IMPACT OF PARASITOLOGICAL, CLINICAL AND RENAL-HEPATIC BIOMARKER RESPONSES IN CHILDREN BELOW FIVE-YEAR OLD CO-INFECTED WITH MALARIA AND HIV IN WESTERN KENYA

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DECLARATION

Declaration by the Candidate

This thesis is my original work and has never been presented for the award of an academic degree in any other university and should not be copied, or reproduced in any format without written authority from the author and/or University of Eldoret.

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DEDICATION

To the children under the age of five years who make research a living testimony. And to my family led by my wife Khadikya Jacqueline, my sons Erick, Elvis and Eddie and my one and only baby girl Mama Angela Elsie Nabwire, who have withstood the loneliness as a result of my many hours and years away during the research project and thesis writing period.

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ABSTRACT

Malaria and HIV remain major causes of morbidity and mortality among children under five years in sub-Saharan Africa. Their co-infection presents a compounded health challenge, particularly in Western Kenya where *Plasmodium falciparum* transmission and HIV prevalence are both high. This study aimed to determine the burden of parasitemia and host biomarker responses in children aged below five years co-infected with *P. falciparum* and HIV. A cross-sectional case-control study involving 138 children aged 6–59 months was conducted at Kakamega County General Teaching and Referral Hospital. Parasitological diagnosis was done by microscopy and rapid diagnostic tests, while biochemical assays evaluated renal and hepatic function. Children co-infected with malaria and HIV were generally younger than those with HIV mono-infection, suggesting that mother-to-child acquired HIV predisposes to increased malaria susceptibility and severity in early life. The co-infected group had significantly higher median parasitemia (1,870 parasites/µL; range: 1,806–80,025), indicating intense transmission. Female children were more affected than males, suggesting possible gender-based differences in exposure, care-seeking behavior, or immune response. Renal markers serum creatinine, urea, and blood urea nitrogen were significantly elevated in the co-infected group, reflecting early renal impairment likely linked to immune complex deposition and microvascular obstruction. Hepatic markers ALT, AST, GGT, total and direct bilirubin were also markedly raised, indicating hepatocellular injury and cholestasis. Total protein, albumin, and globulins were significantly higher in co-infected children, suggesting polyclonal B-cell activation and hypergammaglobulinemia driven by chronic immune stimulation. Among the biochemical markers, LDH, creatinine, and ALP exhibited high sensitivity and specificity in predicting organ dysfunction, while GGT, bilirubin, and total protein demonstrated high sensitivity but lower specificity. Receiver Operating Characteristic (ROC) analyses showed modest predictive value (AUC 0.43–0.69) for these markers in identifying renal and hepatic dysfunction. The findings suggest that combining hepatic and renal markers could enhance diagnostic accuracy in co-infected children. *P. falciparum* and HIV co-infection in children under five years significantly disrupts renal and hepatic function, reflecting compounded immune and metabolic stress. Elevated creatinine, bilirubin, and transaminases indicate potential for these markers to serve as adjunct diagnostic and prognostic tools in endemic areas. The study underscores the need to integrate biochemical assessment into pediatric malaria management, especially in HIV-prevalent regions. Routine monitoring of renal and hepatic function is recommended for timely identification of co-infected children at risk of severe outcomes. Further longitudinal and multi-center studies should investigate the mechanistic pathways underlying biomarker alterations and validate context-specific diagnostic thresholds for clinical use.

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ABBREVIATIONS, ACRONYMS AND SYMBOLS

AIDS: Acquired Immunodeficiency Syndrome

AL: Artemether Lumefantrine

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

DOMC: Division of Malaria Control

GGT: Gamma-Glutamyl Transferase

Hb: Haemoglobin

HIV: Human Immunodeficiency Virus

HDP: High Density Parasitemia

IFN: Interferon

IL: Interleukin

KCGTRH: Kakamega County General Teaching and Referral Hospital

LDH: Lactate Dehydrogenase

MLs: Millilitres

PCR: Polymerase Chain Reaction

RBS: Random Blood Sugar

RDT: Rapid Diagnostic Test

SSA: Sub-Saharan Africa

WHO: World Health Organization

OPERATIONAL DEFINITION OF TERMS

Accuracy: A comparison between the disease conditions (target condition) estimated by a test of interest (index test) and the best estimate of the actual disease state (reference standard).

Algorithm: A set of rules or a process that has/have to be followed when one is performing calculations or going through other problem-solving operations.

Analyte: A substance (marker) that was measured in serum from the study participants.

Area under the curve (AUC): An area bounded by a curve, the x-axis and two vertical lines (or ordinates) at specific x-values used to find the accumulated value of a function over a given interval.

Biochemical marker: Molecules produced during the disease process, either at the initiation of the disease or during progression and which therefore indicates the presence of the disease.

HIV-infected: An individual who has been in contact with the HIV has been confirmed through testing that they are HIV infected.

Liver function markers: Enzymes and proteins in blood that provide the physiological functional status of the liver.

Malaria: A life threatening disease spread to humans by infected female *Anopheles* mosquitos.

Receiver Operating Characteristics (ROC): a curve that includes all the possible decision thresholds from a diagnostic test result.

Reliability: The extent to which a test produces consistent results across different times, different raters, or different settings.

Renal function markers: Chemical or biological agents in body fluids that are used to assess the normal functioning of the kidneys.

Sensitivity: The ability of a test to designate a disease affected individual as being positive for the disease (disease present or true positive).

Specificity: The ability of a test to designate a disease affected individual as being negative for the disease (no disease or true negative).

Validity: A sensitivity, specificity or area under the curve (AUC) threshold value of a biochemical marker that predicts a specific clinical outcome.

CHAPTER ONE

INTRODUCION

1.1 Background Information

Malaria and Human Immunodeficiency Virus (HIV) continue to impose a tremendous health and socioeconomic burden on populations living in sub-Saharan Africa (Deng *et al*., 2023). The two diseases overlap geographically, interact biologically, and together exacerbate morbidity and mortality, especially among vulnerable groups such as young children and pregnant women (Obase et al., 2023; Roberds et al., 2021a). In areas like Western Kenya, where both *P. falciparum* transmission and HIV prevalence are persistently high, their convergence forms a significant obstacle to achieving national and global child survival targets (Hollowell *et al*., 2023; Jaffer & Kingwara, 2023). Despite major strides in prevention, diagnosis, and treatment, malaria–HIV co-infection remains a neglected frontier in public health research, particularly in children under five years of age, who represent the demographic most affected by both infections.

Historically, malaria has shaped human civilization, influencing settlement patterns, agricultural practices, and even the course of empires. Ancient Chinese writings and Egyptian papyri describe fevers resembling malaria, while the disease's presence in the Mediterranean basin was well known by 2700 B.C (Miao, 2025; Talapko *et al*., 2019). The Romans referred to it as mala aria bad air believing it arose from swamp vapors. The modern understanding of malaria emerged through the pioneering work of Charles Laveran, who identified the parasite in human blood in 1880, and Ronald Ross, who

demonstrated mosquito transmission in 1898 (Boualam *et al*., 2021). These discoveries laid the foundation for vector control strategies that remain central to malaria prevention today (Talapko *et al*., 2019).

Globally, malaria remains one of the most lethal parasitic diseases. Despite extensive control efforts, it causes between 200 and 250 million clinical cases annually, resulting in over 600,000 deaths, primarily in sub-Saharan Africa (WHO, 2025). Children under five account for nearly 80% of these deaths, reflecting their limited immunity and high exposure risk. The disease is caused by protozoan parasites of the genus Plasmodium, transmitted through bites of infected Anopheles mosquitoes. Among the five species infecting humans *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. *P. falciparum* is responsible for the most severe and fatal infections in Africa (Lee *et al*., 2022). The parasites invade red blood cells, leading to their destruction and subsequent anemia, and can cause microvascular obstruction, tissue hypoxia, and multi-organ dysfunction in severe cases.

In Kenya, malaria transmission varies by geography and climate, with five major endemic zones: the Lake Region, Coastal Region, Highland Epidemic Zone, Arid and Semi-Arid Zone, and the Central Low-Risk Region (Nyawanda *et al*., 2024). Western Kenya especially around Lake Victoria is one of the highest transmission zones, where malaria remains hyperendemic throughout much of the year. The disease contributes significantly to the health system burden, accounting for roughly 12% of all outpatient visits, up to 19% of inpatient admissions, and 8% overall prevalence (Mategula & Gichuki, 2023). In this region, malaria is responsible for an estimated 27% of deaths among children under five years, and in Africa as a whole, one child dies of malaria every 45 seconds (WHO, 2022).

Parallel to malaria, HIV remains a pervasive epidemic. As of 2022, approximately 39 million people were living with HIV worldwide, of whom 25.6 million reside in sub-Saharan Africa. Children under the age of 15 represent about 1.5 million of these cases, mainly resulting from mother-to-child transmission during pregnancy, delivery, or breastfeeding (UNAIDS, 2023). Despite expanding antiretroviral therapy (ART) coverage, the burden remains high in many rural and resource-limited settings. HIV infection impairs immune function by progressively depleting CD4+ T lymphocytes and activating chronic inflammation, thereby compromising the host's ability to control other infections including malaria.

The relationship between malaria and HIV is multifaceted and synergistic. HIV-induced immunosuppression increases the risk of malaria infection, enhances parasite replication, and raises the probability of severe complications such as severe anemia, cerebral malaria, and renal impairment (Zhang *et al*., 2025). On the other hand, malaria can transiently elevate HIV viral loads by inducing immune activation, which may accelerate progression to AIDS. This interplay is especially pronounced in children, whose immune systems are immature and less capable of mounting effective responses (Roberds et al., 2021b). Studies in Kenya and other parts of Africa show that HIV-infected children experience higher parasite densities, more frequent malaria episodes, and more severe anemia than HIV-negative counterparts (Akech et al., 2020; Milner et al., 2020).

Malaria–HIV co-infection in children also complicates diagnosis. Both diseases may present with overlapping symptoms such as fever, fatigue, and anemia, making it difficult

to distinguish one from the other based solely on clinical features. Furthermore, asymptomatic parasitemia is common in endemic areas, and fever in HIV-infected children may arise from other causes bacterial, viral, or fungal. The presence of HIV may also blunt typical immune and inflammatory responses to malaria, leading to atypical clinical manifestations and delayed recognition of severe disease (Teer et al., 2025).

Accurate laboratory diagnosis is therefore essential. Microscopy remains the gold standard for malaria detection, while rapid diagnostic tests (RDTs) based on parasite antigens such as histidine-rich protein 2 (HRP2) and lactate dehydrogenase (LDH) have improved access to testing in resource-limited settings (Alemayehu et al., 2020; Rogier et al., 2022). However, both methods have limitations: microscopy requires expertise and can miss low-density infections, while RDTs can yield false negatives due to HRP2 gene deletions or false positives due to antigen persistence after treatment. In co-infected individuals, reduced immunity and drug interactions may further alter parasitemia and test performance, highlighting the need for complementary laboratory markers to improve diagnostic accuracy.

Renal and hepatic biomarkers provide an additional window into disease pathophysiology. In malaria, hemolysis and microvascular obstruction can lead to liver dysfunction and renal impairment. Elevated levels of serum creatinine and urea indicate impaired kidney function, while increased bilirubin and transaminases (ALT, AST) reflect hepatocellular injury and hemolysis (Kubanek et al., 2024). In severe cases, such abnormalities correlate with poor outcomes, prolonged hospitalization, and mortality (Brookes & Power, 2022). Similarly, HIV can cause chronic hepatic and renal changes, either directly or through ART

toxicity. Consequently, measuring these biomarkers can help identify children at risk of severe illness, especially when co-infection magnifies systemic inflammation and metabolic stress.

Beyond conventional markers, host immune and inflammatory biomarkers such as cytokines (IL-6, TNF-α), C-reactive protein (CRP), and acute-phase enzymes offer deeper insight into disease dynamics (Donniacuo et al., 2025; Menzel et al., 2021). For instance, elevated CRP and LDH often parallel parasitemia levels and tissue injury, while hypoalbuminemia may signal disease severity or malnutrition. Integrating these biochemical indices with parasitological data could enhance diagnostic accuracy, allowing clinicians to differentiate between uncomplicated malaria, severe malaria, and malaria–HIV co-infection.

Despite substantial research on malaria and HIV separately, integrated biomarker-based studies of co-infection remain limited, especially in pediatric populations in sub-Saharan Africa. Most existing studies are cross-sectional, small-scale, or focused on adults. As a result, the clinical utility of renal and hepatic biomarkers in diagnosing or predicting malaria–HIV co-infection remains poorly defined. Moreover, standard reference ranges for these biochemical markers in African children are lacking, and few studies have examined how ART, nutritional status, and concurrent infections influence these parameters in malaria-endemic regions.

In Kenya, where laboratory infrastructure varies widely between counties, routine use of biochemical markers for malaria risk stratification is rare (Otambo, Olumeh, et al., 2022;

Robert et al., 2024). Surveillance systems focus mainly on parasitological testing, leaving organ dysfunction and biomarker trends largely undocumented. There is thus an urgent need for studies that characterize renal and hepatic changes in malaria–HIV co-infected children, define diagnostic cutoffs relevant to the local population, and assess their predictive value for disease severity and treatment outcomes.

This study therefore seeks to address these knowledge gaps by examining the burden of *P. falciparum* parasitemia and associated changes in renal and hepatic biomarkers among children under five years co-infected with HIV in Western Kenya. Specifically, it will evaluate how biomarkers such as serum creatinine, urea, ALT, AST, and bilirubin vary across demographic profiles and infection categories, and determine their diagnostic and prognostic value in identifying co-infection and disease severity. By integrating parasitological, biochemical, and clinical data, the study aimed to generate evidence that can strengthen laboratory-based diagnosis, guide early clinical intervention, and inform policy on integrated management of malaria and HIV in endemic regions. Ultimately, the findings will contribute to better surveillance, improved case management, and reduced mortality among children affected by these two major diseases.

1.2 Statement of the Problem

Malaria and HIV/AIDS continue to exert an enormous toll on global health, particularly in sub-Saharan Africa, where their overlapping distribution and biological interactions amplify disease severity and complexity of care (Kwenti, 2018). Despite major advances in malaria control and HIV management through vector control programs, effective antimalarial drugs, and widespread access to antiretroviral therapy (ART), these two

diseases remain leading causes of childhood morbidity and mortality. Their convergence in the same populations particularly among children under five years of age creates a compounded burden that threatens to undermine progress toward achieving Sustainable Development Goal 3, which targets an end to epidemics of major infectious diseases by 2030 (Raina et al., 2023).

In malaria-endemic regions such as Western Kenya, *P. falciparum* remains the dominant parasite species, responsible for most malaria-associated deaths in children (Ondeto et al., 2022a; Osborne et al., 2024). At the same time, HIV-1 infection continues to affect a significant proportion of children, mainly through vertical transmission from infected mothers. Although scaling up of prevention of mother-to-child transmission (PMTCT) programs and pediatric ART coverage has reduced new infections, thousands of children still acquire HIV each year (Mwau et al., 2017). These overlapping epidemics have resulted in a growing cohort of children simultaneously exposed to both infections, often in settings marked by poverty, malnutrition, and weak health systems.

The co-existence of *P. falciparum* and HIV-1 profoundly alters disease dynamics and host-pathogen interactions. HIV-induced immunosuppression compromises both innate and adaptive immune mechanisms that are critical for controlling malaria parasitemia (Munyenyembe et al., 2020). This leads to higher parasite loads, prolonged infection, more severe anemia, and an increased likelihood of developing life-threatening complications such as cerebral malaria, metabolic acidosis, and acute kidney injury. Conversely, malaria episodes trigger systemic immune activation and transient increases in HIV viral load, which may accelerate progression to AIDS and worsen immunological recovery even

among children on ART. These interactions create a vicious cycle where each infection intensifies the pathophysiological impact of the other.

Despite the clinical importance of malaria–HIV co-infection, data characterizing the biological and immunological responses to concurrent infection in children remain scarce. Most existing studies have examined malaria and HIV separately, yielding a fragmented understanding of their combined effects (Yibeltal et al., 2020). Few investigations have quantified how parasitemia levels correlate with host immune and biochemical markers such as pro-inflammatory cytokines, anti-inflammatory cytokines, acute-phase proteins, hemoglobin concentration, and markers of liver and renal function in co-infected pediatric populations (Musa et al., 2021; Yibeltal et al., 2020). These biomarkers could serve as early indicators of disease severity, predict treatment outcomes, and support differential diagnosis in settings where malaria and HIV frequently co-exist. However, in many sub-Saharan contexts, including Western Kenya, the distribution, dynamics, and diagnostic value of these markers have not been systematically evaluated.

This knowledge gap poses major clinical and public health challenges. In children under five years, malaria and HIV often present with overlapping symptoms such as fever, pallor, and fatigue, making clinical differentiation difficult. The lack of reliable laboratory markers that reflect co-infection severity leads to delayed or inappropriate treatment. Moreover, diagnostic tools such as microscopy and RDTs for malaria may have reduced sensitivity in immunocompromised children due to altered immune responses, while routine biochemical testing for liver and kidney function is rarely integrated into pediatric case management.

Consequently, many cases of co-infection remain undetected or are treated inadequately, contributing to poor outcomes and perpetuating the cycle of morbidity.

Furthermore, the absence of locally validated reference ranges for key biomarkers in African children complicates clinical interpretation. Factors such as malnutrition, concurrent bacterial or viral infections, and genetic differences can influence biomarker levels, yet these are seldom accounted for in diagnostic algorithms. The interplay between ART regimens, cotrimoxazole prophylaxis, and antimalarial drugs adds another layer of complexity, as these treatments can independently alter hepatic and renal enzyme levels, potentially masking true disease severity.

Understanding the distribution of parasitemia and corresponding host biomarker responses among children co-infected with *P. falciparum* and HIV-1 is therefore essential for several reasons. It will help clarify how immune dysregulation and organ function impairment evolve during co-infection. Additionally, it will identify biochemical and hematological markers that can aid in early recognition of severe disease and guide timely therapeutic interventions. Also, such evidence can inform the development of integrated diagnostic and treatment guidelines that reflect the unique physiological and epidemiological realities of co-endemic regions like Western Kenya.

Without robust epidemiological and biomarker-based data, current interventions risk remaining fragmented and suboptimal. Health workers may continue to rely on nonspecific clinical features, leading to both underdiagnosis and overtreatment. Children with mild disease may receive unnecessary medications, while those with severe co-infection may

not be promptly identified for advanced care. This not only increases mortality but also undermines confidence in existing diagnostic tools and weakens the health system's ability to respond effectively to future malaria or HIV outbreaks.

The present study therefore addressed an urgent gap in understanding how malaria parasitemia interacts with host biomarker responses in children under five years of age living in Western Kenya. By exploring the relationship between parasitemia levels and renal, hepatic, hematological, and immunological markers, the research aims to elucidate the biological basis of disease severity in malaria–HIV co-infection. Findings from this work will provide an evidence base for improving diagnostic accuracy, refining case management protocols, and informing public health strategies aimed at reducing mortality and enhancing quality of care among children in malaria- and HIV-endemic settings.

1.3 Objectives of the Study

1.3.1 Broad Objective

To determine the burden of parasitemia and host biomarker responses in children aged less than five years co-infected with *Plasmodium falciparum* and HIV in Western Kenya.

1.3.2 Specific Objectives

The specific objectives of the study were: -

1) To determine the burden of parasitemia in children under five years co-infected with malaria and HIV in Western Kenya.

2) To compare the concentration of renal and hepatic function markers across demographic profiles between HIV mono-infected and HIV-Malaria co-infected children aged less than five years in Western Kenya.
3) To establish the accuracy and validity of renal and hepatic function markers in the diagnosis of paediatric malaria and HIV co-infection in children aged less than five years in Western Kenya.

1.4 Research Questions

The study sought to answer the following research questions: -

1) How does malaria infection burden significantly differ in malaria-HIV co-infected children aged less than five years in Western Kenya?
2) Would renal and hepatic function markers significantly differ in malaria-HIV-1 co-infected and in HIV-1 mono-infected in children aged less than five years?
3) Would the renal/hepatic markers in the malaria-HIV co-infected children aged less than five years have any significant diagnostic value difference?

