Antiretroviral therapy is highly effective in reducing vertical transfer of HIV infection, sparing many thousands of children premature death from AIDS. However, accumulating evidence indicates that perinatal exposure to antiretroviral agents may place them at elevated risk of developing cancer later in life, owing to potential carcinogenic effects of the agents. An initial experimental evaluation clearly demonstrated that AZT was a genotoxin and transplacental carcinogen of intermediate potency in CD-1 mice. This issue of Environmental and Molecular Mutagenesis contains reports of recent studies designed to confirm and extend earlier findings, and to provide further perspective that will facilitate development of strategies through which the adverse effects might be mitigated. The studies focused on various aspects of the genotoxicity and carcinogenicity of antiretroviral agents, including: mutagenesis in several in vitro experimental systems; mutations and clastogenic effects induced by transplacental administration in mice; transplacental carcinogenesis and mutations in oncogenes and tumor suppressor genes in tumors of mice; and genotoxicity and clastogenicity following perinatal exposure of HIV-infected mothers and their uninfected infants. Collectively, the results obtained provide convincing biological plausibility for the postulate that perinatal exposure to nucleoside analogs puts children at elevated risk of developing cancers later in life. They further emphasize the importance of continued surveillance of these children for increased cancer risk and indicate a need for efforts to develop less genotoxic alternative agents. Environ. Mol. Mutagen. 48:000–000, 2007.

Key words: HIV; AZT; genotoxicity

The incidence of several cancers is greatly increased in persons infected with HIV [IARC, 2000]. Non-Hodgkin lymphoma incidence in AIDS patients is increased by nearly 100-fold, the majority of tumors being of B cell origin. Available evidence suggests that the increase may involve coinfection with Epstein-Barr virus and results from dysregulation of immune function caused by HIV infection. Greatly increased risk for Kaposi sarcoma also is associated with HIV infection. Effective combination therapy has been shown to improve immunocompetence, which in turn results in reduced risk for Kaposi sarcoma and, to a lesser extent, non-Hodgkin lymphoma. While increased incidence of these cancers is a direct consequence of the infection, there is a possibility that offspring of HIV-infected mothers also may be at elevated cancer risk emanating from therapeutic measures designed to prevent maternal transfer of the virus. Nucleoside reverse transcriptase inhibitors such as zidovudine (AZT) are essential components currently used in the highly effective combination therapy referred to as highly active antiretroviral therapy (HAART).

The efficacy of antiretroviral therapy in reducing maternal HIV transmission has been shown in many studies at the population level. In one representative study, HIV transmission from mother to infants was found to be 20% in women not receiving prenatal therapy; 10% in those treated with AZT monotherapy; and 1.2% in those treated with multiple agents. The protective effect increased with the complexity and duration of the regimen [Cooper et al., 2002]. Treatment protocols used in such studies reflect current guidelines for therapy to minimize maternal transmission of HIV, as described in the pediatric AIDS clinical trials group (PACTG) 076 AZT regimen (http://www.pactg.org).
www.hivatus.org/atisinfo.html). This involves administration of AZT to pregnant HIV-infected women, at a daily dose of 500 mg, initiated at 14–34 weeks of gestation and continued throughout the pregnancy; intravenous infusion of 1 mg/kg body weight during labor; and oral administration of AZT to the neonate at 2 mg/kg every 6 hr beginning at 8–12 hr after birth and continuing for the first 6 weeks of life. Abundant additional evidence demonstrates that this type of therapy is highly effective in reducing vertical transfer of HIV infection, sparing many thousands of children premature death from AIDS. However, accumulating evidence indicates that the perinatal exposure associated with this type of treatment may place these children at elevated risk of developing cancer later in life, owing to the potential carcinogenic effects of the therapeutic agents.

