

CORRESPONDENCE



Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception

TO THE EDITOR: Since August 2014, the Botswana Harvard AIDS Institute Partnership has conducted birth outcome surveillance at eight government hospitals throughout Botswana. A primary ongoing aim of the surveillance is to evaluate the prevalence of neural-tube defects associated with exposure to antiretroviral drugs from the time of conception (the risk period for neural-tube defects ends approximately 28 days after conception). At each site, trained government midwives perform surface examinations of consecutive live-born and stillborn infants who are born in the hospital to women infected with human immunodeficiency virus (HIV) and to women without HIV infection. As part of an institutional review board–approved research protocol, research assistants photograph major abnormalities after obtaining written informed consent from the mother; a medical geneticist reviews photos quarterly, without knowledge of mothers' HIV infection status or exposure to antiretroviral drugs. In May 2016, Botswana changed its first-line antiretroviral therapy from tenofovir–emtricitabine–efavirenz to tenofovir–emtricitabine–dolutegravir for all adults, a change that allowed for the inclusion of dolutegravir in surveillance.

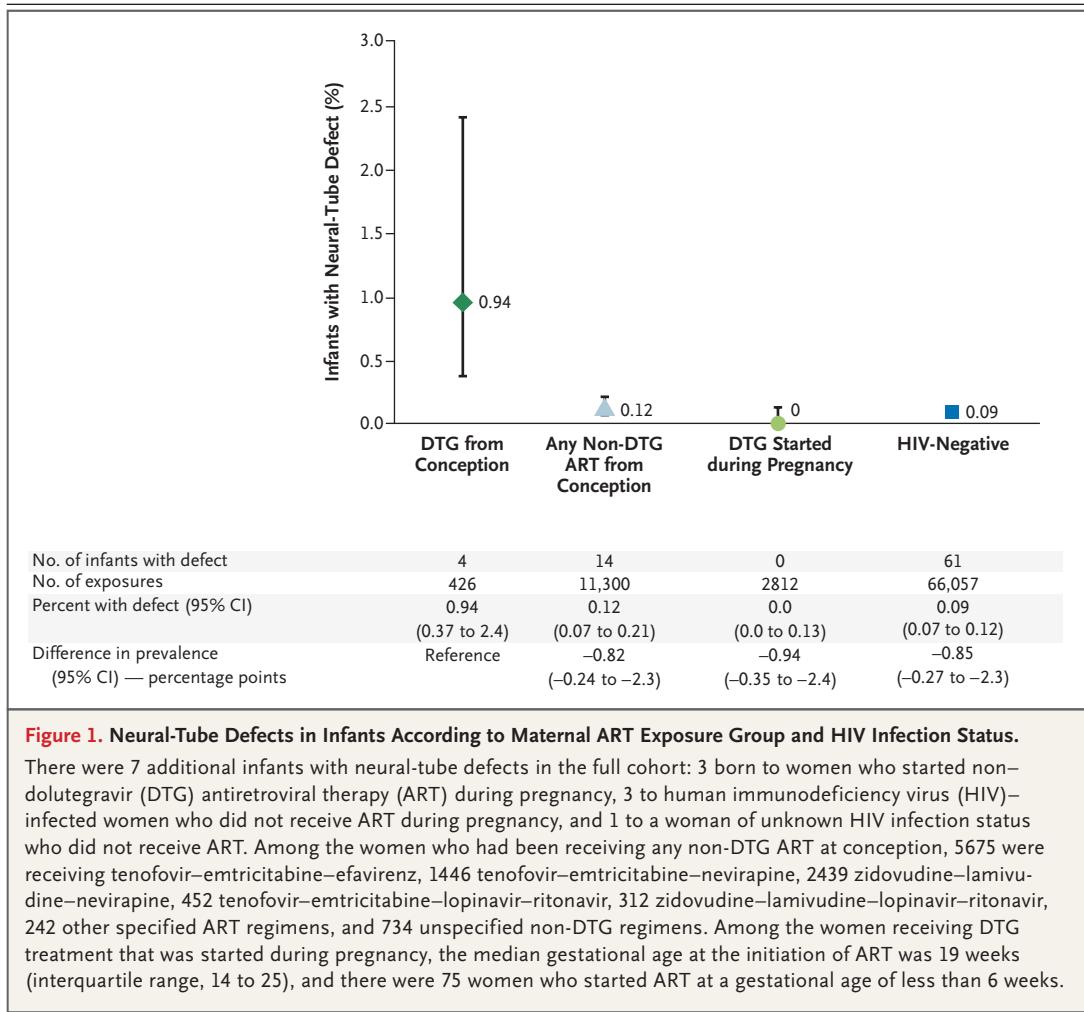
We recently reported that the risk of adverse birth outcomes or congenital abnormalities among women who started dolutegravir-based antiretroviral therapy after conception (including therapy initiated during the first trimester of pregnancy) was not higher than the risk among women who started efavirenz-based therapy after conception.¹ However, in April 2018, we detected a higher-than-expected number of neural-tube defects among infants born to women who started treatment with dolutegravir before conception. We performed an

unplanned interim analysis to compare the prevalence of neural-tube defects among infants born to women who had been receiving dolutegravir-based antiretroviral therapy from the time of conception with the prevalence in other exposure groups. For each exposure group, we calculated the prevalence of neural-tube defects (and 95% confidence interval, calculated with the Wilson method) and the difference in prevalence relative to the group with dolutegravir-based therapy from the time of conception (and 95% confidence interval, calculated with the Newcombe method).²