1.5 Justification of the Study

The justification for this study arises from the urgent need to improve diagnostic accuracy and case management of malaria, particularly in malaria-endemic regions where HIV infection is also highly prevalent. For decades, presumptive treatment of fever as malaria was a widely accepted clinical practice in sub-Saharan Africa (Omondi et al., 2023). This approach was initially justified by the high mortality associated with delayed treatment and

the limited availability of diagnostic infrastructure. However, as malaria transmission patterns have changed and other infectious diseases have become more common, this strategy has increasingly proven inadequate and potentially harmful (Aborode et al., 2025). The continued reliance on clinical diagnosis alone risks both overtreatment of non-malarial fevers and underdiagnosis of other serious infections, leading to misallocation of limited resources, antimicrobial resistance, and preventable deaths among children.

The WHO now recommends parasitological confirmation of malaria in all suspected cases before treatment is initiated(WHO, 2022). Despite this global policy shift, microscopy and RDTs still face operational challenges in many endemic countries, including Kenya (Cole et al., 2025; Omondi et al., 2023). Microscopy, though considered the gold standard, requires skilled personnel, high-quality reagents, and well-maintained equipment resources that are often scarce in rural health facilities (Mutabazi et al., 2021). RDTs, while simple and rapid, have varying sensitivity and specificity depending on parasite density, storage conditions, and the presence of gene deletions affecting target antigens such as histidine-rich protein 2 (HRP2). Consequently, both techniques may produce false-negative or false-positive results, particularly in children with low-level parasitemia or recent treatment (Beshir et al., 2022). This limits their effectiveness in guiding treatment decisions, especially in co-infection settings where immune responses are altered by other diseases like HIV.

HIV infection complicates the diagnosis of malaria in multiple ways. Children living with HIV are more likely to present with fever due to a wide range of causes beyond malaria, including opportunistic infections (such as bacterial sepsis, tuberculosis, or fungal

infections), inflammatory responses related to immune reconstitution, or adverse drug reactions from antiretroviral therapy (Nikjeh et al., 2025). As a result, the presence of fever in an HIV-positive child cannot automatically be attributed to malaria. Furthermore, immunosuppression may alter the clinical presentation of malaria, mask typical signs such as splenomegaly or high-grade parasitemia, and interfere with serological or antigen-based detection methods (Afrane et al., 2024). These factors can lead to both underdiagnosis and overdiagnosis of malaria, undermining effective case management and contributing to poor outcomes.

Given these diagnostic complexities, there is a pressing need to strengthen existing malaria diagnostic approaches by incorporating additional laboratory markers that can enhance accuracy and provide complementary information on disease severity. Renal and hepatic biomarkers such as serum creatinine, urea, bilirubin, ALT and AST have demonstrated potential diagnostic and prognostic value in identifying malaria-related organ dysfunction (Basire et al., 2025). Similarly, hematological markers such as hemoglobin levels, platelet counts, and white blood cell differentials can help distinguish malaria from other febrile illnesses and identify children at risk of severe disease (Jumba et al., 2024; von Wedel et al., 2025). Integrating these biochemical and hematological indices into routine diagnostic protocols could refine the clinical interpretation of test results, particularly in children with HIV, who may present with atypical patterns of infection.

The justification for this study is further grounded in the need for context-specific evidence from high-burden regions like Western Kenya. Many existing studies on malaria diagnostics have been conducted in general populations, with limited focus on how HIV

co-infection influences diagnostic accuracy and biomarker profiles. Data on renal and hepatic dysfunction in co-infected children remain sparse, and local laboratories rarely use these tests as adjuncts in malaria diagnosis. By generating new evidence on how HIV modifies the reliability of malaria microscopy, RDTs, and related biochemical markers, this study provides essential insights for adapting diagnostic strategies to high HIV prevalence settings.

Improving diagnostic precision has several downstream benefits. First, it enables clinicians to make more informed decisions, ensuring that antimalarial therapy is reserved for confirmed cases while other causes of fever are appropriately investigated and treated. Second, it reduces unnecessary drug use, which in turn helps slow the emergence of antimalarial resistance and reduces healthcare costs. Third, accurate diagnosis minimizes patient morbidity by allowing timely management of co-existing or alternative conditions such as bacterial sepsis, which can be fatal if misclassified as malaria. Finally, improved diagnostic practices contribute to health system efficiency by reducing treatment failures, repeated consultations, and unnecessary hospital admissions.

Beyond clinical implications, this study aligns with Kenya's and global health priorities aimed at strengthening integrated disease management in line with WHO's Test–Treat–Track policy. By addressing diagnostic challenges in malaria–HIV co-infection, the findings directly support the Kenya Malaria Strategy and HIV Strategic Framework, both of which emphasize the need for evidence-based case management and the reduction of under-five mortality. Furthermore, accurate and reliable malaria diagnosis contributes to achieving the Sustainable Development Goals (SDGs) specifically Goal 3, which seeks to

end preventable deaths of newborns and children under five years of age, and to combat communicable diseases by 2030.

In essence, this study was justified by the dual necessity of improving malaria diagnostic performance in the context of HIV and enhancing the interpretation of laboratory findings in co-infected children. By exploring the diagnostic value of renal, hepatic, and hematological biomarkers alongside standard parasitological tests, it sought to fill critical knowledge gaps that hinder effective clinical decision-making in endemic, resource-limited settings. The resulting evidence is expected to guide the development of more precise, integrated diagnostic algorithms, reduce childhood morbidity and mortality, and advance progress toward national and global health targets.

1.6 Significance of the Study

The significance of this study lies in its potential to bridge critical gaps in the diagnosis, management, and prognostication of malaria among children living with HIV infection in Western Kenya. Both malaria and HIV remain leading causes of morbidity and mortality among children under five years in sub-Saharan Africa, and their co-infection significantly complicates clinical management. In regions such as Kakamega County, where Plasmodium falciparum transmission is intense and HIV prevalence remains high, children are frequently exposed to both infections concurrently. The resulting overlap in clinical symptoms particularly fever, anemia, and hepatosplenomegaly makes it difficult to distinguish malaria from other causes of illness. Consequently, misdiagnosis and inappropriate treatment are common, undermining the effectiveness of public health

interventions. This study provides an important step toward addressing these diagnostic challenges through the identification and validation of renal and hepatic function markers as complementary laboratory tools.

One of the major contributions of this study is its role in improving diagnostic accuracy. Current malaria diagnosis in Kenya and much of sub-Saharan Africa still relies heavily on blood smear microscopy and RDTs. While these tools are indispensable, their performance can be limited by several factors including low parasite density, operator error, antigen persistence, and gene deletions in P. falciparum. In HIV-infected children, the diagnostic complexity is further compounded by altered immune responses that may suppress parasitemia or lead to atypical clinical presentations. By examining biochemical indicators such as serum creatinine, urea, bilirubin, and transaminases (ALT and AST), this study provides valuable evidence on whether these markers can serve as reliable adjuncts to parasitological methods. Establishing their diagnostic sensitivity and specificity enhances the clinician's ability to make accurate, evidence-based decisions, thereby reducing both underdiagnosis and overdiagnosis of malaria in HIV-positive children.

The study is also significant for its potential contribution to treatment monitoring and prognostication. Malaria and HIV co-infection often lead to organ dysfunction—particularly affecting the liver and kidneys due to a combination of direct parasite and viral effects, systemic inflammation, hemolysis, and drug toxicity. Measuring renal and hepatic function markers allows for early detection of organ impairment, enabling prompt intervention before irreversible damage occurs. In clinical practice, tracking these markers during treatment can provide real-time information on disease progression and response to

therapy. This is especially relevant in children on combined antimalarial and antiretroviral therapy, where drug–drug interactions can further strain hepatic and renal systems. Thus, integrating biochemical monitoring into routine care not only improves immediate patient outcomes but also supports long-term management by identifying children at risk of chronic complications or treatment-related toxicity.

From a public health perspective, the study's findings are valuable for strengthening integrated disease management strategies. Kenya's health system, like many in sub-Saharan Africa, faces the challenge of managing multiple overlapping infectious diseases within limited resource settings. The identification of affordable and readily measurable biochemical markers offers a practical means of enhancing diagnostic and prognostic capacity in county hospitals and peripheral health facilities. By generating locally relevant baseline data for renal and hepatic function in co-infected children, the study supports the development of reference ranges and context-specific guidelines that reflect the unique physiological and epidemiological realities of the Kenyan pediatric population. These data can also inform policy formulation under national frameworks such as the Kenya Malaria Strategy (2019–2023) and the Kenya HIV Strategic Framework (2022–2027), both of which emphasize evidence-based interventions and integrated care.

At a global level, the study aligns with the WHO "Test, Treat, Track" initiative for malaria control, which advocates for universal parasitological confirmation and effective treatment monitoring. By demonstrating how biochemical markers can complement existing diagnostic methods, this research contributes to achieving Sustainable Development Goal (SDG) 3 ensuring healthy lives and promoting well-being for all, particularly through the

reduction of child mortality and the control of communicable diseases. The study's outcomes can also support the design of diagnostic algorithms applicable to other high-burden countries in sub-Saharan Africa, thereby extending its relevance beyond Kenya's borders.

In addition to its diagnostic and clinical implications, the study holds significant research value. It establishes a foundation for future investigations into the biochemical and pathophysiological interactions between *P. falciparum* and HIV-1 in pediatric populations. The baseline data obtained from this work can serve as a reference point for longitudinal studies assessing the impact of treatment regimens, nutritional interventions, or immunological status on renal and hepatic function during co-infection. Furthermore, by identifying laboratory parameters that correlate with disease severity and treatment response, the study opens avenues for developing predictive models and risk stratification tools that can guide personalized medicine approaches in pediatric infectious diseases.

The study's outcomes also carry educational and capacity-building significance. Conducting such laboratory-based research at Kakamega County General Teaching and Referral Hospital contributes to strengthening local diagnostic and research infrastructure, enhances laboratory personnel skills in biochemical and parasitological techniques, and promotes evidence-based clinical practice. These benefits extend beyond the study itself, fostering a culture of scientific inquiry and continuous improvement within the health facility.

Ultimately, the significance of this study lies in its potential to transform how malaria and HIV co-infection is diagnosed and managed in children. By characterizing renal and hepatic function profiles, determining their diagnostic performance, and providing locally relevant baseline data, the study enhances the precision and reliability of clinical assessment in this vulnerable population. The findings will help clinicians recognize disease severity earlier, tailor treatments appropriately, and monitor recovery more effectively. In doing so, the research contributes to reducing childhood morbidity and mortality in Kenya's malaria-endemic regions and advances broader global health objectives aimed at ending preventable deaths among children under five by 2030.

1.7 Scope and Limitations of the Study

This study was undertaken to establish the renal and hepatic function marker profiles among children under five years of age co-infected with malaria and HIV at Kakamega County General Teaching and Referral Hospital. It sought to determine how biochemical indices such as serum creatinine, urea, bilirubin, ALT, AST and ALP vary among co-infected children compared to those with malaria or HIV infection alone. The work also aimed to assess the diagnostic performance specifically the sensitivity and specificity of these laboratory indices as potential adjuncts to standard parasitological tests for malaria. The findings were expected to provide baseline data that could guide clinicians in early detection, monitoring, and prognosis of malaria in pediatric HIV patients.

The study was limited in scope to children under five years of age, a group that bears the greatest risk of malaria-related illness and mortality. It was conducted in a single tertiary

referral hospital, focusing on laboratory analysis and clinical correlations rather than long-term outcomes. The investigation was designed to generate baseline biochemical data and did not extend to immunological, nutritional, or molecular analyses that could have provided a deeper understanding of host-pathogen interactions.

While the study adds valuable information on malaria–HIV co-infection, several limitations must be acknowledged. Many children presenting at the hospital had already received over-the-counter or home-based antimalarial treatment before admission, a common practice in the region. Such pre-treatment may have reduced parasite densities or altered biochemical and hematological responses, thereby influencing the observed relationships between malaria parasitemia and organ function markers.

Another constraint was the exclusion of other prevalent comorbid conditions such as malnutrition, intestinal helminthiasis, bacterial infections, and viral hepatitis. These conditions are widespread in Western Kenya and are known to influence biochemical parameters like liver enzymes, bilirubin, and serum proteins. Their omission means that some of the observed alterations in renal and hepatic markers could have been due to underlying or concurrent illnesses rather than malaria–HIV co-infection alone. Similarly, the study did not account for nutritional status, which can independently affect biochemical and hematological profiles in children.

The hospital-based, cross-sectional design also limited the ability to infer causality or track changes over time. Data were collected at a single point during hospital presentation, which may not reflect fluctuations in biochemical indices as the disease progressed or improved

with treatment. Because most participants were symptomatic enough to seek care at a referral facility, the findings may overrepresent moderate and severe cases while underrepresenting mild or asymptomatic infections within the community.

Although microscopy and rapid diagnostic tests were employed to confirm malaria infection, both techniques have inherent limitations. Microscopy may miss infections with low parasite density, while RDTs can produce false positives from antigen persistence or false negatives due to genetic deletions in Plasmodium falciparum. Without molecular confirmation such as polymerase chain reaction (PCR), some diagnostic misclassification may have occurred. The absence of HIV viral load and CD4 count data also limited the capacity to interpret how immunosuppression might have influenced the biochemical outcomes observed.

Because the study was confined to one hospital in Western Kenya, generalization of the results to other malaria-endemic areas should be made with caution. Variations in transmission intensity, healthcare access, environmental conditions, and population health characteristics across regions could lead to differences in biomarker patterns.

Despite these limitations, the study provides meaningful baseline information on renal and hepatic function changes in children co-infected with malaria and HIV. It highlights the potential role of biochemical markers in supplementing microscopy and RDTs, improving diagnostic accuracy, and guiding management of co-infected children. The findings also emphasize the need for larger, multi-site, and longitudinal studies that incorporate

nutritional, immunological, and molecular factors to better define the complex interplay between malaria, HIV, and host organ function.

CHAPTER TWO

LITERATURE REVIEW

2.1 The Burden of Malaria and HIV Co-Infection

Malaria and HIV remain among the most significant infectious diseases globally, particularly in sub-Saharan Africa where their co-existence has intensified morbidity and mortality (Ssentongo et al., 2020). Both diseases have profound epidemiological and pathophysiological interactions, influencing each other's transmission dynamics, clinical outcomes, and treatment responses (Ryu et al., 2022). Understanding their burden and overlap is critical in guiding prevention and control strategies in endemic regions.

2.1.1 Malaria Epidemiology and Pathophysiology

Human malaria is caused by protozoan hemoparasites of the genus Plasmodium notably *P. falciparum, P. vivax, P. malariae, P. ovale,* and in rare zoonotic cases, *P. knowlesi* (Talapko et al., 2019). Among these, *P. falciparum* is the most virulent and predominant in Africa, accounting for most malaria-related deaths.

Transmission occurs through bites from infected female Anopheles mosquitoes, which inject sporozoites into the bloodstream. These migrate to the liver where they invade hepatocytes, mature into schizonts, and release merozoites that infect red blood cells. The erythrocytic cycle produces the clinical symptoms of malaria such as fever, anemia, and in severe cases, cerebral malaria (Patel et al., 2020).

Globally, malaria remains a major public health challenge. In 2021, approximately 247 million malaria cases were reported across 84 endemic countries, resulting in an estimated 619,000 deaths 76% of which occurred among children under five years (WHO, 2022). Sub-Saharan Africa bore 95% of these cases, emphasizing the persistent disease burden in the region.

In Kenya, malaria transmission varies across five epidemiological zones highland epidemic-prone, lake endemic, coast endemic, seasonal transmission, and low-risk areas. About 70% of the population lives in malaria-risk regions, with an estimated 6.7 million cases in 2021. Children aged 6–14 years exhibit the highest infection rates, reaching up to 19% in lake-endemic zones. The disease also accounts for approximately 13–15% of all outpatient consultations nationwide (Elnour et al., 2023).

2.1.2 HIV Epidemiology and Pathophysiology

HIV is a retrovirus that targets the human immune system, primarily infecting CD4+ T lymphocytes, monocytes/macrophages, and dendritic cells. The virus attaches to CD4 receptors and co-receptors (CXCR4 and CCR5), enabling entry and replication. Persistent viral replication causes progressive depletion of CD4+ cells, weakening the immune response and predisposing individuals to opportunistic infections (Connell et al., 2020; Masenga et al., 2023).

Globally, 39 million people were living with HIV by 2022, including 1.5 million children under 15 years. Sub-Saharan Africa remains the epicenter, harboring 25.6 million of these

infections (UNAIDS, 2023). In the same year, the region recorded 109,000 new pediatric HIV infections and 4,500 AIDS-related deaths among children. Kenya alone had approximately 1.4 million people living with HIV, with 68,000 being children under 15 years. Alarmingly, vertical transmission including breastfeeding accounted for an 8.64% infection rate in 2022 (Kozhobekov et al., 2025; Mutisya et al., 2022).

Although antiretroviral therapy (ART) coverage has expanded, challenges persist. Only about 57,000 of the 68,000 HIV-positive children in Kenya were on ART in 2022, revealing significant treatment gaps. AIDS-related mortality continues to create a generation of orphans, with an estimated 590,000 children aged 0–17 years losing parents to HIV/AIDS in 2022 (UNAIDS, 2023).

2.1.3 Interaction Between Malaria and HIV

The co-existence of malaria and HIV has far-reaching clinical and epidemiological implications. HIV infection increases susceptibility to malaria by impairing cell-mediated immunity, while malaria-induced immune activation enhances HIV replication and accelerates disease progression (Kwenti, 2018). Pregnant women, children, and immunocompromised individuals are disproportionately affected by this dual burden. Co-infected individuals tend to experience more severe malaria episodes, higher parasite densities, and increased treatment failures (Minwuyelet et al., 2025). Conversely, malaria infection in HIV-positive individuals is associated with transient spikes in viral load, which can elevate transmission risks (Nnimbo et al., 2023). The overlap of geographic distribution

further complicates disease control, as both infections thrive under similar socio-economic and environmental conditions.

2.1.4 The Burden in Sub-Saharan Africa and Kenya

Sub-Saharan Africa continues to experience the highest global burden of both diseases. Socioeconomic challenges, weak health systems, and limited access to preventive and therapeutic interventions perpetuate this dual epidemic. In Kenya, malaria and HIV co-infection is most common in western and coastal regions, where high malaria transmission coincides with elevated HIV prevalence rates (Bashir et al., 2025). The dual infection exacerbates anemia, increases hospitalization, and heightens mortality, especially among pregnant women and children. HIV-infected pregnant women are at greater risk of placental malaria, leading to low birth weight, preterm delivery, and increased infant mortality (Ssentongo et al., 2020). For individuals with advanced HIV disease, recurrent malaria episodes often occur despite prophylaxis, contributing to poor clinical outcomes.

The overlap between malaria and HIV remains a major public health concern in Africa. Both diseases reinforce each other's impact through complex immunological and epidemiological mechanisms (Gumel et al., 2021). Despite substantial global progress in prevention and treatment, the persistence of co-infection underscores the need for integrated control strategies that combine vector management, ART scale-up, and strengthened health systems (Toma et al., 2025). In Kenya, focusing on high-transmission zones and improving access to preventive and therapeutic interventions among vulnerable populations is crucial in reducing the burden of malaria–HIV co-infection.

2.2 Parasitological and Clinical Outcomes of Malaria and HIV Co-Infection

Malaria and HIV co-infection remains a serious health problem. Across Africa, children with HIV are more likely to get malaria. Their immune systems are weaker, allowing the parasites to thrive (Mirzohreh et al., 2022a). In Nigeria, HIV-positive children had much higher parasite densities (Okonkwo et al., 2018).The study showed an average of 118.7 parasites per microlitre of blood. HIV-negative children had only about 87.3 parasites per microlitre. This difference highlights how HIV increases malaria severity and persistence.

A Tanzanian study found similar results among hospitalized children. Malaria was confirmed in 31.8% of HIV-infected children (Smart et al., 2016). Among HIV-negative children, the rate was just 9.5%. This suggests that HIV greatly increases malaria susceptibility in young children. In Bungoma, Kenya, malaria prevalence among children aged 2–10 years reached 73% (Chiuya et al., 2022). Children living with HIV had especially high parasite densities. They often presented with prolonged fever and severe anemia. This pattern is common in malaria-endemic regions where HIV rates are high.

