Prevention of mother-child transmission programs work but infants need checking for drug resistance

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Genetic mutations that lead to antiretroviral (the drugs used to treat HIV/AIDS) resistance in HIV-infected infants may develop as a result of exposure to low doses of maternal antiretroviral drugs via breastfeeding rather than being acquired directly from the mother. This key finding from a study by Clement Zeh from the US Centers for Disease Control and Prevention, Kisumu, Kenya, and colleagues, published in this week's *PLoS Medicine,* is important as it may impact the choice of drug regimen given to HIV-infected breastfeeding mothers and their infected infants—an effective intervention which has been shown to substantially reduce the overall rate of mother-to-child transmission of the HIV virus.

The authors conducted a secondary analysis (or substudy) of The Kisumu Breastfeeding Study—a trial in Kisumu, Kenya by Timothy Thomas and colleagues from the Kenya Medical Research Institute (KEMRI) and CDC, Kisumu, Kenya, and colleagues also reported in this week's PLoS Medicine. The Kisumu Breastfeeding Study assessed the safety and transmission rates of a triple-antiretroviral regimen (zidovudine, lamivudine, and either nevirapine or nelfinavir) given to HIV-infected women a few weeks before giving birth (34 wk gestation) through 6 months of breastfeeding. The study documented transmission rates of 7% at 24 months, most of them due to transmission in-utero or during delivery, which is considerably lower than the 25% - 48% transmission rates reported in the absence of antiretrovirals. The authors concluded that this combination of drugs was safe and feasible in

resource-limited settings.

In their secondary analysis, Clement Zeh and colleagues investigated the possible causes of the emergence of maternal ARV-associated resistance among the 24 infants who were infected with HIV either at delivery or during 6 months of breastfeeding and thus exposed to maternal ARVs.

The authors took regular blood samples from these infants and from their mothers to look for the presence of HIV drug resistance mutations. The authors found that various mutations were present in samples taken from all the HIV-positive infants whose mothers who had received nelfinavir but in only half of those taken from infants whose mothers who had received nevirapine. However exposure to nevirapine resulted in a wider range of ARV resistant mutations. In contrast, most of the mothers of HIV-positive infants had no HIV drug resistance mutations, and only one mother-infant pair had an overlapping pattern of HIV drug resistance mutations. This pattern of mutations suggests that drug resistance most likely arose through exposure of the infants to low levels of ARVs in breast milk rather than through mother-to-child transmission of drug-resistant HIV virus.

These findings need further confirmation through future studies but suggest that infants exposed to antiretroviral drugs through breast milk—a situation that may become increasingly common given the encouraging results of The Kisumu Breastfeeding Study and similar trials that show a reduction in mother-to-child-transmission—should be carefully monitored for HIV infection. Providers should consider the mother's regimen when choosing treatment for infants who are found to be HIV infected while breastfeeding and closely monitor response to therapy.

Clement Zeh and colleagues say: "The low mother-to-child HIV transmission rates observed in the trial support the role of triple-

combination maternal antiretroviral therapy as a successful [Prevention of Mother-to-Child Transmission] intervention among breastfeeding HIV-infected mothers. However, the data from this secondary analysis suggest that ingestion of antiretroviral drugs through breast milk may have contributed to the emergence of HIV drug resistance mutations in the infants, as we observed an increasing frequency of infants with HIV drug resistance mutations over the first 6 months of life when maternal antiretroviral therapy was given during breastfeeding."

They add: "[Prevention of Mother-to-Child Transmission] programs providing maternal antiretroviral therapy during breastfeeding and those caring for infants exposed to antiretroviral through breast milk will need to be cognizant of this issue and consider monitoring these infants more closely and tailoring their treatment accordingly."

More information: Zeh C, Weidle PJ, Nafisa L, Lwamba HM, Okonji J, et al. (2011) HIV-1 Drug Resistance Emergence among Breastfeeding Infants Born to HIV-Infected Mothers during a Single-Arm Trial of Triple-Antiretroviral Prophylaxis for Prevention of Mother-To-Child Transmission: A Secondary Analysis. PLoS Med 8(3): e1000430. doi:10.1371/journal.pmed.1000430