Rekindled HIV infection

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researchers to propose that they actively avoided each other (*9*, *10*). However, there is no evidence that the Late Dorset changed their traditional camping locations, as would be expected had they been trying to avoid the Thule. It is hard to imagine a cultural barrier so impermeable that the complete reproductive isolation documented by Raghavan *et al.* could have been maintained between these small and scattered hunter-gatherer populations. Maybe the absence of Paleo-Eskimo haplotypes among the Thule and their descendants is indirect evidence that the Dorset had died out before the Thule arrived, and that the apparently overlapping radiocarbon dates are erroneous.

Just over a thousand years ago, the arrival of Norse Vikings in the North American Arctic completed the expansion of humanity around Earth's circumference. Sutherland has argued that there was extensive interaction, including trade, between the Dorset and the Norse Vikings in Baffin Island (*11*, *12*). Yet, the lack of evidence for intermarriage documented by Raghavan *et al.* is almost impossible to explain if such interactions took place. The problem may lie in the radiocarbon dating, and the Dorset may have died out before the Norse arrived. In this and other cases, Raghavan *et al.*'s findings are likely to influence models of prehistoric migrations and cultural contacts in the North American Arctic for some time to come. ■

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AIDS/HIV

Rekindled HIV infection

What does the "Mississippi baby" tell us about curing HIV-1 infection?

By **Janet D. Siliciano**[1] *and* **Robert F. Siliciano**[1,2]

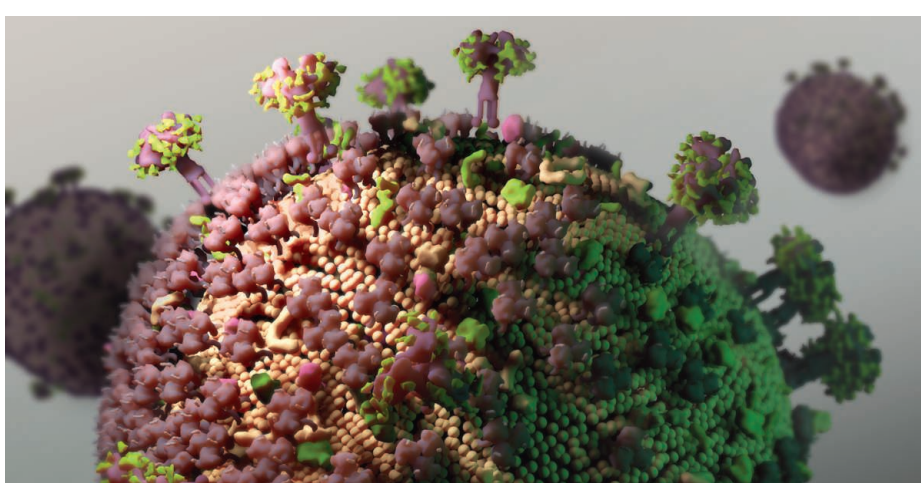
Palpable disappointment accompanied the news last month of a child (the "Mississippi baby") who was thought to be cured of HIV-1 infection by early antiretroviral treatment, but suddenly had detectable virus in the blood 2 years after the treatment was stopped. This setback followed the report of similar delayed viral rebounds 3 to 8 months after antiretroviral treatment was ended in two HIV-1–infected adults who had received bone marrow transplants (*1*). These findings have been viewed as a blow to HIV-1 eradication efforts. Although disappointing, the late rebounds are of enormous scientific importance. They reaffirm the concept that HIV-1 can persist by establishing latent infection and point to this challenge as the major hurdle in achieving a cure for HIV-1 infection.

The Mississippi baby was born to an HIV-1–infected mother who had no prenatal antiviral treatment. The infant tested positive for virus in the blood and was started on antiretroviral therapy 30 hours after delivery (*2*). The amount of virus in the blood (viremia) fell rapidly to below the limit of detection. At 18 months, treatment was stopped (against medical advice), but subsequent testing failed to reveal a rebound in viremia, which normally occurs 2 weeks after treatment interruption. There was widespread excitement that early therapy prevented the establishment of stable viral reservoirs in this infant. However, viremia suddenly rebounded 27 months after treatment interruption.

The two HIV-1–infected adults were given bone marrow transplants for other conditions while on antiretroviral therapy. The antiretroviral drugs protected donor cells from infection while host immune cells, including infected cells, were largely eliminated by chemotherapy and graft-versus-host disease (in which immune cells in the grafted tissue attack the host's immune cells) (*1*). Antiretroviral therapy was eventually stopped, and initially there was no viral rebound, raising hopes for cure. However, both patients later experienced sudden and dramatic rebounds in viremia.

The major barrier to cure is a small but extremely stable pool of resting memory $CD4^+$ T cells that carry an integrated but transcriptionally silent viral genome (*3*–*6*). Upon cellular activation, these latent proviruses are transcribed and replication-competent virus is released. Strategies for curing HIV-1 infection involve early antiretroviral therapy to prevent the establishment of a reservoir of latently infected cells, and a "shock and kill" approach (in which latency is reversed so the infected cells can be eliminated) (*7*). Due to the associated risks, bone marrow transplantation is only a curative strategy in patients requiring a transplant for other conditions.