Ugandan studies have also shown striking effects of co-infection. HIV-infected children were more likely to develop cerebral malaria (Imani et al., 2011). This severe form affects the brain and can be fatal. Other research from Uganda found that malaria episodes raised HIV viral load (Whitworth et al., 2000). The rise in viral load may speed up HIV progression and transmission. In Burkina Faso, malaria was identified as a major cause of death among HIV-positive patients (Ouédraogo et al., 2023). This underscores how the two infections worsen each other’s outcomes. HIV-infected children also experience higher

rates of severe anemia (Menberu et al., 2024). Anemia in such cases results from red cell destruction and bone marrow suppression (White, 2018). It remains one of the most common complications in co-infected patients. For many years, malaria was assumed to cause most childhood fevers. WHO therefore advised that all fevers be treated as malaria (WHO, 2022). This was reasonable when transmission rates were extremely high. However, malaria cases have decreased in many regions over time. This means more children are now misdiagnosed and mistreated. Some may actually suffer from pneumonia, typhoid, or viral infections.

In Kenya today, malaria prevalence averages 3.5% nationwide (Nyawanda et al., 2024). In highly endemic areas such as the lake region, it stands at about 7%. Despite these reductions, co-infection with HIV remains common. Children with both infections face longer recovery and more hospital visits. They are at greater risk of death from anemia or severe malaria. Effective control requires integrating malaria and HIV programs in endemic zones.

2.3 Rates of Malaria Transmission

Malaria transmission has declined considerably in Africa since the early 2000s, with parasite prevalence among children aged 2–10 years dropping from earlier highs to much lower levels in recent years (Bashir et al., 2025). This progress reflects the impact of insecticide-treated nets, indoor residual spraying, improved case management, and wider access to diagnostics and treatment (Pryce et al., 2022). However, this decline has not been uniform, and recent trends show stagnation or even slight increases in some regions

due to climate variability, conflict, and gaps in health system capacity. Children under five years of age continue to carry the highest risk of severe disease and death, accounting for most malaria admissions in endemic areas.

Although hospital data show fewer overall cases, 69–85% of malaria admissions in East African endemic zones still occur among children under five. This pattern reflects their limited immunity and continuous exposure in areas of high transmission (Kamau et al., 2022). As overall transmission declines, however, a shift in disease burden toward older children and school-aged populations has been observed. This change complicates disease control because these age groups are often excluded from preventive strategies such as chemoprevention and routine screening (El Gaaloul et al., 2024). Continuous surveillance is therefore needed to identify shifting transmission patterns and adapt interventions accordingly.

Diagnosis remains a major challenge in malaria management. For many years, health workers in endemic regions treated fever presumptively as malaria. While this approach once saved lives during times of high transmission, it has become less effective as case numbers fall (Omondi et al., 2023). Many fevers in children are now caused by other infections such as pneumonia or bacterial sepsis, but these are often overlooked once antimalarial drugs are administered. This leads to delayed or missed treatment for other serious illnesses, increasing morbidity and mortality. Confirming malaria through laboratory diagnosis is therefore critical, yet microscopy and rapid diagnostic tests vary in quality across facilities (Fitri et al., 2022). Microscopy remains the gold standard but is limited by workload, insufficiently trained personnel, and poor-quality assurance in many

rural health centres. Rapid diagnostic tests have improved access to testing but face challenges from emerging Plasmodium falciparum gene deletions that can cause false-negative results.

The introduction of malaria vaccines, including RTS,S/AS01 and the newer R21/Matrix-M, marks an important advancement in prevention, especially for children living in high-transmission zones (Laurens, 2019). Early evidence shows that these vaccines reduce clinical malaria and hospital admissions (Kigongo et al., 2025; Sallam et al., 2025). However, data on their long-term effectiveness and impact in areas where transmission is already declining remain limited. Understanding how vaccination interacts with existing control measures such as bed nets, indoor spraying, and seasonal chemoprevention is an important research gap.

Overall, while malaria transmission has fallen substantially over the past two decades, the disease remains a major health challenge in sub-Saharan Africa. Weak surveillance systems, inconsistent diagnostic quality, and limited adaptation to changing epidemiological patterns hinder control efforts (Kamau et al., 2020). There is a need for more reliable subnational data, integration of malaria testing with broader fever management programs, and regular monitoring of diagnostic test performance. Research should also focus on how best to target emerging risk groups, improve microscopy quality assurance, and evaluate the combined effects of vaccines and traditional control tools on reducing malaria transmission.

2.4 Clinical Diagnosis of Malaria

Clinical diagnosis based on fever alone is unreliable in most settings. Combining symptoms and simple labs improves accuracy, but performance varies with age, season, and transmission intensity (Attai et al., 2024). Work from West and East Africa showed that multivariable clinical scores can approach expert judgment when tests are unavailable. Even then, many febrile children without malaria would still receive antimalarials if clinical signs are used in isolation (Koliopoulos et al., 2024; Nyaoke et al., 2019; Orimadegun et al., 2022). This is because fever, chills, sweats, headache, and malaise are nonspecific and overlap with pneumonia, sepsis, typhoid, rickettsioses, arboviral infections, and urinary tract infections. As transmission declines and asymptomatic parasitemia persists, the specificity of symptom-based diagnosis falls further. Many children carry parasites without current illness, so clinical signs plus a light parasitemia may not indicate malaria as the cause of fever.

Hematological patterns can help but should not be used as stand-alone tests. Thrombocytopenia is common in acute malaria and often resolves with clearance of parasitemia (Antwi-Baffour et al., 2023). Mild to moderate anemia, leukopenia or normal total leukocyte counts with relative lymphopenia, and elevated lactate in severe disease are frequently described. Simple full blood counts therefore add discriminatory value when paired with symptoms and epidemiologic context. However, anemia is also driven by nutritional deficiencies, helminth infections, and chronic inflammation, while thrombocytopenia occurs in dengue and sepsis (B. P. Gupta et al., 2025). The same marker

can mean different things in low versus high transmission areas, so thresholds need local calibration.

The move from presumptive treatment to the “Test, Treat, Track” approach reflects these limitations. Parasitological confirmation by microscopy remains the reference standard when quality is assured, allowing parasite detection, staging, and quantification. In routine practice, rapid diagnostic tests enable timely decisions and have reduced overtreatment where adhered to (Alegana et al., 2020). Yet both modalities have caveats. Routine microscopy accuracy fluctuates with slide workload, training, and quality assurance, particularly in primary facilities. Rapid tests detect circulating antigens rather than live parasites, remain positive for days after cure, and can miss non-falciparum species depending on the target. Emerging hrp2/hrp3 deletions in some regions produce false-negative HRP2-based tests, which pushes clinicians back toward symptoms unless pLDH-based alternatives are available (Alegana et al., 2020). In settings with high prior antimalarial use, measured temperature may be normal at presentation, and caregiver-reported fever becomes the only sign, compounding uncertainty.

Predictive models that blend clinical features with basic labs show promise but need careful external validation. Scores incorporating age, axillary temperature, history of fever, splenomegaly, prostration, respiratory rate, platelet count, hemoglobin, and season can stratify risk better than symptoms alone (Tanase et al., 2024). Machine-learning models built from electronic records sometimes outperform simple scores, yet their transportability is limited. Models derived in high-transmission rural settings often underperform in urban clinics or peri-urban areas where disease ecology and care-seeking differ(Yang et al.,

2022). Few models address adolescents and adults, who account for a growing share of cases as transmission falls. Very few tools explicitly adjust for background asymptomatic parasitemia, prior antipyretic use, or coinfections like invasive bacterial disease and dengue that mimic malaria.

Several gaps remain. First, there is inadequate, standardized, subnational validation of clinical-laboratory algorithms across transmission strata, seasons, and age groups. Second, programs rarely link clinical prediction with quantified parasite density to distinguish incidental parasitemia from malaria as the cause of fever, which leads to misclassification in both directions (McGuinness et al., 1998; Tangpukdee et al., 2009). Third, frontline facilities need stronger microscopy quality assurance and routine monitoring of rapid test performance, including periodic surveillance for hrp2/hrp3 deletions and ready access to alternative test types. Fourth, fever case management pathways for rapid-test–negative patients are often underspecified, so children with sepsis or pneumonia may receive neither timely antibiotics nor appropriate observation. Fifth, research on integrating point-of-care markers such as CRP or procalcitonin with malaria testing is limited in African primary care, despite evidence that such markers can guide antibiotic decisions and reduce missed bacterial infections (Nsobya et al., 2021; Thang et al., 2022). Finally, as transmission patterns shift and school-age children and adults contribute more to transmission, clinical algorithms and training materials remain disproportionately focused on under-fives, creating a mismatch between guidance and epidemiology (Rek et al., 2022). Addressing these gaps will improve diagnostic precision, reduce missed non-malarial fevers, and align clinical practice with the evolving malaria landscape.

2.5 Laboratory Diagnosis of Malaria

Microscopy misses malaria for predictable technical and occasional biological reasons. Low parasitemia at the time of sampling reduces smear sensitivity, especially early in infection or after partial treatment (Tamir et al., 2025). Poor smear preparation, inadequate staining, and rushed reads further erode performance. Thick films improve sensitivity but demand skill; thin films aid speciation yet miss light infections. Workload, night calls, and lack of external quality assessment all contribute (Tegegne et al., 2020). Despite these weaknesses, good-quality microscopy remains the reference because it quantifies parasites, shows stages, and detects non-falciparum species.

Pathophysiology can also hide parasites from view. In falciparum malaria, mature trophozoites and schizonts sequester in deep vasculature, so peripheral smears underrepresent true biomass (Khoury et al., 2014). Sampling during afebrile intervals may occur between schizogony bursts, giving falsely low densities. Prior self-medication with artemisinin combinations reduces circulating parasites before facility presentation, pushing densities below detection (Obonyo et al., 2024). These dynamics explain why repeated smears 12–24 hours apart often outperform a single draw in symptomatic patients.

Ancillary laboratory signals help anchor suspicion. Thrombocytopenia is common and often profound in acute malaria. Mild leukopenia with relative lymphopenia, falling hemoglobin, rising unconjugated bilirubin, and elevated LDH are frequently observed (Obonyo et al., 2024; Zniber et al., 2025). In severe disease, lactate rises and coagulation factors may fall. These changes are not specific dengue, sepsis, typhoid, and hemolytic

states can mimic them but in the right epidemiologic context they increase the post-test probability of malaria when parasitemia is low or intermittently detectable.

Rapid diagnostic tests were introduced to stabilize frontline diagnosis when slide quality is variable. In many studies they match expert microscopy for detecting falciparum malaria and are faster, simpler, and more scalable (Maturana et al., 2022). They have limitations. HRP2-based tests may stay positive for days after cure, inflating apparent prevalence and prompting unnecessary retreatment. High antigen loads can produce a prozone effect with false negatives unless procedures are followed (Lynch et al., 2022). Deletions in pfhrp2 or pfhrp3 genes lead to missed infections where these variants circulate. pLDH-based tests help but may be less sensitive at very low densities and have shorter positivity windows. Non-falciparum detection varies by brand and target.

The move from presumptive treatment to universal parasitological confirmation ("test, treat, track") was rational, yet implementation remains uneven. Stock-outs, lack of electricity or microscopes, and thin staffing still push clinicians toward empiric therapy (Mohanlal, 2020). In under-fives with danger signs, delays for testing can be harmful; in practice, clinicians often give antimalarials first and backfill diagnostics when feasible. This creates a paradox where partial treatment degrades both smears and some antigen tests, complicating confirmation and monitoring.

Nucleic-acid tests offer a way out of the sensitivity trap. PCR and ultrasensitive qPCR detect subpatent infections that microscopy and standard RDTs miss. Loop-mediated isothermal amplification (LAMP) has near-PCR sensitivity with simpler workflows and

could serve referral centers (Feleke et al., 2021; Opoku Afriyie et al., 2023). However, costs, supply chains, and training limit widespread use. Turnaround times matter in acute care; a test that returns after a child has been discharged is of little clinical value.

Clinical–laboratory algorithms can bridge gaps. Scores that combine age, history of fever, axillary temperature, splenomegaly, prostration, season, platelet count, hemoglobin, and simple chemistry improve discrimination over symptoms alone (Doucoure et al., 2024). Adding CRP or procalcitonin can help triage RDT-negative febrile children toward or away from antibiotics while repeat malaria testing is arranged. Yet most scores are derived in single settings and rarely validated externally (Bonko et al., 2022). Performance often drops when moved from rural high-transmission clinics to peri-urban or low-transmission areas, or when applied to school-age children and adults who increasingly carry the burden as transmission falls.

These realities create a programmatic dilemma. Completely abandoning presumptive treatment risks missing severe malaria or delaying care where tests are unavailable or unreliable. Persisting with empiric antimalarials for most fevers drives overtreatment, masks sepsis, and wastes resources. A pragmatic compromise is a tiered pathway: immediate RDT for all febrile patients, same-visit microscopy when feasible for severe or RDT-negative but high-suspicion cases, repeat testing after 12–24 hours if symptoms persist, and clear protocols for managing non-malarial fevers with safety-net review (Ghai et al., 2016). Concurrent investment in microscopy quality assurance, routine lot-testing and field-monitoring of RDTs, and periodic surveillance for hrp2/hrp3 deletions is essential.

Key gaps remain. Microscopy quality varies widely; many facilities lack regular proficiency testing, slide rechecking, and mentorship (C. da Silva et al., 2024). Data linking parasite density and ancillary indices to causal attribution of fever are sparse, so programs struggle to distinguish incidental parasitemia from malaria disease. RDT portfolios in several countries still rely heavily on single-antigen HRP2 tests despite known deletion hotspots. External validation of clinical–laboratory scores across seasons, age groups, and transmission strata is limited, and few tools explicitly account for prior antimalarial or antipyretic use. Point-of-care molecular or LAMP assays are not yet integrated into tiered diagnostic networks at scale (Diallo et al., 2025). Finally, care pathways for RDT-negative febrile children remain under-specified, leading to missed bacterial infections or unnecessary antibiotics. Closing these gaps would improve diagnostic precision, target treatment more effectively, and reduce mortality from both malaria and non-malarial febrile illnesses.

2.6 Biomarkers of Malaria Infection

Malaria triggers a broad set of hematological and biochemical changes that reflect parasite biomass, hemolysis, tissue hypoxia, and endothelial injury. The most consistent hematologic signals are anemia and thrombocytopenia. Anemia is usually normocytic and can be profound in severe disease because of red cell destruction, dyserythropoiesis, splenic clearance, and marrow suppression (Antwi-Baffour et al., 2023). Platelet counts often fall below 100,000 per microlitre and recover with parasite clearance, making thrombocytopenia a useful supportive marker when parasite density is low on smear

(Attaher et al., 2024). Leukocyte counts are typically normal or low, with relative lymphopenia, while severe disease may show neutrophilia from secondary inflammation. Red cell distribution width tends to increase during hemolysis, and reticulocyte responses can be blunted early and rebound after treatment.

Biochemical abnormalities mirror the pathophysiology. Hyperbilirubinemia is common, driven by hemolysis with a mixed pattern in severe cases. Transaminases can rise but usually not to levels seen in acute viral hepatitis. Elevated lactate and low bicarbonate indicate impaired perfusion and are among the strongest correlates of severity and mortality (Shah et al., 2023). Acute kidney injury appears as rising urea and creatinine and may reflect hypovolemia, hemoglobinuria from massive hemolysis, or microvascular obstruction. Electrolyte derangements are frequent in children with vomiting or diarrhea and in adults with severe intravascular hemolysis (Bradshaw et al., 2019). These patterns, taken together, increase the posttest probability of malaria when slides are negative or density is very low.

Parasite derived markers add diagnostic and prognostic value beyond routine chemistries. Histidine rich protein 2 in plasma reflects circulating and sequestered *P. falciparum* biomass (Uyoga et al., 2020). Quantitative HRP2 and parasite lactate dehydrogenase levels correlate with density and often with severity, though persistence of antigens after cure can complicate interpretation (Tiono et al., 2014). Molecular assays detect parasite DNA at densities far below microscopy and can clarify whether fever is malaria related or an incidental parasitemia. In research settings, ultrasensitive antigen and DNA assays have

uncovered a substantial reservoir of low-density infections that maintain transmission and occasionally progress to clinical disease.

Host response biomarkers help distinguish severe from uncomplicated disease. High C reactive protein is common in acute malaria but lacks specificity. Procalcitonin may help flag invasive bacterial coinfection in parasitemic children who remain febrile with a negative blood culture (Wilairatana et al., 2021). Angiopoietin 2 and the angiopoietin 2 to angiopoietin 1 ratio, soluble ICAM 1, and markers of endothelial glycocalyx shedding such as syndecan 1 track endothelial activation and microvascular dysfunction and have repeatedly associated with severe malaria and death (Barber et al., 2021). Plasma cell free hemoglobin, haptoglobin consumption, and hemopexin depletion capture hemolysis mediated nitric oxide scavenging and vascular stress. In cerebral malaria, combinations of lactate, base deficit, and endothelial markers improve risk stratification compared with clinical signs alone.

Hematology analyzers already present in many county and sub county hospitals can yield platelet count, hemoglobin, RDW, and reticulocyte indices within minutes. When these are interpreted alongside lactate or bicarbonate and simple liver and kidney function tests, clinicians can classify risk, anticipate complications like severe anemia or acute kidney injury, and decide who needs admission, transfusion, or parenteral therapy (Daves et al., 2024). In RDT positive but smear negative cases, a profile of thrombocytopenia with rising lactate and bilirubin supports true malaria disease rather than incidental antigenemia (Megnekou et al., 2018). Conversely, normal platelets with high procalcitonin in an RDT positive child should prompt a careful search for bacterial sepsis.

Several gaps limit the translation of these markers into routine decision making in Kenya. Thresholds are not standardized by age, transmission intensity, and comorbidity, so a platelet count of 90,000 per microlitre may carry different implications in a holoendemic county than in a low transmission highland setting (P. Gupta et al., 2019). Most biomarker studies were derived in single hospitals and have not been externally validated across seasons or facilities with different case mix, which reduces transportability. Few algorithms jointly model parasite density, HRP2 or pLDH levels, and host markers to decide when parasitemia is causal versus incidental (Wasena et al., 2025). Quality assurance for lactate and bicarbonate is uneven, and point of care lactate meters are not consistently available in primary facilities. Quantitative HRP2 and molecular tests remain largely research tools without clear procurement pathways, costs, or turnaround time compatible with acute care.

There is also limited guidance for integrating biomarker panels into the current test treat track policy. Frontline guidelines specify how to act on RDT and microscopy results but are less explicit about how to combine platelet count, lactate, creatinine, and bilirubin to triage febrile children who are RDT negative yet clinically unwell. Training materials still emphasize under-fives, while school age children and adults form a growing share of cases as transmission falls. Finally, surveillance rarely captures biochemical or hematologic data alongside parasitology, which means health managers cannot easily evaluate how biomarker guided care affects outcomes.

Practical next steps are clear. Establish locally validated cutoffs for platelet count, lactate, bilirubin, and creatinine that predict transfusion, acute kidney injury, or death, stratified by

age and county level transmission (Xu et al., 2019). Incorporate a basic biomarker bundle into fever pathways at hospital triage stations and high-volume health centers, with simple traffic light decision aids. Pilot combined algorithms that use RDT or smear plus platelet count and lactate to drive admission and repeat testing, and prospectively measure reductions in missed severe disease and unnecessary admissions (Elrobaa et al., 2024). Build a referral tier for quantitative HRP2 or LAMP in county laboratories to adjudicate difficult cases and monitor low density infections during elimination focused activities. With these steps, biomarkers can move from descriptive studies into everyday decisions that reduce mortality and improve targeting of scarce resources.

2.7 Algorithms in Malaria Diagnosis

Clinical algorithms for malaria work unevenly across ages and settings. Findings from coastal Kenya showed that rule-based approaches added little value in patients older than 15 years, where symptoms are less specific and alternative diagnoses are common (Kapesa et al., 2018; Otambo, Onyango, et al., 2022). In contrast, work from West Africa during the rainy season suggested that very high fever of short duration without another obvious focus strongly predicts malaria in young children (Diouf et al., 2022). These contrasting results reflect how transmission intensity, age-acquired immunity, season, and circulating pathogens shape the performance of any bedside rule.