Direct evidence in humans regarding the possible carcinogenicity of antiretroviral agents is fragmentary and inconclusive, since available data have emanated from trials in adult HIV-infected patients designed to establish therapeutic efficacy, not to assess cancer risk. Interpretation of such data is compromised by multiple factors, including limited survival time, small numbers of participants, insufficient information regarding immunodeficiency, and under-reporting of cancer occurrence [IARC, 2000]. A recent multicenter study [European Collaborative Study, 2003] investigated the association between antiretroviral therapy exposure, perinatal problems, and major health events later in life. Median follow-up was 2.2 (0–15.9) years. Among 1,008 infants exposed to therapy at any time, 90% were exposed antenatally, 83% neonatally, and 74% both antenatally and neonatally. Exposure was not significantly associated with a pattern or prevalence of congenital abnormalities or low birth weight, but anemia in early life and prematurity were associated with antenatal exposure to combination therapy, with or without a protease inhibitor. There was no evidence of an association with clinical manifestations suggestive of mitochondrial abnormalities. Although the absence of serious adverse effects in this large cohort of uninfected children exposed to prophylactic antiretroviral therapy in the short to medium term is reassuring, the period of follow-up was too short to permit conclusions with respect to cancer risk.

Features of the current perinatal therapeutic regimen are pertinent in the context of the initial experimental evaluation of AZT transplacental carcinogenicity in mice [Olivero et al., 1997]. In that experiment, pregnant CD-1 mice received 0, 12.5, or 25 mg AZT by gavage on days 12–18 of gestation. Offspring were not treated further. No neoplasms were found in offspring necropsied after 3 or 6 months, but after 1 year, dose-related increases in liver and lung tumors were observed in both males and females, together with an increased incidence of neoplasms of the ovary, uterus, and vagina in females. Incorporation of AZT into nuclear and mitochondrial DNA was detected in multiple organs of transplacently-exposed mice, and the incorporation was associated with telomere shortening in liver and brain. These results clearly demonstrated that AZT was a genotoxin and transplacental carcinogen of intermediate potency in CD-1 mice, and focused increased attention on the subject over the past decade. This issue of *Environmental and Molecular Mutagenesis* contains reports of recent studies designed to confirm and extend earlier findings, and to provide further perspective that will facilitate development of strategies through which the adverse effects might be mitigated. These studies have focused on various aspects of the genotoxicity and carcinogenicity of antiretroviral agents, including: mutagenesis in several in vitro experimental systems; mutations and clastogenic effects induced by transplacental administration in mice; transplacental carcinogenesis and mutations in oncogenes and tumor suppressor genes in tumors of mice; and genotoxicity and clastogenicity following perinatal exposure of HIV-infected mothers and their uninfected infants. The following is a summary of the major findings produced by these studies.

Wang et al. [2007] examined the genotoxicity of AZT in cultured mouse lymphoma (L5178Y) cells. The drug caused a significant, dose-related increase in mutant frequency at the thymidine kinase (tk) locus in both large and small colony mutants following 24 hr of treatment. Mutants were analyzed for loss of heterozygosity (LOH) using a heteromorphic microsatellite locus located in the tk allele together with eight other microsatellite markers spanning the entire mouse chromosome 11, and real-time PCR was used to analyze gene dosage. Results showed that more mutants induced by AZT than spontaneous mutants contained tk LOH, and induced mutants also showed distinct chromosome 11 LOH patterns. The mutation spectrum of induced mutants was significantly different from that of spontaneous mutants, and also contained more deletions and fewer intragenic mutations. Collectively, these findings showed that in this cell type AZT induced primarily LOH mutations, a large number of which resulted from deletions.

Carter et al. [2007] determined the relative mutagenic potencies of the nucleoside analogues didanosine (ddI), lamivudine (3TC), and stavudine (d4T) (see [Olivero, 2006] review for structures), alone or in combination, on cell survival and mutagenesis of the hypoxanthine phosphoribosyltransferase (HPRT) and thymidine kinase (TK) genes in cultured human lymphoblastoid TK6 cells. Three-day treatments with ddI, 3TC or d4T + 3TC at concentrations of 0–300 μM, or with d4T or d4T + 3TC at 100–300 μM resulted in significant increases in mutant frequencies at both loci. Comparison of these data to mutagenicity studies of other nucleoside reverse transcription inhibitors indicate that the relative mutagenic potencies for all drugs tested to date are: AZT + ddI > d4T + 3TC > AZT + 3TC = AZT + 3TC + abacavir > AZT > d4T + 3TC > 3TC > d4T ≥ abacavir. The authors inter-
interpret these data to indicate that some nucleoside analogues or combinations may impose less health risks than others for humans based on their lesser mutagenicity.

