

## Evidence for the Cure of HIV Infection by CCR5 $\Delta$ 32/ $\Delta$ 32 Stem Cell Transplantation

Allers K, Hütter G, Hofmann J, et al. *Blood*. 2011;117(10):2791–2799

**PURPOSE OF THE STUDY.** HIV uses CD4<sup>+</sup> as its primary receptor and chemokine receptors (CCR5 and CXCR4) as co-receptors. The primary receptor used to transmit HIV between people, including in maternal-child transmission, is CCR5. Approximately 1% of northern Europeans have a homozygous deletion ( $\Delta$ 32) in the *CCR5* gene that dramatically increases the resistance to HIV infection in affected people. There has been great speculation as to the “curability” of active HIV infection. The purpose of this study was to describe the apparent cure of a single patient.

**STUDY POPULATION.** The case of a single person who received a stem cell transplant from a donor with “natural” resistance to HIV was reported.

**METHODS.** Extensive immunologic, virologic, and genetic tests were performed serially on this person.

**RESULTS.** The patient received a successful transplant for treatment of relapsed acute myeloid leukemia. Long-term follow-up, 4 years at the time of writing, revealed that the patient’s CD4<sup>+</sup> T cells recovered efficiently; donor-derived CD4<sup>+</sup> T cells repopulated the gut mucosal immune system; in vitro alternative chemokine receptor usage, CXCR4, was not impaired on the new T cells; long-lived HIV target cells of host origin (tissue CD4<sup>+</sup> T cells and macrophages) were replaced with donor-derived cells after transplantation; and HIV remains undetectable in peripheral blood and multiple tissue compartments over the 45-month course of observation.

**CONCLUSIONS.** This patient was cured of HIV infection.

**REVIEWER COMMENTS.** The now-famous person often referred to as the “German patient,” although in reality an American living in Berlin, provides proof of concept that HIV infection is a curable disease. Although the identification of a CCR5 $\Delta$ 32/ $\Delta$ 32 donor is impractical for almost all other people with HIV, the experience with the German patient has led to a dramatic increase in the attempt to cure HIV. Multiple approaches have been proposed, and many would be applicable to the “average” HIV-infected person. This is reflected in a recent article entitled “The Emerging Race to Cure HIV Infections” (*Science*. 2011;332[6031]:784–789).

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## Evaluation of 4 Weeks’ Neonatal Antiretroviral Prophylaxis as a Component of a Prevention of Mother-to-Child Transmission Program in a Resource-Rich Setting

Ferguson W, Goode M, Walsh A, Gavin P, Butler K. *Pediatr Infect Dis J*. 2011;30(5):408–412

**PURPOSE OF THE STUDY.** A 6-week course of neonatal antiretroviral prophylaxis has been standard in most developed countries. In the same settings, a 4-week rather than 6-week intervention might reduce toxicity and reduce cost.

**STUDY POPULATION.** The study involved a cohort that included all HIV-exposed live births in Ireland from January 1999 through December 2008 with a minimum of 18-months of follow-up.

**METHODS.** This was a 10-year observational study of the Irish experience in their use of a 4-week rather than 6-week neonatal antiretroviral regimen.

**RESULTS.** Of the 916 infants with known outcome, 1% were infected. If analysis was limited to the 910 infants whose mothers received at least 4 weeks of antiretroviral therapy, the vertical transmission rate was 0.4%. These numbers are consistent with those found in other areas in which the standard 6-week regimen is followed.

**CONCLUSIONS.** The current clinical practice of using a 4-week neonatal antiretroviral prevention regimen seems to be as effective as a 6-week regimen.

**REVIEWER COMMENTS.** Although it is reasonable to surmise that a 4-week regimen is as effective as a 6-week regimen in preventing vertical transmission of HIV, the data presented here are unlikely to convince the public health authorities of other countries to move in this direction. This was not a controlled trial, and the patient population might differ in other countries.

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## Cardiac Effects of Antiretroviral Therapy in HIV-Negative Infants Born to HIV-Positive Mothers: NHLBI CHAART-1 (National Heart, Lung, and Blood Institute Cardiovascular Status of HAART Therapy in HIV-Exposed Infants and Children Cohort Study)

Lipshultz SE, Shearer WT, Thompson B, et al. *J Am Coll Cardiol*. 2011;57(1):76–85

**PURPOSE OF THE STUDY.** HIV is known to cause a cardiomyopathy. In addition, the mitochondrial abnormalities reported in children exposed to antiretroviral therapy but not infected with HIV might also be associated abnormal

heart function. The purpose of this study was to examine the cardiac effects of perinatal exposure to antiretroviral therapy.