As transmission declines, symptom patterns change and asymptomatic parasitemia becomes more frequent. Algorithms that label any fever plus parasitemia as “malaria” risk misattributing illness when parasites are incidental (White, 2022). Conversely, in high-

transmission settings, a purely clinical rule tends to overtreat non-malarial fevers such as pneumonia, invasive bacterial disease, rickettsioses, typhoid, or arboviral infections (Chiuya et al., 2022). This tension is why policies shifted from presumptive treatment toward universal parasitological testing, with rapid tests at the point of care and microscopy where available. Even so, test results still need clinical interpretation. HRP2-based RDTs can remain positive after cure or miss infections where hrp2/hrp3 deletions circulate, and routine smear quality varies with workload and training (Kong et al., 2021). Algorithms that combine test results with a few low-cost indices platelet count, hemoglobin, lactate or bicarbonate, and basic renal and liver tests consistently outperform symptoms alone for triage and prognostication.

Several groups have proposed pragmatic scores that blend age, axillary temperature, duration of fever, season, splenomegaly, prostration, respiratory rate, platelet count, and hemoglobin. In under-fives, these scores can approach expert clinical judgment when laboratory capacity is limited, and they help flag children who need admission, repeat testing, or parenteral therapy (Kasbekar et al., 2021). Adding C-reactive protein or procalcitonin can also help separate likely bacterial sepsis from malaria in RDT-positive children who remain ill, improving early antibiotic decisions (Wilairatana et al., 2021). Machine-learning tools trained on routine electronic records sometimes outperform simple rules, but gains often vanish when models are moved across facilities or seasons because case-mix and testing practices differ.

Implementation details matter as much as model choice. Algorithms that mandate same-visit RDT for all febrile patients, reserve urgent microscopy for severe or RDT-negative

but high-suspicion cases, and require repeat testing after 12–24 hours if symptoms persist can reduce both missed malaria and missed non-malarial fevers. Embedding these steps in triage flow, with clear escalation for danger signs and hypoxia, makes them usable on busy pediatric wards. Regular microscopy quality assurance, routine field monitoring of RDT performance, and access to pLDH-based alternatives in deletion areas are essential scaffolds for any algorithm to work reliably.

Important gaps remain. Most published algorithms were derived in single-site studies and lack external validation across counties, seasons, and transmission strata, especially for school-age children and adults who now account for a larger share of cases as transmission falls. Few tools explicitly model background asymptomatic parasitemia or prior antimalarial use, both of which degrade specificity. Guidance is thin on integrating simple biomarkers into current “test, treat, track” pathways, so clinicians often lack clear thresholds for admission, repeat testing, or antibiotics when results are discordant. There is limited evaluation of algorithm impact on hard outcomes such as mortality, transfusions, readmissions, and antibiotic stewardship, and very little cost-effectiveness work comparing clinical-only, clinical-plus-labs, and molecular add-ons. Finally, frontline systems rarely collect the data needed to recalibrate algorithms over time, including parasite density, platelet counts, lactate, and bacterial culture results. Addressing these gaps—through multicentre validation, age-specific recalibration, explicit handling of incidental parasitemia, and routine quality assurance would make algorithms a safer, more dependable backbone for malaria case management.

2.8 Malaria and HIV Infection

Malaria–HIV co-morbidity is shaped by setting, age, and immune status, which helps explain why studies report divergent patterns. In some adult cohorts, including Maputo, malaria represented a smaller share of febrile illness among people with HIV than among HIV-negative adults, likely because advanced immunosuppression broadens the differential toward bacterial, mycobacterial, and fungal infections (Roberds et al., 2021). In high-transmission areas, however, children with HIV often carry higher parasite densities, experience more frequent episodes, and present with severe anemia or cerebral malaria more often than their HIV-negative peers (Kwenti, 2018). These contrasts underscore that the influence of HIV on malaria is not uniform and that local transmission intensity, prior exposure, and access to care shape clinical expression.

Fever in people living with HIV has many competing causes. Opportunistic infections, occult bacterial sepsis, tuberculosis, disseminated fungal disease, and arboviral infections can all mimic malaria (Justiz Vaillant & Naik, 2025). Antiretroviral therapy can further complicate assessment through immune reconstitution inflammatory syndrome and drug reactions. In endemic regions, asymptomatic parasitemia is common, so finding parasites does not always mean malaria is the cause of fever (Afrane et al., 2024). This creates a high risk of misclassification in both directions: true malaria episodes missed because attention shifts to HIV-related causes, and non-malarial fevers treated as malaria because a light parasitemia is detected.

Cotrimoxazole prophylaxis provides partial protection against malaria and lowers episode frequency in many HIV-infected children, but its effects vary with local resistance patterns and adherence (Mbeye et al., 2014). In pregnancy, HIV increases placental malaria risk, reduces trans-placental antibody transfer, and worsens maternal anemia and low-birth-weight outcomes, yet intermittent preventive therapy and insecticide-treated nets still confer benefit (Agyeman et al., 2020). The widespread rollout of antiretroviral therapy has changed the landscape: better immune reconstitution generally reduces malaria incidence and severity, but intermittent viral rebound, poor adherence, or late presentation continue to sustain vulnerability in a sizable minority.

Diagnostic performance can differ in people with HIV. Rapid diagnostic tests may remain positive after parasite clearance and can miss infections where hrp2/hrp3 deletions circulate; routine microscopy is affected by low densities after partial treatment and by variable slide quality (Mekonen et al., 2024a). In advanced HIV, atypical presentations with absent splenomegaly, blunted fever, or coexisting bacterial infection can erode the predictive value of clinical scores derived in immunocompetent children. Ancillary laboratory findings marked thrombocytopenia, rising lactate, metabolic acidosis, hyperbilirubinemia, and acute kidney injury improve triage and prognostication but are not specific and require local thresholds (Cyrino et al., 2021). Algorithms that pair parasitological testing with simple biomarkers and clear pathways for managing RDT-negative but ill children are more reliable than symptom-based rules alone.

There are important epidemiologic and methodological gaps. Much of the evidence linking HIV and malaria comes from single-site or short-duration studies with limited external

validity, sparse adjustment for confounders such as anemia, malnutrition, or prior antimalarial use, and inconsistent case definitions across eras of changing transmission (Ssentongo et al., 2020). Few studies stratify results by CD4 count, viral load, or ART regimen, yet immune status and drug–drug interactions likely modify risk and treatment response. Data on the performance of RDTs and microscopy specifically in HIV-infected children are thin, especially in contexts with hrp2/hrp3 deletions or high asymptomatic carriage. Kenyan data remain patchy, with limited linkage between clinical records, laboratory indices, and parasitological confirmation, making it hard to separate incidental parasitemia from malaria disease in febrile HIV-infected patients.

These gaps point to clear priorities for the present study. Systematically comparing hematologic and biochemical profiles in HIV-positive versus HIV-negative parasitemic children, while recording parasite density, CD4 count, and ART status, can clarify how HIV alters laboratory signatures and clinical presentation. Incorporating repeat testing at 12–24 hours for initially negative smears will reduce false negatives from fluctuating parasitemia. Embedding a standardized fever pathway RDT for all, targeted microscopy, and predefined thresholds for admission based on platelet count, lactate, bilirubin, and creatinine will produce actionable evidence on diagnostic yield (Bruxvoort et al., 2017). Finally, documenting non-malarial diagnoses in RDT-negative, HIV-infected children will quantify the hidden burden of bacterial and viral infections that currently masquerade as malaria and will help tailor integrated care in Kenyan facilities.

2.9 Prognostic Value of Biochemical Markers in Predicting Disease

Evidence from paediatric malaria shows that routine renal and hepatic tests carry real prognostic signal, but thresholds and models vary widely and external validation is scarce. In severe falciparum malaria, rising creatinine and urea, low estimated GFR (Schwartz formula), and oliguria mark evolving acute kidney injury and correlate with prolonged admission, need for transfusion or dialysis, and mortality (Basire et al., 2025). Hyperbilirubinemia often mixed hemolytic and hepatocellular tracks parasite biomass and hemolysis; very high total bilirubin associates with severe disease and longer recovery. Transaminases (ALT/AST) tend to be modestly elevated compared with viral hepatitis; marked rises usually flag multi-organ dysfunction or coinfection (Tripathi & Jialal, 2025). Hypoalbuminemia is common in critically ill children and associates with edema, longer stay, and death, but it is nonspecific and confounded by malnutrition and systemic inflammation. When available, lactate and bicarbonate outperform most single liver/kidney tests for short-term mortality prediction, yet creatinine and bilirubin add incremental information to stratify risk among children with similar acid–base status (Soeters et al., 2019).

In paediatric HIV cohorts, liver and kidney indices have been used mainly to monitor treatment toxicity and opportunistic disease rather than to predict short-term mortality from febrile illness. Before and during ART, elevated ALT/AST or bilirubin can reflect hepatitis coinfection, drug reactions, or immune reconstitution; persistent abnormalities predict later treatment changes, growth faltering, and hospitalizations (Strauss et al., 2025). Tenofovir-associated kidney injury is a concern in adolescents, while trimethoprim elevates creatinine via tubular secretion without true GFR loss and atazanavir can raise unconjugated bilirubin both important diagnostic confounders (Mtisi et al., 2019). As a result, renal and hepatic

markers in HIV-infected children carry prognostic value for medium-term morbidity, but their interpretation during an acute fever episode requires careful adjustment for regimen and adherence.

For malaria–HIV co-infection specifically, published prognostic models are sparse. Studies often report that co-infected children present with higher parasite densities, more severe anemia, and higher risks of acidosis and AKI than mono-infected peers, but few derive or validate multivariable tools that combine biochemistry with clinical and parasitological data (Ssentongo et al., 2020). Where models exist, they typically adapt severe-malaria predictors (e.g., lactate, coma score) and add creatinine or bilirubin, without HIV-specific factors such as CD4 count, viral load, ART class, or cotrimoxazole use (Mirzohreh et al., 2022). Almost none address whether renal and hepatic indices improve discrimination beyond rapid diagnostic testing, parasite density, and simple bedside signs in co-infected under-fives.

Three themes emerge from cross-study synthesis. First, renal markers are strongest for near-term adverse outcomes in malaria: even mild creatinine rises above age-adjusted norms predict complications. Serial trends over 24–48 hours outperform single values, but few studies collect paired measurements. Second, bilirubin is a consistent severity correlate, yet the prognostic weight differs by context: hemolysis-driven indirect hyperbilirubinemia in high-transmission settings versus mixed patterns when sepsis or hepatitis co-occur (Batte et al., 2025a). Fractionating bilirubin adds value but is inconsistently reported. Third, transaminases add little alone, but in combination with albumin, INR (where available), and bilirubin they reflect hepatic reserve and endothelial stress and can refine admission decisions.

Key gaps limit clinical use and policy uptake. Age- and context-specific cut-offs are poorly standardized; many papers apply adult thresholds to children or ignore height-adjusted eGFR. Confounding is under-handled: dehydration, malnutrition, hemoglobinopathies, G6PD deficiency, bacterial sepsis, hepatitis viruses, and drug effects all shift liver/kidney tests and are rarely modeled explicitly (Alao et al., 2025). Most cohorts are single-site, small, and cross-sectional, so calibration and transportability are unknown. Outcomes are heterogeneous some use composite "severe malaria," others mortality or length of stay—making meta-comparison difficult. Crucially, co-infection models almost never integrate HIV disease control (CD4, viral load) or medications, though these modify both marker baselines and risk (Shilabye et al., 2025). Laboratory quality is another weak link: few studies report external quality assurance, pediatric reference ranges, or timing of blood draw relative to fluids or antimalarials.

A practical research path for Western Kenya would close these gaps. Build a prospective cohort of febrile under-fives with universal RDT, targeted microscopy, and standardized panels at presentation and 24 hours: creatinine (eGFR), urea, electrolytes, bilirubin fractions, ALT/AST, albumin, bicarbonate or venous CO_2, and lactate where feasible (Robert et al., 2024). Record parasite density, HRP2 line intensity or quantitative HRP2 if available, HIV status, CD4, viral load, ART class, and cotrimoxazole. Define clear outcomes transfusion, dialysis/AKI by KDIGO pRIFLE, ICU transfer, 7- and 28-day mortality and derive parsimonious prediction models for (a) any severe outcome and (b) mortality (Fisher et al., 2023). Compare performance in malaria mono-infection, HIV mono-infection, and co-infection. Use age-adjusted z-scores for creatinine and albumin, and decision-curve analysis to judge clinical utility. Externally validate across at least two hospitals and a highland versus lake-endemic site, and prespecify how marker thresholds

trigger actions (repeat testing, admission, antibiotics, transfer). Finally, report assay QA, reference ranges, and sampling times to support replication.

Renal and hepatic function tests already carry actionable prognostic information in paediatric malaria and HIV, but co-infection-specific tools are largely missing. Locally derived and validated models that incorporate both parasite and HIV variables, use serial measurements, and align with bedside decisions are the next step to turn these routine labs into reliable risk stratifiers.

2.10 Diagnostic Utility of Renal and Hepatic Biomarkers in Paediatric Infections

Renal and hepatic chemistries carry prognostic signal in paediatric malaria, but as diagnostic tools for malaria–HIV co-infection their performance is indirect and context-dependent. In severe falciparum malaria, creatinine and urea rises identify acute kidney injury and track short-term risk; KDIGO-defined AKI in children is common and strongly associated with adverse outcomes, and point-of-care creatinine measurements can detect AKI at admission and during early evolution of disease (Mambo et al., 2023). These markers, however, reflect organ dysfunction rather than malaria itself, and their thresholds vary with age, hydration, and baseline nutrition, which limits their diagnostic specificity for co-infection.

Bilirubin and transaminases add complementary information. Total and unconjugated bilirubin correlate with hemolysis and parasite biomass, while ALT/AST are usually modestly elevated in malaria compared with viral hepatitis; marked transaminase elevations typically imply multi-organ dysfunction or coexisting processes (Ojo et al., 2022). The “malarial hepatopathy” construct uses bilirubin with transaminases to flag

severe disease, but reported cut-offs and timelines differ across cohorts, restricting direct comparison and bedside application in children.

Against this backdrop, established malaria antigens remain the primary diagnostic biomarkers. HRP2 is highly sensitive for *P. falciparum* and underpins most rapid tests in Africa, with pediatric sensitivities frequently in the high-80s to mid-90s against PCR or expert microscopy in endemic settings, though specificity can fall when antigen persists after cure (Rogier et al., 2022). LDH-based tests detect active parasite metabolism and clear more quickly after treatment; their sensitivity is generally lower than HRP2 in field studies, especially at low densities, but they offer a critical alternative where pfhrp2/3 deletions compromise HRP2 tests (Alemayehu et al., 2020). These patterns are seen in comparative evaluations of HRP2 versus LDH RDTs and in head-to-head studies of conventional and "ultrasensitive" HRP2 assays for low-density infections.

When the goal is to predict disease severity rather than detect infection, renal and hepatic indices add incremental value to malaria biomarkers. Creatinine (or eGFR) and bilirubin frequently improve risk stratification beyond HRP2 positivity or parasite density, helping identify children likely to require transfusion, dialysis, or intensive monitoring; serial trends over 24–48 hours outperform single measurements for this purpose (Leonard et al., 2022). Still, most pediatric studies report associations or AUROCs rather than calibrated cut-offs with bedside decision thresholds, and few specify how these markers should alter management when rapid tests are positive but smears are negative or densities are low.

For HIV-infected children, interpretation becomes more complex. ART and cotrimoxazole can shift creatinine (via tubular secretion effects) and bilirubin (e.g., atazanavir-related

unconjugated hyperbilirubinemia) without true organ failure; HIV disease stage also modifies baseline liver and kidney indices (Panagopoulos et al., 2017a). Consequently, the sensitivity and specificity of creatinine, urea, ALT, AST, or bilirubin for predicting malaria–HIV co-infection are not well defined and likely poor if used alone; their primary utility is prognostic once parasitemia is confirmed. Published pediatric models that explicitly combine malaria antigens (HRP2 or LDH), parasite density, and renal/hepatic chemistries with HIV variables (CD4, viral load, ART class) are scarce (Sanyaolu et al., 2013a). Comparisons across biomarkers highlight a practical hierarchy. For detecting *P. falciparum* infection, HRP2 remains most sensitive but vulnerable to false negatives in deletion hotspots and false positives post-treatment; LDH is less sensitive at low densities but better reflects active infection and is not affected by HRP2 persistence (Mekonen et al., 2024b). For grading severity, creatinine/eGFR and bilirubin outperform transaminases and urea, and they complement lactate or bicarbonate when available. In cohorts where hrp2/3 deletions are emerging, mixed HRP2/LDH RDT portfolios plus targeted microscopy provide better diagnostic coverage than reliance on a single antigen.

Several gaps limit clinical uptake, especially for co-infection. First, pediatric sensitivity, specificity, and predictive values for renal/hepatic tests are seldom reported against clear outcomes in febrile children stratified by HIV status; most studies are single-site and cross-sectional (Tiruneh et al., 2022). Second, few analyses adjust for key confounders malnutrition, dehydration, hemoglobinopathies, hepatitis viruses, prior antimalarial or antibiotic exposure that shift these chemistries (Donovan et al., 2021). Third, quantitative or ultrasensitive HRP2 assays and LDH measurements are not routinely linked to organ-dysfunction panels to create actionable, validated scores. Fourth, emerging pfhrp2/3

deletions necessitate ongoing surveillance and contingency plans for antigen choice; without them, sensitivity estimates derived elsewhere will not transport (Sambe et al., 2025). Addressing these gaps will require prospective pediatric cohorts that collect antigen tests, parasite density, creatinine/eGFR, urea, bilirubin fractions, ALT/AST, and HIV variables at presentation and 24 hours, with predefined severity outcomes and decision-curve analysis to quantify clinical utility.

HRP2 (with LDH as a complement) remains best for detecting infection, while creatinine/eGFR and bilirubin are the most informative routine chemistries for grading severity once malaria is confirmed. In HIV-infected children, these organ markers should be interpreted through the lens of ART and immune status, and used to refine triage rather than to “diagnose” co-infection on their own.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Area

Western province which comprises of Busia, Bungoma, Vihiga and Kakamega counties is a malaria holo-endemic rural area. The highest rainfall is registered in the months of April to September, a time when malaria transmission is highest. The hospitals in this region serve a catchment area of approximately 1,500,000 people. It has four general referral hospitals for the region according to the government classification; these are Busia, Bungoma, Vihiga and Kakamega County Referral Hospitals. Kakamega County Teaching and Referral Hospital (KCTRH) is located in Kakamega town, Kakamega County in the western region of Kenya. The county is divided into Thirteen sub-counties with 12 constituencies namely: Butere, Ikolomani, Khwisero, Likuyani, Lugari, Lurambi, Malava, Matungu, Mumias East, Mumias West, Navakholo and Shinyalu. Kakamega County has a population of 1,660, 651 people (Kenya National Bureau of Statistics-KNBS, 2010). The county is the second most populous after Nairobi County (KNBS, 2010). Kakamega town has a population of about 99,987 (KNBS, 2010). The town is 51 kilometers north of Kisumu, elevation of 1,535 meters above sea level. The inhabitants are mainly of the Luhya tribe whose economic activities chiefly include farming, fishing and small-scale businesses.

