneously mutate in slightly different strains in a short time. Resistant mutants have an altered genetic make up, and survive, either by using alternative metabolic pathways to those blocked by the drug or by preventing the entry of the drug into the cell. Other predisposing factors may include sustained under dosage of chemotherapeutic drugs (21).

1.2.10. Drug Response Grading in Malaria infection

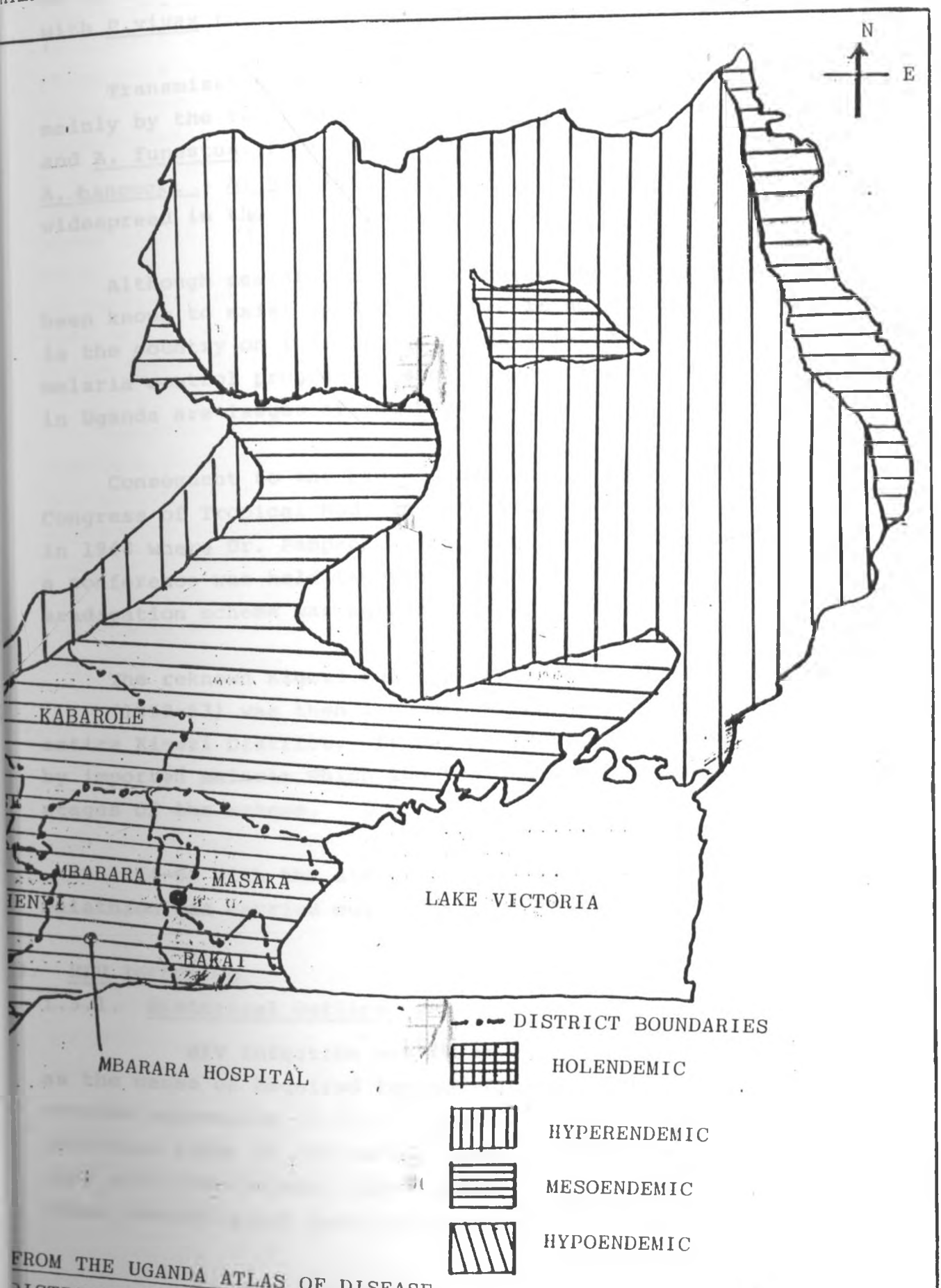
The following system of grading the responses to asexual p.falciparum to normally recommended doses of chemotherapy has been proposed (21).

Response	Recommended Symbol	Evidence
Sensitive	S	Clearance of asexual forms within 7 days of initiation of treatment without subsequent recrudescence.
Resistance	RI	Clearance of asexual parasitaemia as in (S) followed by recrudescence
	RII	Marked reduction of asexual pararitaemia but no clearance.
	RIII	No marked reduction of asexual parasitaemia

1.2.11. Malaria in Uganda

Malaria disease was first described in Uganda by Cook in 1901. (34) Since then numerous studies on malaria have been carried out in the country. Langlands and Hall (9) attempted to map the endemicity of the disease in the country. They showed existence of all four types of endemicity, namely hypo-, meso-, hyper-, and holoendemicity. (Map 3). They reported the presence of all the four species of plasmodia and that P.falciparum was responsible for the great majority of malaria infections in the country. It was reported to be the commonest cause of severe illness especially among children and considerable infant mortality, anaemia in pregnancy, and low birth weight.

ALARIA ENDEMICITY IN UGANDA (1968)



FROM THE UGANDA ATLAS OF DISEASE
DISTRIBUTION (1975) BY LANGLANDS & HALL

P.malariae was reported as the next most prevalent, alone, or in combined infections with P.falciparum. It was reported with P.vivax to account for no more than 3% of all the infection.

Transmission of malaria in Uganda was also reported to be mainly by the two species of Anopheles mosquito, namely A.gambiae and A. funestus. Four other minor vectors namely, A.pharoensis, A. hancocki, A. gibbinsi and A. moucheti were reported to be widespread in the country.

Although resistanceto chemotherapy by P.falciparum has been known to exist in Uganda there is no published work done in the country on this aspect of malaria infection. Vigorous malaria control programmes such as use of residual insecticides in Uganda are issues of the past.

Consequent to the proceedings of the fourth International Congress of Tropical Medicine and Malaria in Washington U.S.A. in 1948 where Dr. Pampana raised the idea of eradicating malaria, a conference was held two years later in Kampala where an eradication scheme was agreed on.

The reknown Kigezi malaria eradication project by De Zulueta[35] (1959-63) was then launched which reaped some success in the entire Kigezi District. It was however, later to be disappointed by imported malaria which led to localised outbreaks in the later stages of the scheme.

In 1964-66 with the aid of WHO a large scale field trial of malathion was carried out in Masaka district with success.

3. HIV INFECTION

1.3.1. Historical Outline

HIV infection was first described in 1981 in U.S.A., as the cause of Acquired Immunodeficiency Syndrome (AIDS) the extreme expression of the infection (36). Suspicion of the infection arose as increasing numbers of patients were being seen with overwhelming opportunistic infections, for which no known immunological deficiency could be found.

This was shortly followed by reports of more similar cases in other centres in U.S.A., U.K., France and North America especially after the Centre for Disease Control(CDC) in Atlanta Georgia had made a diagnostic definition. More cases were subsequently reported from African countries. The virus responsible for the infection was isolated by two independent groups of workers in U.S.A. and France. Those in U.S.A. called it Human - T - Lymphotropic Virus Type III (HTLV-III) and the French called it Lymphadenopathy Associated Virus (LAV). Subsequent studies showed that LAV and HTLVIII were antigenic strains of the same retrovirus. In 1986 an International Committee on Taxonomy of viruses proposed that the virus be officially designated as Human Immunodeficiency Virus (HIV).

Clummeck N. in 1983, and Sonnet in 1983, and Brunnet (37) were the first to report the variations in risk factors between the infection in Africa, mainly, heterosexual promiscuity as opposed to homosexuality in Europe and America. The ratio male to female is 1:1 in Africa and 19:1 in America. Other risk factors in Africa include blood transfusion and other parenteral manoeuvers where screening and sterility techniques are still lacking.

3.2. The World Situation

There is no doubt that since the infection was first reported in the U.S.A. in 1981 HIV has rapidly become one of the world's major public health problem. By June 1989, 149 countries of the world had reported about 159,000 cases of AIDS to WHO. Of these 100,000 cases were from U.S.A., 25,000 from Africa, 22,000 from Europe, 8,000 from South America, 1,400 from Australia and 400 from Asia. At that time it was estimated that upto 250,000 people could have died of AIDS worldwide. A figure of 750,000 deaths due to AIDS is estimated for the year 2000. For every case of AIDS it has been estimated that there are 30 to 300 individuals infected by the virus, who may exhibit acute or chronic features of the infection or remain asymptomatic. The disease is certainly on the move (38,39).

1.3.3. The Agent

HIV belongs to the Retroviridae family of viruses. This family is characterised by their ability to encode their genetic information in RNA by using a unique enzyme reverse transcriptase. By this means they are able to copy their genome into the host cell genome as a provirus. Once the virus has entered the host cell it is capable of evading the host immune mechanism causing persistent infection.(2,39).

1.3.4. Transmission

Available data to date indicate that HIV is transmitted through a limited number of ways which include sexual, parenteral and vertical from mother to infant. In sexual and parenteral transmission the virus is transmitted through body fluids from which it gets access to the blood circulation. (37).

1.3.5. Pathogenesis

HIV gains access to the body cells through the (CD4) receptor site of the T - helper (T4) lymphocytes. Other cells which have this receptor such as monocytes are affected. The virus enters the cell coated and once inside the cell it is uncoated. The viral reverse transcriptase makes an initial complementary single-stranded DNA copy of the viral RNA molecule. This is followed by the generation of circular double-stranded DNA called proviral DNA, some of which is integrated into the hosts chromosomal DNA. New viral messenger RNA molecules (mRNA) are expressed by transcription of proviral DNA, the mRNA is subsequently translated into different viral capsids proteins.(2,39).

1.3.6. Clinical Picture of HIV Infection

HIV infection manifests itself through a spectrum of signs and symptoms. At one end there is the AIDS, an extreme expression of the infection. At the other end there are those individuals who are infected with the virus,

carry antibodies and also the virus itself, but remain symptomless and healthy. Between these extremes falls a large number of cases who show a wide variety of clinical and immunological effects of the infection. These symptoms may include chronic swollen lymphnodes, recurrent fevers, unexplained weight loss, chronic diarrhoea, oral thrush and lethargy. The incubation period of the disease is 2-7 years. (2,37,39).

3.7. HIV Infection Diagnosis

The best confirmatory test for HIV infection is isolation of HIV in the individual by culture. This however, is extremely difficult and there are several other easier ways.

a) Serology

This entails detection of serum antibodies to HIV. It is done by using the enzyme linked immunosorbent assay (ELISA) technique. (40) It is basically an optical density technique. Detection of HIV antibody can also be achieved by the Western Blot (WB) assay in which specific polypeptides are fractionated according to molecular weight by electrophoresis technique on a polyacrylaride slab gel, in presence of sodium dodecyl sulphate (SDS). The separated HIV polyptides are then transferred from the gel to a nitrocellulose membrane via electrophoretic blotting. The presence of HIV specific immunoglobulin in serum is indicated by in situ labelling of HIV specific proteins. Reacted strips may be used to determine the presence of antibodies to the major HIV antigens including p17, p24, p41, p3, p5, p55, p66. GP120 and GP160. A positive WB test may be any strip that has all bands, p24, with any other, GP41, p55 or any other. These antigens correspond to the genes for the HIV virus. 'Gap' coded by p55, p24, p17, 'pol' coded by p66, p51, p31, 'env' coded by GP160, GP120, GP41.

