

**DETERMINATION OF PROHYLACTIC ACTIVITY OF HIV-PROTEASE  
INHIBITORS AND THEIR INTERACTIONS WITH ANTIMALARIALS.**

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**DECLARATION**

Student's declaration

This proposal is my original work and has not been presented for the award of a degree in any other university.

Signature.....


Date.....26/9/2013

Name: Dominic Thuku Mburu

156/21458/2012

Supervisor's declaration

This proposal has been submitted with our approval as university supervisor.

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## ABSTRACT

Malaria is a leading cause of morbidity and mortality in sub-Saharan Africa with children under 5 years and pregnant women at the highest risk. Over years, there has been an enhanced effort all over the world to find an effective drug or a vaccine against the protozoa. However most antimalarial drugs have been countered by increased resistance by parasite to the drugs rendering them ineffective. Among potential targets for new modes of chemotherapy are malarial proteases, which appear to mediate processes within the erythrocytic malarial life cycle, including the rupture and invasion of infected erythrocytes and the degradation of hemoglobin by trophozoites. Aspartic proteases play a key role in the biology of malaria parasites and human immunodeficiency virus type 1 (HIV-1). Most antivirals used in HIV therapy target these proteases that cleave a viral polyprotein precursor into individual mature proteins. *Plasmodium falciparum*, the most virulent human malaria parasite, expresses a number of aspartic proteases, known as plasmepsins. The convergence in dependence of the two parasites on the aspartic proteases makes them similar targets for chemotherapy. Malaria and AIDS share a wide geographical overlap in occurrence both being more prevalent in sub-Saharan Africa and the interaction of the two diseases results in co-infection which clearly has major public health implication. Given their known dependence on proteases, it appears the protease inhibitors (PI) in the treatment certainly exert a certain degree of antimalarial effect. This has also been demonstrated in *in vitro* and *in vivo* with the most potent compound, lopinavir, active against parasites at concentrations well below those achieved by ritonavir-boosted lopinavir therapy. The objective of this study will therefore be to assess the antimalarial activity of protease inhibitors in mice models, and assess if they have protective role when taken before malaria infections and whether their co-use with the malarial drugs has any interactions that would affect their utilization. Three HIV protease inhibitors Ritonavir, Saquinavir mesylate and Nelfinavir mesylate hydrate (Sigma Aldrich) currently available in Kenyan markets will be used. Mice (5 for each group) infected with *Plasmodium berghei* will be treated with each of the protease inhibitors (PIs). Parasitaemia will be determined every 3 days by microscopy and cure/survival rate over a period of 30 days recorded. Another group will be treated with a combination of ritonavir and conventional antimalarial drug artemether-lumefantrine (coartem) to assess their interaction and another prophylactic assay. The effects of inhibitors on *P. berghei* morphology (shape and cell integrity) will be assessed by light microscopy of Giemsa-stained smears. Data will be entered in excel spreadsheet and analyzed with student's T-test and ANOVA to determine whether the observed differences between the mean parasitaemia of the treatment groups is significant and testing significance within and between groups respectively. Statistical significance will be considered at  $P < 0.05$ . Results of this study will generate useful information that can be used by malaria control programs especially in areas where both HIV/AIDS and malaria are endemic hence co-infection is high.