The in vivo mutagenicity of antiretroviral agents has been investigated by several groups. Von Tungeln et al. [2006] studied transplacental drug transfer and frequencies of tk and hpert lymphocyte mutants and of micronuclei in peripheral blood cells of mice treated with AZT and 3TC. Mice were treated daily by gavage with each drug alone or in combination from gestational day 12 to parturition. AZT was found at much higher levels than two of its principal metabolites in the blood of both dams and fetuses. In neonates, AZT and the AZT + 3TC mixture caused increases in nucleated red blood cells, and also increased the tk mutant frequency in males. The induced mutations resulted from loss of the wild-type tk allele through LOH, which was accompanied by a pattern of discontinuous LOH. The prominent role of LOH in these results is in agreement with the data of Wang et al. [2007] (see above) and emphasizes that the increased number of mutants resulting from AZT treatment is due mainly to large-scale genetic alterations.

Mutagenesis induced by AZT, 3TC, and ABC alone or in combination also was studied following in vitro exposure of cultured human lymphoblastoid TK6 cells and in utero exposure of CD-1 mice by Torres et al. [2007]. Dose-related increases in mutations in both the HPRT and TK genes were found following 3 days of exposure of cells to AZT or 3TC alone at levels of 33–300 μM, or to equimolar amounts of AZT + 3TC. Coexposure to the mixture generally produced higher increases in mutation frequency. Experiments with abacavir were unsuccessful due to the extreme toxicity of the drug. Exposure of cells to peak, plasma-equivalent levels of AZT + 3TC for an extended period (10 μM, 30 days) resulted in similar increases in mutant frequency as short-term, high-dose treatment. In mice necropsied 13–21 days postpartum, hpert mutation frequencies in T-cells were significantly elevated in both AZT-only and AZT + 3TC treated groups at 13 days of age. These results further confirm the in vitro and in vivo mutagenicity of AZT, and suggest that the response is driven by cumulative dose.

Dobrovolsky et al. [2007] investigated hpert mutagenesis and micronucleus formation in p53-haploid mice treated perinatally with AZT alone or in combination with 3TC. Pregnant mice were treated from gestation day 12 through parturition with each drug alone or in combination, and haploid (p53+/−) offspring were treated daily after birth through postnatal day 28. Frequencies of micronucleated erythrocytes in peripheral blood were determined at intervals, and the frequency of mutant hpert spleen lymphocytes was measured at postnatal day 28. Micronucleus formation was increased in treated animals at all time points, and was maximal at 10 days. Somewhat greater responses were detected in mice treated with AZT + 3TC than with AZT alone, especially in p53+/− animals. Both treatment regimens induced small but significant increases in hpert mutant frequency in p53+/− mice, whereas only the combination caused an effect in p53+/+ animals. These data add to the evidence of the mutagenicity and genotoxicity of these agents, and also demonstrate that p53 haplodeficiency affects their genotoxicity, although the effects were relatively small.

The transplacental carcinogenicity of AZT was initially demonstrated in Swiss CD-1 mice, and animals of this strain also were used in each of the in vivo genotoxicity experiments summarized above. To extend this evidence, Walker et al. [2007] characterized responses to AZT treatment in mice of a second strain, B6C3F1, and also in the F344 rat, animals that are widely used in carcinogenesis bioassays. Pregnant females of both species were gavaged daily with AZT at doses of 80–480 mg/kg body weight during the last 7 days of gestation. At 2 years postpartum, male and female offspring were necropsied for gross and microscopic tissue examinations. Significant increases and dose-related trends were found in the incidences of hemangiosarcomas in male mice and mononuclear cell leukemia in female rats at all three dose levels of AZT. A positive trend and increased incidence of hepatic carcinoma in the high dose AZT group of male mice provided further evidence of carcinogenic activity. Confirming and extending those of previous transplacental exposure studies in mice, these findings further attest to the carcinogenic properties of AZT.