A number of other immunological assay methods have been developed so far.

b) Hematological

This is based on the pathophysiology of the infection - destruction of the T-4 helper/effector lymphocytes. HIV causes a drastic drop in T-helper (OKT4 or LEU3) lymphocytes and in the T-helper to T-suppressor (OKT8 or LEU2) lymphocyte ratio. The ratio T4/T8 in healthy individuals is between 1.5 and 2. (39).

c) CDC/WHO Clinical Case Definition

This mainly defines AIDS case which is the extreme expression of the HIV infection. It excludes the symptomless cases. In the absence of known causes of immunosuppression an AIDS case in an adult exists if there are at least two of major signs associated with one minor sign. (41):

Major Signs

(a) Weight loss of greater or equal to 10% body weight.
(b) Chronic diarrhoea for longer than one month.
(c) Prolonged fever for longer than one month's duration.

Minor Signs

(a) Persistent cough for one month or more.
(b) Generalised pruritic dermatitis
(c) Recurrent herpes zoster.
(d) Oral-pharyngeal candidiasis.
(e) Chronic progressive and disseminated herpes simplex.
(f) Generalised lymphadenopathy.

The presence of Kaposi's Sarcoma with HIV antibody is enough to make the diagnosis of AIDS.

In children, it should be two signs with at least two minor in the absence of a known cause of immuno-suppression.

Major signs

(a) Weight loss or abnormally slow growth.
(b) Chronic diarrhoea over one month.
(c) Prolonged fever one month.

Minor Signs

(a) Generalised lymphadenopathy
(b) Oral-pharyngeal candidiasis.
(c) Repeated common childhood infections e.g. otitis media.
(d) Generalised dermatitis.
(f) Confirmed HIV infection.

d) ARC (AIDS Related Complex)

Some persons who are infected with HIV do not meet the CDC definition of AIDS. They do however, show a variety of symptoms and physical/laboratory findings. These may include haematological abnormalities such as leucopaenia, thrombocytopaenia and anaemia, with a dysplastic bone marrow. Symptoms may include; chronic swollen lymphnodes, recurrent fevers, unexplained weight loss, chronic diarrhoea, minor alterations of the immune system (less severe than those that occur in AIDS) and oral thrush.

1.3.8. HIV Infection in Uganda

The epidemiology of HIV in Africa was extensively described by Quin. (42) The presence of the infection in Uganda was first reported towards the end of 1982 when the first deaths due to AIDS were first confirmed in Rakai District bordering Tanzania. From 1983 onwards the disease spread to other Districts and major towns through the Trans African highway. The number of AIDS cases increased from year to year and by July 31st 1989 a total of 9145 cases of AIDS had been reported. (43)

The disease in Uganda presents in a rather peculiar clinical form with predominant symptoms of chronic diarrhoea and extensive weight loss. (44) The disease has earned the name "slim" in Uganda on the basis of this striking loss of weight.

Bond C. and Widi-Wirski (45) have confirmed a widespread distribution of the infection in the country. Naamara (46) in his study on a rural population in Rakai district reported a point seroprevalence of the infection ranging from 67% among highly promiscuous town residents, 17% among less promiscuous rural/urban residents to 1.1% among children aged 2-15 years.

He found a female: male ratio of 1.1, thus confirming heterosexual transmission.

1.9 HIV Infection Control in Uganda

Activities geared towards HIV infection control are coordinated through the Uganda National AIDS Control Committee (ACP), at the Ministry of Health Headquarters, Entebbe, Uganda. The major strategies in the control are mainly through mass health education programmes and measures geared at reducing the parenteral transmission. These include screening blood for transfusion.

1.4 PREVIOUS STUDIES ON THE ASSOCIATION BETWEEN HIV AND P.FALCIPARUM INFECTIONS

A number of studies, motivated by initial concern that there might be an association between HIV and P.falciparum malaria infections have been carried out elsewhere. One study of adult hospital patients aged 12 years and above in Ndola, Zambia (44) failed to show any significant difference in the prevalence of P.falciparum parasitaemia between HIV seropositive and seronegative patients. The study also found no significant difference in P.falciparum antibodies and P.falciparum mean parasite densities between HIV seropositive and seronegative patients. The results of this study therefore did not provide evidence for increased susceptability to P.falciparum malaria in individuals infected with HIV.

Another study by Nguyen Dihn (48) in Kinshasa showed a spurious association between HIV and P. falciparum infections because of transfusing children anaemic due to P.falciparum infection with HIV infected blood. Another study reported by the same group failed to show any significant difference in the HIV seropositive rate of 164 children presenting with P.falciparum malaria and 169 healthy controls. They also failed to show any association between P. falciparum slide positivity and HIV seropositivity among 1046 children presenting to Mamayemo Hospital in Kinshasa, Zaire. (49) Studies by Biggar R.J. (50) which had showed significant association between malaria infection and HIV were later thought to have been due to many false positive results

with earlier ELISA's and to difficulties in interpreting Western blots. (51)

HIV antibodies were found more frequent in Venezuelan patients with acute malaria than in healthy blood donors from the same area. (52).

CHAPTER 2

THE RESEARCH PROBLEM

2.1. PROBLEM DEFINITION

The epidemiology of severe P.falciparum infections in the non-immune, who include almost all the adult individuals from non-malaria endemic regions of the world and the majority of children from endemic and non-endemic regions, can almost wholly be explained by lack of naturally acquired immunity to malaria infections. The semi-immunity acquired from repeated exposure to malaria infections in the endemic areas, however, protects the majority of adult individuals in these regions from severe malaria. Indeed severe P.falciparum infection in adults has been rare in the endemic regions of East Africa as reflected by its little mention in the medical literature.

In the recent past however there have been reports of unexplained increase in the incidences of this severe malaria in Uganda (Downing, personal communication 1988 Kitovu hospital and the author's personal observations 1987/88 Bushenyi Uganda). A similar situation seems to be prevailing in Kenya. Dr Kayima reported seeing an increase in the numbers of such cases in indigenous Kenyans at Aga Khan hospital, Nairobi, Kenya (personal communication, 1988).
In 1988, within a period of 6 months Owuor reported seeing 59 cases of severe P.falciparum malaria in adults at Kenyatta National Hospital (KNH), Nairobi.[53] Within 8 months between July 1989 and February 1990, Tombe reported having seen 32 adult patients with severe P.falciparum malaria at the same hospital[54], and within 6 months between January and June 1990, over 100 cases were reported to the Ministry of Health (MOH), Kenya Government from Uasin district, Kenya[55]. Malaria has been endemic in East Africa and in Uganda it is endemic in all regions (9). Severe adult malaria in these regions therefore suggests an alteration in the population immunity to malaria infections. HIV causes functional defects in the immune system, mainly T-4 Lymphocyte dysfunction in the helper/effector Lymphocyte subset[39].

The important immune mechanisms in malaria infections are lymphocyte dependent (13). HIV infection has now reached epidemic proportions in Uganda (43, 45). A possible association between HIV infection and this severe adult malaria was conceived in view of this background evidence.

2.2. STUDY OBJECTIVES AND HYPOTHESES

Reports of severe P.falciparum malaria in adults in Uganda have been largely anecdotal. The aim of and motivation for this study were to confirm this phenomenon and to investigate its possible association with HIV infection in an adult population aged 18-60 years living in a meso-endemic malaria region in Western Uganda.

Specifically the study was to determine whether:-

1. HIV infection is associated with an increased risk or severity of infection with P.falciparum malaria.

2. HIV infection is associated with a slower clinical and or parasitological response to chemotherapy for P.falciparum malaria.

The Specific Hypotheses were :-

1. Ho: HIV infection is not associated with an increased risk or severity of infection with P.falciparum.

   Vs

   HA: HIV infection is associated with an increased risk or severity of infection with P.falciparum.

2. HO: HIV infection is not associated with a slower clinical and/or parasitological response to chemotherapy for P.falciparum infection.

   Vs

   HA: HIV infection is associated with a slower clinical and/or parasitological response to chemotherapy for P. falciparum infection.

2.3. RATIONALE FOR THE STUDY

The studies carried out elsewhere on the association between HIV and malaria infections have been carried out in areas where the HIV seroprevalence was low. It was necessary to carry out the study in an area of higher HIV seroprevalence like Uganda and compare results.

From 1971-1986 Uganda went through a debilitating political turmoil. The Health sector including medical research and the Health Information System had their share of this political upheaval. With return of peace and favourable political atmosphere since early 1986, the government has embarked on the task of formulating plans and policies for rehabilitating the health sector. At the moment HIV and malaria are major public health challenges in the country. This study was therefore timely and appropriate, as its results will be considered in the overall planning and policy making for the health care programmes.

CHAPTER 3

3. STUDY AREA

3.1. GEOGRAPHY

The study was conducted at Mbarara Hospital in Mbarara district in South Western Uganda. The Republic of Uganda is located in East Africa and lies astride the equator (see map 1). It is a landlocked country bordering Kenya in the East, Tanzania and Rwanda in the South, Zaire in the West and Sudan in the North. The country has an area of 241,038 square kilometres, 18 percent of which is open water and swamps and 12 percent is forest reserve and gameparks. Lake Victoria, the third largest lake in the world, makes up most of the open water area and is shared by Kenya and Tanzania.

Uganda has a favourable climate because of its relatively high altitude. Temperatures range between 17^{o}c and 26^{o}c. The Central, West and South West regions receive heavy rainfall during the months of March through May and light rainfall between September and December. The soil composition varies accordingly, being generally fertile in the Central, West and SouthWest regions and becoming less fertile as one moves from the East to the North. Due to these combinations of climatic conditions, Uganda has tropical rain forest vegetation in the South and savanna woodlands and semi-desert vegetation in the North. These climatic conditions favour the breeding and flourishing of mosquitoes, the vectors for transmission of malaria parasite.

At the present Uganda is divided into 34 districts which do not necessarily represent tribal groupings but were created for the ease of administration.

3.2. ECONOMIC AND DEMOGRAPHIC PROFILE

The country has a basically agricultural economy with 90 percent of the population dependent on agriculture and agro-based industries. Agricultural produce contributes 98 per cent of Uganda's exports and the country is basically self sufficient in food. From 1960 to 1970, Uganda had an expanding economy with a Gross Domestic Product (GPD) growth rate of 5 per cent per annum, compared to a population growth rate of 2.6 per cent per annum. From 1970-85 however, the country experienced a period of civil and military unrest with the resultant destruction of social infastructure and disruption of the economy. This has had a tremendous negative impact on the economy, educational and health situation of the general population.
The Health Information System is still so bad that it is difficult to collect meaningful health data from available health records.