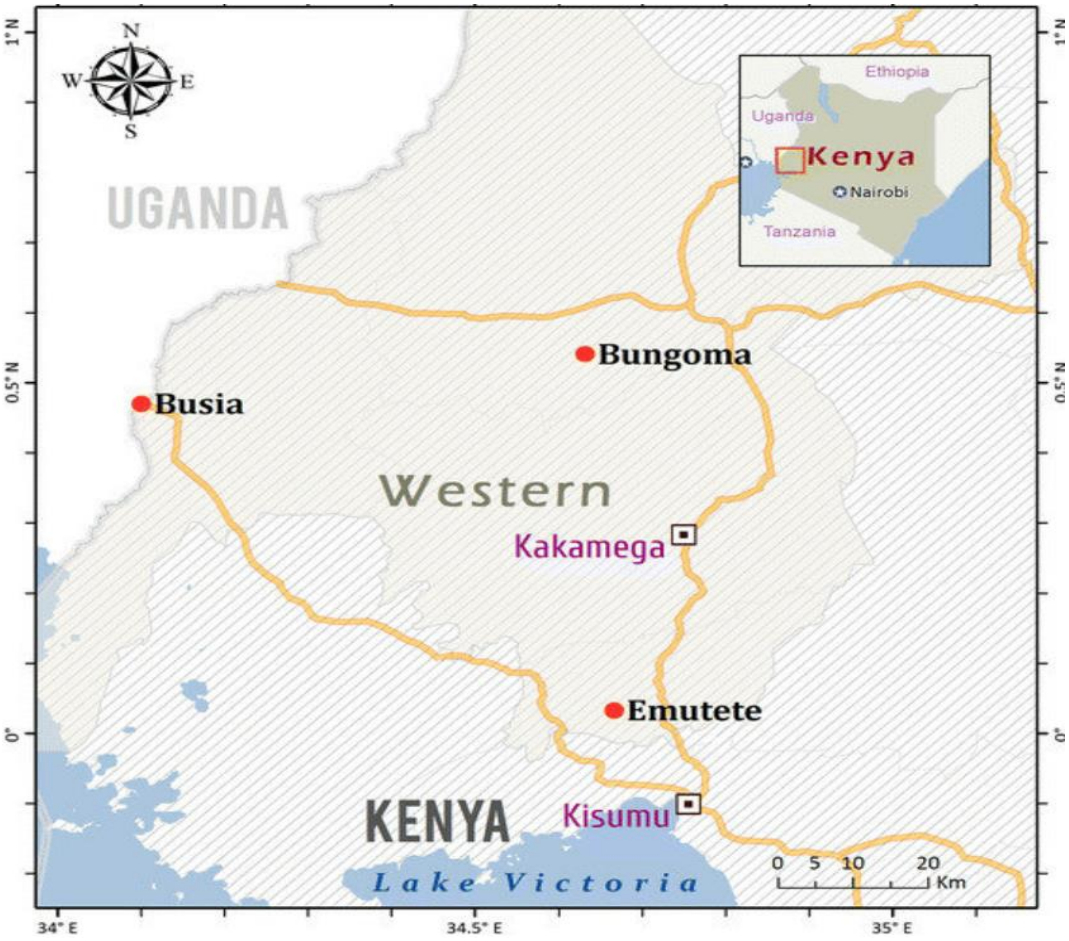

Figure 3.1: Map of Western Kenya.
Showing the study sites including Kakamega, Bungoma, Busia, and Vihiga counties. The region borders Uganda to the west and Lake Victoria to the south, with the inset map indicating Kenya's location within East Africa. Kakamega County General Teaching and Referral Hospital, located centrally within this malaria–HIV co-endemic zone, served as the primary study site. The area experiences perennial malaria transmission with seasonal peaks influenced by rainfall patterns and represents a major referral catchment for pediatric cases from surrounding rural and peri-urban communities.

3.2 Study Design

The study design adopted was mixed cross sectional (by providing demographics in form of age, gender and parasitemia) and case control (by assessing analytes between malaria positive and malaria negatives). No follow up of the subjects was made and the data was collected at a point in time.

3.3 Ethical Considerations

Consent was obtained from parents or guardians before collecting any data or samples from the children. To protect confidentiality, no names were recorded; instead, each participant was assigned a unique code. Once blood slides were examined, the results were shared promptly with the child's primary caregiver, in line with the turnaround times of Kakamega County Teaching and Referral Hospital laboratory. All information relevant for the child's management was disclosed to the caregiver. The study received approval from the appropriate authorities. Ethical clearance was granted by the Masinde Muliro University of Science and Technology (MMUST) Institutional Ethics and Research Committee (IERC), reference number MMUST/IERC/027/2022. A research permit was also issued by the National Commission for Science, Technology, and Innovation (NACOSTI), reference number NACOSTI/P/22/16599. Participants and caregivers were informed of their right to withdraw from the study at any time. To reduce discomfort during sample collection, trained phlebotomists were engaged, and only 5 mL of blood was drawn from each child. Children who tested HIV positive were started on first-line antiretroviral therapy (ART), and their caregivers were offered counseling. HIV-positive parents also received medical education, and their viral loads and CD4+ T cell counts were monitored. Children who tested positive for malaria were treated with oral Artemether-Lumefantrine in accordance with WHO and Ministry of Health guidelines.

3.4 Study Population

This comprised of children sampled at the outpatient department of KCTRH during the study period. It included both general outpatient and the HIV paediatric clinic and also the children aged less than 5 years in the catchment area of the hospital, who sought treatment at the hospital. Children with auxiliary temperatures of more than 37.5^0C were recruited.

3.4.1 Inclusion Criteria

HIV-1 infected children aged between 6-59 months, whose guardians/parents gave consent and with malaria positive slides and malaria negative slides were recruited into the study.

3.4.2 Exclusion Criteria

Children whose parents/guardians declined to give consent and those on anti-malarial and antiretroviral treatments at the time of sampling were excluded from the study. The study also excluded those who were HIV negative and malaria negative since these were considered being normal individuals. In addition, malaria positive but HIV negative were excluded since the study focused mainly on the co-infected.

3.5 Sampling Technique

Consecutive random and purposive sampling techniques were utilized. Consecutive random because the study participants were sampled as and when they visited the hospital. Purposive sampling was used to enroll children aged between 6 months and 59 months and who were positive for malaria by microscopy and malaria rapid diagnostic test (mRDT) and only in HIV positive children (malaria and HIV are conditions known to bring about fever, especially in children).

3.5.1 Sampling Strategy

The study lasted 24 months (July 2021 – June 2023). A whole 2 calendar years were chosen to take care of the seasonal variations in malaria transmission, which is during the rainy and dry seasons. Children between 6 months and 59 months seen at the county referral hospitals' outpatient department and who fulfilled the inclusion criteria during the study period were eligible and sampled.

3.6 Sample Size Determination

The minimum sample size was calculated using Cochran's Basic Formula for Large Populations (1977) as follows:

$$n = \frac{z^2pq}{D^2}$$

$$n_0 = \frac{Z^2\,p\,q}{D^2}$$

Where:

- $Z = 1.96$ (for 95% confidence interval)
- $p = 0.10$ (expected prevalence of malaria parasitemia among febrile children)
- $q = 1 - p = 0.90$
- $D = 0.05$ (desired precision level)

p = Malaria parasite prevalence among febrile children (10%)(Mazigo et al., 2025).

$$n_0 = \frac{(1.96)^2 \times 0.10 \times 0.90}{(0.05)^2}$$

$$n_0 = \frac{3.8416 \times 0.09}{0.0025} = \frac{0.345744}{0.0025} = 138.3$$

Thus, the **minimum required sample size** before correction is **≈138**.

Adjusting for a Finite Population

The total population of eligible children during the study period was 193 cases, the finite population correction (FPC) formula applies:

$$n = \frac{n_0}{1 + \frac{n_0 - 1}{N}}$$

Substituting values:

$$n = \frac{138}{1 + \frac{138-1}{193}}$$

$$n = \frac{138}{1 + 0.714} = \frac{138}{1.714} = 80.5$$

So after correction, the **final adjusted sample size = 81**.

To account for possible non-response, missing data, or attrition, a 15% buffer is added:

$$n_{final} = 81 \times 1.15 = 93.2 \approx 93$$

$$n_{adjusted} = 93 + 45\,(\text{seasonal buffer}) = 138$$

3.6.1 Subject Enrolment

The investigator was stationed at the pediatric outpatient department of the KCGRH (triage area) each 1st and 3rd Monday of the month. Likewise, we also sampled in the pediatric HIV clinic every 1st and 3rd Tuesday of the month. The triage nurse was requested to send all the children with temperature above 37°C to the investigator's bench. Consecutive sampling was done until the desired sample size was attained. Auxiliary temperature of these children was taken using a digital thermometer. Those with temperature of >37.5^{0}C were recruited and parents or guardians requested for consent. Complete history and physical examination was performed as per the data proforma (voluntary and prompted history) (Appendix 2). A questionnaire was used to come up with views on the causes of fever, and what they use to treat malaria

This information was entered into the study data collection sheet (Appendix 2). Blood samples were taken and transported to the KCTRH laboratories for analysis immediately. Four samples were taken; one for HIV rapid test, one for clinical chemistry analytes, one for mRDT, and one for the thick and thin peripheral blood smear. The participant would then go through the normal management process by the hospital staff. A study number was assigned to each study subject to ensure confidentiality.

3.6.2 Sample Collection Techniques

This was done by the investigator and trained phlebotomists at the collection points. A vacutainer blood collection system was used. It consisted of double pointed needle, a plastic holder and a series of vacuum tubes with rubber stopper of various colors. The

patient's vein was punctured with a sterile needle attached to an aspirating device after cleaning the site with alcohol wipes (70% isopropyl alcohol). 5 mL of blood were drawn and 3 mL dispensed into a red-top (no additive) tube each (Red-top for chemistries). Blood smears and malaria RDTs for malaria diagnosis and RDTs for HIV-1 diagnosis were made from the 2 mL of the same blood dispensed into an EDTA vacutainer tube. Adhesive tape was used to protect the venipuncture site after sample collection. The vacutainer tubes were all BD (Becton Dickinson, Franklin Lakes, USA). The tubes were then labeled with the participant's codes, date and time of sample collection. The blood samples in the EDTA tubes was used for malaria peripheral blood film and also malaria and HIV rapid diagnosis tests (RDTs). The blood in the plain vacutainer tubes was allowed to clot and the serum extracted was then used for the clinical renal and hepatic function assays.

3.6.3 Laboratory Procedures

Blood samples collected in the red-top bijou-bottles were used for biochemistry analysis where renal and hepatic function tests were performed using a chemistry auto-analyzer. The chemistry analyzer was quality controlled as per the manufacturer's recommendations. The machine was validated and routinely calibrated to ensure biomarker accuracy. The results from this machine were used as the chemistry indices or biomarkers of the malaria parasite-HIV co-infections. Blood films (thin and thick, combined on the same glass slide) were prepared and stained with 4% Giemsa stain and examined using power 100 lens under oil immersion objective for malaria parasites. A laboratory technologist examined the slides separately and the investigator, being a parasitologist, authenticated the results so as to resolve discrepancies for purpose of quality assurance. The dual reading (technologist +

investigator) of slides in addition to blinded re-reads for discordant slides and following standard staining standard operating procedures ensured quality control for microscopy. Laboratory records were also reviewed for that day to check the number and results of the blood slides and chemistry tests ordered for that particular day.

3.6.3.1 Malaria Diagnosis and Parasite Density

Malaria RDTs were used to screen for the presence of the malaria parasites. mRDTs were used together with microscopy to cross-validate the results. Malaria RDTs contain a strip with antibodies against malaria parasites. If malaria parasite antigens are present in the blood sample, two bands will form on the test strip; the control band and a positive test band. In the absence of the malaria parasite antigens, only the control band will form or appear on the test cassette. Briefly, the patients' details were labelled on the test strip. A drop of blood from the EDTA tube was the transferred into the test well (membrane) on the test cassette. In the first reagent well, a buffer solution was applied as per the manufacturer's instructions. Results were then read at the recommended time. So as to confirm malaria positivity, microscopy being the gold standard procedure in malaria diagnosis, was then performed.

Peripheral blood films (both thick and thin smears) were prepared on the same glass slide and stained with 4% Giemsa. To estimate parasitemia, the number of asexual parasites (trophozoites) was counted against 200 white blood cells. A diagnosis of *Plasmodium falciparum* infection was confirmed under the microscope after examining at least 200 high-power fields. In addition, to parasite identification, changes in red blood cell morphology including size, shape and staining characteristics were assessed as part of

the diagnosis. Parasite density was then expressed as the number of parasites per microliter of blood.

3.6.3.2 HIV Diagnosis

Participants were tested for HIV-1 using two rapid immunochromatographic kits: the Determine™ test (Abbott Laboratories, Tokyo, Japan) and the First Response™ test (Trinity Biotech Plc, Bray, Ireland). Following the National HIV testing algorithm, one kit was used for initial screening and the other as a confirmatory test. A participant was considered HIV-1 positive only if both tests gave positive results. For each test, about two drops of blood (roughly 50 µL) were placed into the sample well of the test cassette, which was labeled with the participant's details. Since whole blood was used in this procedure, 5 drops of the chase buffer was then applied to the sample and test results read after the stipulated time as per the manufacturer's instructions.

3.6.3.3 Clinical Chemistry Measurements

Kidney and liver function tests were carried out using an automated analyzer, the Mindray™ BS-200 Clinical Chemistry Analyzer (Mindray Medical International, Shenzhen, China), following the manufacturer's guidelines and the standard operating procedures of Kakamega County Teaching & Referral Hospital laboratories. Quality controls were run alongside the samples, and any parameters that failed were recalibrated before testing continued. For each test, 1000 µL of serum was pipetted into a clean Mindray™ BS-200 cuvette and placed in the sample chamber of the analyzer. The machine then measured serum creatinine and urea as indicators of kidney function. It also measured

liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total bilirubin, albumin, total proteins and immunoglobulins.

3.7 Data Management and Analysis

All statistical analyses were performed using Microsoft Excel and SPSS version 24.0 (IBM) . Descriptive data for febrile children who were both malaria- and HIV-positive, as well as those who were HIV-positive but malaria-negative, were summarized using the median and range. Group comparisons for continuous variables were done using the Mann-Whitney U test. Kidney function was assessed using serum creatinine and urea levels. Elevated creatin ine (hypercreatinaemia) was defined as values above 59.0 µmol/L, while normal creatinine (normocreatinaemia) was ≤59.0 µmol/L. Elevated urea (hyperuricaemia) was defined as >12.4 mmol/L, while normal levels (normouricaemia) were ≤12.4 mmol/L (Stirnadel-Farrant *et al*., 2015). Liver function was evaluated using several biomarkers based on standard reference values. Alanine aminotransferase (ALT) was considered high if >63.0 IU/L, aspartate aminotransferase (AST) if >95.0 IU/L, alkaline phosphatase (ALP) if >392.0 IU/L, gamma-glutamyl transferase (GGT) if >111.0 IU/L, and lactate dehyd rogenase (LDH) if >170.0 IU/L (Zakowski, 2016). Total protein, albumin, and globulins were also measured, with elevated levels defined as >92.0 g/L, >79.0 g/L, and >53.0 g/L respectively. Normal ranges for each marker were also applied. Receiver operating characteristic (ROC) curve analysis was used to evaluate how well these kidney and liver function markers could distinguish between abnormal (high/low) and normal values in both HIV-positive children with and without malaria. The area under the ROC curve (AUC) was

the main measure of test performance, showing the balance between sensitivity (correctly identifying abnormal cases) and specificity (correctly identifying normal cases). An AUC of 1.0 indicates perfect discrimination, while an AUC of 0.5 means no better than chance. Test accuracy was classified as excellent (0.9–1.0), good (0.8–0.9), fair (0.7–0.8), poor (0.6–0.7), or fail (0.5–0.6). Generally, tests with an AUC ≥0.85 are considered accurate (Kumar & Indrayan, 2011). Youden's index was also used, with values closer to 1 indicating stronger potential for use as a diagnostic or screening tool (Hui, 2021).

CHAPTER FOUR

RESULTS

4.1 The Burden of Parasitemia among the Co-Infected Children

Table 4.1 summarizes the parasitemia levels and demographic characteristics of the study participants. Children who were both HIV-exposed and malaria-positive were significantly younger than the HIV-exposed but malaria-negative controls (median age 14.4 months, range 5–48 months vs. median 24 months, range 6–54 months; P = 0.039). Out of the 138 children enrolled, there were notable gender differences between the groups. Among the HIV-exposed malaria-positive cases, females were the majority (64.2%) compared to males (35.8%), while in the HIV-exposed malaria-negative controls, males were more common (58.8%) than females (41.2%)—a difference that was statistically significant (P = 0.014). Microscopic examination of malaria-positive cases showed a median parasite density of 1,870 parasites per microliter of blood, with counts ranging from 1,806 to as high as 80,025 parasites/μL. Within this group, 10.1% of the children had high-density parasitemia.

Table 4 1: Parasitemia levels and participant demographics

Characteristic	HIV-positive and malaria-negative, n=69	HIV-positive and malaria-positive, n=69	*P*
Parasitaemia/μL of blood	0 (0)	1,870 (1,806-80,025)	-
HDP	-	7 (10.1)	-
Age (range), months	24.0 (6.0-54.0)	14.4 (5.0-48.0)	**0.039**
Gender, n (%)			
Female	19 (35.8)	34 (64.2)	**0.014**
Male	50 (58.8)	35 (41.2)	

Results are presented as number (n) for parasitaemia and also as number and proportion (%) of subjects for gender as well as median (range) for age. HIV, human immunodeficiency virus. μL, microlitre. HDP, high density parasitaemia is defined as >10,000 parasites/μL of blood. *P*-values in bold indicate significant differences.

4.2 Renal Function Markers

Figures 4.1 to 4.4 present the serum creatinine and urea concentrations and their abnormalities. Kidney function analysis showed that children who were both HIV-positive and malaria-positive had significantly higher serum creatinine (median 93.0 μmol/L; range 24.0–1935.0) and urea levels (median 4.9 mmol/L; range 1.4–34.5) compared to HIV-positive but malaria-negative controls (creatinine: median 80.0 μmol/L; range 46.0–205.0; P = 0.001; urea: median 3.7 mmol/L; range 1.7–8.4; P < 0.0001). The proportion of children with elevated creatinine (hypercreatinaemia) was high in both groups and did not differ significantly (75.4% in cases vs. 71.0% in controls; P = 0.564). However, elevated

urea (hyperuraemia) was much more common in the malaria-positive cases (26.1%) compared to the controls (1.4%), a difference that was statistically significant (P < 0.0001).

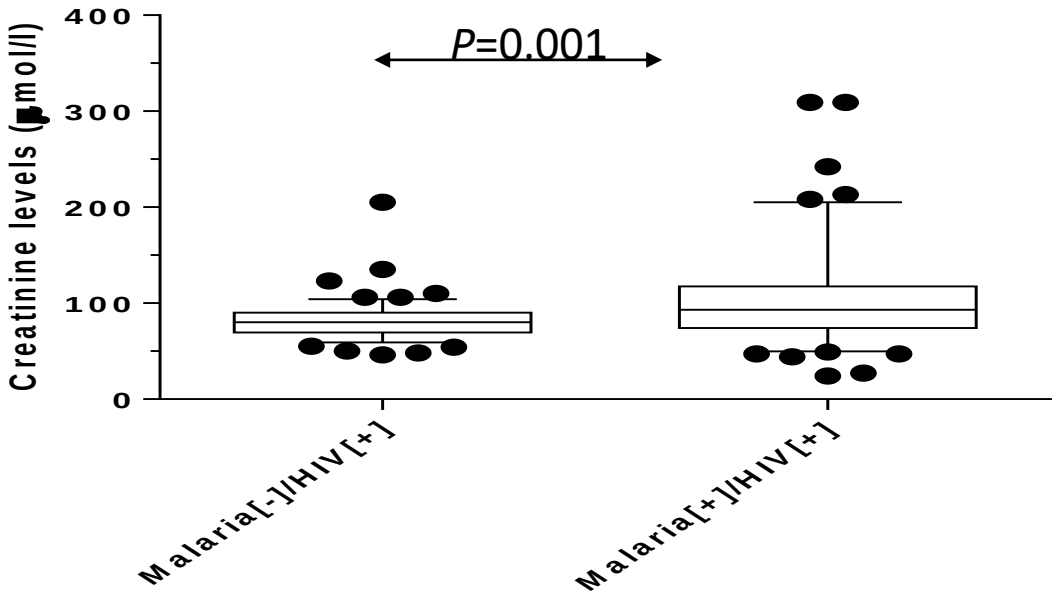

Figure 4 1: Concentrations and alteration in serum Creatinine and Urea

Results are presented as median (range) for serum Creatinine levels. HIV, human immunodeficiency virus. µmol/l, micromole/litre. *P*-values <0.05 indicate significant *P*-values.

