HIV lessons from the Mississippi Baby

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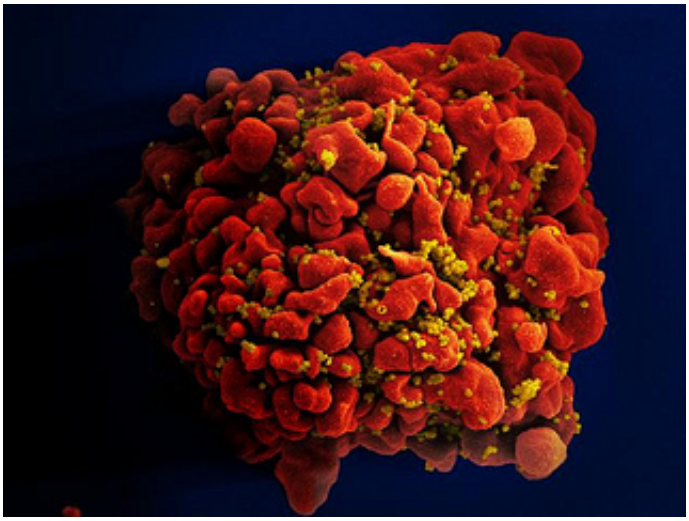

Scanning electron micrograph of an HIV-infected H9 T cell. Credit: NIAID

(Medical Xpress)—The news in July that HIV had returned in a Mississippi toddler after a two-year treatment-free remission dashed the hopes of clinicians, HIV researchers and the public at large tantalized by the possibility of a cure.

But a new commentary by two leading HIV experts at Johns Hopkins argues that despite its disappointing outcome, the Mississippi case and two other recent HIV "rebounds" in adults, have yielded critical lessons about the virus' most perplexing—and maddening—feature: its ability to form cure-defying viral hideouts.

Writing in the Aug. 28 issue of the journal *Science*, HIV research duo

Robert Siliciano, M.D., Ph.D., and Janet Siliciano, Ph.D., note that such "failures" are in fact stepping stones to new understanding of what "cure" may look like and new therapies that tame the virus into long-term remission.

"Heartbreaking as these three cases are clinically, they provide a dramatic illustration of the real barrier to an HIV cure and illuminate important therapeutic strategies," says Robert Siliciano. "This is not the end of the story but the beginning of a new chapter."

The 27-month off-treatment remission experienced by the Mississippi toddler is, in and of itself, a laudable therapeutic goal, the Silicianos write, and is what cure of HIV may look like in the foreseeable future. Finding ways to induce long-term remission and to closely monitor its course will be the next frontier in HIV treatment, they write.

The ability to put the virus in remission and go off treatment for months or years at a time is an important goal, because it can spare HIV-infected people from a lifetime of daily antiviral regimens, which can be difficult to tolerate and hard to follow. Failure to comply with the strict treatment protocol, which occurs often, can lead to viral mutations that make HIV resistant to drugs.

All three cases, the Silicianos write, also reaffirm that the single most important hurdle to eradicating HIV is a tiny but extremely stable pool of virus tucked away in a handful of immune cells known as memory CD4+ T cells.

Memory T cells are the immune system's combat-trained sentinels, responsible for fighting invaders they have encountered in the past. Much of the time, memory T cells lie dormant and become active only when the body is invaded by old foes they are specifically trained to recognize. HIV invades memory T cells early in the infection, and as

long as the T cells lie quiet, so does HIV inside them.

However, as soon as memory T cells get stirred up by an invader, the HIV DNA inside them wakes up, cranks out new virus and reignites infection. Because antiviral drugs work only against actively replicating virus, such silent viral hideouts remain out of therapy's reach. Thus, reducing the number of latently infected cells or precluding their formation altogether is an important and—as the three recent cases suggest—realistic strategy, the Silicianos say.

"These cases paint several clinical scenarios where a substantial reduction of viral reservoirs would allow some patients to come off treatment for prolonged yet uncertain periods of time, but they also raise the critical question of how to best monitor them for relapse so they can resume therapy swiftly when the virus rebounds," says Janet Siliciano.

In the widely reported case of the Mississippi baby, a child born to an HIV-infected mother received a full-treatment regimen of antiviral drugs within hours of birth, instead of the customary prophylactic regimen typically used in suspected but unconfirmed newborn infections. The baby's HIV infection was subsequently confirmed. The child was lost to follow-up and went off treatment but later returned to clinic. A series of standard and ultrasensitive tests failed to detect HIV in the child's blood. In total, the child remained free of HIV infection—with undetectable viral loads and free of HIV antibodies—for 27 months despite receiving no treatment. By contrast, most HIV-infected people experience dramatic viral rebound within a few weeks of treatment cessation.

Described as the first documented instance of HIV remission in a child, the Mississippi case suggested that very early treatment with antiretroviral drugs quashed the formation of viral reservoirs. The child was followed by a University of Mississippi pediatrician, a University of Massachusetts immunologist and a Johns Hopkins pediatric HIV expert,

Deborah Persaud, M.D., who was also the lead author on case report published Nov. 7, 2013, in The *New England Journal of Medicine*.

In two other "remission" cases reported in 2013, HIV ultimately rebounded in two adults after months without antiviral therapy and following bone marrow transplantation for cancer. Both patients received antiviral drugs while undergoing transplantation to prevent the donors' immune cells from becoming infected with HIV. The patients' own HIV-infected immune cells were killed off by chemotherapy and by graft-versus-host disease, a common post-transplant phenomenon in which the donor's immune cells attack and destroy the recipient's organs, tissues and cells. When antiretroviral treatment was stopped, the patients went into remission for several months, but the virus came roaring back later on, according to published reports.

"Clearly, neither approach managed to eradicate all latently infected cells, and what these cases underscore is the ability of even a few such cells to rekindle infection after prolonged remission," Robert Siliciano says.

The three cases also lend urgency to the search for better ways to monitor the presence of and measure the number of such dormant HIV reservoirs, which could be used as a rough gauge of how long remission might last. Latently infected cells can evade detection by even the most sophisticated tests, which are so exquisitely sensitive that they can sniff the presence of a single HIV-infected cell. The problem is not lack of test sensitivity, the Silicianos explain, but the size of the blood sample tested. Latent HIV reservoirs exist in a few out of millions of immune cells, but a mere 2 percent of memory T cells that harbor such reservoirs are circulating in the blood at any given time. Thus, even large blood samples may not capture the few infected cells harboring dormant virus—a feat that becomes even more challenging as the number of reservoirs is reduced.

Even though research indicates that remission duration is linked to the amount of latently infected cells, the Silicianos caution remission time is bound to vary widely from patient to patient. Its length would depend on individual biologic factors and the occurrence of other infections that might coax latently infected immune cells out of dormancy and trigger a rebound. A few patients may never relapse, the Silicianos say, but no patient is safe from rebound as long as he or she harbors even a single latently infected T cell. The unpredictable nature of remission and rebound will therefore require frequent blood monitoring to detect the earliest signs of viral reactivation.

"It is not too soon to begin planning for this type of 'cure' scenario," the authors conclude.

More information: "Rekindled HIV infection," by J.D. Siliciano et al. *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1259452

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