Since 1986, however the National Resistance Movement Government has introduced and implemented a recovery programme which is steadily moving the country towards economic prosperity.

The population of Uganda, estimated at more than 16 million, is increasing 2.8 per cent per year. The land's population carrying capacity is closely related to the agricultural potential which is determined by the climatic conditions.

Table 1.1 summarises the basic socio-economic indicators in Uganda.

Table 1.1 Basic Socio-Economic Indicators, Uganda, Various Years.

Indicator	Year	Value
Population (thousands)	1988	15,947.8
Total area (sq.km.)	1988	241,038
Land area (sq. km.)	1988	197,100
Women of child bearing age as per cent of total population	1985	23
Population growth rate/year	69/80	2.8
Life expectancy - male	1969	145.6
- female	1969	46.9
Hospital beds	1981	20,136
Beds for 10,000 population	1981	15
Population for physician	1981	23,000

Source: Ministry of Planning and Economic Development, Uganda, Various Development Plans

3.3. HEALTH PRIORITIES AND PROGRAMMES

Health services in Uganda are provided by the Ministry of Health, the Ministry of Local Government and non-governmental organizations (NGOs), particularly religious groups. The Ministry of Health is responsible for planning and developing health policies and for providing health care in all government hospitals. The Ministry of Local Government is in charge of health care delivery at the district level and below. NGOs provide services both to hospitals and to smaller medical units. In its continuing efforts to expand services to the majority of the population, the government is gradually shifting away from costly curative services to cost-effective, preventive services.

The government is developing a health policy with the goal of health for all people by means of a nationwide network of preventive and curative health services in a self-sustaining cost recovery system. Particular emphasis is placed on maternal and child health services, environmental sanitation, provision of essential drugs, water supply and health education. The goal of the system is to extend health coverage to all Ugandan citizens by the turn of the century through community participation. Through this approach it is hoped that most of the endemic diseases such as malaria and HIV could be brought under control in the near future. (56)

3.4. MBARARA HOSPITAL

This is a government run institution with about 200 bed capacity. It serves as one of the referral units for most of the private clinics in the large town of Mbarara and for most dispensaries and health centres within the district. Referral is extended to the neighbouring districts of Bushanyi and Rakai. In this way the hospital shares in serving a population of about 1,500,000 for the three districts (see map 2)..

CHAPTER 4

4. MATERIALS AND METHODS

4.1. EXPLORATORY VISIT AND PERIOD OF STUDY

After developing the protocol at the Department of Community Health (DCH), University of Nairobi, Kenya, a preliminary visit was made to Uganda between August and October 1989. The purpose of the visit was;

1. To obtain permission from the ACP and the Ugandan National Research Council to carry out the research in the country;
2. To obtain the necessary demographic, economic and health data from the ACP, Ministry of Health and Ministry of Planning and Economic Development;
3. To get acquainted with the general situation at Mbarara Hospital and to establish operational understanding with District Administrator (DA), District Medical Officer (DMO), the Hospital Superintendent (HS), physicians, laboratory and pharmaceutical personnel at the hospital;
4. To assess availability of resources such as transport, laboratory and storage facilities, electricity and personnel for utilization in the study.

The visit was successfully completed and after sponsorship was obtained the project was finally commenced in January 1990 and completed in May 1990.

4.2. STUDY DESIGN

Two inter-related studies were designed to evaluate the potential associations between P.falciparum malaria and HIV infections. Study A, a case-control study design, tested the hypothesis; whether HIV infection increases the risk or severity of infection with P.falciparum malaria by comparing the prevalence of HIV infection (as denoted by presence of HIV antibodies) in selected patients aged between 18-60 years with symptomatic P. falciparum malaria infection of different degrees of severity, and in asymptomatic patients.

Study B, a follow up study design, tested the hypothesis, whether HIV infection is associated with a slower clinical and or parasitological response to anti-malarial chemotherapy by comparing the prevalence of HIV infection in the malaria patients with different rates of clinical and or parasitological response to the chemotherapy.

4.3. SAMPLE SIZE

W. Naamara found a point seroprevalence for HIV of 17.7% in a population in Lyamtonde, a town only 60 kilometres away from Mbarara town.(46) A 10% seroprevalence of HIV for Mbarara population was assumed and in regard to the following specifications a statistically large enough sample size was calculated.

Specifications:

1. Desired level of significance of test = 95% therefore, α error = 0.05
2. Desored minimum increase in risk of severe malaria due to HIV infection to be detected
   i.e. Relative Risk (Odd's ratio = 3)
3. Desired power of the test = 90%
   therefore B error = 0.1
4. Assumed relative frequency (f) of exposure of HIV among controls in the target population (i.e. prevalence of HIV in study population) is 10%).

From sample size tables for case-control studies* and using the above specifications, n, the minimum statistically large enough number for each group of cases and controls is given as = 68. Therefore N, minimum number of total participants viz.; = 3n = 204. (N.B. 3n = 2 groups of P.falciparum case. one group severe cases, one group non-severe cases and one group of non-malaria controls). They were matched 1:1:1 for age and sex.

*SCHLESSELMAN, J.J.
Sample size requirements in cohort and case-control studies of disease. Amer. J. Epid. 1974.

4.4 STUDY POPUALTION

Patients admitted to the medical wards or seen at the outpatient clinic at Mbarara hospital constituted the study population.

4.4.1 Inclusion and Exclusion Criteria

Patients aged 18 years or more, indigenous residents of the districts or Rakai, Mbarara or Bushenyi and had given informed consent were recruited into the study. Those who had signs and symptoms of severe malnutrition and/or were known to have the inherited disorders of sickle cell trait or G-6-P-D deficiency were excluded from the study.

4.4.2 Case control study group (A)

Patients, if they had demonstrable P.falciparum parasitaemia accompanied by symptoms suggestive of malaria for which no other cause could be identified, were recruited as cases of malaria. They were classified into severe and non-severe groups according to criteria laid down in section 1.2.7. They were recruited by a system of frequency matching for age (5 year bands) and sex.

By the same system a comparable control group was recruited from patients asymptomatic for P.falciparum malria. These included patients who had come for medical, surgical or gynaecological reasons unrelated to malaria disease. Detailed medical history, including duration of present malaria symptoms, antimalarial treatment already taken and demographic data were enquired into from the patient or accompanying attendant. Then a physical examination was carried out by the principal investigator and the findings recorded on the proforma as shown in appendix I. Venous blood samples were then collected and for those patients with altered levels of consciouses a lumbar puncture was performed and cerebral spinal fluid (c.s.f) collected for examination to exclude other causes of menngitis. Then blood was obtained by pricking a finger of the patient with a lancet needle and slide smears prepared for malaria parasite examination.

4.4.3. Follow-up study group (B)

Patients with P.falciparum malaria infection as ascertained in group A, were recruited into this group. Those who were very sick, especially the severe malaria cases were admitted, others were seen on outpatient basis. Treatment with antimalarial drugs was started and the patients were grouped according to the specific antimalarial treatment they received.

The choice of antimalarial chemotherapy to give to the patient depended on the type of antimalarial drug the patient had taken prior to presentation, (if this could be known), severity of the malaria infection and availability of the medicine. Severe P.falciparum malaria cases received quinine therapy mostly.

4.4.3. 1 Specific treatment groups

Group BI received chloroquine only.
Group BII received chloroquine and Fansidar together.
Group BIII received Quinine therapy only.

The treatment regimen shown in table 2 was maintained throughout the study period, parenteral quinine hydrochloride was given diluted in 500mls of normal saline or 5% dextrose and infused over a 6-8 hour period per unit.

TABLE: 2, TREATMENT REGIMEN

Drug name and dosage	Groups					
	BI		BII		BIII	
	Admitted	Outpatient	Admitted	Outpatient	Admitted	Outpatient
Chloroquine	-Intial inj.im. 200mg -6hrs. later inj.im. 100mg -then daily 2 tabs or inj.im. 100mg x 3 days	Initial inj.im. 200mg 6hrs. later 2 tabs then daily 2 tabs x 3 days				
Chloroquine and Fansidar			Initial inj. im. 200 mg chloro-quine followed by Fansidar 3 tablets immediate-ly then 3 tablets next day	Initial inj.im. 200mg chloro-quine followed by Fansidar 3 tablets immediate-ly then 3 tablets next day		
Quinine					iv 650 mg 8hrly x 24hrs, then inj/ tab 650mg daily x 10 days	iv 650mg ,the tab 650mg daily x 10-13day

Inpatients were reviewed daily and outpatients were asked to return on day 3 and day 7 for review and their clinical/parasitological responses to treatment assessed and recorded on the follow-up sheet shown in appendix 2.

On day 7 a blood slide smear was taken from the patient and read for P.falciparum parasites.

4.4.3.2 Supportive Treatment

1. Other drugs
Patients were advised not to use any other antilalarials or analgesics. For those who complained of severe headaches one or two doses of paracetamol (2 tablets) were allowed.

2. Anaemia
Those whose haemglobin levels were below 7.1g/dl were transfused with whole blood.

3. Coma; Comatose patients were appropriately nursed.

A urinary bladder catheter was inserted for urinary output determination.

4. Hyperthermia

Tepid sponging and body exposure were advised for patients whose axillary temperatures rose to or above 39^{o}C.

5. Dehydration

Dehydrated patients were encouraged to consume plently of oral fluids or received appropriate intravenous fluid therapy.

4.5. LABORATORY STUDIES

4.5.1. Parasitaemia

Patients suspected of having malaria infection had thick blood slides prepared and presence of malaria parasites ascertained on Giemsa staining of the slides. When enrolled for the study a thin slide smear was prepared for parasite counting. For thick smears a drop of blood was placed in the centre of a clean glass slide and teased with the edge of another glass slide to make a smear of about 1 cm diameter. For thin smears a drop of blood was placed near one end of a clean glass slide. A glass slide cover was then brought backwards into the drop of the blood at an angle of about 30 degrees, and then pushed forward in a steady movement to produce a film with two straight edges.

After the films were made they were dried by waving in the air, and kept with the blood facing downwards to prevent airborne contamination. Then thin films were fixed in methylalcohol for about 30 seconds and then stained in a 10% solution of Giemsa stain in ph buffered water. The thick films were stained with Field's stain. The slides were read with the help of an experienced laboratory technician. Parasites were counted on the thin smear against 500 erythrocytes.

4.5.2. HIV Serology

Venous blood was obtained from the patients using 8mls vacutainers. Serum was immediately separated and stored in a refrigerator at $-20^{\circ}C$ after careful labelling. Serology for HIV was performed with the DU-PONT Kits by ELISA. A specimen was considered positive for HIV antibodies if it was repeatedly (twice) reactive on the ELISA.