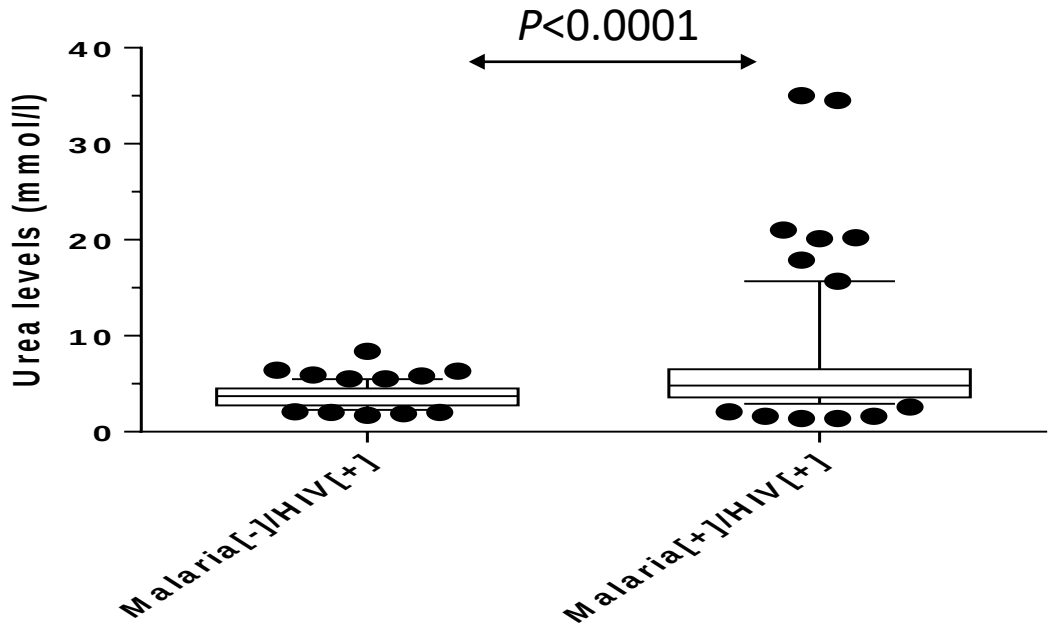

Figure 4 2: Concentrations and alteration in Blood Urea Nitrogen

Results are presented as median (range) for serum Urea levels. HIV, human immunodeficiency virus. mmol/l, millimole/litre. *P*-values <0.05 indicate significant *P*-values.

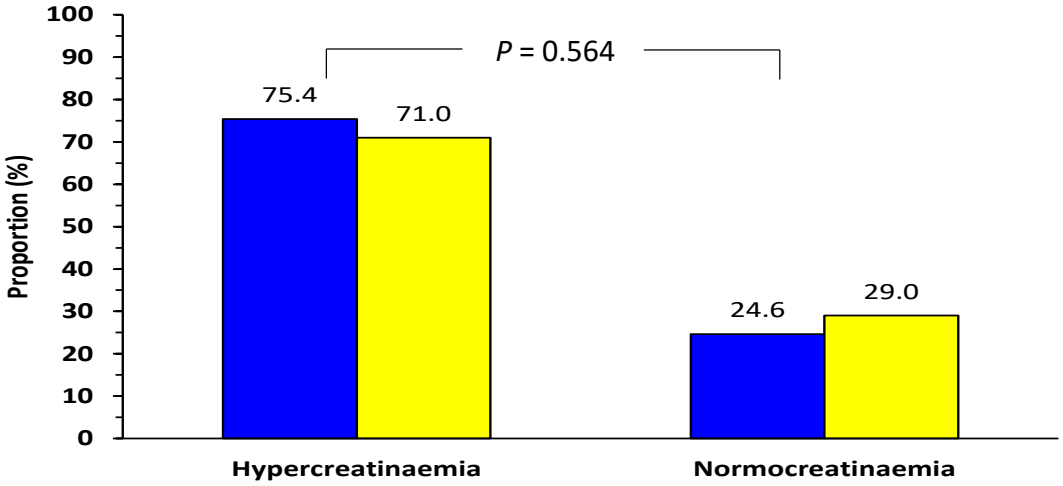

Figure 4 3: Rates of dysfunction in serum Creatinine

Dysfunctions in Creatinine levels were defined as hypercreatinaemia (serum Creatinine, >59.0 µmol/l); and normocreatinaemia (serum Creatinine, ≤59.0 µmol/l). Blue bars represent Malaria [+] HIV [+] and Yellow bars indicate Malaria [-] HIV [+].

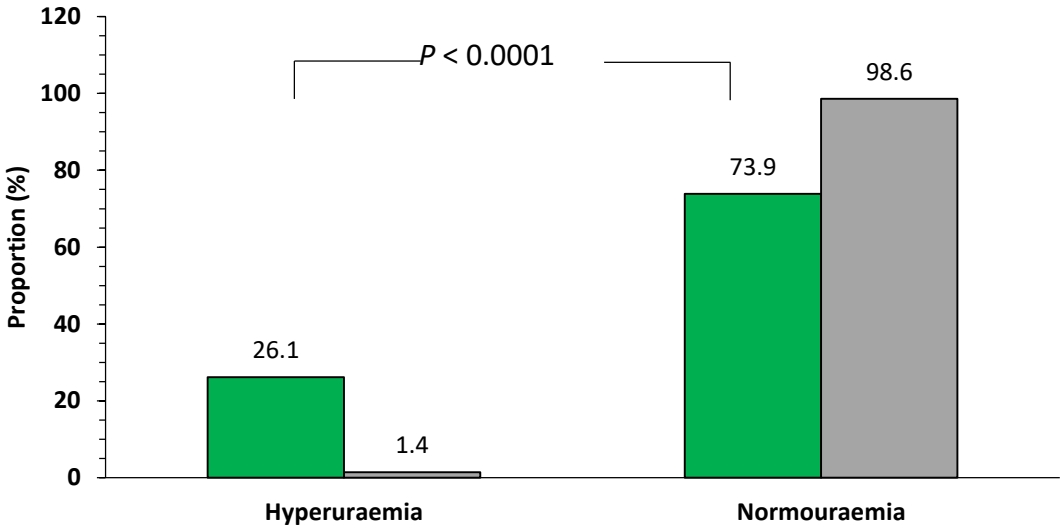

Figure 4 4: Rates of dysfunction in Blood Urea Nitrogen

Dysfunctions in Urea levels were defined as hyperuricaemia (serum Urea, >12.4 mmol/l); and normouricaemia (serum Urea, ≤12.4 mmol/l). Green bars represent Malaria [+] HIV [+] and Gray bars indicate Malaria [-] HIV [+].

4.3 Hepatic Function Markers

Table 4.2 summarizes the levels and abnormalities in liver enzyme markers among the study groups. Analysis of hepatic function showed that children co-infected with HIV and malaria had significantly higher levels of several liver enzymes compared to those who were HIV-positive but malaria-negative. Specifically, alanine aminotransferase (ALT) was higher in the co-infected group (median 16.0 IU/L; range 2.0–135.0) than in the controls (median 11.0 IU/L; range 2.0–43.0; P = 0.031). Aspartate aminotransferase (AST) levels were also elevated (median 19.5 IU/L; range 3.0–340.0 vs. median 16.5 IU/L; range 5.0–36.0; P = 0.010). Gamma-glutamyl transferase (GGT) showed the most marked difference, with the co-infected group having a median of 38.0 IU/L (range 5.0–423.0) compared to 23.5 IU/L (range 6.0–170.0) in the HIV-only group (P < 0.0001). When looking at the

proportions of children with abnormally high enzyme values, the co-infected group also showed a significantly higher burden. Elevated ALT was present in 21.7% of the co-infect ed group compared to only 2.9% of HIV-only children (P = 0.001). Similarly, elevated AST was observed in 33.3% versus 5.8% (P < 0.0001), and elevated GGT in 72.5% versus 50.7% (P = 0.013). These findings indicate that HIV and malaria co-infection is strongly asso ciated with liver enzyme abnormalities. On the other hand, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels did not differ significantly between the two groups. Median ALP values were 76.0 IU/L (range 29.0–572.0) for co-infected children and 73.0 IU/L (range 28.0–559.0) for HIV-only children (P = 0.262). Similarly, LDH medians were 359.1 IU/L (range 75.6–1009.6) versus 326.5 IU/L (range 95.5–720.3; P = 0.113). The proportions of children with high ALP (68.1% vs. 82.4%; P = 0.075) and LDH (89.9% vs. 91.3%; P = 0.999) were also comparable between the groups.

Table 4 2: Levels of Hepatic Enzymatic Proteins

Marker	HIV-positive and malaria-negative, n=69	HIV-positive and malaria-positive, n=69	*P*
ALT, IU/l	11.0 (2.0-43.0)	16.0 (2.0-135.0)	**0.031**
High	2 (2.9)	15 (21.7)	**0.001**
Normal	67 (97.1)	54 (78.3)	
AST, IU/l	16.5 (5.0-36.0)	19.5 (3.0-340.0)	**0.010**
High	4 (5.8)	23 (33.3)	**<0.0001**
Normal	65 (94.2)	46 (66.7)	
ALP, IU/l	73.0 (28.0-559.0)	76.0 (29.0-572.0	0.262
High	56 (82.4)	47 (68.1)	0.075
Normal	13 (17.6)	22 (31.9)	
GGT, IU/l	23.5 (6.0-170.0)	38.0 (5.0-423.0)	**<0.0001**
High	35 (50.7)	50 (72.5)	**0.013**
Normal	34 (49.3)	19 (27.5)	
LDH, IU/l	326.5 (95.5-720.3)	359.1 (75.6-1009.6)	0.113
High	63 (91.3)	62 (89.9)	0.999
Normal	6 (8.7)	7 (10.1)	

Results are presented as median and range for liver enzymes test levels. HIV, human immunodeficiency virus. IU/l, international units/litre. *P*-values in bold indicate significant *P*-values.

Analysis of liver markers linked to hemolysis showed that HIV and malaria co-infected children had significantly higher bilirubin levels than those with HIV alone. Total bilirubin

was nearly double in the co-infected group (median 20.5 µmol/L; range 4.3–60.0) compared to the mono-infected group (median 9.5 µmol/L; range 3.5–26.0; P < 0.0001). Direct bilirubin followed the same trend, with higher values in the co-infected group (median 6.7 µmol/L; range 2.0–46.4) compared to HIV-only children (median 3.7 µmol/L; range 0.9–13.4; P < 0.0001). The proportion of children with abnormal bilirubin levels was also notably higher among those with both infections. Almost half of the co-infected children (49.3%) had elevated total bilirubin compared to just 5.8% in the HIV-only group (P < 0.0001). Similarly, 68.1% of the co-infected group had high direct bilirubin levels ve rsus 30.4% of the mono-infected group (P < 0.0001). These findings, summarized in Table 4.3, suggest that co-infection greatly increases the risk of hyperbilirubinemia.

Table 4 3: Tetrapyrrole molecule (Bilirubin) levels

Marker	**HIV-positive and malaria-negative, n=69**	**HIV-positive and malaria-positive, n=69**	***P***
Total bilirubin, µmol/l	9.5 (3.5-26.0)	20.5 (4.3-60.0)	**<0.0001**
Hyperbilirubinaemia	4 (5.8)	34 (49.3)	**<0.0001**
Normobilirubinaemia	65 (94.2)	35 (50.7)	
Direct bilirubin, µmol/l	3.7 (0.9-13.4)	6.7 (2.0-46.4)	**<0.0001**
Hyperbilirubinaemia	21 (30.4)	47 (68.1)	**<0.0001**
Normobilirubinaemia	48 (69.6)	22 (31.9)	

Results are presented as median and range for bilirubin test levels. HIV, human immunodeficiency virus. µmol/l, micromole/litre. *P*-values in bold indicate significant *P*-values.

Protein analysis showed that all serum markers of liver protein metabolism were significantly higher in children co-infected with HIV and malaria compared to those with HIV alone. Total protein levels were elevated (median 90.0 g/L; range 35.0–160.0) in the co-infected group versus 82.0 g/L (range 69.0–115.0) in the HIV-only group ($P < 0.0001$). Albumin was also higher in co-infected children (median 55.0 g/L; range 30.0–68.0) compared to 50.0 g/L (range 37.0–61.0; $P < 0.0001$). Similarly, globulin levels were raised (median 36.0 g/L; range 18.0–160.0) relative to 29.5 g/L (range 16.0–61.0; $P = 0.006$). These findings are summarized in Table 4.4.

The co-infected children also had higher proportions of protein dysfunction. Hyperproteinaemia was more common (76.8% vs. 55.1%; $P = 0.018$), as was hyperalbuminaemia (24.6% vs. 2.9%; $P < 0.0001$) and hyperglobulinaemia (15.9% vs. 2.9%; $P = 0.004$). Overall, these results show that malaria co-infection in HIV-positive children is linked with significant disturbances in protein metabolism.

Table 4 4: Metabolic Protein levels

Marker	**HIV-positive and malaria-negative, n=69**	**HIV-positive and malaria-positive, n=69**	***P***
Total protein, g/l	82.0 (69.0-115.0)	90.0 (35.0-160.0)	**<0.0001**
Hyperproteinaemia	38 (55.1)	53 (76.8)	**0.018**
Normoproteinaemia	31 (44.9)	16 (23.2)	
Albumin, g/l	50.0 (37.0-61.0)	55.0 (30.0-68.0)	**<0.0001**
Hyperalbuminaemia	2 (2.9)	17 (24.6)	**<0.0001**

Normoalbuminaemia	67 (97.1)	52 (75.4)	
Globulins, g/l	29.5 (16.0-61.0)	36.0 (18.0-160.0)	**0.006**
Hyperglobulinaemia	2 (2.9)	11 (15.9)	**0.004**
Normoglobulinaemia	67 (97.1)	58 (84.1)	

Results are presented as median and range for protein test levels. HIV, human immunodeficiency virus. g/l, grams/litre. *P*-values in bold indicate significant *P*-values.

4.4 Validity of Renal and Hepatic Markers in Malaria and HIV Co-Infection Diagnosis

The results of the ROC curve analyses are presented in figure 4.5 and Table 4.5, respectively. The ROC-AUC analysis results were fair (0.7-0.8) for total bilirubin, poor (0.6-0.7) for urea, ALT, AST, GGT, direct bilirubin, total protein and albumin; and fail (0.5-0.6) for creatinine, ALP and LDH. The cut-off points for markers were: Creatinine (71.0 µmol/l), urea (6.4 mmol/l), ALT (30.0 IU/l), AST (28.0 IU/l), ALP 100.0 IU/l), GGT 23.0 IU/l), LDH 170.0 IU/l), total bilirubin (20.5 µmol/l), direct bilirubin (5.1 µmol/l), total protein (8.0 g/l), and albumin (5.8 g/l). Based on the Youden's index of ≤50.0% which denotes inability of the marker to detect disease or health (Rota *et al*., 2015), all the laboratory markers had no diagnostic value except LDH with a Youden's index of 82.2%. The specificities and sensitivities were, respectively: creatinine (75.8% and 71.0%), urea (26.1% and 1.4%), ALT (21.5% and 1.6%), AST (33.8% and 5.9%), ALP (68.1% and 82.4%), GGT (71.6% and 50.0%), LDH (91.0% and 91.2%), total bilirubin (49.3% and 5.8%), direct bilirubin (67.7% and 30.6%), total protein (76.5% and 54.4%) and albumin (23.5% and 2.9%). The positive predictive value and negative predictive value for the markers were: creatinine (50.5% and 55.6%), urea (94.7% and 57.1%), ALT (93.3% and

54.5%), AST (85.2% and 58.7%), ALP (45.6% and 35.3%), GGT (58.5% and 64.2%), LDH (49.6% and 50.0%), total bilirubin (89.5% and 65.0%), direct bilirubin (69.8% and 67.2%), total protein (58.4% and 66.0%) and albumin (88.9% and 56.3%). The accuracy to correctly identify malaria in HIV infection was creatinine (51.9%), urea (62.3%), ALT (59.1%), AST (64.0%), ALP (43.1%), GGT (60.7%), LDH (49.6%), total bilirubin (71.7%), direct bilirubin (68.5%), total protein (61.0%) and albumin (60.6%).

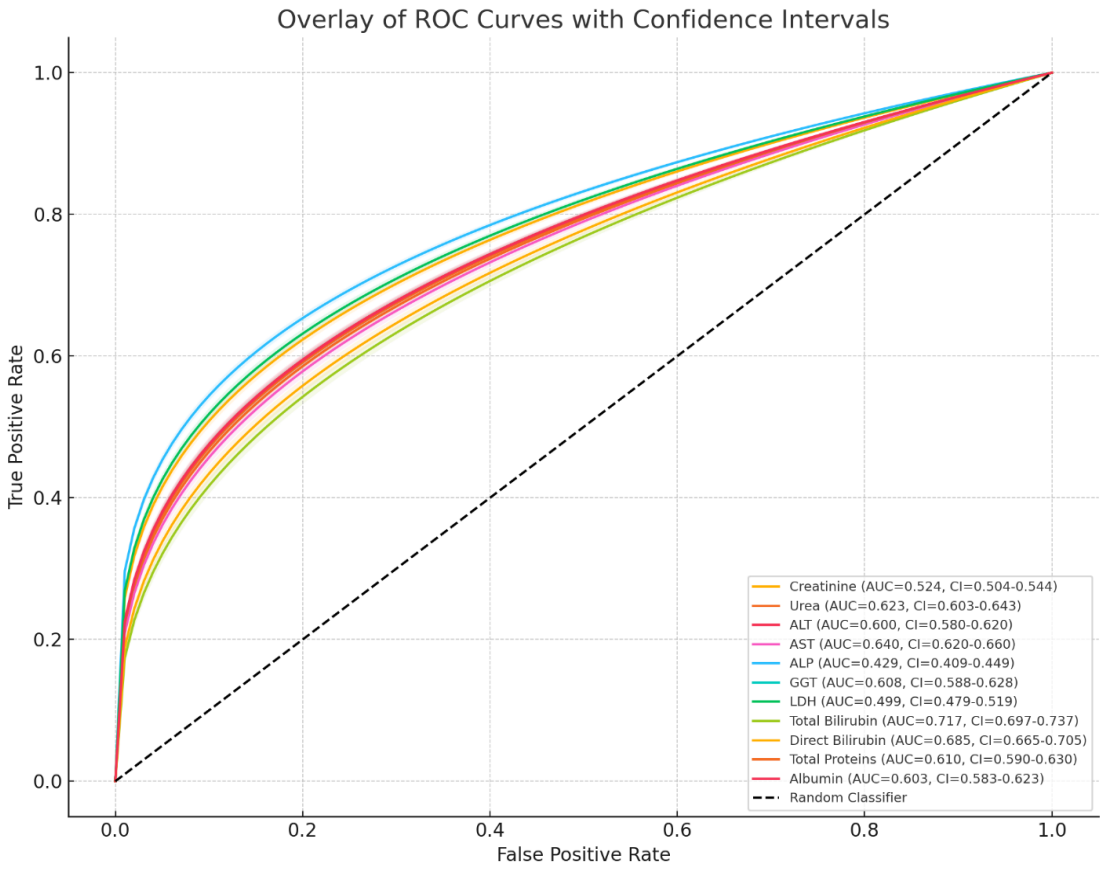

Figure 4 5: An overlay of the Receiver Operating Characteristics with Confidence Intervals

Total Bilirubin stood out with the highest AUC and relatively narrow confidence bounds, suggesting strong and reliable performance. LDH, despite having a low AUC (~0.5), showed a steep ROC shape—driven by its high Youden Index—indicating peculiar test characteristics. Markers like Albumin and ALT showed poor discrimination, clustering near the random classifier line.

Table 4 5: Receiver Operating Characteristics curve analyses for the laboratory markers

Marker	AUC (95% CI)	Cut-off levels of the marker	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
Creatinine	0.524 (0.426-0.621)	71.0	75.8	71.0	50.5	55.6
Urea	0.623 (0.529-0.717)	6.4	26.1	1.4	94.7	57.1
ALT	0.600 (0.509-0.698)	30.0	21.5	1.6	93.3	54.5
AST	0.640 (0.546-0.733)	28.0	33.8	5.9	85.2	58.7
ALP	0.429 (0.333-0.525)	100.0	68.1	82.4	45.6	35.3
GGT	0.608 (0.513-0.704)	23.0	71.6	50.0	58.5	64.2
LDH	0.499 (0.402-0.597)	170.0	91.0	91.2	49.6	50.0
Total bilirubin	0.717 (0.630-0.804)	20.5	49.3	5.8	89.5	65.0
Direct bilirubin	0.685 (0.592-0.779)	5.1	67.7	30.6	69.8	67.2
Total protein	0.610 (0.515-0.705)	8.0	76.5	54.4	58.4	66.0
Albumin	0.603 (0.508-0.698)	5.8	23.5	2.9	88.9	56.3

Data are presented as proportions (%). AUC, area under the curve, sensitivity, specificity, +PV, positive predictive value. -PV, negative predictive value.

