Drug used to prevent HIV transmission from mother to child damages DNA

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HIV transmission from mother to child can occur in utero, during labor or from breastfeeding. If left untreated, approximately 25 percent of newborns exposed to the virus from their infected mothers will become infected themselves and potentially develop AIDS. Fortunately, antiretroviral drug combinations, which typically include AZT (zidovudine), a nucleoside reverse transcriptase inhibitor (NRTI), have reduced the rate of transmission from mother to child to less than 2 percent in infants who are not breast fed.

NRTIs work by inhibiting the viral reverse transcriptase and by incorporating into the viral DNA and terminating nascent strands, thus preventing the virus from duplicating. However, previous research has shown that NRTIs also incorporate into the DNA of host cells, causing damage that could have long-term health consequences for those exposed to the drugs.

Two new animal studies have examined the cancer-causing effects of transplacental exposure to AZT in mice and rats and found increased rates of tumors and tumors with gene changes that frequently occur in human cancer. In addition, two human studies are the first to observe the induction of mutations and large scale chromosomal damage in red blood cells of newborns exposed to NRTIs in utero.

These, and other, studies were published in April 2007 in a special issue of *Environmental and Molecular Mutagenesis* that examines the latest research on DNA damage and potential health risks related to the use of

NRTIs. Besides the effects of NRTIs on nuclear DNA and cancer risk, the issue also contains recent findings on the toxicity of these drugs toward mitochondrial DNA. *Environmental and Molecular Mutagenesis*, the official journal of the Environmental Mutagen Society, is published by John Wiley & Sons, Inc.

Researchers led by Dale M. Walker of Experimental Pathology Laboratories in Herndon, VA, administered AZT in varying doses to female mice and rats during the last 7 days of gestation and examined the tissue of their offspring two years later. They found clear evidence of an AZT-induced increase in the incidence of hemangiosarcoma (cancer originating in cells that line the blood vessels) in male mice and mononuclear cell leukemia in female rats.

There was also some evidence of increased liver cancer and reproductive tumors. "Although the implications of these findings for the long-term health of human children exposed tranplacentally to AZT are uncertain, the possibility of increased cancer risk for a subset of these children in mid and late adulthood appears highly plausible," the authors state. The carcinogenic effects of AZT were further demonstrated by a study on mice led by Hue-Hua Hong of the National Institute of Environmental Health Sciences in Research Triangle Park, NC. This study found mutations in the K-ras and p53 cancer genes that are often mutated in human lung tumors. The development of lung cancer in these mice suggests that the incorporation of AZT or its metabolites into DNA, oxidative stress, and genomic instability may be the contributing factors to the pattern of mutations observed in the study, according to the authors. They conclude, "The cumulative mutagenesis data suggest that infants exposed transplacentally to AZT may be at increased risk for cancer as they age."

In the first of the two human studies, researchers led by Patricia A. Escobar of the University of Pittsburgh, in Pittsburgh, PA, measured

DNA damage caused by AZT in the blood of newborns. They found increased frequencies of glycophorin A mutations in the red blood cells of newborns who had been exposed to AZT plus lamivudine (another type of NRTI) in utero, and these changes persisted for the most part through one year of age. The researchers note that although the combination of the two NRTIs is more effective at preventing transmission of HIV from mother to fetus, it is also more genotoxic than AZT alone. They conclude that "there is a need for careful monitoring of the future health of children who received peripartum AZT-based therapies, the development of new safer NRTIs, and the identification of antimutagenic drugs that will mitigate the side effects of NRTI-based highly active antiretroviral therapy."

In the second study involving humans, researchers led by Kristine L. Witt of the National Institute of Environmental Health Sciences in Research Triangle Park, NC measured the frequency of immature red blood cells (reticulocytes; RET) containing micronuclei (MN), indicators of chromosomal damage, in blood samples of HIV-infected women and their infants exposed to antiretroviral drugs during pregnancy. Most, but not all, of the prenatal treatment regimens in this study included AZT. At birth, the researchers observed ten-fold increases in the frequencies of micronucleated reticulocytes (MN-RET) in the women and infants whose prenatal drug regimen included AZT. No increases were detected in the women and infants who did not receive prenatal AZT. The frequency of MN-RET in the AZT-exposed newborns decreased over the first 6 months of life to levels seen in nonexposed infants. These findings imply a strong potential for AZT-induced genetic damage in the developing fetus. The authors state "We are concerned about the long-term health implications for these infants because the MN increases noted in this study add to the growing body of evidence that ZDV [AZT] readily induces genetic damage," The authors conclude by emphasizing that they do not advocate eliminating the use of AZT in the treatment of HIV because it is highly effective in preventing mother to child

transmission of the virus. However they recommend long-term monitoring of AZT-exposed infants who are HIV uninfected.

Source: John Wiley & Sons