Hong et al. [2006] describe findings in animals from another transplacental carcinogenesis study in CD-1 mice. Pregnant mice were treated by gavage daily with AZT at doses of 50–300 mg/kg body weight/day, through an 18- to 19-day gestation period. At the end of 2 years, incidences of alveolar/bronchiolar adenomas and carcinomas in the 200 and 300 mg/kg/day male treatment groups were significantly elevated above controls. Benign and malignant neoplasms were evaluated for the presence of point mutations in the K-ras and p53 genes. DNA isolated from formalin-fixed, paraffin-embedded tissue was analyzed by sequencing of PCR-amplified fragments. K-ras mutations were detected in 66% of AZT-induced lung tumors, the predominant mutation being codon 12 G → T transversions. p53 mutations were detected in 84% of lung tumors, in which the major mutations were in exon 8, codon 285 A → T transversions, and exon 6, codon 198 T → A transversions. No mutations in either gene were found in spontaneously occurring tumors. The authors conclude that the pattern of observed mutations suggest that incorporation of AZT or its metabolites into DNA, oxidative stress, and genomic instability may be contributing factors to the mutation profile and development of lung tumors in these mice.

In addition to these experimental studies, results of three investigations in human subjects also are reported.
In an observational cohort study, Meng et al. [2007] evaluated plasma and cellular markers of AZT metabolism as indicators of its incorporation into nuclear DNA of mononuclear cells from mother–child pairs receiving prepartum therapy with AZT, with or without 3TC. Several systemic and cellular markers were measured concurrently in blood samples from uninfected mothers and their HIV-positive mothers who received AZT-based therapies. Relationships between these pharmacological endpoints, levels of AZT incorporation into DNA, and mutagenic responses were evaluated. AZT incorporation into DNA was found in nuclear DNA from 56% (30–100%) of mothers exposed to AZT alone compared to 100% exposed to AZT + 3TC. The average incorporation in infants exposed to AZT alone was significantly (four fold) lower than that in AZT + 3TC-exposed infants. Incorporation of AZT into DNA of exposed infants correlated positively with plasma levels of AZT-triphosphate. These results demonstrate transplacental transfer of AZT and its incorporation into cellular DNA of the newborn, and also that the efficiency of these processes is enhanced in the presence of 3TC.

Escobar et al. [2007] investigated the genotoxicity of AZT and AZT + 3TC in vitro in cultured human H9 lymphoblastoid cells and also in peripheral or cord blood cells from perinatally-exposed HIV-infected mothers and their infants. Exposure of H9 cells to AZT for 24 hr produced dose-dependent increases in Comet assay tail moment when the assay was conducted at pH 13, but not at other pHs. These results indicate that AZT induces alkali-labile sites (e.g., apurinic sites) in DNA rather than direct DNA strand breaks. The magnitude of DNA damage was directly correlated with AZT incorporation, measured independently. Levels of DNA damage in cord blood mononuclear cells, detected by Comet assay, were similar in newborns exposed to AZT in utero and unexposed controls. In contrast, the glycoporin A (GPA) somatic cell mutation assay, which screens for large-scale DNA damage of red cell precursors, showed significant increases in the frequency of \( \text{GPA N/N} \) variants arising from chromosome loss and duplication, somatic recombination, and/or gene conversion in infants and their mothers who received prepartum AZT + 3TC therapy compared to controls. Elevations in variant frequency generally persisted through one year of age in exposed children, but not in controls. These findings provide clear in vivo as well as in vitro evidence of the genotoxicity of the agents.

