Research Letter

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Cancer risk among HIV-exposed uninfected children in the United States

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***In utero* exposure to didanosine was associated with increased risk of brain cancer in a French study. We used United States health department records to assess cancer risk among 13 617 children exposed to HIV *in utero*, who remained HIV-uninfected after birth (1990–2017). Risk of brain tumors was borderline elevated among these children (standardized incidence ratio 2.2, 95% confidence interval 0.8–4.8, $P = 0.12$, based on six cases). Risk was not significantly increased for leukemia or other cancers.**

Administration of combination antiretroviral therapy (cART) to pregnant women living with HIV and to their infants immediately after birth is the most effective way to prevent mother-to-child-transmission (PMTC) of HIV [1]. Globally, as the number of children who acquire perinatal HIV infection has decreased through wider access to cART during pregnancy (Option B+) [2], the number of children exposed to HIV *in utero*, who remain HIV-uninfected after birth (i.e., HIV-exposed, uninfected [HEU] children), is rising, bringing with it concerns about their long-term health outcomes [3].

Although cART is highly effective for PMTC [4,5], exposure of children to antiretroviral (ARV) medications *in utero*, at birth, and during early infancy may increase their cancer risk. In a French cohort study of 15 163 HEU children, the incidence of cancer among those perinatally exposed to the nucleoside reverse transcriptase inhibitor (NRTI) didanosine was twice the rate in the general population [6], pointing to potential carcinogenicity of this drug and possibly others within the same mechanistic class. NRTIs can incorporate into human nuclear and mitochondrial DNA and may interfere with host DNA synthesis, leading to point mutations, loss of chromosomal integrity, and shortened telomeres [7]. Zidovudine, an NRTI introduced in 1994 for PMTC [8], is considered a possible human carcinogen [9]. However, several additional smaller studies of HEU children have not detected excess cancer risk in relation to ARV exposure [10–13].

The study linked health department data on HEU children in six US states/territories during 1990–2017 to cancer registry data in the same regions (Supplemental Materials, http://links.lww.com/QAD/C757). Follow-up started at birth and ended at the earlier of age 20 years, death, or end of cancer registry coverage. We calculated standardized incidence ratios (SIRs) to measure relative risk compared with the general population. The study was approved by institutional review boards at study sites, as required.

In the cohort of 13 617 HEU children, most were exposed to maternal ARVs during pregnancy or labor and/or delivery (Supplemental Table, http://links.lww.com/QAD/C757). Children were followed for a total of 133,667 person-years (median 9.3 years, interquartile range 4.4–15.2 years, with a maximum of 20 years). During this follow-up, 18 cancers were diagnosed, of which six were brain tumors (Table 1), five leukemias, and seven other cancers (Supplemental Materials, http://links.lww.com/QAD/C757). Median age at cancer diagnosis was 2.5 years (interquartile range 1–7 years).

Risk was borderline elevated for cancer overall (SIR 1.6, 95% confidence interval [95% CI] 0.9–2.4, $P = 0.10$), which was related to a suggestive increase in brain tumor risk (SIR 2.2, 95% CI 0.8–4.8; $P = 0.12$) and, specifically, for astrocytomas (SIR 2.8, 95% CI 0.8–7.1; $P = 0.12$, based on four observed cases). Risk was not statistically significantly increased for leukemia (SIR 1.6, 95% CI 0.5–3.8, $P = 0.40$) or other miscellaneous cancers (SIR 1.2, 95% CI 0.5–2.5, $P = 0.74$).

Four children with brain tumors were exposed to zidovudine- and lamivudine-containing regimens *in utero*, and zidovudine during labor and delivery, and three were exposed to zidovudine in the postnatal period (Table 1). Two children with brain tumors were also exposed to nevirapine, one to nelfinavir, and one to efavirenz *in utero*.

Our study suggests that HEU children may have twice the risk of developing a brain tumor and, specifically, nearly three times the risk of astrocytoma, compared with the general population, although the findings were of borderline significance and should be considered cautiously, especially given the rarity of the cancer outcomes. There were no statistically significant associations with leukemia or other cancers.

In the prior French study [6], HEU children exposed to didanosine had 2.5-fold elevated risk of cancer compared to the general population, and cancer risk was elevated 5.5-fold with first trimester exposure compared to other NRTI regimens [6]. In addition, the cohort of HEU children overall exhibited borderline increased risk for

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Table 1. Demographic and tumor characteristics, and ARV medication exposure, for six HEU children diagnosed with brain tumors.

Sex	Age group (years)	Tumor histology	ARV medication exposure		
			In utero	Labor and delivery	Postnatal
Female	0–4	Pilocytic astrocytoma	Zidovudine, lamivudine, nevirapine	Zidovudine	Zidovudine
Female	0–4	Pilocytic astrocytoma	Unknown	Unknown	Unknown
Male	5–9	Pilocytic astrocytoma	Zidovudine, lamivudine, nelfinavir	Zidovudine	Unknown
Male	5–9	Oligoastrocytoma	Unknown	Unknown	Unknown
Female	0–4	Ependymoma	Zidovudine, lamivudine, efavirenz, nevirapine	Zidovudine	Zidovudine
Female	>10	Craniopharyngioma (benign)	Zidovudine, lamivudine	Zidovudine	Zidovudine

ARV, antiretroviral; HEU, HIV-exposed uninfected.

astrocytoma (SIR 3.7, 95% CI 1.0–9.4) and a significantly increased risk of pineoblastoma (SIR 100, 95% CI 20–290, based on our calculations; two of the three observed cases were exposed to didanosine) [6]. Didanosine is no longer recommended for use during pregnancy due to its toxicity [14,15]. Four children with brain tumors in our study were exposed to zidovudine and lamivudine, but this observation could be a coincidence, since the regimen has been widely used for preventing mother-to-child transmission [14]; two had unknown exposures. Zidovudine is no longer preferred as part of a cART regimen in pregnancy, while lamivudine is still recommended [14].

With 13 617 individuals and 133 667 person-years of follow-up, our study is among the largest to study cancer risk among HEU children. Most prior studies of cancer risk in HEU children after *in utero* ARV exposure were smaller and had shorter follow-up [10–13], which would hinder detection of rare events and cancers that occur later in childhood. An important limitation of our reliance on public health surveillance data in this study is the lack of systematic information on individual ARV medications and start-stop dates. This precluded formal analysis of cancer risk for specific ARV regimens, drug classes, and exposure windows.

The suggestively increased risk for brain tumors that we observed should be considered in the context of the substantial benefits provided by ARV medications for PMTC and protecting the mothers' health. With optimal treatment, ARVs can reduce the risk of perinatal transmission from 25% to 30% to less than 1% [4], and transmission is 0% among women with undetectable viral load in high resource settings [5]. In absolute terms, the occurrence of brain tumors among the HEU children in our study was a rare event (incidence 4.5 cases per 100 000 person-years), and, if the association were causal, only half of these cases would be attributable to the children's exposure to ARVs (i.e., attributable fraction = [2.20–1]/2.20 = 54% based on the SIR).

Though the number of pregnant women with HIV every year in the United States is small (approximately 5000) [16], globally, there were 1.3 million pregnant women with HIV in 2020, 85% of whom received ARVs for PMTC [17]. Given the growing size of the HEU population and morbidity associated with pediatric cancers, our suggestive findings on risk of brain tumors warrant further assessment.

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Conflicts of interest

There are no conflicts of interest.

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