4.5.3. C.S.F. Analysis

C.S.F. from patients with altered mental status was analysed for

a) cells
b) sugar
c) protein

4.6. ETHICAL CONSIDERATION.

This study involved human subjects. A number of ethical requirements had therefore to be met.

a) The proposal was passed by the ethical committee of the Uganda Medical Research Council (see Apendix 4)

b) Informed consent was obtained from the study participants after an attempt was made to explain to them what the study was about and its value to them (See Appendix 5). Pretest counselling sessions were held for each consented participant. Post test counselling sessions were held for all the participants whose HIV screening result was positive.

c) Because of the stigma that is associated with HIV or AIDS the following precautions were taken.

i) The study was discussed with the DMO, DA and MS of the hospital plus the lab. technician only. Throughout the period of the study the principle investigator kept a low profile with the rest of the hospital staff especially on matters pertaining to the study.

ii) Demographic data and medical histories were obtained from the participants or their attendants by the principle investigator alone who also carried out the physical examinations needed for the study.

iii) No results of the blood tests were ever to be made known to anybody or to any study participants especially if they did not insist on knowing.

vi) Throughout the study, the laboratory technician was not aware of the names of the participants. Codes and not names were used to label specimens. Codes were later dropped when lab. results were obtained

d) A new and separate venepuncture set was used for each study participant.

e) Used syringes, needles, swabs etc. were properly disposed of at the end of each days work.

f) In liason with other medical staff at the hospital participants with medical conditions were properly managed. Alternative forms of antimalaria therapy were administered to those who proved resistant. Untoward effects of quinine such as hypotension, tinnitus,hypoglycaemia etc. were monitored in those who recieved the treatment with a view to correcting them. Collaborative management of the patients ensured that there was no delay in treating any patient if the principal investigator was busy or absent. Patients were properly handed over to other physicians at the hospital at the end of the study for continued management.

4.7 STUDY LIMITATIONS

The major constraint in this study was supervision. The study was conducted quite far away from the DCH in Nairobi. This made supervision limited as travel by supervisors to Uganda was at times difficult.

Other constraints included inadequate laboratory facilities. It was not possible to carry out pre-recruitment urine or blood concentrations of antimalarials and prior ingestion was only assumed from patient reports. Serial parasitaemia determinations in the progress of patient response to treatment was not possible. Western blot confirmatory tests on sera that reacted positive for HIV antibodies on ELISHA could not be done because of expenses of the kits. The non-malaria control as selected from hospital patients yielded a biased control sample. Selection of this group from non-hospitalised individuals such as hospital staff, patients' attendants or the general population would have yielded a non-biased control group. This was not possible because of the stigma associated with HIV. Healthy individuals were not so readily willing to undergo voluntary HIV screening tests. Exclusion of cryptococcal meningeal infection was not possible because of lack of Indian ink stains for CSF.

On several occasions lack of intravenous fluids especially dextrose and saline raised much anxiety in the management of patients. The effects of frequent fluctuations in electric power supply at the point of

study on stored sera is difficult to assess. Screening for G-6-P-D defficiency and haemoglobin-S could not be carried out.

4.8 DATA ANALYSIS

Clinical and laboratory data were recorded on the proforma shown in appendix 1, 2 and 3. The services of a computer were not immediately available and information gathered from the field was primarily analysed by hand using an ordinary electronic calculator. A computer was also utilized during data analysis. Student's t and z -tests of significance were done on the corresponding means and proprtions respectively. Chi-square test of significance were done on rates. Odds ratio , an estimate of relative risk was calculated to determine the strengh of association. A statistical test was considered significant if it's p-value was < 0.05 and non-significant if it was ≥ 0.05.

CHAPTER:5

RESULTS

A total of 207 participants were recruited into the study and matched for sex and age in the three groups namely; severe P.falciparum cases, non-severe P.falciparum cases and non-malaria controls. Each group had 69 participants.

AGE AND SEX DISTRIBUTION

Of the total participants ,105 (50.7%) were females and 102 (49.3%) were males, and their sex (F:M) ratio was 1:1. None of the females was pregnant. The overal mean age for the participants was 27 ± 10 (mean $\pm$ S.D). These findings are summarised in tables 3 and 4 and depicted in figure 1.

COMPARISON OF THE GROUPS BY THEIR LEVELS OF EDUCATION

The level of education attained by each participant was enquired into and the following five categories were obtained.

A: No formal education

B: 1-5 years of Primary Education

C: Completed Primary Education (i.e. up to P.7)

D: Had some post-primary education (Junior 2,3 - Senior 4)

E: Had more than senior 4 education (i.e. higher, university or had training after senior 4).

Tables 5, 6a and 6b summarise the distribution of the study participants according to their levels of education. There were no statistically significant differences in the levels of education among these groups.

TABLE 3: SEX DISTRIBUTION OF THE PARTICIPANTS

SEX	P.FALCIPARUM CASES		NON-MALARIA CONTROLS	TOTAL n (%)
	SEVERE n	NON-SEVERE n	n	
FEMALES	35	35	35	105 (50.7)
MALES	34	34	34	102 (49.3)
TOTAL	69	69	69	207 (100)

Female-Male Ratio = SEX RATIO = 1:1

n = NUMBER WITHIN THE GROUP

TABLE 4

PARTICIPANTS AGE DISTRIBUTION

Age-Groups AGE-GROUP	P.FALCIPARUM CASES		NON-MALARIA	TOTAL (%)
	SEVERE	NON-SEVERE		
18 - 22	27	27	27	81 (39)
23 - 27	17	17	17	51 (25)
28 - 32	6	6	6	18 (9)
33 - 27	7	7	7	21 (10)
38 - 42	6	6	6	18 (9)
43 - 47	3	3	3	9 (4)
48 - 52	2	2	2	6 (3)
53 - 57	1	1	1	3 (1)
TOTAL	69	69	69	207 (100)
MEAN	26.7	27	26.6	27 YEARS
S.D.	10	9.5	9.8	10 YEARS

FIGURE 1: HISTOGRAM OF AGE DISTRIBUTION FOR THE PARTICIPANTS

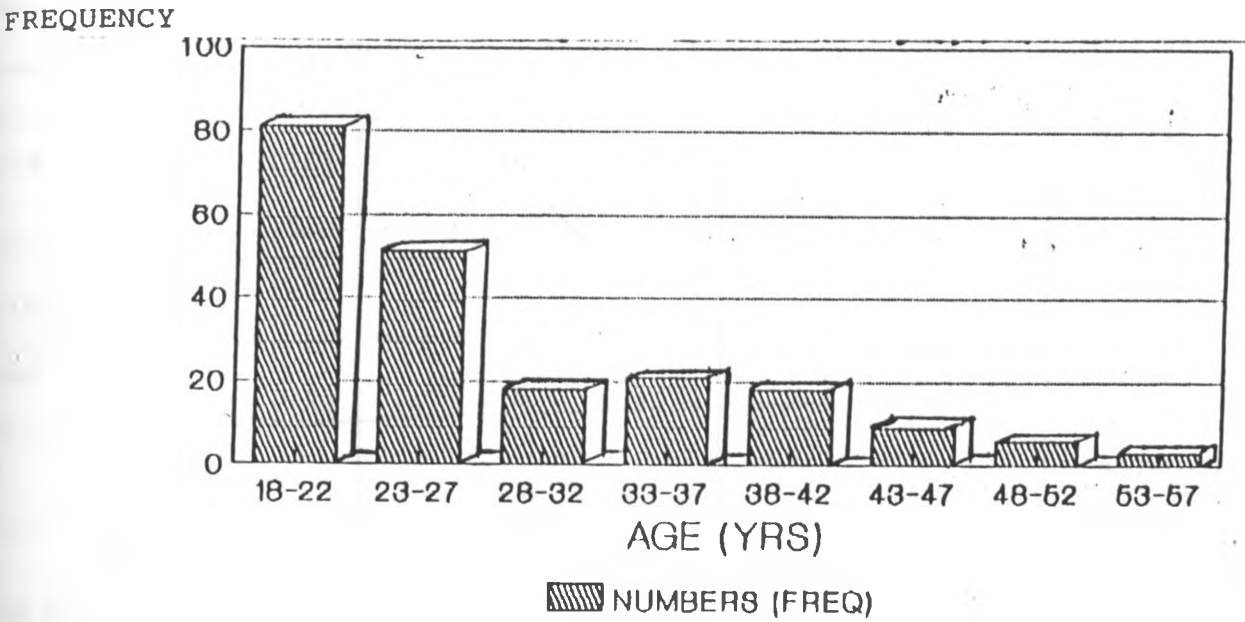


TABLE:5 DISTRIBUTION OF STUDY PARTICIPANTS BY THEIR LEVELS OF EDUCATION

OF TION	P.FALCIPARUM CASES		NON-MALARIA CONTROL	TOTAL n(%)
	SEVERE n (%)	NON-SEVERE n (%)	n (%)	
formal ation	25 (35)	19 (27)	27 (38)	71 (34)
5 years	30 (38)	27 (34)	22 (28)	79 (38)	
o Std 7	6 (26)	10 (42)	8 (33)	24 (12)
-Primary	5 (25)	8 (40)	7 (35)	20 (10)
than S.4 tion	3 (22)	5 (39)	5 (39)	13 (6)
AL	69	69	69	207 (100)

TABLE 6(a): COMPARISON OF STUDY GROUPS BY LEVEL OF EDUCATION

OF TION	P.FALCIPARUM CASES		NON-MALARIA CONTROL	TOTAL n * (%)	STATISTICAL SIGNIFICANCE
	SEVERE n (%)	NON-SEVERE n (%)	n (%)		
	25 (35)	19 (27)	27 (38)	71 (34)	$X_2^2 = 2.22$
D+E	44 (32)	50 (37)	42 (31)	136 (66)	P> 0.100 * N.S
L	69	69	69	207 (100)	

N.S. = NOT SIGNIFICANT

TABLE 6(b): COMPARISON OF STUDY GROUPS BY LEVEL OF EDUCATION

LEVEL OF EDUCATION	P. FALCIPARUM CASES		NON-MALARIA CONTROL	TOTAL n(%)	STATISTICAL SIGNIFICANCE
	SEVERE n (%)	NON-SEVERE n (%)	n (%)		
A+B	55 (37)	46 (31)	49 (33)	150 (72%)	$X_2^2 = 3.051$
C+D+E	14 (25)	23 (40)	20 (35)	57 (28%)	$P > 0.100$ NS
TOTAL	69	69	69	207 (100%	

COMPARISON OF THE GROUPS BY THEIR PLACES OF RESIDENCE

The place of residence was enquired into for each study participant. Table 7 summarises the results of these enquiries. Of the total participants, 64% were rural residents, 32% urban residents and 4% dual residents (i.e. partly rural and partly urban.) There were no statistically significant differences in places of residence for the three groups of participants.

DISTRIBUTION OF SEVERE P.FALCIPARUM INFECTION BY AGE

A total of 69 cases of severe P.falciparum malaria were recruited into this study. Their distribution by age group is shown in table 4 and figure 2. There was an inverse relationship between the numbers of these cases with age, i.e. the number of cases decreased with advanced age.

DURATION OF P.FALCIPARUM SYMPTOMS PRIOR TO PRESENTATION

A history of duration of malaria symptoms prior to presentation was enquired into for both the severe and non-severe P.falciparum cases. The mean duration of these symptoms was 2.75 $\pm$ 2.2 (mean $\pm$ S.D.) days for the severe cases and 4.2 $\pm$ 2.12 (mean $\pm$ S.D.) days for the non-severe cases (table 8 and figure 3). The difference in mean duration of P.falciparum symptoms for the two groups was highly statistically significant ($P' < 0.001$).

