

MOLECULAR ASSOCIATION OF POLYMORPHISMS IN *PLASMODIUM FALCIPARUM* DHFR/DHPS GENES AND PYRIMETHAMINE/SULFADOXINE RESISTANCE.

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Chloroquine resistance is well established in Africa and, the synergistic antifolate fixed combination, sulfadoxine-Pyrimethamine (SP) has become the drug of choice for the treatment of uncomplicated *falciparum* malaria. Pyrimethamine (PYR) is a competitive inhibitor of dihydrofolate reductase (DHFR) while sulfadoxine (SDX) inhibits dihydropteroate synthase (DHPS); key enzymes in the biosynthesis of DNA and some proteins. Several reports have indicated that point mutations in DHFR (at codon 108,51, 59) [triple mutant DHFR] and in DHPS (at codon 437, 540) [double mutant DHPS] are associated with clinical SP resistance. We sought to assess the impact of these markers in relation with clinical SP efficacy on *P. falciparum* samples collected in Kilifi between 1999-2000 as part of a broad study meant to evaluate the clinical efficacy of SP-Artesunate combination. The samples were collected before treatment and within 28 days of treatment failure. Detection of the DHFR and DHPS point mutations was done using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism method. Our results showed a rise in Tp-DHFR from 54.55% before treatment to 74.36% after treatment. The same trend was observed with Db-DHPS rising from 61.70% before treatment to 88.37% after treatment. Only 2.27% Wt-DHFR was found before treatment while there was none after treatment; indicating its clearance in the course of treatment. A decrease of Wt-DHPS from 34.04% before treatment to 6.98% after treatment was also observed. The Tp- DHFR - Db-DHPS genotype combination (the genotype strongly associated with SP resistance) showed a substantial increase from 32.56% before treatment to 64.86% after treatment. In conclusion, our findings confirm a high selection pressure for DHFR/DHPS mutations in the course of treatment with SP and that Tp-DHFR-Db-DHPS genotype combination is associated with SP resistance as previously reported.