More on Nicotine Poisoning in Infants

TO THE EDITOR: Bassett et al. (June 5 issue)[1] describe a case of a child who was poisoned by e-cigarette refill liquid. In California, we have also seen a dramatic increase in telephone calls to poison control centers because of exposures to nicotine solution; there were 35 total cases of exposure in the period from 2010 through 2012[2] and 105 cases in 2013 alone. In 2013, exposure to nicotine refill solution was involved in 18% of all cases. Reported exposure to this solution in 10 children resulted in hospital evaluation in 7 and mild nicotine poisoning in 3. Children were not the only victims; 4 adults mistakenly instilled nicotine refill solution into their eyes instead of eyedrops, resulting in considerable but transient irritation in each case. In addition, systemic symptoms of nicotine poisoning developed in 3 adults after they spilled nicotine refill solution on their skin. There is currently no federal legislation with respect to labeling or packaging of nicotine refill solution. Given the high toxicity of nicotine and the widespread availability of nicotine refill solution, perhaps these products should fall under the umbrella of the Poison Prevention Packaging Act and thus be sold in child-resistant packaging.

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No potential conflict of interest relevant to this letter was reported.

1. Bassett RA, Osterhoudt K, Brabazon T. Nicotine poisoning in an infant. N Engl J Med 2014;370:2249-50.
2. Cantrell FL. Adverse effects of e-cigarette exposures. J Community Health 2014;39:614-6.

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THE AUTHORS REPLY: Cantrell and Clark's description of exposures to nicotine refill solution mirrors our own experience with poison control centers. Poison control centers are vigilant in epidemic surveillance, and broader poison control center–based data are available from the National Poison Data System of the American Association of Poison Control Centers.[1] Since poison control centers rely on voluntary reporting, it is important to view their data within the context of other data sources such as the National Electronic Injury Surveillance System of the U.S. Consumer Product Safety Commission (derived from emergency department visits) or medical examiners' offices. Additional data characterization is valuable, but we know enough already from decades of research on injury prevention to realize that potent, dangerous neurotoxicants such as liquid nicotine should not be sold to consumers without safety warnings in the packaging and should not be marketed attractively as food or with candy flavors.

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Since publication of their letter, the authors report no further potential conflict of interest.

1. American Association of Poison Control Centers. E-cigarette devices and liquid nicotine (http://www.aapcc.org/alerts/e-cigarettes).

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Shift of HIV Tropism in Stem-Cell Transplantation with *CCR5* Delta32 Mutation

TO THE EDITOR: Infection with the human immunodeficiency virus (HIV) requires entry into target cells by binding of the viral envelope to the CD4 receptor and to either the chemokine (C-C motif) receptor 5 (CCR5) or the chemokine (C-X-C motif) receptor 4 (CXCR4). Homozygosity for a 32-bp deletion in the *CCR5* allele (*CCR5* delta32) prevents cellular entry of CCR5-tropic (R5-tropic) HIV type 1 (HIV-1) strains. In 2009, there was a report[1] about an HIV-1–infected patient with acute myeloid leukemia in whom the viral load remained undetectable after allogeneic stem-cell

transplantation from a donor who was homozygous for the *CCR5* delta32 mutation and after the discontinuation of antiretroviral therapy. This case gave rise to hope for new strategies for eradicating HIV-1 infection. However, this case has remained unique. Furthermore, in HIV-1–infected patients undergoing allogeneic stem-cell transplantation from donors with nonmutated *CCR5*, viral rebound has been reported.[2]

Here, we present the case of a 27-year-old patient with HIV-1 infection and anaplastic large-cell lymphoma. Because of a poor prognosis after progression of the T-cell lymphoma, stem-cell transplantation was planned, and a donor who was homozygous for the *CCR5* delta32 mutation was identified. We determined the viral tropism of HIV-1 by genotyping the V3 amino acid sequence and applying geno2pheno bioinformatic software to predict viral coreceptor use,[3] which indicates the probability of classifying

