Prolonged nevirapine in breast-fed babies prevents HIV infection but leads to drug-resistant HIV

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Babies born to HIV-positive mothers and given the antiretroviral drug nevirapine through the first six weeks of life to prevent infection via breast-feeding are at high risk for developing drug-resistant HIV if they get infected anyway, a team of researchers report. But the investigators highlight the proven superiority of the six-week regimen in preventing mother-to-child HIV transmission in breast-fed infants.

In a study led by researchers at Johns Hopkins Children's Center, risks of drug resistance in the first year of life were compared in Indian infants getting a standard single dose of nevirapine at birth and those on the six-week regimen.

"While extended nevirpaine prophylaxis dramatically reduces HIV transmission during the first six weeks of life, our data show that if infection does occur, it will most likely be with strains resistant to nevirapine, making HIV much harder to treat early with nevirapine," says senior investigator Deborah Persaud, M.D., a pediatric HIV expert at Hopkins Children's. "But until other interventions become available, the extended nevirapine regimen remains a reasonable way to prevent infections through breast-feeding."

Published in the Jan.1 issue of *Public Library of Science One* (*PLoSOne*), the research report emphasized that in the developing world especially, where bottle feeding is not safe, too expensive or simply unavailable, the

extended nevirapine therapy remains one of the best ways to reduce mother-to-child transmission of HIV through breast milk.

Given the high risk of death from HIV in infancy, the benefits of fewer infections still outweigh the risk of increased resistance, the researchers conclude.

The findings also suggest that because of their higher risk for acquiring resistant HIV strains, infants given extended courses of nevirapine—should they get infected—should receive treatment with protease inhibitors (PIs), which are effective against nevirapine-resistant strains.

"In the developing world testing for resistance is not available or too expensive," Persaud says, "so if extended nevirapine regimens become widespread, PIs should be made available as a first line of treatment early on for all infants who get infected despite prophylaxis."

The new report comes on the heels of two separate multi-center studies from Johns Hopkins and other institutions, published in 2008, showing that a six-week regimen with nevirapine or a 14-week regimen with nevirapine slashed the risk of HIV infection from breast-feeding by 46 percent and 66 percent, respectively.

For the current study, investigators analyzed samples from 74 Indian babies infected with HIV before, during or after birth. Of the 74 infants, 22 were infected before birth, 19 were infected during birth or during early breastfeeding (three to six weeks after birth) and 33 were infected during late breast-feeding (around six months after birth). Of the 19 infants infected through breastfeeding in the first six weeks of life, four were given daily nevirapine for six weeks, and 15 received a single dose at birth. All four babies on extended nevirapine developed resistant strains of the virus, while only four of the 15 given a single dose tested

positive for resistant strains after infection.

It is important to keep in mind that while the risk of resistance is higher with extended nevirapine regimens once infection occurs, the risk of acquiring HIV with extended regimens is dramatically reduced, the investigators say. Thus, in the long run, extended nevirapine regimens do not lead to more resistant cases than the single-dose regimens because single-dose regimens also carry some risk of resistance and are also less effective in preventing new infections.

Indeed, when researchers compared resistance among infants infected during late breast-feeding, the gap in resistance risk virtually disappeared. Fifteen percent of the 13 infants given extended nevirapine developed resistance, and so did 15 percent of the 20 infants who received a single dose of the drug.

When investigators used more sensitive assays to detect nevirapine-resistant mutations that are normally not detected by standard tests, the proportion of infants with resistant strains who had received single-dose nevirapine went up from 38 percent to 59 percent among the 29 infants who got the single dose, but remained unchanged in the group receiving the six-week regimen, 92 percent of 12. Likewise, the proportion of infants testing positive for resistance went up in the group infected after six weeks of age. In that group, 31 percent of 13 infants on the extended regimen tested positive for resistant strains, and 40 percent of 20 infants who got the single dose had resistant strains. However, researchers say, the clinical significance of mutations that are not detected by standard testing remains unclear.

The infants in this trial were infected with HIV subtype C, but previous studies have shown that the six-week regimen increases resistance in infants who get infected with other HIV subtypes as well.

Despite the risk of HIV transmission, breast-feeding for at least six months is widely encouraged by the World Health Organization (WHO) and other organizations as a proven factor in better infant survival. In 2007 alone, 420,000 infants acquired HIV in utero, during birth or during breast-feeding, according to WHO estimates. HIV infection is estimated to occur in 1 out of 10 breast-fed infants, with many of the infections occurring in the first six to 14 weeks of life.

Source: Johns Hopkins Medical Institutions