TABLE 7: COMPARISON OF STUDY GROUPS BY THEIR PLACES OF RESIDENCE

PLACE OF RESIDENCE	P.FALCIPARUM CASES		NON-MALARIA CONTROLS	TOTAL	STATISTICAL SIGNIFICANCE
	SEVERE n (%)	NON-SEVERE n (%)	n (%)	n (%)	
RURAL (R)	39 (57)	49 (70)	44 (64)	132 (64)	A) TOTAL MALARIA CASES VS CONTROL $X^2_1 = 1.89$ p> 0.100 N.S.
URBAN (U)	26 (37)	20 (30)	21 (30)	67 (32)	B) SEVERE MALARIA VS NON-SEVERE MALARIA $X^2_1 = 1.34$ p> 0.100 N.S.
R/U*	4 (6)	0 (0)	4 (6)	8 (4)	C) SEVERE MALARIA VS CONROLS
TOTAL	69 (100)	69 (100)	69 (100)	207 (100)	$X^2_1 = 0.50$ p > 0.100 N.S.

*R/U = Rural/Urban

FIGURE 2: DISTRIBUTION OF SEVERE P.FALCIPARUM MALARIA BY AGE

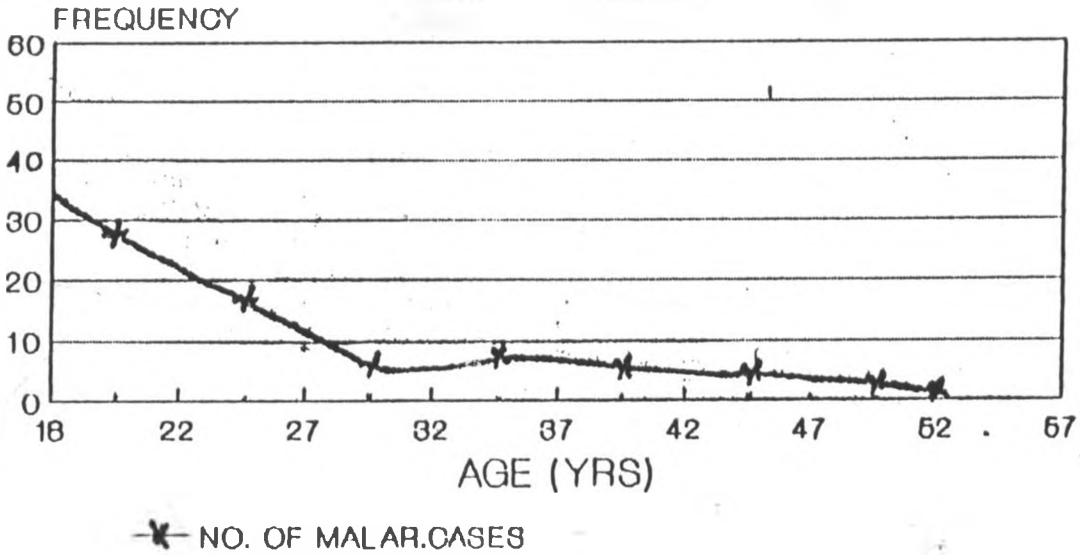


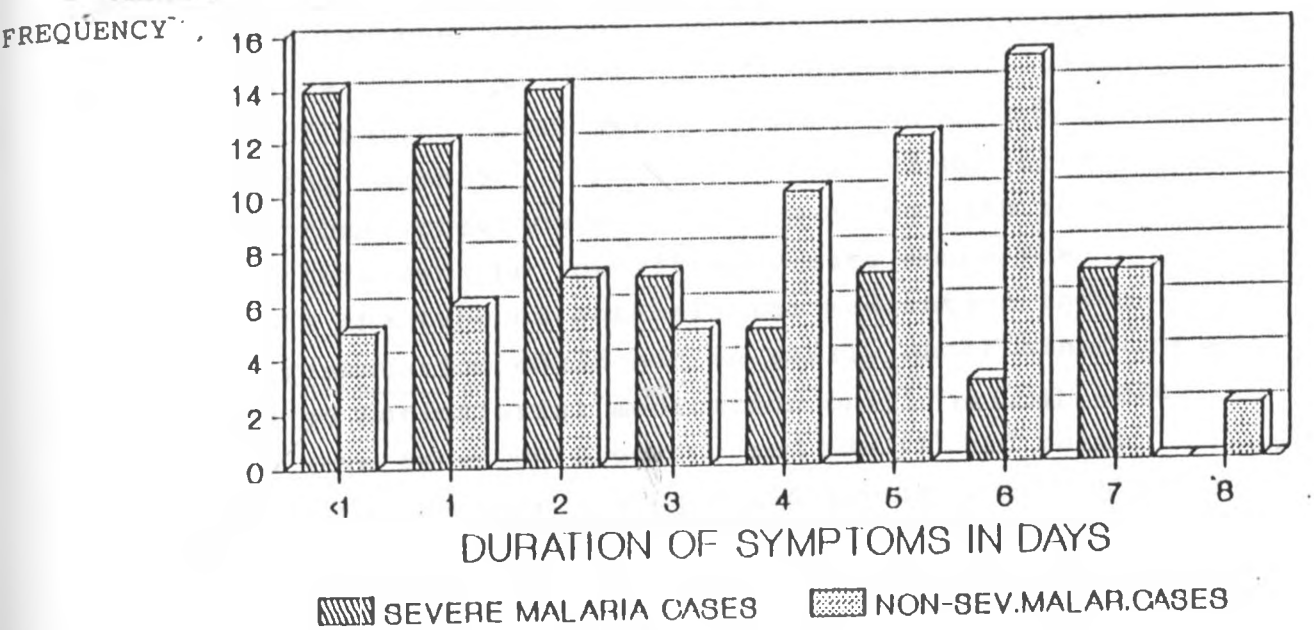
TABLE 8: DURATION OF MALARIA SYMPTOMS PRIOR TO PRESENTATION

DURATION OF SYMPTOMS (DAYS)	SEVERE P. FALCIPARUM CASES	NON-SEVERE P.FALCIPARUM CASES
<1	14	5
1	12	6
2	14	7
3	7	5
4	5	5
5	7	10
6	3	15
7	7	7
8	0	2
MEAN	2.75 DAYS	4.24 DAYS
S.D.	2.2 DAYS	2.12 DAYS
T - STATISTIC (D.F. = 136)	4.1	
P. VALUE	<0.001	H.S.
95% C.L.	1.49 ± 0.72	
OVERAL MEAN ± S.D.	3.5 ± 0.72	

H.S. = HIGHLY SIGNIFICANT

D.F. = DEGREE OF FREEDOM

FIGURE 3: DURATION OF MALARIA SYMPTOMS PRIOR TO PRESENTATION



HISTORY OF ANTIMALARIAL INGESTION

A history of antimalarial ingestion within 48 hours prior to presentation was enquired into for each P.falciparum malaria cases. A total of 115 or(83%) patients volunteered a history of having taken antimalarials and 23 or(17%) denied having taken any. Most patients did not carry medical records of their previous medications along with them. Because of this and the low literacy rate among the participants the type of antimalarial medication taken prior to presentation could not be easily ascertained. Of those who had taken antimalarial medication only 27 or(23%) were certain to have taken Chloroquine and 9(or 8%) had taken Chloroquine and Fansidar. None could remember having taken Quinine.

Among the severe P.falciparum 54(or 78%) had taken antimalarial medication and 15 (or 22%) had not taken any prior to presentation. Of the non-severe P.falciparum 61(or 88%) had taken some form of antimalarial medication and 8 or (12%) had not taken any.

These findings are summarised in table 9. The ddifference in proportions of patients who had taken antimalarial medication prior to presentation in the groups was not statistically significant.

TABLE 9: COMPARISON OF PRIOR ANTIMALARIAL INGESTION BY GROUP

ANTIMALARIALS TAKEN	P.FALCIPARUM CASES				TOTAL		STATISTICAL SIGNIFICANCE
	SEVERE		NON-SEVERE				
	n	(%)	n	(%)	n	(%)	- Z TEST
YES	57	(78)	61	(88)	115	(83)	Z= 1.58
NO	15	(22)	8	(12)	23	(17)	p = 0.114
							$\chi^2_1 = 1.58$
TOTAL	69	(100)	69	(100)	138	(100)	95% cl = 0.1 ± 0.123

HIV SEROPREVALENCE

Of the 207 participants, 85(or 41%)were seropositive for HIV antibodies on ELISA and 122(or 59%) tested negative. The severe P.falciparum group had a seropositivity rate for HIV antibodies of 44.0%, the non-severe P.falciparum group had a rate of 40.6% and the control group had a rate of 37.7%. HIV seroprevalance among the study groups is shown in table 10. The differences in the seroprevalance rates of these groups were not statistically significant.

DISTRIBUTION OF AIDS RELATED COMPLEXES (ARC)

Of the 85 HIV seropositive participants only one satisfied the WHO/CDC criteria for AIDS. 27(or 32%) manifested with ARC. The distribution of ARC by group is shown in table II. None of the HIV seropositive patients with cerebral malaria manifested with signs and symptoms suggestive of ARC.

COMPARISON OF ARC BY GROUP

Table 12 depicts the results of the comparison of the study groups by their ARC status.

(a) SEVERE MALARIA CASES COMPARED WITH CONTROL GROUP

ARC did not appear to increase the risk of severe malaria, (X^2 = 1.73, P > 0.05, 95% CL:0.54 -15.18).

(b) ALL AMALARIA COMPARED WITH NON-MALARIA CONTROLS

ARC appeared toincrease the risk of malaria (X^2 = 5.79, P< 0.905, 95%CL:1.25 - 16.13)

SEVERE MALARIA COMPARE WITH NON-SEVERE MALARIA CASES

C) Patients with ARC were more likely to be non-severe cses than severe cases.

(x^2= 5.04, P < 0.05, 95% CL: 0.11 - 0.97)

D) NON-SEVERE MALARIA CASES COMPARED WITH CONTROLS

ARC appeared to increase the risk of non-severe malaria (x^2 = 9.86, P < 0.05 OR = 5.66, 95% CL: 1.84 - 24.61)

DISTRIBUTION OF P.FALCIPARUM PARASITAEMIA BY HIV SEROSTATUS

P.falciparum malaria parasite densities expressed as percent of infected red blood cells at presentation were determined for severe and non-severe P.falciparum cases. Their distribution by HIV serostatus are depicted in table 13 and figure 4 and 5.

The mean parasite density for the severe cases of P.falciparum was 7.15 ± 3.8 (mean ± S.D.) and 2.2 ± 1.1 (mean ± S.D.) for the non-severe cases.

Within the severe cases of P.falciparum the mean parasite density for the HIV seropaositive cases was 7.4 ± 3.7 (mean ± S.D.) and 6.9 ± 3.6 (mean ± S.D.) for the HIV seronegative cases. The difference in these means, however, was not statistically significant (t = 0.54. P > 0.1).