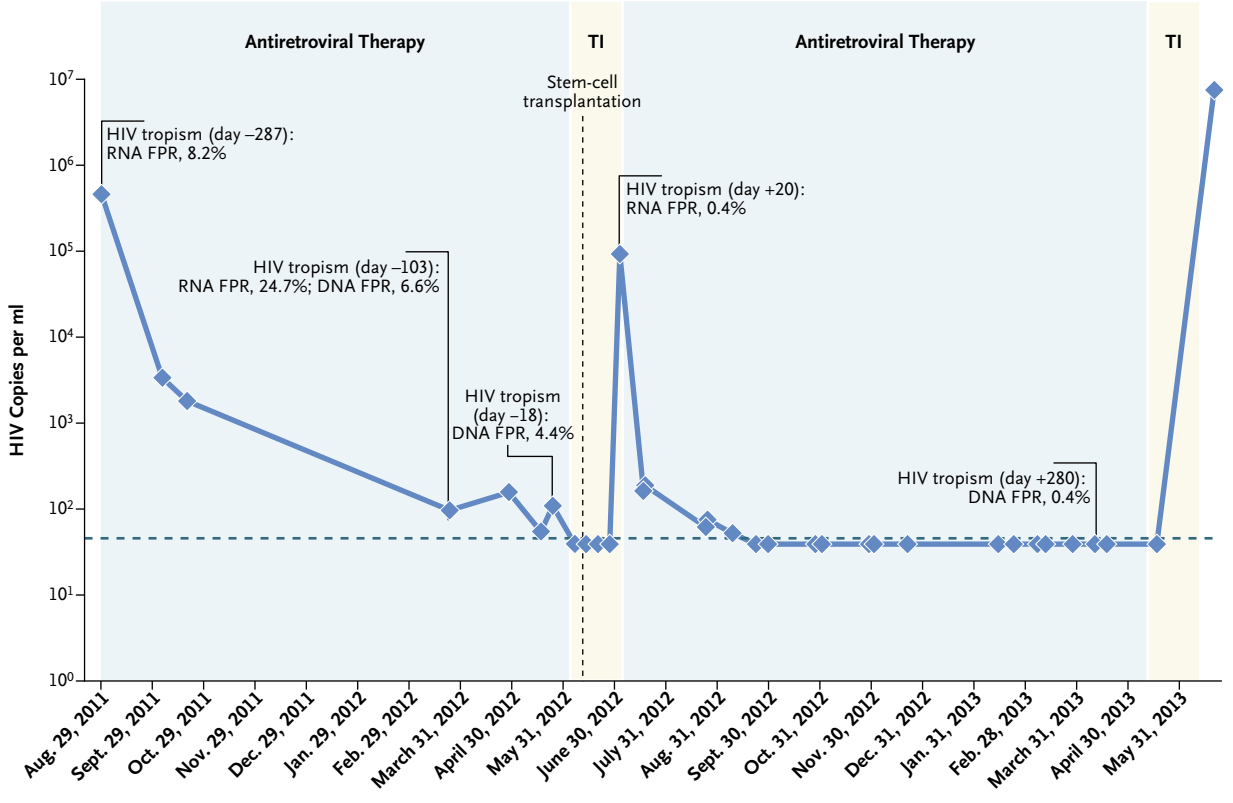

Figure 1. Human Immunodeficiency Virus (HIV) Levels, HIV Tropism, and Effect of Antiretroviral Therapy in a Patient with Anaplastic Large-Cell Lymphoma.

HIV tropism is determined by genotyping the V3 amino acid sequence and applying geno2pheno bioinformatic software to predict viral coreceptor use, which indicates the probability of classifying a CCR5-tropic (R5-tropic) virus falsely as CXCR4-tropic (X4-tropic). On the basis of the false positive rate (FPR), viruses are categorized as X4-tropic, intermediate, or R5-tropic. In our patient, analyses revealed an intermediate HIV tropism before the restart of antiretroviral therapy consisting of lopinavir–ritonavir, tenofovir, and emtricitabine 287 days before the patient underwent allogeneic stem-cell transplantation. During antiretroviral treatment and 103 days before the transplantation procedure, the HIV tropism from RNA was classified as R5-tropic, whereas the HIV tropism from DNA was again intermediate. Eighteen days before transplantation, the HIV tropism test from DNA indicated the presence of X4-tropic viruses with an FPR slightly below the cutoff (FPR, <5%). Twenty days after transplantation and during antiretroviral therapy interruption (TI), HIV tropism from RNA indicated the replication of clearly X4-tropic viruses (FPR, 0.4%). Reinitiation of antiretroviral therapy — which started with lopinavir–ritonavir, tenofovir, and emtricitabine, was switched to lopinavir–ritonavir, lamivudine, and abacavir in December 2012, and finally was switched to lamivudine, abacavir, and raltegravir in April and May 2013 — led to sustained suppression of viral replication before antiretroviral therapy was finally stopped. (Details regarding HIV-1 genotypes of protease, reverse transcriptase, and amino acid changes in the V3 sequence of viral RNA and proviral DNA, as compared with the consensus subtype B sequence, are provided in the table in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

an R5-tropic virus falsely as a CXCR4-tropic (X4-tropic) virus (false positive rate of <5%, X4-tropic; false positive rate of 5 to 10%, intermediate; false positive rate of >15%, R5-tropic). Before the patient underwent transplantation, the tropism from viral RNA was predicted to be either R5-tropic (false positive rate, 24.7%) or intermediate (false positive rate, 8.2%), whereas the V3 sequence from proviral DNA was classified as intermediate (false positive rate, 6.6%) or X4-tropic (false positive rate, 4.4%).

The patient discontinued antiretroviral therapy before the initiation of myeloablative treatment but resumed therapy 3 weeks after transplantation because of a rebound of 93,390 copies of HIV RNA per milliliter (Fig. 1). The V3 sequence was related to the previous genotypes from this patient, as indicated by the presence of identical mutations in all V3 sequences (see the table in the Supplementary Appendix); it also carried several specific mutations resulting in the prediction of an X4-tropic virus (false positive rate, 0.4%). Antiretroviral therapy effectively suppressed viral replication until the patient had a relapse of the T-cell lymphoma, when antiretroviral therapy was again stopped. Two weeks before the patient died, the HIV-1 RNA level was 7,582,496 copies per milliliter.

The genotypic analyses of HIV-1 variants in this patient showed a shift from a dominantly R5-tropic HIV before stem-cell transplantation toward an X4-tropic HIV after transplantation. This shift of tropism was probably driven by transplantation with stem cells homozygous for the *CCR5* delta32 mutation. This case highlights the fact that viral escape mechanisms might jeopardize CCR5-knockout strategies to control HIV infection.[4]

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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