Witt et al. [2007] also studied genotoxicity in infants exposed in utero and postpartum to AZT-based therapeutic regimens. To determine if chromosomal damage was induced by AZT in infants exposed transplacentally, they evaluated micronucleated reticulocyte frequencies in 16 HIV-infected mother–infant pairs; 13 women received therapy containing AZT and three therapy without AZT. Tenfold increases in micronucleus frequency (1.67% ± 0.34% vs. 0.16% ± 0.06%) were observed in women and infants who received AZT-containing therapy prenatally; no increase was observed in women and infants not exposed to AZT. Micronucleus frequency in AZT-exposed infants decreased over the first 6 months of life to levels comparable to cord blood from control (unexposed) infants. These results are in general agreement with those of Meng et al. [2007] and Escobar et al. [2007] summarized above. Taken together, they clearly demonstrate that transplacental AZT exposure is genotoxic in humans.

Extensive use of high-dose AZT regimens and increasingly complex mixtures of antiretroviral agents to minimize maternal HIV transmission could increase cancer risk in children exposed in utero and neonatally when they reach young adulthood or middle age [Olivero et al., 1997; IARC, 2000]. Abundant evidence from studies on experimental animals lends credence to that possibility. It is well established that carcinogen-induced tumor incidence and tumor sites are dependent on the age of the animal at the time of carcinogen treatment, irrespective of the tendency for development of spontaneous tumors. Prenatal and neonatal susceptibility to chemical carcinogenesis is typically much greater than that of adults, and both higher tumor incidence and shorter latency are found in the offspring of rodents and nonhuman primates than are found in pregnant or nonpregnant adult animals [Rice, 1981; Anderson, 2004]. In addition Vesselinovitch et al. [1971] compared urethan-induced tumor incidence in mice treated during prenatal and neonatal stages, and found that animals treated during the neonatal period developed tumors of many adult tissues more readily than those exposed in utero. An age-related pattern of response is especially prominent with respect to carcinogen-induced liver tumors. Early experiments [Vesselinovitch, 1990] demonstrated that the neonatal mouse possesses particularly high susceptibility to hepatocarcinogenesis from the day of birth to weaning, i.e., the first 3 weeks of postnatal life. In specific cases, including dimethylnitrosamine and aflatoxin, the carcinogens induced liver tumors when administered during the first 15 days postnatally, but were quite ineffective in 30 to 40-day-old animals, even at much higher doses.

A substantial body of additional evidence [Fu et al., 2000] clearly establishes the sensitivity of the neonatal mouse to carcinogenesis induced by genotoxic agents. This evidence has particularly relevant implications for assessing potential carcinogenic risks posed by AZT, since exposure through the HAART regimen takes place perinatally, the period of maximal sensitivity of mice to other genotoxic carcinogens. However, extrapolation of these experimental data to evaluation of risk in humans poses a complex and difficult problem. In the initial study of the carcinogenicity of AZT [Olivero et al., 1997], mice were treated transpla-
centrally during the last 7 days of gestation. The cumulative
dose to the mice in this study was similar to that received
by HIV-1-infected pregnant women treated according to
the CDC Guideline for the last 6 months of pregnancy. The
authors point out the difficulty in extrapolation of this type
of exposure data in assessing the relevance of the findings
to humans, and concluded that the available literature does
not allow accurate estimation of the human risk implied.
Nonetheless, in its evaluation IARC found that evidence from
studies in experimental animals accumulated prior to
2000 justified classification of AZT and dideoxycytidine
(ddC) as "possibly carcinogenic to humans" (Group 2B)
[IARC, 2000].

As summarized above and in the preceding review [Olivero,
2006], available evidence now indicates that AZT is
incorporated into nuclear and mitochondrial DNA in multi-
ple organs in mice and monkeys and in the leukocytes of
infants following transplacental exposure. Genotoxic mani-
festations of AZT incorporation into DNA appear to result
from oxidative damage, in addition to chain termination
deriving replication. Unremoved damage results in deletions
and point mutations as well as clastogenic events, micronu-
rus formation, sister chromatid exchanges, and other
manifestations of genomic instability. Molecular mecha-
nisms underlying these effects remain largely unidentified.
Collectively, these data provide convincing biological
plausibility for the postulate that perinatal exposure to
nucleoside analogs puts children at elevated risk of devel-
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