Within the non-severe cases of P.falciparum, mean parasite density for the HIV seropositive cases was 2.2 ± 0.95 (mean ± S.D.) and 2.17 ± 1.06 (men ± S.D) for HIV seronegative cases. The difference in these mean parasite densities was not statistically significant (t = 0.46, P > 0.1).

TABLE 10: COMPARISON OF HIV SEROSTATUS BY GROUP

ELISA	P.FALCIPARUM MALARIA CASES				NON-MALARIA CASES		TOTAL		STATISTICAL SIGNIFICANCE
	SEVERE		NON-SEVERE						
	n	(%)	n	(%)	n	(%)	n	(%)	
+	31	(44.9)	28	(40.6)	26	(37.7)	85	(41)	A) SEVERE VS CONTROLS $X_1^2 = 0.75$ P> 0.100 N.S. OR = 1.35 95% cl = 0.68-2.66
-	38	(55.1)	41	(59.4)	43	(62.3)	122	(59)	B) NON-SEVERE VS CONTROLS $X_1^2 = 0.122$ p>0.100 NS OR = 1.13 95% cl = 0.57-2.24
TOTAL	69	(100)	69	(100)	69	(100)	207	(100)	C) ALL MALARIA CASES VS CONTROLS x_1^2 0.48, OR = 1.24 95/C.L. 0.68 - 2.23 P> 0.100 NS.

TABLE 11: DISTRIBUTION OF ARC BY GROUP

ARC MANIFESTATION	P.FALCIPARUM CASES		NON-MALARIA CONTROLS	TOTAL
	SEVERE n	NON-SEVERE n	n	
DIARRHOEA	2	7	0	9
EXTRA INGUINAL LYMPHADENOPATHY	1	4	1	6
CHRONIC CAUGH	0	2	0	2
WEIGHT LOSS	2	2	1	5
SKIN RASHES	1	2	0	3
HERPES ZOSTER (PAST OR PRESENT)	1	0	1	2
TOTAL	7	17	3	27

TABLE 12. COMPARISON OF ARC DISTRIBUTION BY GROUP

ARC	P.FALCIPARUM CASES		NON- MALARIA CONTROLS	TOTAL	STATISTICAL SIGNIFICANCE
	SEVERE n (%)	NON-SEVERE n (%)	n (%)	n (%)	
+	7 (10)	17 (25)	3 (4)	27 (13)	A. SEVERE VS CONTROL X_1^2 = 1.73 P = 0.32 N.S OR = 2.48 95% CL: 0.54-15.18
-	62 (90)	52 (75)	66 (96)	180 (87)	B. ALL MALARIA VS CONTROL X_1^2 = 5.79 P = 0.016 H.S OR = 4.63 95% CL: 1.25-16.13
TOTAL	69 (100)	69 (100)	69 (100)	207 100	SEVERE VS NON-SEVERE X_1^2 = 5.04 P = 0.04 H.S OR = 0.113 95% CL . 0.11-0.97 D. NON-SEVERE VS CONTROL X_1^2 = 9.88 P = 0016 H.S OR = 5.66 95% CL: 1.84-24.61

: NOT SIGNIFICANT

= HIGHLY SIGNIFICANT

TABLE 13: DISTRIBUTION AND COMPARISON OF P.FALCIPARUM PARASITAEMIA BY GROUP AND HIV SEROSTATUS

PARASITE DENSITY (%)	SEVERE P.FALCIPARUM CASES		NON-SEVERE P.FALCIPARUM CASES	
	ELISA		ELISA	
	+ FREQUENCY	- FREQUENCY	+ FREQUENCY	- FREQUENCY
<1	1	0	2	3
1	1	3	5	8
2	2	3	12	14
3	2	2	8	9
4	4	2	3	5
5	5	5		
6	1	4		
7	0	3		
8	2	1		
9	2	4		
10	3	3		
11	4	2		
12	3	4		
13	2	2		
n	31	38	30	39
MEAN	7.4	6.9	2.2	2.17
S.D.	3.7	3.6	0.95	1.06
MEAN*	7,5		2.2	
S.D.**	3,8		1.1	
S.E.	0.92		0.065	
T.STATISTIC	0.54		0.46	
P. VALUE	≥0.10 N.S.		>0.10 N.S.	
95% CL	0.5^{+}_{-} 1.84		0.03^{+}_{-} 0.12	

FIGURE 4: DISTRIBUTION OF MALARIA PARASITES DENSITIES IN PATIENTS WITH SEVERE MALARIA

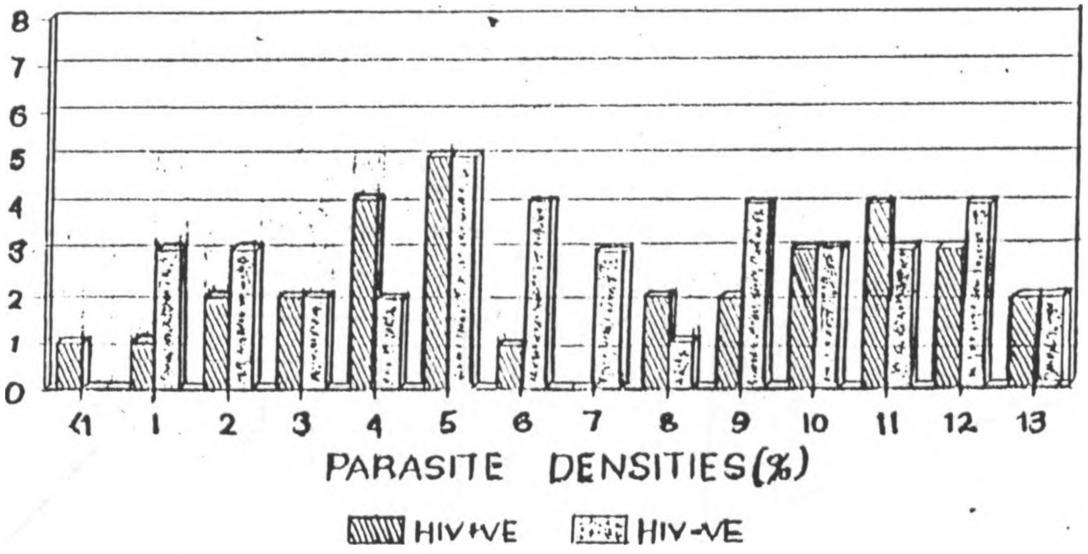
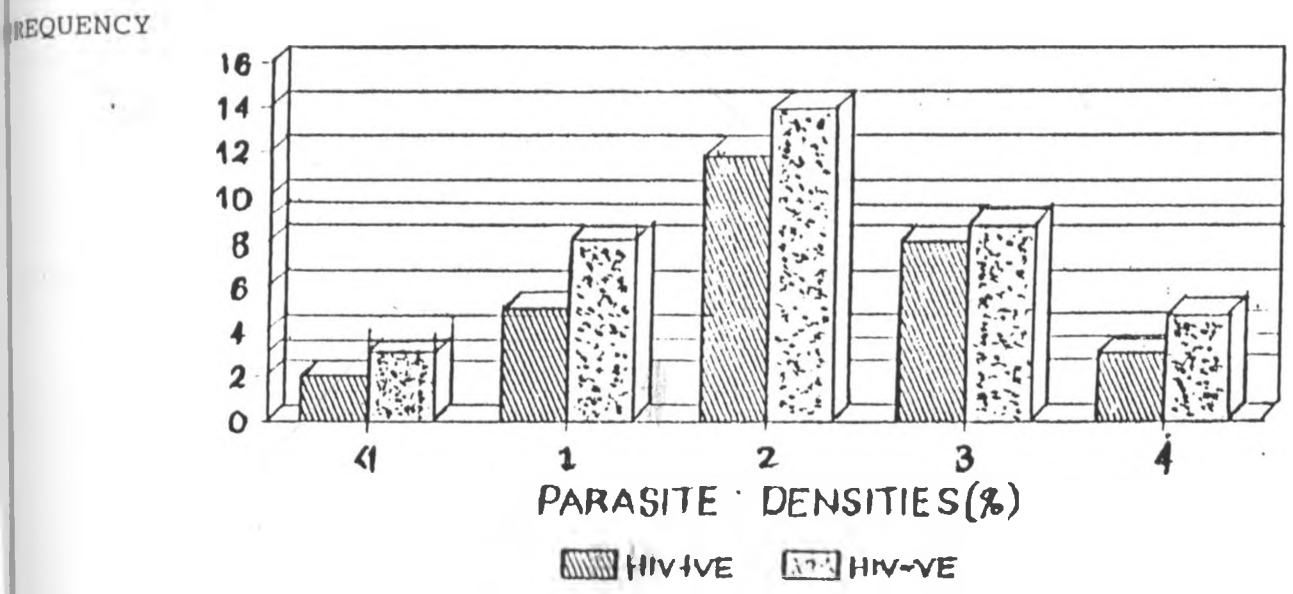


FIGURE 5: DISTRIBUTION OF MALARIA PARASITES DENSITIES IN PATIENTS WITH NON-SEVERE MALARIA.



SYMPTOMS OF SEVERE P.FALCIPARUM MANIFESTATION BY HIV SEROSTATUS

Severe P.falciparum cases manifested with more than one symptom. Of the 69 cases, 42(or 60%)manifested with hyperpyrexia, 25(or 36%) , satisfied the definition of cerebral malaria,15(or 22%) manifested with : anaemia, 13(or 19%) with - jaundice and 13(or 19%)with hyperparasitaemia. The grouping of these symptoms by HIV serostatus is shown in table 14. Tables 14A, 14B, 14C, 14D and 14E show the relationship between the HIV serostatus and these symptoms. HIV infection did not appear to be associated with any of the symptoms manifested by severe P.falciparum malaria.

TABLE 14: DISTRIBUTION OF SYMPTOMS OF SEVERE P. FALCIPARUM MALARIA BY HIV SEROSTATUS

SYMPTOM	ELISA				TOTAL	
	+		-			
	n_1	(%)	n_2	(%)	n	(%)
HYPERPYREXYA	20	(65)	22	(58)	42	(60)
CEREBRAL MALARIA	11	(36)	14	(37)	25	(36)
ANAEMIA	5	(16)	10	(26)	15	(22)
JAUNDICE	4	(13)	9	(24)	13	(19)
HYPERPARASITAEMIA	5	(16)	8	(21)	13	(19)

TOTAL CASES N= 69, n_1 = TOTAL ELISA+ = 31 n_2 = TOTAL ELISA - = 38 X_1^2 =1.79 N.S.

TABLE 14A: COMPARISON OF HIV SEROSTATUS IN HYPERPYREXIC CASES

ELISA	HYPERPYREXIA		TOTAL	STATISTICAL SIGNIFICANCE
	PRESENT	ABSENT		
+	20	11	31	X_1^2 = 0.314, p> 0.100
-	22	16	38	OR = 1.32
TOTAL	42	27	69	95% cl = 0.497 - 3.52 N.S.

TABLE 14B: COMPARISON OF HIV SEROSTATUS IN CEREBRAL MALARIA CASES

ELISA	CEREBRAL MALARIA		TOTAL	STATISTICAL SIGNIFICANCE
	PRESENT	ABSENT		
+	11	20	31	X_1^2 = 0.0136, p>0.100
-	14	24	38	OR = 0.942
TOTAL	25	44	69	95% cl=0.351 - 2.53
				N.S.