CHAPTER FIVE

DISCUSSION

5.1 Parasitemia Burden and Demographic Characteristics

The findings from this study revealed that HIV and malaria co-infected children were significantly younger than those presenting with HIV mono-infection. This pattern suggests that perinatally acquired HIV infection may increase susceptibility to malaria early in life, likely due to impaired immune development and inadequate acquisition of malaria-specific immunity. Infants born with HIV or exposed to maternal HIV infection often exhibit delayed maturation of humoral and cellular immune responses, which limits their ability to mount effective protection against *Plasmodium falciparum*. This observation aligns with earlier reports from Bungoma County, Kenya, which documented a higher prevalence of malaria among HIV-positive children aged 2–10 years compared to their HIV-negative counterparts (Rutto et al., 2015). It also supports hospital-based findings from Tanzania, where HIV-seropositive children aged 3–12 years had significantly higher odds of malaria infection than HIV-seronegative peers (Smart et al., 2016). Collectively, these findings emphasize that HIV-induced immune dysfunction heightens malaria risk even in early childhood and underscore the need for targeted malaria preventive measures such as intermittent preventive therapy and bed net distribution among HIV-exposed and HIV-infected infants.

The median parasitemia level of 1,870 parasites/μL (range: 1,806–80,025) observed in co-infected children indicates moderate to high parasite burdens, consistent with endemic transmission in Western Kenya. These values closely mirror findings from Rutto et al.

(2015), who reported mean parasite densities of approximately 2,008.9 ± 7,602.3 parasites/μL in a region of comparable malaria intensity. Interestingly, the levels were higher than those observed in hypo-endemic regions such as Benin, where average parasitemia in HIV-positive children was about 118.7 parasites/μL (Okonkwo et al., 2018). Such regional variations likely reflect differences in transmission intensity, host immune adaptation, and vector ecology. The relatively elevated parasite densities in the current study highlight the persistent high transmission in Western Kenya and suggest that co-infection with HIV may impair effective parasite clearance, possibly due to reduced macrophage activation and decreased cytotoxic T-lymphocyte responses. From a clinical perspective, these findings underline the importance of early malaria testing and aggressive management of febrile illness among HIV-infected children, as delayed diagnosis in this group can quickly lead to severe anemia or other complications.

A notable finding was the higher prevalence of co-infection among female children compared to males. This sex-based disparity is consistent with a Tanzanian study reporting that 61.9% of HIV-positive pediatric malaria cases were female (Smart et al., 2016). Conversely, earlier work in Western Kenya indicated that male children under 14 years of age had higher malaria parasite densities than females (Ondeto et al., 2022). Several factors may explain this discrepancy. Biologically, sex-related differences in immune function particularly the influence of sex hormones can shape susceptibility to infectious diseases. Estrogen is known to modulate both innate and adaptive immunity, which could alter the inflammatory and antibody-mediated responses to malaria. Social and cultural determinants may also play a role. In many rural communities, male children often receive more attentive healthcare and preventive services. Evidence from Western Kenya shows

that full vaccination coverage is higher among male children compared to females (Calhoun et al., 2014), suggesting gender-based disparities in healthcare access and health-seeking behavior. Consequently, delayed care and underutilization of preventive services among female children may increase their exposure to infection and risk of developing co-infection. These findings have implications for health policy, calling for equitable child health interventions that address gender disparities in malaria prevention and access to care.

The immunological mechanisms underlying these findings further reinforce the interaction between HIV and malaria. Effective control of *P. falciparum* infection depends on robust Th1-mediated immune responses, particularly the production of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12). In HIV-infected individuals, this Th1 response is often compromised due to progressive CD4+ T-cell depletion. Concurrently, there is an upregulation of Th_2 cytokines such as IL-4 and IL-10, which suppress macrophage activation and limit parasite clearance (Mandala et al., 2021). This cytokine imbalance contributes to higher parasitemia, recurrent malaria episodes, and more severe clinical outcomes in co-infected children. The observed immune modulation underscores the need for integrating immunological assessment into the clinical management of malaria among HIV-positive pediatric populations.

From a public health perspective, these results carry several implications. Clinically, healthcare providers should maintain a high index of suspicion for malaria in all febrile HIV-infected children, regardless of age or sex, and ensure that laboratory confirmation is performed before treatment (Sanders et al., 2014). Strengthening routine screening for malaria at pediatric HIV clinics could allow early detection and timely management,

minimizing complications and hospitalizations. Policy-wise, the findings advocate for tailored malaria prevention programs for HIV-exposed and HIV-infected children, including the use of insecticide-treated nets, chemoprophylaxis, and community-based education on early fever management. Moreover, given the observed sex-related differences, interventions should incorporate gender-sensitive approaches to address unequal healthcare access and caregiver behavior.

Further research is needed to elucidate the immunopathological pathways linking malaria and HIV co-infection in children, particularly the role of cytokine regulation and immune cell dynamics. Longitudinal studies should explore how ART initiation and sustained viral suppression modify malaria risk and parasite density. Future investigations should also assess the impact of socioeconomic, nutritional, and environmental factors on the observed disparities. Overall, the current findings highlight the complex interplay between host immunity, infection burden, and demographic factors, providing a foundation for refining both clinical practice and public health strategies aimed at reducing malaria-related morbidity in HIV-infected children.

5.2 Renal Function Markers

The present study demonstrated that children co-infected with HIV and malaria exhibited significantly elevated serum creatinine levels compared to those with HIV infection alone, indicating a greater degree of renal dysfunction in co-infected individuals. This observation is consistent with the well-documented relationship between *P. falciparum* infection and acute kidney injury (AKI), a common complication of severe malaria (Katsoulis et al.,

2021; Kubanek et al., 2024). Although malaria-associated renal impairment is historically more prevalent among adults, emerging evidence suggests that children, particularly in high-transmission settings, are also vulnerable to malaria-related kidney injury (Batte et al., 2025b; Tembo et al., 2022). The elevated creatinine levels observed in this cohort align with these reports and highlight the burden of renal complications in pediatric malaria, especially when compounded by HIV infection.

Previous studies have reported that HIV infection on its own can contribute to renal abnormalities, including microalbuminuria, proteinuria, and elevated serum creatinine or cystatin C levels (Edward et al., 2025; Nasuuna et al., 2024). These findings suggest that chronic immune activation and viral replication may damage renal glomeruli and tubules. HIV-associated nephropathy, characterized by focal segmental glomerulosclerosis, remains one of the most common renal pathologies in HIV-infected children. The combination of HIV and malaria, therefore, represents a dual insult to the kidneys through overlapping but distinct pathogenic mechanisms one driven by immune-mediated inflammation and direct viral injury, and the other by microvascular obstruction and hemolysis.

The median serum creatinine level of 93 µmol/L recorded in co-infected children exceeded both the values observed in HIV-only participants (80 µmol/L) and the upper limits of standard reference ranges for children (44–80 µmol/L for females, 62–106 µmol/L for males) (Ghasemi et al., 2021). This elevation likely reflects the cumulative renal burden imposed by both infections. In malaria, kidney injury is typically caused by the sequestration of parasitized red blood cells within small renal vessels, which impairs

microcirculation and leads to ischemic injury. This process is further exacerbated by intravascular hemolysis and inflammatory responses that release vasoactive substances such as thromboxane, catecholamines, and endothelin, contributing to endothelial dysfunction and hemodynamic instability (da Silva et al., 2017). In HIV, elevated creatinine is often associated with low CD4 counts, chronic inflammation, and metabolic abnormalities related to body mass index and lipid levels ((Duangrithi & Silathong, 2025; Phalane et al., 2018). Additionally, prolonged use of nephrotoxic antiretroviral agents particularly tenofovir disoproxil fumarate can independently contribute to renal impairment (Venter et al., 2018). The convergence of these mechanisms in co-infected children likely amplifies kidney injury, explaining the higher creatinine levels observed in this study.

These findings underscore the importance of routine kidney function monitoring in HIV-infected children living in malaria-endemic regions. Early detection of elevated creatinine or urea can guide timely intervention and prevent progression to severe AKI. Clinicians should be particularly vigilant during malaria episodes or ART initiation, when renal stress is highest. Screening protocols that include serum creatinine and urea testing alongside malaria diagnostics could improve comprehensive case management and reduce renal complications in this high-risk group.

In addition to creatinine, this study found significantly elevated serum urea levels among children with HIV–malaria co-infection compared to those with HIV mono-infection. Urea, measured clinically as blood urea nitrogen (BUN), serves as an indicator of nitrogen metabolism and renal excretory function (Salazar, 2014; Seki et al., 2019). The elevated urea observed in this study suggests impaired renal clearance and increased protein

catabolism. Normal BUN levels range from 2.1 to 8.5 mmol/L, although this can vary depending on age, hydration, and nutritional status (Hosten, 1990). In severe *P. falciparum* infection, high urea and creatinine levels often occur together, reflecting acute tubular necrosis and glomerular injury caused by reduced renal perfusion and the deposition of immune complexes within renal capillaries (Basire et al., 2025).

HIV infection can also independently elevate urea levels, particularly in untreated or ART-naïve children. Studies in Nigeria, Ghana, and Ethiopia have reported increased urea concentrations and early renal impairment in HIV-infected pediatric populations, attributed to chronic inflammation and cytokine-mediated injury (Kefeni et al., 2021; Obiri-Yeboah et al., 2018). The pathophysiology involves dysregulation of renal immune mechanisms, including the action of unconventional T cells (γδ T cells) and cytokines such as IL-17, IL-23, IFN-γ, and TNF-α, which are critical for maintaining glomerular and tubular integrity (Kalyan & Kabelitz, 2014; Li et al., 2010). HIV disrupts these regulatory pathways, promoting glomerular sclerosis and elevated nitrogenous waste accumulation (Olusola et al., 2020).

When HIV and malaria occur together, these mechanisms likely have an additive or even synergistic effect, leading to the markedly higher urea levels observed in this study. The finding of concurrent elevation in creatinine and urea points to a hyper-catabolic state, in which increased protein breakdown and impaired renal excretion coexist. Experimental models have demonstrated that malaria induces broad metabolic disturbances, including increased amino acid turnover and urea cycle activation (Das et al., 2021; Saiki et al., 2013). Human studies in Bangladesh have reported similar disruptions, with decreased circulating

amino acids and accumulation of ammonia, supporting the hypothesis of malaria-induced hyper-catabolism (Colvin & Joice Cordy, 2020; Leopold et al., 2019). These biochemical alterations, when compounded by HIV-associated inflammation and nephropathy, create a metabolic environment that exacerbates renal strain and dysfunction in co-infected children.

From a clinical and public health perspective, these findings carry several implications. First, they highlight the importance of integrating renal function tests specifically serum creatinine and urea into routine evaluation of HIV-positive children, especially in malaria-endemic areas. Second, they suggest that malaria infection should be considered a potential cause of renal deterioration in children receiving ART, particularly those on nephrotoxic regimens such as TDF-based therapies. Third, the results point to the need for revising pediatric HIV–malaria co-management guidelines to include renal monitoring as part of comprehensive care. This approach would enable early identification of kidney dysfunction, prompt dose adjustments, and timely referral for nephrological assessment.

At the policy level, the findings support Kenya's efforts under the National Malaria Strategy and the HIV Strategic Framework to strengthen integrated disease surveillance and management of co-morbid infections. Incorporating renal biomarker monitoring into existing pediatric HIV and malaria programs could enhance patient outcomes and reduce long-term complications. For future research, longitudinal studies are needed to assess how ART duration, parasite load, and nutritional status influence renal outcomes in co-infected children. Investigations into the reversibility of biochemical abnormalities after treatment could also inform follow-up protocols and therapeutic interventions.

This study provides strong evidence that both HIV and malaria independently impair kidney function but act synergistically when co-infection occurs. Elevated serum creatinine and urea levels in co-infected children signal significant renal stress and metabolic disturbance, reflecting the combined pathophysiological burden of both diseases. Routine monitoring of these markers should therefore be prioritized in pediatric populations living in malaria-holo-endemic regions, both for early diagnosis of renal complications and for guiding effective, integrated management of malaria and HIV co-infection.

5.3 Hepatic Function Markers

This study found that children co-infected with *P. falciparum* and HIV exhibited significantly elevated liver enzymes alanine ALT, AST and GGT alongside raised total and direct bilirubin levels compared to those with HIV alone. These findings point to hepatic dysfunction and mirror previous reports from Ghana, southern Nigeria, and Cameroon, where HIV–malaria co-infected children and adults showed elevated liver enzyme profiles (Liu et al., 2022; Yadav et al., 2022). The consistency across studies underscores that hepatic involvement is a key manifestation of malaria–HIV co-infection, likely reflecting additive or synergistic hepatic stress from both pathogens.

Malaria alone has long been linked to liver injury, with elevated ALT, AST, ALP, and GGT being hallmarks of hepatocellular damage (Megabiaw et al., 2022; Reuling et al., 2018). The mechanisms are multifactorial. During *P. falciparum* infection, parasitized red blood cells sequester in hepatic sinusoids, reducing portal circulation and oxygenation. The

resultant hypoxia, coupled with oxidative stress and inflammatory cytokine release, leads to hepatocyte apoptosis, microvesicular steatosis, and cholestasis (Fabbri et al., 2013). Autopsy studies have shown hemozoin pigment deposition within Kupffer cells and hepatocytes, Kupffer cell hyperplasia, and focal necrosis (Deroost et al., 2014; Hirako et al., 2022). The accumulation of malaria pigment impairs macrophage function and stimulates pro-inflammatory cytokines such as macrophage migration inhibitory factor (MIF), amplifying hepatic inflammation. These cellular disruptions align with the elevated enzyme patterns observed in this study.

HIV infection independently contributes to liver injury through several mechanisms. It causes direct viral cytopathic effects on hepatocytes, chronic immune activation, and dysregulated cytokine production. HIV also promotes oxidative stress, mitochondrial damage, and metabolic disturbances that further compromise liver integrity ((Amegashie et al., 2025). Elevated liver enzymes have been reported in both ART-naïve and ART-treated HIV-infected individuals, with some studies in Africa and Asia documenting early fibrosis in pediatric cases (Rose et al., 2022). Additionally, antiretroviral therapy itself particularly protease inhibitors and nucleoside analogues can contribute to hepatotoxicity through mitochondrial toxicity and impaired lipid metabolism.

The co-occurrence of malaria and HIV therefore exposes the liver to dual pathogenic insults: malaria-related ischemic and inflammatory damage on one hand, and HIV-mediated oxidative and metabolic stress on the other. The significantly elevated ALT, AST, and GGT levels observed in co-infected children compared to HIV mono-infected peers reinforce the notion of compounded hepatic injury. From a pathophysiological standpoint,

these changes may reflect hepatocellular necrosis and inflammation triggered by simultaneous parasite sequestration and viral replication within hepatic tissue.

The raised bilirubin levels observed in co-infected children further support the presence of hepatocellular dysfunction. Both total and direct bilirubin were significantly higher than in HIV mono-infection, with many children exhibiting biochemical evidence of hyperbilirubinemia. This observation is consistent with prior findings showing a positive correlation between malaria parasite density and bilirubin concentration (Okon et al., 2022). Elevated bilirubin in malaria stems primarily from hemolysis of both parasitized and non-parasitized erythrocytes and impaired conjugation or excretion by damaged hepatocytes (Woodford et al., 2018). Although HIV mono-infection is not typically associated with jaundice, certain ART drugs such as atazanavir and indinavir can inhibit bilirubin conjugation, leading to indirect hyperbilirubinemia (Panagopoulos et al., 2017). Thus, the combination of malaria-induced hemolysis and ART-related hepatocellular stress may explain the high bilirubin levels observed in co-infected children.

In addition to enzyme and bilirubin alterations, the study noted elevated total protein, albumin, and globulin concentrations in the co-infected group compared to HIV-only children. While hyperproteinemia and hyperglobulinemia have been reported in both malaria and HIV, their pathophysiological origins differ. In malaria, elevated serum proteins likely reflect an acute-phase response and increased production of inflammatory proteins such as haptoglobin, fibrinogen, and complement components (Rosa-Fernandes et al., 2025). Experimental studies in *Plasmodium chabaudi*-infected mice have similarly demonstrated transient hyperproteinemia associated with increased immunoglobulin

synthesis (Gbaguidi et al., 2024). In HIV infection, chronic antigenic stimulation and B-cell hyperactivation drive polyclonal and sometimes monoclonal gammopathies (Wang et al., 2024). The coexistence of both infections likely amplifies immune dysregulation, resulting in exaggerated protein synthesis and release into circulation.

These findings have several clinical and public health implications. The elevation of hepatic enzymes and bilirubin in co-infected children indicates that liver dysfunction is common and potentially underrecognized in pediatric populations living in co-endemic regions. Routine liver function monitoring should therefore be integrated into the clinical management of HIV-positive children, particularly during malaria episodes or when initiating ART. Early detection of hepatocellular injury would allow for timely interventions, such as adjusting ART regimens, providing hepatoprotective therapy, or optimizing malaria treatment to reduce hepatic stress.

From a policy perspective, the results underscore the need for integrated screening protocols that assess both hepatic and renal function in HIV–malaria co-management programs. National malaria and HIV control frameworks should incorporate biochemical monitoring into pediatric care guidelines, especially in regions like Western Kenya where co-infection rates remain high. This would support rational drug use, minimize adverse drug reactions, and improve overall treatment outcomes.

Further research should aim to clarify the temporal dynamics of hepatic injury during co-infection specifically, whether these enzyme elevations resolve after malaria treatment or persist due to chronic HIV-related inflammation. Longitudinal studies incorporating

imaging and histopathological assessments could help distinguish transient hepatic stress from progressive liver disease. Additionally, future investigations should explore the molecular pathways underlying combined liver injury, including oxidative stress markers, mitochondrial DNA damage, and cytokine signaling patterns.

This study demonstrates that HIV–malaria co-infection in children exerts an additive effect on liver physiology, leading to pronounced increases in liver enzymes, bilirubin, and serum proteins. These biochemical alterations reflect overlapping mechanisms of hepatocellular injury, hemolysis, and immune activation. Recognizing and managing hepatic dysfunction early in co-infected children is essential for improving prognosis and ensuring safer, more effective therapeutic regimens in malaria-holo-endemic regions.

5.4 Validity of Laboratory Markers in Malaria and HIV Co-Infection Diagnosis

This study evaluated the diagnostic and prognostic performance of several renal and hepatic biomarkers in children co-infected with *P. falciparum* and HIV. Among all markers analyzed, serum LDH, creatinine, and ALP demonstrated the highest diagnostic performance, with LDH showing the greatest sensitivity (91.0%) and specificity (91.2%) at a cut-off value of 170 IU/L. These results suggest that LDH, a marker of tissue injury and hemolysis, may serve as a useful adjunct indicator for detecting malaria–HIV co-infection and assessing disease severity. Elevated LDH levels in co-infected children likely reflect widespread hemolysis and hepatic cell injury triggered by both malaria parasitemia and HIV-induced systemic inflammation. This finding aligns with prior work showing that LDH rises significantly during malaria infection, correlating with parasite density and red

cell destruction (Sanyaolu et al., 2013). It also parallels reports of increased LDH in HIV-positive individuals, particularly those with advanced disease stages, due to high viral replication and immune cell turnover.

Similarly, elevated creatinine levels demonstrated strong sensitivity (75.8%) and specificity (71.0%) at a threshold of 71.0 µmol/L, reinforcing its role as a reliable marker of renal dysfunction in co-infected children. The increase in creatinine mirrors earlier findings in both malaria and HIV mono-infections, where renal impairment stems from different but complementary mechanisms malaria-induced tubular obstruction from parasitized erythrocytes and HIV-associated nephropathy driven by chronic inflammation (Venter et al., 2018). The relatively high diagnostic accuracy of creatinine observed in this study supports its potential inclusion as part of a broader diagnostic panel for identifying renal complications in children with co-infection, particularly in settings where advanced diagnostics are unavailable.