The recent cases of delayed rebound suggest that even a small number of latently



Silent reservoir. HIV-1 may establish a latent infection in T cells that is unaffected by antiretroviral therapy. The virus may rebound later.

ILLUSTRATION: V. ALTOUNIAN/*SCIENCE*

infected cells established in early infection or persisting after transplantation may be sufficient to rekindle viral replication. But there has been some promising news too. Established simian immunodeficiency virus infection in nonhuman primates was cleared by vaccine-induced T cell responses (*8*). There is also evidence that a histone deacetylase inhibitor can perturb the latent HIV-1 reservoir in humans, potentially making the infected cells vulnerable to immune clearance (*9*). In addition, the well-known "Berlin patient"—an HIV-1–infected adult who developed leukemia—remains virus-free after being off of antiretroviral therapy for 5 years. This patient received a bone marrow transplant from a donor who did not express C-C chemokine receptor type 5, a co-receptor for HIV-1 (and was therefore resistant to commonly transmitted forms of HIV-1) (*10*).

> ***"The rebound cases also provide insight into the likely outcome of cure strategies."***

There has been lingering concern that HIV-1 persistence in patients who are on antiretroviral therapy might be due in part to low amounts of viral replication, occurring perhaps in an anatomical site with low drug concentrations (*11*). If persistent replication were occurring in these patients during therapy, rebound should have occurred rapidly after treatment interruption, particularly because HIV-1–specific immune responses were absent or diminished (*1*, *2*). The finding that viremia can remain undetected with the most sensitive assays for months to years in patients off therapy before a dramatic and sudden rebound to high concentrations (>2,000,000 copies/ml in the transplant patients) can only be explained by the persistence of a latent form of HIV-1. It is not clear where the rebound virus came from in the Mississippi baby or in the two adults, but the latent reservoir in resting memory $CD4^+$ T cells is present in every patient and persists indefinitely even in patients on suppressive antiretroviral therapy (*12*).

The recent cases illustrate a major challenge: measuring the latent reservoir. This reservoir was initially defined using a quantitative viral outgrowth assay (QVOA), which measures the frequency of resting $CD4^+$ T cells that produce replication-competent virus after the T cells are activated. Typical values are ~1 per 10^6 resting $CD4^+$ T cells. Measurement of HIV-1 DNA by polymerase chain reaction (which amplifies a targeted DNA sequence) gives higher frequencies for infected cells because both replication-competent and defective viral genomes are detected (*13*, *14*). Before rebound, the QVOA was negative in the recent cases, and HIV-1 DNA was at or below the limit of detection. Thus, viral rebound occurred even though the best available assays for persistent HIV-1 were negative. The problem is not assay sensitivity. Both the QVOA and polymerase chain reaction can detect a single latently infected cell. The limitation is the size of the tissue sample tested. Even large blood or tissue samples may be devoid of such cells although they persist elsewhere in the patient.

The rebound cases also provide insight into the likely outcome of cure strategies. For example, if treatments that produce multilog reductions in the latent reservoir can be found, patients may interrupt therapy and remain aviremic for months to years, during which time assays for viral persistence would be negative (because of sample size). However, rebound could occur in a sudden and unpredictable fashion at late time points after interruption (*15*). Although the time to rebound will increase with reservoir reduction, enormous patient-to-patient variation in time to rebound can be expected because of the stochastic nature of the reactivation of latently infected cells. Thus, frequent monitoring of viremia over long periods of time would be needed. However, patients can only be considered safe from rebound if all latently infected cells are eliminated. It is much more likely that we will be able to achieve partial reductions, allowing a prolonged but uncertain interval off therapy—something that many patients would welcome. It is not too soon to begin planning for how to monitor this type of cure scenario. ■

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RESEARCH FUNDING

Demystifying central government R&D spending in China

Should funding focus on scientific research?

By **Yutao Sun**[1,2] *and* **Cong Cao**[2]*

China has become a powerhouse in research and development (R&D) spending. In 2012, its gross domestic expenditure on R&D (GERD) topped yuan renminbi (RMB) 1 trillion ($163 billion in current dollars). Measured by purchasing power parity, China's GERD reached $294 billion, behind the United States' $454 billion and the European Union's $341 billion but ahead of Japan's $152 billion (*1*). China's GERD as a percentage of gross domestic product (GERD/GDP) reached 1.98%; it more than tripled since 1995, surpassing the 28 member states of EU, which together managed 1.96% (*1*, *2*).

POLICY

China's recent requirement that central government agencies release their departmental annual reports (DARs) indicates that the nation is catching up to international norms in disclosing the government's expenditure, including its R&D expenditure profile, emphasizing not only aggregate statistics but also the structure of, and government's contribution to, the expenditure. Taking advantage of this disclosure, we disaggregate and analyze China's central R&D expenditure [see supplementary materials (SM)], to opening the "black box" of China's government R&D expenditure (fig. S1). We pinpoint the roles of agencies with missions in R&D in China's national innovation system. The analysis also promotes transparency through normalizing China's R&D expenditure statistics as a whole.

APPROPRIATION AND EXPENDITURE. Rather than aligning with international norms in reporting R&D expenditure, the Chinese government embeds R&D expen-