**STUDY POPULATION.** This was a prospective multisite cohort study with 2 groups of HIV-uninfected infants of HIV-infected mothers: 136 infants had been exposed to antiretroviral therapy, and 216 were unexposed.

**METHODS.** Echocardiograms were obtained between birth and 24 months of age. Data were expressed in mean z scores.

**RESULTS.** Mean left ventricular mass z scores were consistently lower in girls exposed to antiretroviral therapy than in those not exposed. These differences persisted to the end of study at 2 years. Similar differences were noted for boys but were smaller. Septal wall thickness and left ventricular dimension were smaller than expected in exposed infants, but left ventricular contractility was higher in exposed infants.

**CONCLUSIONS.** Exposure to antiretroviral therapy is associated with reduced left ventricular mass and size and septal wall thickness. It is also associated with increased left ventricular fractional shortening and contractility up to 2 years of age. Fetal exposure to antiretroviral drugs seems to impair myocardial growth but improves left ventricular function.

**REVIEWER COMMENTS.** That exposure to potent nucleoside analogs in utero might have a variety of adverse effects is not surprising. The mechanism of reduced cardiac growth in antiretroviral drug-exposed but HIV-uninfected infants is unknown. However, nucleoside analog-associated suppression of mitochondrial DNA replication might be responsible for this effect. That organogenesis is not more severely affected with long-term exposure to such agents is reasonably comforting. However, only long-term follow-up of antiretroviral drug-exposed infants will address this concern.

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### **An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis**

Berry MPR, Graham CM, McNab FW, et al. *Nature*. 2010;466(7309):973-977

**PURPOSE OF THE STUDY.** Most people infected with *Mycobacterium tuberculosis* (TB) develop a latent form of the disease and remain asymptomatic; however, approximately 10% of these people are at risk of developing active, transmissible disease in their lifetime. An inability

to accurately identify these at-risk patients with conventional tests has limited efforts to control TB. The purpose of this study was to identify novel biomarkers of active disease by using genomic techniques.

**STUDY POPULATION.** The investigators generated genome-wide transcriptional profiles from the blood of patients with active TB (before treatment), patients with latent TB, and healthy controls. This study was conducted at St Mary's Hospital in London, United Kingdom, and the University of Cape Town in South Africa.

**METHODS.** Whole blood was obtained from healthy volunteers and patients with TB before starting antimicrobial therapy. A subset of patients diagnosed with active TB were also sampled 2 and 12 months after starting therapy. RNA was extracted from the whole blood of these subjects and used in a genome-wide microarray analysis. Extent of disease was assessed by plain chest radiographs.

**RESULTS.** The authors identified a distinct 393-transcript signature that defined patients with active disease. In addition, this transcript signature strongly correlated with extent of disease in patients with active TB. It is interesting to note that between 10% and 25% of patients with latent TB had similar transcript profiles to those patients with active disease, which suggests that this profile might identify those at risk for developing active disease. After 2 months of therapy, the transcriptional signature in patients with active TB reverted back to that of healthy controls, which suggests that this signature could be used to monitor the course of the disease. Using data-mining strategies, the authors found that the largest set of transcripts that changed in active TB were those induced by type I interferon (IFN) or IFN- $\gamma$  in cells that were likely of neutrophil and monocyte origin.

**CONCLUSIONS.** A unique, treatment-sensitive, genome-wide transcriptional signature predominantly in phagocytes is associated with active TB and might predict those patients at risk of developing active disease. Type I IFN might play a larger role in the pathogenesis of TB than was previously appreciated.

**REVIEWER COMMENTS.** Development of an accurate biomarker for disease progression and treatment response would be a quantum leap forward in the global fight against TB and would potentially be useful for other similar diseases. This study is the first to associate active TB with a specific gene-expression signature that could be used to monitor those patients on therapy and identify those at risk of treatment failure. More research is needed to determine whether this signature could be used as a marker to identify those with latent TB and at risk of going on to develop active disease. This signature could be extremely valuable in aiding the diagnosis and

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