ALP also demonstrated appreciable diagnostic utility, with sensitivity and specificity values of 68.1% and 82.4%, respectively. This pattern is consistent with previous studies in West Africa showing that malaria and HIV co-infection increases cholestatic enzyme activity due to intrahepatic inflammation, hepatocellular damage, and disrupted bile excretion (Obase et al., 2023). ALP elevation is particularly relevant in pediatric populations, where it may signal hepatic injury or early cholestasis linked to systemic infection. Its moderate predictive value in this study reinforces its role as a supportive, though not standalone, marker of hepatic involvement in co-infection.

In contrast, GGT, direct bilirubin, and total protein exhibited higher sensitivities but lower specificities. While GGT had a sensitivity of 71.6% and specificity of 50.0%, direct bilirubin showed 67.7% sensitivity but only 30.6% specificity. Total protein achieved relatively good sensitivity (76.5%) but moderate specificity (54.4%). These findings suggest that although these markers are responsive to infection-related hepatic stress, they may lack diagnostic precision when used alone. Elevated bilirubin and GGT are known consequences of malaria-associated hemolysis and hepatocellular dysfunction, while total protein rises due to immune activation and hypergammaglobulinemia (Chughlay et al., 2020). The low specificity of these markers implies they may also respond to other inflammatory or infectious processes common in children from endemic regions, such as bacterial or viral co-infections, thereby limiting their diagnostic reliability in isolation.

Receiver Operating Characteristic (ROC) curve analysis provided further insight into the diagnostic value of these biomarkers. LDH, creatinine, and GGT exhibited area under the curve values ranging between 0.499 and 0.608, suggesting fair predictive performance for detecting co-infection-related organ dysfunction. Direct bilirubin, with an AUC of 0.685, had the highest overall discriminative ability, indicating that bilirubin levels may serve as a practical biochemical indicator of hepatic impairment in co-infected patients. Although these AUCs were modest, their combined interpretation suggests that panels integrating both renal and hepatic markers may yield more accurate diagnostic and prognostic predictions than single tests.

These findings align with earlier evidence from Nayebi et al. (2022), who demonstrated that elevated high-sensitivity C-reactive protein (hs-CRP), another hepatic inflammatory

marker, achieved sensitivities above 96% and specificities exceeding 79% in malaria prediction (Nayebi et al., 2022). Both studies underscore that systemic inflammation, driven by malaria pigment deposition, immune activation, and viral replication, underlies the observed biochemical changes. The inflammatory response likely amplifies hepatocellular enzyme release and disrupts renal filtration, producing the characteristic laboratory abnormalities identified here.

The current results also resonate with broader studies examining prognostic indicators in infectious diseases. For example, Lowlaavar et al. (2016) developed a prognostic model among Ugandan children with malaria and other infections that achieved high predictive accuracy (AUC 0.85) when incorporating HIV co-infection and clinical parameters such as coma score and undernutrition (Lowlaavar et al., 2016). Similarly, Hazard et al. (2022) demonstrated that composite clinical-laboratory indices such as the Universal Vital Assessment (UVA) score achieved better mortality prediction in HIV–malaria-endemic populations than single physiological measures (Hazard et al., 2022). In contrast, systemic inflammatory response syndrome (SIRS) criteria performed poorly across multiple countries (Santacroce et al., 2024), suggesting that laboratory-based markers alone may be insufficient without integrating clinical variables. The present study supports this view, emphasizing that biochemical indices such as LDH, creatinine, ALP, and bilirubin should be used alongside clinical assessments to improve diagnostic precision in pediatric co-infection.

The findings have several implications for clinical practice and policy. First, the strong sensitivity and specificity values of LDH and creatinine indicate their potential for use as

inexpensive, readily available diagnostic adjuncts in low-resource settings. Incorporating these tests into routine pediatric malaria and HIV evaluations could enhance early detection of organ dysfunction and guide appropriate management. Second, the study highlights the value of multi-marker diagnostic algorithms that combine hepatic and renal indices with clinical observations. Such integrative approaches could improve case classification, reduce misdiagnosis, and support timely intervention in co-endemic areas.

From a policy standpoint, these results support efforts to strengthen laboratory capacity in regional hospitals to include biochemical profiling as part of integrated malaria–HIV management. National health programs could benefit from developing standardized diagnostic protocols that utilize these markers for risk stratification and monitoring of pediatric patients. Additionally, the moderate predictive performance observed suggests the need for refining biomarker thresholds specific to local populations, considering differences in endemicity, nutritional status, and ART exposure.

For future research, longitudinal studies should explore the temporal dynamics of these biomarkers during acute infection and convalescence to determine their prognostic value for recovery and long-term organ function. Investigations into combined biomarker models integrating inflammatory, metabolic, and hematological parameters could provide a more comprehensive picture of co-infection pathophysiology. Furthermore, evaluating how ART regimens and antimalarial therapies modulate these markers over time would inform safer and more personalized treatment strategies for co-infected children.

This study demonstrated that elevated LDH, creatinine, and ALP are reliable indicators of organ dysfunction in pediatric malaria–HIV co-infection, while GGT, bilirubin, and total protein offer supplementary diagnostic value. The combined use of hepatic and renal biomarkers enhances the understanding of disease severity and provides a practical framework for improving diagnosis and management of co-infected children in malaria-holoendemic regions.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

This study demonstrated that malaria and HIV co-infection in children under five years is associated with significant alterations in renal and hepatic function markers. The elevated biochemical parameters observed among co-infected children suggest multi-organ involvement driven by systemic inflammation and parasitic–viral interactions. The key parameters that were consistently elevated included serum creatinine and urea for renal function, as well as bilirubin, total protein, and several hepatic enzymes for liver function.

6.1.1 Parasitemia Burden and Demographic Characteristics

The findings showed that malaria–HIV co-infected children were generally younger and predominantly female, with higher parasitemia levels compared to their HIV-only counterparts. This pattern may reflect lower immune competence in early childhood, gender-related disparities in healthcare access, and possible immunological differences between sexes. The results underscore the heightened vulnerability of young and female children to malaria infection in the context of HIV-induced immune suppression.

6.1.2 Renal Function Markers

Children co-infected with malaria and HIV exhibited significantly elevated serum creatinine and urea concentrations, indicative of renal impairment. The presence of

hyperuricemia further supports evidence of malaria-associated kidney dysfunction. These findings suggest that renal injury in co-infected children may result from a combination of malaria-induced microvascular obstruction, hemolysis, and immune complex deposition, compounded by HIV-related nephropathy and chronic inflammation.

6.1.3 Hepatic Function Markers

Hepatic dysfunction was evident in the co-infected children, as reflected by elevated serum ALT, AST, GGT, total and direct bilirubin, total protein, albumin, and globulins. These abnormalities likely resulted from hepatocellular damage, cholestasis, and excessive immune activation. The increased synthesis of hepatic enzymes and proteins suggests ongoing hepatocellular stress, likely triggered by malaria pigment deposition and HIV-mediated inflammatory responses.

6.1.4 Validity of Renal and Hepatic Markers in Malaria and HIV Co-Infection Diagnosis

The diagnostic reliability of the measured biomarkers varied across parameters. Elevated serum LDH, creatinine, and alkaline phosphatase (ALP) exhibited higher sensitivity and specificity in detecting co-infection-related dysfunctions, whereas GGT, direct bilirubin, and total protein showed high sensitivity but lower specificity. Although these biomarkers demonstrated weak predictive accuracy (AUCs below 0.70), their combined use could improve diagnostic performance in identifying malaria–HIV co-infection and associated organ dysfunction.

6.2 Recommendations

6.2.1 Recommendations for Action

The higher vulnerability of younger and female children to elevated malaria parasitemia during HIV co-infection calls for strengthened, targeted public health interventions. Healthcare providers in malaria–HIV co-endemic regions should adopt age- and gender-sensitive diagnostic, treatment, and preventive strategies to reduce the burden of malaria among HIV-infected children. Routine presumptive treatment should be discouraged; instead, every febrile illness should be confirmed through laboratory diagnosis using microscopy or rapid diagnostic tests to ensure appropriate case management and minimize overtreatment.

The consistent elevation of renal biomarkers creatinine and urea highlights the need to incorporate renal function assessment into the routine clinical management of pediatric malaria–HIV co-infection. These markers can support early detection of renal complications, monitor disease progression, and guide clinical decision-making, particularly in resource-limited rural healthcare settings.

Similarly, hepatic biomarkers ALT, AST, GGT, bilirubin, albumin, and total protein—should be validated and integrated into pediatric care protocols as part of comprehensive evaluation, monitoring, and prognosis in co-infected children. These enzymes reflect hepatocellular stress and can serve as early indicators of complications requiring medical intervention.

Although the diagnostic accuracy (AUC–ROC) of LDH, creatinine, ALP, GGT, direct bilirubin, and total protein was modest, their high sensitivities and specificities suggest

potential utility in identifying early organ dysfunction. Therefore, these parameters should be considered for inclusion in clinical algorithms for screening and classification of renal and hepatic injury among children co-infected with HIV and malaria, especially at referral facilities and pediatric care centers.

6.2.2 Suggestions for Further Research

Further research should prospectively examine the relationships between parasitemia levels, immune status, and demographic characteristics in children co-infected with malaria and HIV. Future studies should explore additional parasitological indicators, such as malaria pigment-containing neutrophils and monocytes, and integrate variables like immunization history, breastfeeding status, and anthropometric indices to better understand risk patterns in pediatric populations.

Expanded renal profiling is recommended, incorporating markers such as urinary total protein, albumin, glucose, ketone bodies, bilirubin, hemoglobin, creatinine clearance, and glomerular filtration rate, along with electrolyte levels (sodium, potassium, chloride). This would provide deeper insight into the nature and progression of renal impairment associated with co-infection.

Further hepatological assessment should include parameters such as fibrinogen, prothrombin time, ferritin, carbohydrate and lipid profiles, and enzymes like 5′-nucleotidase and cholinesterase. Such studies would help elucidate the complex hepatic pathophysiology of malaria–HIV co-infection.

Lastly, larger, multicenter clinical validation studies on biomarkers such as LDH, creatinine, ALP, GGT, direct bilirubin, and total protein are necessary to confirm their diagnostic and prognostic utility. Establishing standardized cut-off values specific to pediatric malaria–HIV co-infection will improve clinical accuracy and enhance evidence-based management in endemic settings.

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APPENDICES

APPENDIX I : INFORMED CONSENT TO PARTICIPATE IN THE STUDY

Study title: PARASITEMIC DISTRIBUTION WITH BIOMARKERS OF *PLASMODIUM FALCIPARUM* AND HIV-1 CO-INFECTION IN CHILDREN BELOW FIVE YEARS, WESTERN KENYA

Background

You are being asked to allow your child to participate in a research. Before you decide, it is important for you to understand the research concept, the risks and benefits of the study to your child and to the community as a whole.

The aim of this study is to understand how laboratories make the diagnosis of malaria without the use of other malaria indices and how accurate this is in the diagnosis. And how these methods can be made more accurate especially in this era of many other diseases. The study will try to understand the value of various clinical laboratory malaria indices in malaria diagnosis.

Study procedure

The research will ask you several questions about your child's illness and examine your child. Only those children with fever are being selected. It will take about 10 minutes to complete this session. The child will be sent to the lab where a blood sample to test for malaria and other blood variables will be taken. Then your child will go through the usual hospital procedure for the treatment. The result will be communicated to the clinician who saw your child at the start.

Risks

Your child will experience some pain when the blood sample is being taken. Sterile procedure will be used.

Benefits

The results of the blood tests will be communicated to your doctor for the benefit of the child. This study will also help come up with a more accurate way of making a diagnosis of clinical malaria.

Confidentiality

All information obtained will be confidential. No names will be used.

Voluntary participation

It is up to you to decide whether your child takes part in the study or not. Refusal to participate or withdrawal from the study will invoke no penalty. It will not affect your relationship with the investigators or the hospital staff and your child will continue with the normal treatment.

Contacts

In case of any questions please contact the principal investigator with these details:

Fidelis A. Mambo
Tel: 0723501979/0733501977
Email: fmambo@mmust.ac.ke/fidelimambo88@yahoo.com

Consent

By signing this consent, I have read/been read to the information in this form and had an opportunity to ask questions. I have understood the purpose and the procedure of the study. I voluntarily accept my child to take part in the study.

(Printed name of parent or guardian and signature/finger print)
Date…….

(Investigators name and signature)…….
Date…….

APPENDIX II : GENERAL SICK CHILD OUT PATIENT CLINIC DATA COLLECTION SHEET

Study participant number……

Date of data collection……

A. Nursing Station Demographic data

1. Age (Date of birth)……

( ) 2 – 3 years ( ) >3 <4 years ( ) > 4 < 5 years

2. Sex:- ( ) Male ( ) Female

3. Resident:- ( ) Kakamega county ( ) Other counties (specify)……

4. Informant:- ( ) Mother ( ) Father ( ) Relative ( ) Other (specify)…….

B. Anthropometric measurements

1. Height (cm)……
2. Weight……. (kg) ( ) below normal for age

( ) appropriate for age ( ) above normal for age

3. Mid upper circumference:- ( ) < 12 ( ) 12 – 13 ( ) > 13

C. Vital disease signs

1. Temperature……^{0}C ( ) >37.5 – 39 ( ) 39.1 – 41 ( ) >41

2. Respiratory Rate…….bpm ( ) below 40bpm ( ) above 40bpm

3. Pulse rate……..bpm ( ) below 80bpm ( ) 80 – 120 ( ) above 120bpm

4. Blood pressure……..

D. Health seeking behavior

1. Referral: ( ) Yes ( ) No

2. If Yes from where

( ) Health centre
( ) Dispensary
( ) Private clinic
( ) Self
( ) Other (specify)…….

3. Prior use of antimalarials for this episode ( ) Yes ( ) No
4. If yes which one or description…….

( ) AL
( ) SP
( ) CQ
( ) Herbal
( ) Others (specify)…….

5. If yes, what was the source of the medication?

( ) Hospital ( ) Health centre ( ) Dispensary ( ) Local pharmacy/retail shop
( ) Others (specify)……..

6. Prior use of antipyretics ( ) Yes ( ) No
7. Recent history of malaria treatment in the last 3 months ( ) Yes ( ) No
8. Use of malaria preventive measures in the last two weeks ( ) Yes ( ) No

If Yes, which one

( ) Bed net
( ) Repellants
( ) Medicines
( ) None
( ) Others (specify)……

Recent history of travel ( ) Yes ( ) No
If Yes, specify…….

E. Laboratory results

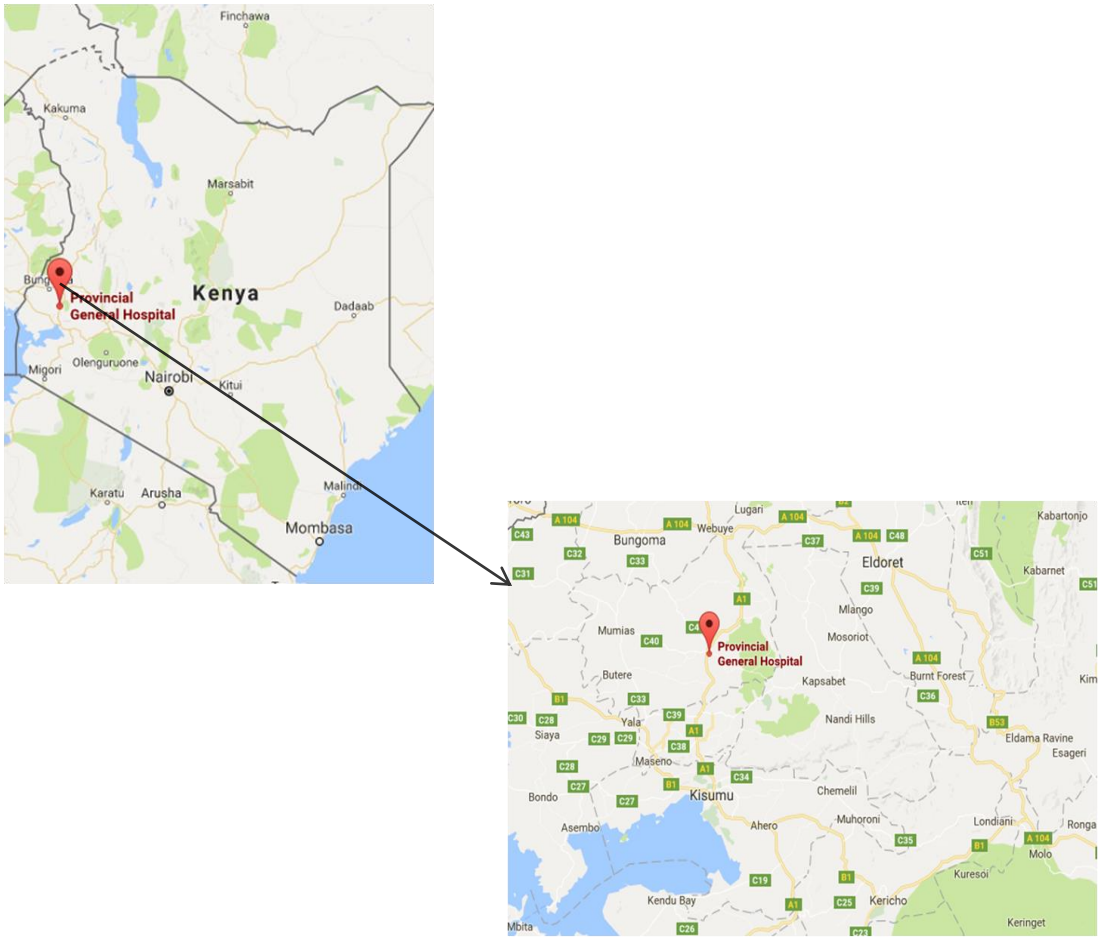
1. Blood slide for malaria parasite ( ) Positive ( ) Negative

2. OptiMAL malaria test results ( ) Positive ( ) Negative

Positive ( ) Pf ( ) Po ( ) Pf/Po combined

3. Chemistries (Machine printouts)

APPENDIX III : MAP OF STUDY SITE



APPENDIX IV : IERC CLEARANCE

MASINDE MULIRO UNIVERSITY OF SCIENCE AND TECHNOLOGY

Tel: 056-31375
Fax: 056-30153
E-mail: ierc@mmust.ac.ke
Website: www.mmust.ac.ke

P. O. Box 190,
50100.
Kakamega,
KENYA

Institutional Ethics and Review Committee (IERC)

REF: MMU/COR: 403012 Vol 6 (01)

Date: March 23rd, 2022

To: Mr. Fidelis Arambe Mambo,

Dear Sir.,

RE: POTENTIAL BIOMARKERS FOR MALARIA PARASITOSIS IN HUMAN IMMUNODEFICIENCY VIRUS EXPOSED UNDER FIVE YEARS CHILDREN IN KAKAMEGA COUNTY, KENYA.

This is to inform you that the ***Masinde Muliro University of Science and Technology Institutional Ethics and Review Committee (MMUST-IERC)*** has reviewed and approved your above research proposal. Your application approval number is **MMUST/IERC/027/2022.** The approval covers for the period between ***March 23rd, 2022*** to ***March 23rd, 2023.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including informed consents, study instruments, MTA will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MMUST-IERC.***
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MMUST-IERC*** within 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MMUST-IERC*** within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MMUST-IERC.***

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours Sincerely,

Prof. Gordon Nguka (PhD)
Chairperson, Institutional Ethics and Review Committee

Copy to:
- The Secretary, National Bio-Ethics Committee
- Vice Chancellor
- DVC (PR&I)

APPENDIX V : NACOSTI LICENSE

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **202770**

Date of Issue: **29/March/2022**

RESEARCH LICENSE

This is to Certify that Mr.. Fidelis Arambe Mambo of Masinde Muliro University of Science and Technology, has been licensed to conduct research in Kakamega on the topic: POTENTIAL BIOMARKERS FOR MALARIA PARASITOSIS IN HUMAN IMMUNODEFICIENCY VIRUS EXPOSED UNDER FIVE YEARS CHILDREN IN KAKAMEGA COUNTY, KENYA for the period ending : 29/March/2023.

License No: **NACOSTI/P/22/16599**

202770

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Director General
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APPENDIX VI : SIMILARITY REPORT

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Certificate of Plagiarism Check for Dissertation

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