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HIV treatment reduces risk of malaria recurrence in children, study shows

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A combination of anti-HIV drugs has been found to also reduce the risk of recurrent malaria by nearly half among HIV-positive children, according to researchers supported by the National Institutes of Health.

The combination of protease inhibitors lopinavir and ritonavir contributed to an overall reduction of 40 percent in the rate of malaria among a group of HIV-positive infants and children up to 6 years old in Uganda who were also being treated with anti-malarial drugs. This reduction was in comparison to malaria incidence among children receiving a drug treatment of one of a class of drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Protease inhibitors interfere with the reproduction of HIV by blocking the protease enzyme of HIV. The protease inhibitor combination used in the study did not appear to inhibit an initial bout of malaria—but reduce the chances of a recurrence of the disease following a successful treatment.

The researchers found that blood levels of anti-malarial drugs were higher in children who had received the protease inhibitors, which may help explain their effectiveness at preventing malaria's return.

"It's possible that these protease inhibitors prevent antimalarial drugs from breaking down or have some other additive effect against the malarial parasite," said Lynne Mofenson, M.D., chief of the Pediatric, Adolescent, and Maternal AIDS Branch at the Eunice Kennedy Shriver

National Institute of Child Health and Human Development, the NIH institute that funded the study. "Laboratory studies also suggest that protease inhibitors can block the malaria parasite outright. Finding out why this drug combination is effective is an area for further study."

Previous studies have shown that the lopinavir–ritonavir combination also is more effective for treating HIV-positive infants than widely used treatment regimens based on the medication nevirapine.

The NNRTI nevirapine is the first-line treatment for HIV recommended by the World Health Organization for children in developing countries. It is less expensive than the protease inhibitor combination and, unlike the protease inhibitors, does not need refrigeration. Compared to nevirapine, the liquid formulation of the protease inhibitor combination is also unpleasant tasting. However, recent changes in the protease inhibitor formulation may overcome these barriers to expanding its use in resource poor settings, Dr. Mofenson said.

"New formulations have been developed for the drug so that it can be sprinkled on food, tastes better, and doesn't need refrigeration," she said. "This may help where it is needed most."

First author Jane Achan, MMed, of Makerere University and the Infectious Diseases Research Collaboration, in Uganda, collaborated with colleagues in Uganda and at the University of California, San Francisco.

Their findings appear in the *New England Journal of Medicine*.

More than 170 HIV-positive infants and children participated in the study. They received either an NNRTI (nevirapine for children under age 3, efavirenz for children over age 3) or the protease inhibitor-based treatment. In addition, the children received insecticide-treated nets to

keep mosquitoes away while they slept, vitamins, a clean source of water, and medication to prevent infection with the malaria parasite, which is transmitted by mosquitoes.

Even with these measures, the researchers found that the children's risk of developing malaria in the first six months of their anti HIV treatment was greater than 40 percent. Although the risk was slightly higher in the nevirapine-treated group, the difference was not significant statistically.

However, of the children who developed malaria and were successfully treated for it during the study, 41 percent of those taking an NNRTI developed another case of malaria within 28 days of clearing their system of the parasite the first time. In contrast, only 14 percent of those on the combination lopinavir–ritonavir treatment developed another case of malaria within this time period.

When comparing the two groups over a 63-day period, the researchers found that 54 percent of the NNRTI group had a recurrence of malaria, compared with 28 percent of the group taking the lopinavir–ritonavir treatment.

In addition, tests conducted one week after the start of malaria treatment showed that blood levels of an anti-malaria drug were higher among children receiving the protease inhibitor combination than among their counterparts taking the nevirapine-based treatment.

"The finding that this protease inhibitor combination not only appears more effective at treating HIV than NNRTIs, but also protects against malaria recurrence, merits its consideration for children living in areas where malaria is rampant," Dr. Mofenson said.

Provided by NIH/National Institute of Child Health and Human

Development