As of May 1, 2018, a total of 89,064 births had been included in our surveillance; 88,755 births (99.7%) had an infant surface examination that could be evaluated, with 86 neural-tube defects identified (0.10% of births; 95% confidence interval [CI], 0.08 to 0.12) (57% identified with a photograph, 43% identified by description). The defects included 42 instances of meningocele or

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myelomeningocele, 30 of anencephaly, 13 of encephalocele, and 1 of iniencephaly. Among the 426 infants born to HIV-positive women who had been taking dolutegravir-based antiretroviral therapy from the time of conception, 4 (0.94%) had a neural-tube defect. The defects in these 4 infants were encephalocele, myelomeningocele (along with undescended testes), and iniencephaly (along with major limb defect), all three of which were identified with photos, and anencephaly, which was identified by description. The 4 mothers delivered in three geographically separated hospitals over a 6-month period; none had epilepsy or diabetes or received folate supplementation at conception. In comparison, neural-tube defects occurred in 14 (0.12%) of 11,300 infants born to women who had been exposed to any non-dolutegravir antiretrovi-

ral therapy from the time of conception, 0 (0.00%) of 2812 infants born to women who had been exposed to dolutegravir treatment that was started in pregnancy, and 61 (0.09%) of 66,057 infants born to HIV-uninfected women (Fig. 1). Seven neural-tube defects occurred in other exposure groups. In the analysis of the prevalence of neural-tube defects associated with exposure to antiretroviral therapy from the time of conception, the difference between non-dolutegravir-based antiretroviral therapy (prevalence, 0.12%) and dolutegravir-based antiretroviral therapy (0.94%) was -0.82 percentage points (95% CI, -0.24 to -2.3).

In conclusion, we found a potential early signal for an increased prevalence of neural-tube defects in association with dolutegravir-based antiretroviral therapy from the time of conception. Our study

is ongoing, and more data are needed to confirm or refute this signal, given the small number of events and the small difference in prevalence.

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High-Risk Clonal Hematopoiesis as the Origin of AITL and *NPM1*-Mutated AML

TO THE EDITOR: Clonal hematopoiesis of indeterminate potential (CHIP) is associated with an increased risk of hematologic neoplasms. CHIP is most common in older patients, who usually carry a single somatic mutation (which provides a fitness advantage) in a minority of hematopoietic cells.^{1,2} Here, we describe the striking sequential onset within 2 years of angioimmunoblastic T-cell lymphoma (AITL) with mutation in the gene encoding ras homolog family member A (*RHOA*)³ and acute myeloid leukemia (AML) with mutation in the gene encoding nucleophosmin 1 (*NPM1*)⁴ in a 45-year-old man with CHIP. The relatively young age of the patient was unusual, because both of these cancers are typically diagnosed in elderly patients. We also describe the common origin of these two neoplasms from high-risk CHIP driven by multiple *TET2* and *ASXL1* mutations in virtually all bone marrow cells. (Additional details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

After the patient presented with AITL (Fig. 1A), molecular studies in formalin-fixed lymph node DNA identified a clonal *RHOA* G17V mutation, which is characteristic of AITL,³ along with four inactivating *TET2* and *ASXL1* somatic mutations that are typical of CHIP.² These four mutations were also documented in the staging aspirate of bone marrow and in purified CD34+ hemato-

poietic cells at frequencies of 7.9 to 49.3%, which were much higher than the frequencies of the *RHOA* G17V mutation (0.04 to 0.24%), which was consistent with minimal bone marrow involvement by AITL.

The patient had a complete remission after six cycles of chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP), followed by autologous hematopoietic stem-cell transplantation. Approximately 1 year after the diagnosis of AITL, the patient received the diagnosis of AML involving the bone marrow and skin, which were infiltrated by leukemic cells that were negative for CD34 and aberrantly positive for cytoplasmic *NPM1*⁵ (Fig. 1B). In both the bone marrow aspirate and skin-biopsy sample, we identified a clonal *NPM1* mutation type A⁴ and two subclonal *KRAS* mutations, along with the same four preleukemic *TET2* and *ASXL1* mutations, but the *RHOA* G17V mutation was either absent or only minimally present. The patient subsequently died of AML despite receiving intensive chemotherapy. (Details regarding this treatment are provided in the Supplementary Appendix.)

Variant allele frequencies in preleukemic bone marrow suggested the first occurrence in a hematopoietic stem cell of the *TET2* Q1654* mutation, resulting in a clone that eventually replaced the entire bone marrow while acquiring additional subclonal mutations (Fig. 2). In particular, a sec-