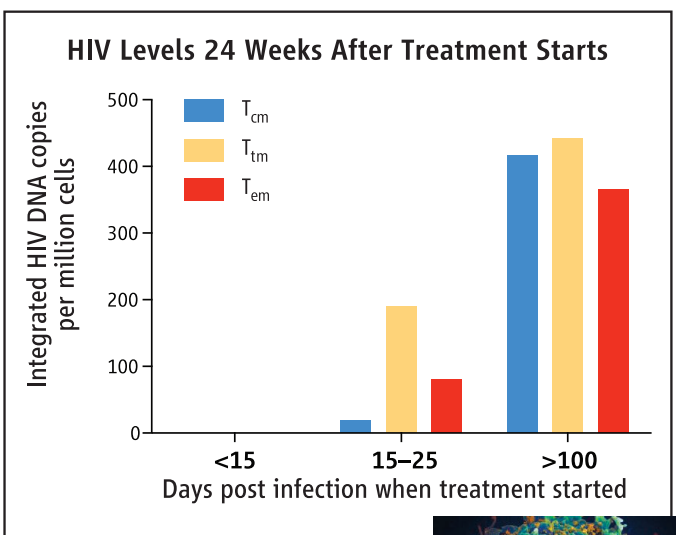
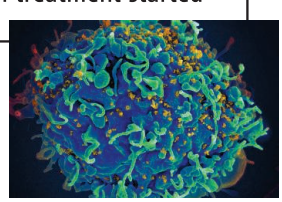
HIV/AIDS

Subset of CD4 Cells May Hold Key To Reaching HIV Cure

ATLANTA—"What do you think of the baby?" became the most asked question at the 20th Conference on Retroviruses and Opportunistic Infections held here last week. But the Mississippi case that grabbed international headlines after a report at the meeting described how a child had been cured of an HIV infection represents a single intriguing observation rather than a significant advance (*Science*, 8 March, p. 1134). New findings about how a subset of CD4+ white blood cells invaded by HIV may control the course of the disease promise to have a far more profound impact on the field. These "central memory cells" might even help explain the underlying mechanism behind the child's apparent cure.





Early does it. HIV invades various subsets of CD4+ T cells (T_{em}, T_{tm}, T_{cm}), but prompt intervention with antiretroviral therapy protects T_{cm} cells from infection.

"At the end of the day, what happens to central memory cells in the context of HIV infection may be the most important determinant of who you'll be able to cure and a patient's long-term outcome," said Steven Deeks of the University of California, San Francisco (UCSF), whose own lab focuses on curing HIV infections.

HIV preferentially invades T lymphocytes that have CD4 receptors on their surfaces. The resulting destruction of CD4 cells over a decade or so cripples the immune system and is the hallmark of AIDS. But the process takes many years because the central memory cell, a type of CD4+ T lymphocyte known in shorthand as T_{cm}, churns out clones of itself and can almost refill the body's pool of CD4 cells as fast as HIV drains it. However, the downside is that some infected T_{cm} cells become reservoirs of latent virus that rekindle infection if antiretrovirals (ARVs) are stopped.

The researchers who presented the case of the Mississippi child contend that success occurred because treatment was started unusually early, 31 hours after birth, which they say may have severely limited the size of the child's reservoir and given the infant's body a better chance to clear those cells. They have no direct evidence for this—but another report at the meeting lends credence to the idea.

At the Thai Red Cross AIDS Research Center in Bangkok, Jintanat Ananworanich and a team from the U.S. Armed Forces Research Institute of Medical Sciences have been identifying people shortly after they become infected and then encouraging them to start ARVs immediately. It typically takes 3 weeks after infection for people to test positive on standard screens for viral proteins and antibodies, but Ananworanich uses more sensitive tests that can identify infections earlier. Some people are so recently infected that the researchers detect only HIV genetic material in their blood, while others who are a little further along have viral proteins, and a third group also has antibodies that are detected by an ultrasensitive test, a sign of a slightly longer infection.

This study separated 75 acutely infected people into these three groups and started them on ARVs within 5 days of taking a blood test. An analysis by immunologist Nicolas Chomont of the Vaccine and Gene Therapy Institute of Florida in Port St. Lucie found that all three groups started out with fewer HIV-infected T_{cm} cells than seen in untreated people who have been infected for several years. What's more, after 24 weeks of treatment, the HIV DNA integrated into the T_{cm} cells remained undetectable or extremely low in each group. "Early [treatment] prevents the seeding of latent reservoirs in long-lived central memory T cells," Ananworanich concluded. She suggested that these people might be "ideal candidates" for future cure studies that she and her colleagues plan to conduct with novel interventions aimed at purging reservoirs. UCSF's Deeks suspects that the Mississippi child's T_{cm} cells were protected by extraordinarily early treatment and that the child's body was able to clear the tiny reservoir that was established.

Some people naturally control HIV better than others and protect their T_{cm} cells without the help of ARVs. Christina Ramirez Kitchen of the University of California, Los Angeles, collaborated with Deeks to look at "elite controllers," HIV-infected people who retain low HIV levels in their blood and high CD4 counts without treatment. The study compared nearly 300 infected people who had low levels of HIV in their blood, two-thirds of whom received treatment. The researchers found that elite controllers stood out in part because their T_{cm} cells downregulated a key receptor that HIV needs for entry and were less permissive to HIV infection. Conversely, Kitchen noted that people whose immune systems did not rebound even though ARVs controlled their infections had T_{cm} cells with impaired function.

In yet another twist involving T_{cm} cells, a poster presentation by Nichole Klatt of the University of Washington, Seattle, examined an unusual group of five people who had been infected for more than 9 years and maintained relatively normal CD4 counts, but, unlike elite controllers, have high levels of HIV in their blood. None took ARVs. The researchers compared these "viremic nonprogressors" to seven recently infected, untreated people with similar viral loads and CD4 counts who they expect will progress. A key difference between the two groups: The viremic nonprogressors had significantly fewer HIV-infected T_{cm} cells, and those cells had the same downregulated receptor found in the T_{cm} cells of the elite controllers that Kitchen studied.

So while the "cured" baby stole the limelight at the retrovirus meeting this year, central memory cells occupied center stage, too.

–JON COHEN

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