TABLE 14C: COMPARISON OF HIV SEROSTATUS IN ANAEMIA CASES

ELISA	ANEMIA		TOTAL	STATISTICAL SIGNIFICANE
	PRESENT	ABSENT		
+	5	26	31	X_1^2 = 1.04, p>0.100
-	10	28	38	OR = 0.538
TOTAL	15	54	69	95% CL = 0.162 -1.785
				N.S.

TABLE 14D: COMPARISON OF HIV SEROSTATUS IN CASES WITH HYPERPARISITAEMIA

ELISA	HYPERPARASITAEMIA		TOTAL	STATISTICAL SIGNIFICANCE
	PRESENT	ABSENT		
+	5	26	31	X_1^2 = 0.271, p> 0.100
-	8	30	38	OR = 0.721
TOTAL	13	56	69	95% CL = 0.209 -2.47 N.S.

TABLE 14E: COMPARISON OF HIV SEROSTATUS IN JAUNDICEDCASES

ELISA	JAUNDICE		TOTAL	STATISTICAL SIGNIFICANCE
	PRESENT	ABSENT		
+	4	27	31	X_1^2 = 1.30 p>0.100
-	9	29	38	OR = 0.477
TOTAL	13	56	69	95% CL = 0.132 -1.732 N.S.

HIV SEROSTATUS BY AGE AND SEX

Table 15 shows the HIV serostatus by age and sex. HIV seropositivity rate declined with advance in age with the majority below the age of 35 years. The Female: Male (F:M) sex ratio generally declies with advance in age. The overal F:M ratio, however, was 1.13:1

HIV SEROSTATUS BY PLACE OF RESIDENCE AND LEVEL OF EDUCATION

Tables 16, 17, 18 summarise the relationship between HIV serostatus, place of residence and level of education of the participants. HIV was not associated with either place of residence or level of education.

TABLE 15 HIV SEROSTATUS BY AGE AND SEX

AGE GROUPE (YRS)	HIV SEROSTATUS				F:M RATIO FOR HIV SEROPOSITIVITY
	+		-		
	F	M	F	M	
18-22	16	4	20	24	4:1
23-27	16	12	18	20	1.3:1
28-32	3	12	7	4	0.25:1
33-37	4	1	2	8	4 : 1
38-42	5	7	8	3	0.72 : 1
43-47	0	2	0	1	0
48-52	1	1	3	1	1:1
53-57	0	1	2	1	0
n	45	40	60	62	
TOTAL	85		122		1.13:1

TABLE 16: COMPARISON OF HIV SEROSTATUS BY PLACE OF RESIDENCE

ELISA	PLACE OF RESIDENCE			TOTAL	STATISTICAL SIGNIFICANCE
	RURAL	URBAN	RURAL/URBAN		
+	47	34	4	85	$X_2^2 = 4.48$ p> 0.100
-	85	33	4	122	N.S.
TOTAL	132	67	8	207	

TABLE 17: COMPARISON OF HIV SEROSTATUS BY LEVEL OF EDUCATION

ELISA	EDUCATION LEVEL					TOTAL	STATISTICAL SIGNIFICANCE
	A	B	C	D	E		
+	13	10	18	24	20	85	$X_4^2 = 0.0377$
-	20	17	26	31	28	12	p> 0.100
TOTAL	23	26	44	55	48	207	N.S.

TABLE 18: COMPARISON OF HIV SEROSTATUS BY GROUP AND PLACE OF RESIDENCE

GROUP	SEVERE MALARIA			NON-SEVERE MALARIA		NON-MALARIA CONTROLS			TOTAL	STATISTICAL SIGNIFICANCE
RESIDENCE	R	U	R/U	R	U	R	U	R/U		
ELISA										
+	17	10	2*	17	4	13	10	2*	85	$X^2_5 = 3.409$
-	22	16	2*	32	6	31	11	2*	122	p> 0.100
TOTAL	39	26	4	49	20	44	21	4	207	N.S.

* R/U excluded as numbers are too small hense x^2 (D.F. =5)

CLINICAL AND PARASITOLOGICAL RESPONSE TO ANTIMALARIA CHEMOTHERAPY GROUPED BY HIV SEROSTATUS

A total of 138 malaria cases received antimalarial chemotherapy. 134 cases were followed for at least 7 days and their clinical and parasitological response to treatment assessed. Those who had no symptoms suggestive of malaria infection and had a negative slide for malaria parasites on day 7 of treatment were regarded as cured. Those who still had a positive slide for malaria parasites were regarded as resistant. 4 patients fell out of the study as 2 of them died within the course of treatment and 2 never returned for follow up.

Group BI

A total of 59 patients were treated with chloroquine only. Of these 4 (or 7%) had severe malaria while 55 (93%) had non-severe malaria infection. The results of their response to chloroquine therapy and grouping of HIV serostatus are shown in table 19. 27 (or 46%) were cured by the 7th day of treatment and 32 (or 54%) were resistant. 12 (or 52%) of the seropositive and 15 (or 42%) of the seronegative were cured while 11 (or 48%) of the seropositive and 21 (or 58%) of the seronegative were resistant. These proportions, however were not significantly different, (χ = 0.76, P = 0.447).

GROUP BII

A total of 16 patients were treated with chloroquine and Fansidar combined.3 (19%) had severe malaria infection while 13 (81%) had non-severe malaria infection. 11 (69%) were cured by the 7th day of treatment and,5 (31%) were resistant. This information is summarised in table 20. 7(or 70%) of the seropositive and 4 or (67%) of the seronegative were cured while 3 or (30%) of the seropositive and 2(or (33%) of the seronegative were resistant. These proportions,however,were not statistically significantly different (Z= 0.125, P= 0.904) ;

GROUP BIII

A total of 59 patients were treated with Quinine only. 52 (88%) of them,had severe malaria infection while 7 (12%) had non-severe malaria infection. The results of their response to Quinine therapy are summerised in table 21. 20(or (87%) of the seropositive and 31 or (86%) of the seropositive were cured while 3 or (13%) of the seropositive and 5(or (14%) of the seronegative were resistant. These proportions however were not statistically different. (Z= 0.11, P = 0.9.12)

TABLE 19: COMPARISON OF RESPONSE TO CHLOROQUINE THERAPY

ELISA	RESPONSE		TOTAL	STATISTICAL SIGNIFICANCE
	CURED n (%)	RESISTANT n (%)	n (%)	2 TAIL Z - TEST
+	12 (52)	11 (48)	23 (39)	SE = 0.13 Z = 0.76 P = 0.44
-	15 (42)	21 (58)	36 (61)	95% CL= 0.1 ± 0.25 N.S.
TOTAL	27 (46)	32 (54)	59 (100)	

TABLE 20: COMPARISON OF RESPONSE TO COMBINED CHLOROQUINE/FANSIDAR THERAPY

ELISA	RESPONSE		TOTAL	STATISTICAL SIGNIFICANCE
	CURED n (%)	RESISTANT n (%)	n (%)	2 TAIL Z - TEST
+	7 (70)	3 (30)	10 (63)	SE = 0.24 Z = 0.125 P = 0.904 95% CL= 0.03 ± 0.470
-	4 (67)	2 (33)	6 (37)	
TOTAL	11 (69)	5 (31)	16 (100)	N.S.

TABLE 21: COMPARISON OF RESPONSE TO QUININE THERAPY

ELISA	RESPONSE				TOTAL		STATISTICAL SIGNIFICANCE
	CURED		RESISTANT				
	n	(%)	n	(%)	n	(%)	2 TAIL Z TEST
+	20	(87)	3	(13)	23	(39)	SE = 0.09
							Z = 0.11
-	31	(86)	5	(14)	36	(61)	p ≤ 0.12
							95% CL = 0.01 ± 176
TOTAL	51	(86)	8	(14)	59	(100)	N.S.

CHAPTER: 6

6. DISCUSSION OF THE RESULTS

6.1. P.FALCIPARUM CASES

6.1.1. Demographic profiles

In this study, 69 consecutive cases of confirmed severe P.falciparum were studied at Mbarara Hospital within a period of 5 months. This is not the actual number of the cases that came to the hospital in that period. A number of other cases were excluded for reasons such as, early death, loss to follow-up, lack of matching pairs and or non-consent to be fully involved in the study. It must be pointed out here that Mbarara hospital, like any other government hospital in the country, is on the disadvantage when it comes to competition with private clinics and or hospitals around, in as far as efficiency and availability of drugs and other medical supplies are concerned, and hence for patients. The fact that over 69 cases of severe P.falciparum were seen at the hospital within this period could mean a larger number of similar cases attended the private medical units, a fact that suggests a high incidence of the illness in the area.

The numbers of these cases declined in the older age groups with more than 60% of them in the age 18-30 years with a mean age 27^{+}-10 (mean^{+}- S.D.).

This mean age is almost similar to that of 29 $\pm$ 10.4 (mean$^{\pm}$ S.D.) years found by Tombe at KNH, Kenya[54]. This could suggest a difference in immunity to malaria with age. It could also be related to the age structure of the population as the greatest majority of adults fall in the age 20-35 years)[56] The sampling criterion definetely contributed to this mean age as participants had to be aged above 18 years.

This age range was chosen in order to be able to include individuals at the greatest risk of HIV infection because of sexual activitiy, as the latter has been shown to be greatest single risk factor for HIV transmission in Africa[40].

The age of 18 years was arbitrarily taken as the minimum age for sexual activity in this area.

Females and males were equally affected as evidenced by a 1:1 ratio for sex, indicating absence of difference in immunity to malaria by sex.

Education and place of residence in this study did not seem to be associated with severity of malaria. If these findings were not simply due to small samples then a likely plausible explanation may be two-fold. It may be likely that the kind of education in this population is not a reflection of the ability to influence acquisition of malaria infection. It is also most likely that conditions prevailing in the rural and urban places of residence reported for these participants are not greatly different in as far as prevention of malaria infection is concerned. Indeed with deterioration in economy and general lowering of living standards in the country as a result of political upheavals, this could most likely be so. Moreover most of the reported urban residences were rural trading centres and some of the urban slums in Mbarara town.

6.1.2. Duration of P.falciparum symptoms prior to presentation.

Severe P.falciparum infection were more acute than the non-severe ones. The information on the durations, however were entirely patient-recall-dependent and were most likely influenced by subjectivity, considering that the symptoms of malaria may not be easily distinguishable from those of other illness by most patients. However, if this was not a biased finding it indeed suggests a reduction or absence of immunity to malaria in these patients. Longer duration of the non-severe infections could mean that these patients had the capacity to contain these infections because of possessing immunity to malaria or had opportunity to take some form of antimalarial therapy prior to presentation.

