

HIV delivers a punch to the guts

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HIV HATES our guts. Evidence is building that the virus deals a body blow to the immune system almost immediately after infection by destroying key cells in the gut lining; in the past, most researchers have assumed that there is a steady battle throughout the course of infection. The new findings have important implications for the development of vaccines and for improving therapies.

"I think AIDS is a two-punch fight," says immunologist Louis Picker of Oregon Health and Science University in Portland, a vocal supporter of the new theory. "The first punch is in the first few weeks - and the issue is not whether you recover from that, but how long you stagger on."

HIV attacks CD4 cells, also known as "helper" T-cells, which help coordinate immune responses. In the blood of infected people, there is a steady fight between viral replication and the production of new CD4 cells to replace those that are lost to the virus. If left untreated, HIV eventually wins this battle, and the immune system collapses.

The most successful treatment for HIV is called highly active anti-retroviral therapy, or HAART, which uses cocktails of drugs that can tip the balance in the blood in the immune system's favour: people with HIV who have now been on the therapy for years seem to remain healthy.

The vast majority of CD4 cells, however, some 98 per cent, are in mucosal tissues, such as those lining the vagina, airways and especially the gut - possibly because pathogens typically enter the body through such tissues. Only about 2 per cent of CD4 cells circulate in the blood.

This may explain why HAART doesn't fix all the damage that HIV causes. The virus hits immune cells in mucosal tissues hard and fast, usually before treatment with HAART even starts. Virologists have recently shown that the number of CD4 cells in the gut lining plummets by up to 60 per cent within the first few weeks of infection.

Now researchers led by Martin Markowitz of the Aaron Diamond AIDS Research Center in New York have shown that HAART does little to reverse this damage, even in people who are treated very early after being infected. Despite being put on drugs within about three weeks, 70 per cent of Markowitz's patients lost more than half of the CD4 cells in their lower gut (*PLoS Medicine*, DOI: 10.1371/journal.pmed.0040484).

Markowitz's team is now picking apart the mechanisms by which HIV wreaks havoc in the gut. Not only does the virus kill gut CD4 cells directly but it gets the immune system to turn on itself: some CD4 cells self-destruct, and others seem to be killed by other T-cells (*Journal of Virology*, DOI: 10.1128/JVI.01739-06). The researchers believe this is linked to the way HIV activates the immune system abnormally.

This damage may also trigger further harmful immune activation throughout the body, says Daniel Douek of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. Douek's work suggests that damage to the gut enables molecules from microbes in the gut to enter the bloodstream. These molecules include some known as lipopolysaccharides,



which are a component of bacterial cell walls and stimulate the immune system (*Nature Medicine*, vol 12, p 1365).

One big unknown is what these findings mean for people with HIV who are on HAART. The worry is that their damaged gut linings may eventually cause them to be laid low by HIV, despite the positive effects of HAART in the blood.

Another possibility, however, is that HAART could keep enough gut CD4 cells alive to make a difference - enough to keep an infected person healthy for the rest of their life, even if the gut's immune system never returns to normal. "We don't want to scare people," says Markowitz.

HAART was introduced in 1995, so the longest anyone with HIV has been on the drug cocktail is about a decade. Markowitz says that it will be important to monitor the health of people on HAART as they grow older to examine the consequences of the immune damage in their guts. For instance, it may be wise to give them more regular colonoscopies to look for the early signs of colorectal cancer, which the immune system normally helps to keep in check.

The new focus on the gut and immune activation also suggests some alternative approaches to therapy. Douek speculates that it may be possible to help people with HIV by blocking cell-surface receptors that respond to lipopolysaccharides.

The most important implications may be for vaccine development. An effective AIDS vaccine will probably have to trigger "mucosal" immunity in the gut lining, in addition to immunity in the blood. Ideally, it would stimulate antibodies capable of knocking out the virus before it enters CD4 cells, as well as directing T-cells to destroy cells that do get infected.

"If we could do that, we'd be very happy," says Gary Nabel, who heads the Vaccine Research Center. "But to be honest, we don't know how at this point."

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