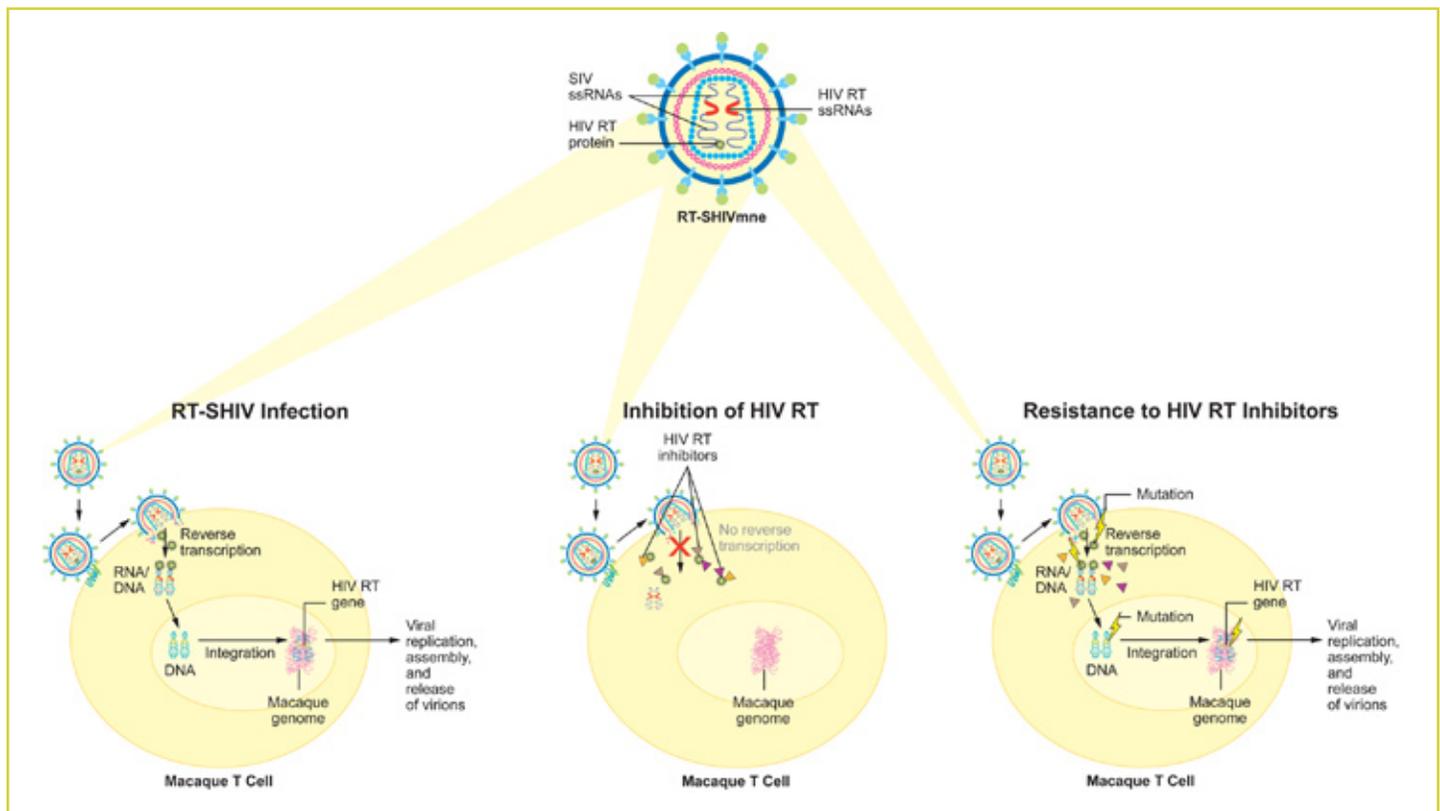


Exposing the Secrets of HIV's Success

An estimated 40 million people were living with HIV and approximately 3 million people died of AIDS worldwide in 2005, making HIV the deadliest infectious agent of the modern era. HIV owes much of its pathogenic success to two factors—its rapid and imprecise replication, which can lead to drug resistance, and its ability to survive at low levels in the presence of antiviral drugs, a phenomenon called persis-

tence. Multipronged treatment—usually a combination of three antiviral therapies—has helped reduce the number of AIDS-related deaths in developed countries, but does not provide a cure. Drug resistance sometimes occurs with long-term combination therapy, and is even more common when suboptimal treatment strategies are employed. Furthermore, if treatment is interrupted, HIV makes a rapid return.

Macaque monkeys infected with SIV (simian immunodeficiency virus) are the preferred model for studying HIV/AIDS infection and disease progression, but investigating drug resistance and persistence has been challenging because drugs used to treat HIV in humans are not effective against SIV. Research led by Vineet KewalRamani, Ph.D., Head of the Model Development Section of NCI's HIV Drug Resistance Program, and Zandrea Ambrose, Ph.D.,



Vineet KewalRamani and colleagues created a new macaque T-cell model that closely mimics human HIV infection and responds to anti-HIV drugs. This model also can be induced to mimic resistance to antiviral therapy.

a research fellow in his lab, has led to the development of a new macaque model that closely mimics human HIV infection and responds to anti-HIV drugs. A study using this model was reported in the September 12, 2007, online edition of the *Journal of Virology*.

KewalRamani and colleagues created a chimeric version of SIV that contains the HIV version of reverse transcriptase (RT), a protein essential for HIV infection and target of many anti-HIV drugs. The researchers determined that macaques infected with the chimeric virus, called RT-SHIVmne, respond to a combination of three drugs—efavirenz (EFV), tenofovir, and emtricitabine (FTC)—commonly used to treat HIV in humans. Furthermore, treatment interruption allowed RT-SHIVmne to quickly regain its foothold, indicating this model may provide an opportunity to learn more about how HIV in humans avoids being eliminated by antiviral drugs.

To determine whether their chimeric virus is capable of developing resistance to anti-HIV drugs, the Kewal-Ramani lab conducted an experiment designed to mimic a suboptimal treatment approach that seems to

facilitate development of drug resistance in humans. RT-SHIVmne-infected macaques underwent short-term treatment with a single antiviral agent—EFV—4 weeks before combination therapy was initiated. Within 1 week of EFV treatment, viruses with mutations known to impart resistance to EFV were detected in two of three EFV-treated animals.

All three EFV-pretreated animals initially responded to subsequent combination therapy, but disease soon began to progress in one of the two macaques that housed EFV-resistant RT-SHIVmne. Viral genomic analysis revealed that treatment failure in this animal correlated with gradual accumulation of virus with mutations associated with resistance to both EFV and FTC. The second macaque that had acquired EFV-resistant mutations did not acquire mutations associated with FTC-resistance and continued to respond to therapy. Resistance-associated mutations were not observed in any of the three macaques that were not pretreated with EFV. These data show that transient treatment of this model with a single antiviral agent facilitates accumulation of drug-resistant mutations as well as

subsequent combination therapy failure, both of which have been observed in humans.

The new macaque model developed by the KewalRamani lab mimics human HIV infection in several important ways: It responds to human antiviral agents. Virus levels rebound if treatment is removed, and suboptimal treatment facilitates the accumulation of drug-resistant virus. The availability of an animal model with these characteristics will allow careful examination of mechanisms that support HIV persistence and resistance in ways that are not possible in human studies and should help develop improved strategies for treating HIV.

Reference

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