6.1.3 Ingestion of antimalarial medications prior to presentation

Prior ingestion of antimalarial medication however, did not seem to be associated with severity of the malaria infection. These findings were not free from the influence of subjectivity as admission to prior ingestion of medication does not necessarily mean antimalarial drugs. It sould mean any other drugs. It was not possible to carry out urine antimalarial assays, which would have -improved the reliability of this information. The majority of the patients admitted having taken some form of medication and yet presented with the infection. This could mean that these medications were largely ineffective, a fact that was supported by finding of high rates of resistance of the malaria infections to the common antimalarial drugs that were later used to treat them.

6.2 HIV INFECTION AND THE RISK OR SEVERITY OF P.FALCIPARUM INFECTION

6.2.1 HIV Point seroprevalence

An average point seroprevalence rate to HIV of 41 for all the study participants was found. The seroprevalence rates reported in the country are 5-20% and 1-5 % for urban and rural popualtions respectively [45]. Namaara[46] in his study in a rural population in Rakai, Uganda, had reported rates of 67% and 17.1% for high and normal risk groups respectively. Although our rate compares well with that of Namaara considereing that our population was a mixture of high and normal risk groups it is a very high rate indeed and could most likely mask an association of HIV infection and malaria, This discrepancy could have arisen from false positive results associated with the low specificity of ELISA which not only differs with different populations but is also affected by cross reactions with malaria antibodies [40]. This was most likely so especially as confirmatory tests with WESTERN BLOT were not done.

6.2.2 Association of HIV seropositivity and risk of severity of P.falciparum malaria

No significant differences were found in the sero-positivity rates for HIV between the three study groups. Absence of a different would imply that HIV is not associated with the risk, or severity , of P.falciparum infection .

It would be fallacious to conclude simply on this evidence since the degrees of immune depression in the HIV seropositive individuals (as would be denoted by T4/T8 ratios, if these were to be determined in the groups) were not assessed and or compared. Indeed in the limitted number of patients whose immunity was presumed to have been severely compromised as indicated by the presence of ARC, the findings were different. Patients with ARC were at an increased risk of P.falciparum infection but more so of non-severe infection. ARC was not associated with higher risk of severe P.falciparum infection. None of the patients with ARC presented with cerebral malaria. This could mean that patients immunocompromised by HIV are protected from cerebral malaria, a situation comparable with that prevailing in severe malnutrition[14]. These findings, however, could simply be the result of small samples in the study groups, while a spurious situation cannot be ruled as some of the ARC manifestations are non-specific. There was, for instance, a large number of cases presenting with diarrhoea especially among the non-severe malaria cases. Malaria per se is known to cause diarrhoea.

These results therefore need to be studied more fully with larger numbers of cases and when other causes of signs and symptoms similar to those of ARC have been carefully excluded.

In this study no significant difference was found in P.falciparum mean parasite densities between HIV seropositive and seronegative patients. These findings are similar to those reported by Simoya et al in Ndola, Zambia[47].

HIV seropositivity was not found to be associated with any of the features manifested by severe P.falciparum. This was expected since seropositivity was not associated with severitiy of P.falciparum malaria.

6.2.3. Demographic profiles and HIV seroprevalence

HIV seropositivity was inversely related to age with greater rates in the age below 35 years. This was expected as this is the age of the greatest sexual activity. This and the finding of a 1:1 sexual ratio are in support of the risk of sexual transmission for HIV in the area as reported earlier by Namara [46] in Uganda and elsewhere in Africa [37].

HIV seropositivity appeared not to be associated with either level of education or place of residence.

In the opinion of the author however, these results could have been greatly influenced by the small samples in the study and need further evaluation with larger populations.

6.3. ASSOCIATION OF HIV INFECTION WITH CLINICAL AND OR PARASITOLOGICAL RESPONSE TO CHEMOTHERAPY FOR P.FALCIPARUM INFECTION

In this study HIV infection did not appear to be associated with the rate of clinical or parasitological response to chemotherapy for P.falciparum infection. Although resistance to chloroquine, Fansidar and quinine was exhibited by malaria patients in this study, this resistance was not associated with HIV seropositivity as such. However, a comparison of these responses in the participants stratified according to their degrees of immune depression would have yielded more rational conclusions on this association.

Resistance to the antimalarial chemothepary in this study could not be graded according to the scheme of "S, RI , RII and RIII", because of failure to carry out serial parasitological determinations or follow up the patients through to the end of the fourth week of treatment.

In view of these short comings, therefore, further investigations of this association are recommended.

CHAPTER 7

7. CONCLUSIONS, RECOMMENDATIONS:

7.1. CONCLUSION

a) Over 69 confirmed cases of severe P.falciparum malaria in adults were seen at Mbarara hospital within a period of 5 months. This is evidence to indicate a high prevalence of this phenomenon of severe adult malaria in this presumably malaria mesoendemic region and of its undoubtedly great public health importance.

b) Although a high seroprevalence to HIV was found, HIV seropositivity per se, was not found to be associated with an increased risk of severe P.falciparum infection. However, ARC appeared to increase the risk of P.falciparum infection although not of the severe infection. Since HIV infection of necessity progresses to ARC or AIDS with time the adverse associations between HIV and malaria in patients with ARC or AIDS could become more common and apparent in future as the HIV epidemic progresses, provided the health care personnel stay aware of and watch for it.

c) Resistance to antimalarial treatment was encountered but this was not associated with HIV seropositivity. There were high rates of resistance to chloroquine and Fansidar. Resistance to quinine was minimal and on the whole severe P.falciparum malaria infection responded quite well to quinine therapy. Malaria severity could be associated with this resistance to chemotherapy.

d) The fact that severe P.falciparum infection were more commonly acute rather than chronic as opposed to the non-severe infection, points to a relative reduction or absence of immunity to malaria in these patients. Since this was not necessarily due to HIV infection, it could be linked to other epidemiological determinants such as changes in malaria endemicity, lack of adult immunity or parasite strain virulence.

7.2. RECOMMENDATIONS

a) Further studies are recommended to obtain proper estimates of the true incidence of severe P.falciparum malaria in the country.

b) More analytical studies are recommended to elucidate the major determinants of severe P.falciparum malaria in the country. Of priority are studies to;

i) Determine the prevalence of antibodies to P.falciparum in the populations,

ii) Determine sensitivity of P.falciparum to various antimalarial drugs for current or future use.

iii) Survey the knowledge, attitude, and use of antimalarial drugs in the country.

vi) Map the current malaria endemicity in the country.

The results of such studies would then form the basis for planning appropriate interventions.

c) More studies are recommended to further elucidate the possible association between P.falciparum and HIV infection . Comparison of severity of P.falciparum in patients with differing degrees of immune depression by HIV such as differing T4/T8 ratios, or ARC or AIDS might be more appropriate and relevant; and so would studies of infants infected with HIV. Determination of incidence rates of malaria infection in HIV infected cohorts by prospective studies might be of rewarding interest.

d) There is urgent need to promote a general well informed awareness of the phenomenon of severe adult P.falciparum malaria among all health care planners and providers, especially of its diagnosis and management, in the region.

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APPENDIX 1.

ADMISSION DATA PROFORMA

1. Demographic data

Name: _____ Serial Number: _____

Age (years): _____ Sex: _____

Parity: _____ LNMP: _____

Education: _____ Religion: _____

Residence and Address: _____

Occupation _____

2. Symptoms of present illness

Fever: _____ Joint aches: _____

Headache: _____ Vomiting: _____

Diarrhoea & duration (days) _____ Loss of wt: _____

Coma: _____ Duration of coma (days): _____

Convusion: _____

Cough: _____

Body itch: _____

Others: _____

_____

3. History of present illness

Duration of symptoms (days) : _____

-previous treatments received

a) H/o antimalarial ingestion
within the past 48 hrs: chloroquine: _____

Fansidar: _____

Quinine: _____

Others: _____

b) Surgery: _____

c) Transfusion: _____

4. Other known medical conditions specifically:

Sickling trait: _____

G-6-P-D- deficiency: _____

5. Clinical signs

General

Tempretature ^{O}c: _____ pallor: _____

Jaundice: _____ Hydration: _____

Skin change: _____ Oral thrush: _____

Lymphadenopathy: _____
(classified by site)

Dehyration (moderate or severe): _____

Pulse: _____ BP: _____
(Beats/minute) (Systolic/Diastolic mmHg)

Dyspnoea: _____

b, Systemic

CNS: Consciousnes: _____ speech: _____

Neck stiffness: _____ Kernigs'sign: _____

Muscle tone: _____ Reflexes: _____

RS _____

Abdominal: Epigastric tenderness
Hepatomegaly (mch in cm)
Splenomegaly
(Hatchet's classification)

Others: _____

_____

6. Laboratory investigations and results

BS: Thick smear for MPS: _____

Thin smear for MPC: _____

Hb: _____ PVC: _____

(g/dl) (ml/100 mls) _____

WCC (cells x 10^9/l)

Electrolytes: sodium (mmol/l) _____

: Potassium (mmol/l) _____

: Urea (mmol/l) _____

: Creatinine (mmol/l) _____

Urine sugar: _____

CSF: Protein (g/l) _____ Glucose mmol/l_____

: Cells: (cells x 10^9/l) _____culture/sensitivity_____

: Indian ink test _____

G-6-P.D. activity _____

ELISA 1st _____

2nd _____

APPENDIX 2

FOLLOW-UP DATA PROFORMA

Name _____ Age _____ Serial number _____

DAY	SIGNS & SYMPTOMS	LAB FINDINGS	TREATMENT INSTITUTED
0			
1			
2			
3			
4			
5			
6			
7			

OUTCOME: CURED _____ RESISTANT _____

APPENDIX 3

LABORATORY REQUEST FORMS

1. Form I:

Name: _____ Age _____

Sex: _____ Registration number _____

Request: BS (Thick) for MPS _____

Results _____

Form: 2

Code name/number _____

Requests		Results
Bs (thin) for MP count	_____	_____
Hb	_____	_____
PCV	_____	_____
WCC	_____	_____
Electrolytes - sodium	_____	_____
- Potassium	_____	_____
- Urea	_____	_____
- Creatinine	_____	_____
Urine Sugar	_____	_____
- Protein	_____	_____
- Cells	_____	_____
Indian inktest	_____	_____
G-6-P-D- deficiency	_____	_____
ELISA		

APPENDIX 4.

NATIONAL RESEARCH COUNCIL,
MINISTRY OF PLANNING AND
ECONOMIC DEVELOPMENT,
P.O BOx 6884,
KAMPALA, UGANDA.

Ref: MV/289

14th, November, 1989.

The District Administrator
MBARARA.

Dear Sir,

RE: Dr. E.K. Mpora

I wish to introduce to you Dr. E. K. Mpora who is going to carry out a research project in your district entitled, "An association Between Human Immuno Deficiency Virus and Plasmodium Falciparum in an Urban Population".

His project has been approved by the National Research Council and cleared by the Office of the President.

The purpose of this letter is to request you to avail him the necessary assistance during the course of his study.

Yours faithfully

D. Kasozi
for: Chief Research Co-ordinator
NATIONAL RESEARCH COUNCIL

APPENDIX 5

CONSENT FORM

I _____ from _____

_____, being of _____years of age

do hereby consent to such studies as will be subjected

to _____, as explained by

Dr Mpora, having fully understood what such studies will entail.

Signed: _____

Witness: Name: _____

Signed: _____

Date: _____