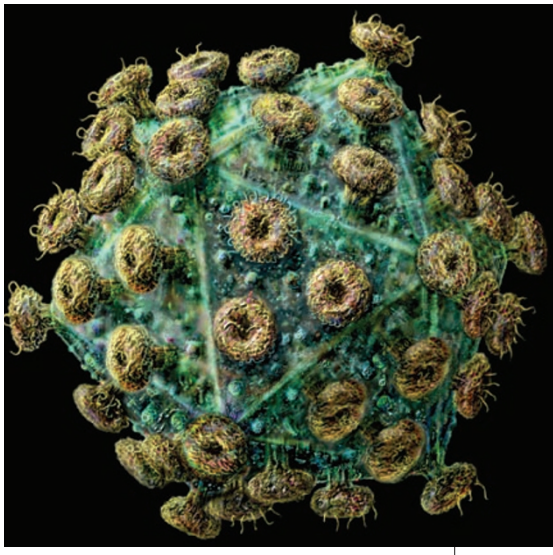
On high alert

HIV keeps the immune system in a hyperactive state, gradually leading to its ruin, reports **Emma Marris**.



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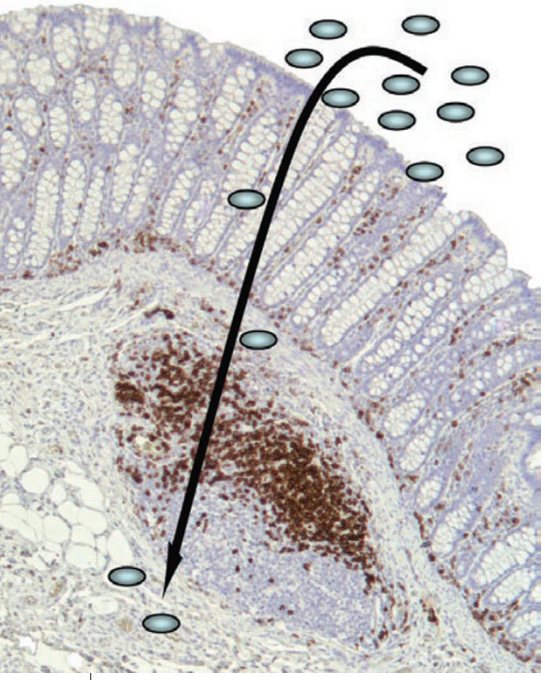
The last time you had a cold, you probably sniffled, coughed and stayed at home in bed for a couple of days. All the while, your immune system fought a quick battle against the cause of the cold: a virus. It was a battle with a foregone conclusion, as many of them tend to be. In most cases, the immune system is triumphant, and mops the floor with the virus within a couple of weeks.

HIV is no ordinary virus, however. After a quick skirmish with the immune system — what researchers call the 'acute phase' of infection — HIV escapes eradication, often living on quietly for years and only much later dragging the immune system to utter ruin.

In the past few years, researchers studying the long road from infection to AIDS have been particularly interested in 'immune activation' — a state in which the immune system stays on high alert and prepared to fight.

In this condition, the immune system marshals many types of cell into an active mode, ready to sense and attack pathogens. The body produces abundant amounts of signalling proteins, known as cytokines and chemokines, and a host of other proteins.



HIV damages the gut and makes it leaky, allowing other pathogens to enter and wreak havoc.

This ready and roused state is short lived in the case of most viruses; however, HIV triggers chronic immune activation. "Practically every arm of the immune system that has been investigated has been shown to be in a hyperactive state," says Jason Brenchley, an investigator at the US National Institutes of Health.

As immune cells are activated, they become targets for HIV, so an active immune system paradoxically amounts to a higher viral load. Cells that constantly replicate when activated eventually become depleted, causing a premature ageing of the immune system. In a process that is still mysterious, chronic immune activation seems to wreck the tissues that produce immune cells[1].

This set of effects has been linked to conditions ranging from heart disease to cancer. Even on its own, immune activation "makes you feel lousy," says Daniel Douek, chief of human immunology at the US National Institute of Allergy and Infectious Diseases' Vaccine Research Center.

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Long road

The basic outline of HIV pathogenesis is well chronicled. The virus enters the body usually through mucosal tissue, such as the lining of the vagina or anus. Once there, it encounters CD4 cells, which orchestrate the immune response. The virus gains entry into these cells, where it insinuates its DNA into host nuclear DNA. For a day or less, each CD4 cell essentially becomes a factory for viruses, and then it dies.

This is what allows HIV to persist where other viruses beat a hasty retreat. Once the acute infection is past, HIV continues to replicate and diversify by mutating into many different forms, each one a new challenge to the immune system (see page S6).

Over years of infection, the average person's CD4 cells slowly decline. HIV takes up residence in quiescent immune cells and possibly in other hideouts (see page S11). The depletion of CD4 cells cripples the immune system, leaving the host vulnerable to any attack, and turning HIV infection into full-blown AIDS.

A key element in this story is pace. The rate of disease progression varies enormously between people, and some 'elite controllers' never reach the milestones that mark AIDS (see page S4). Scientists can roughly predict disease course by looking at virus levels in the blood. As far back as 1993, however, researchers found that elevated levels of $CD38^+$ $CD8^+$ cells — a subset of immune cells that correlate with immune activation — are a better harbinger of AIDS' arrival[2].

"Immune activation is one of the oldest ideas in HIV research," notes Carl Dieffenbach, director of the Division of AIDS at the US National Institute of Allergy and Infectious Diseases. "We have just rediscovered this more times than I care to think about."

Recurring theme

When researchers first began thinking about immune activation, they saw it primarily as a symptom of the illness.

"At the time before we had good drugs, or any drugs at all, I think that most people thought that [if] we got a good drug and knocked out the virus, that immune activation would go away," says Susan Plaeger, director of basic research in Dieffenbach's division. As therapies that control the virus became available, however, it was clear that immune activation lingers even when viral numbers are down.

Several new findings have brought immune activation back to centre stage, according to researchers.

First, scientists discovered, about a decade ago, that sooty mangabeys and African green monkeys, 'natural hosts' of the HIV-like simian immunodeficiency virus (SIV), do not show immune activation and do

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not get sick. Rhesus macaques, the experimental model for HIV vaccines, do have immune activation, however, and develop AIDS (see page S5).

Second, researchers reported in 2008 that elite controllers, despite their seemingly good health and negligible viral loads, show some abnormal immune activation[3]. Finally, many HIV-infected individuals taking antiretroviral drugs have low viral loads but suffer from inflammation-related diseases of ageing — heart disease, liver disease, cancer and perhaps even dementia — earlier than do their uninfected peers.

One trial, called Strategies for Management of Anti-Retroviral Therapy (SMART), which was designed to study drug scheduling in HIV-positive people, found that protein markers of inflammation were higher in those who died during the trial[4]. The implication is that immune activation contributes to mortality from conditions not typically classified as AIDS-related, says Douek.

Overall, evidence from natural host monkeys and clinical observations suggest that viral infection and immune activation are both needed for progression to AIDS.

Persistence of memory

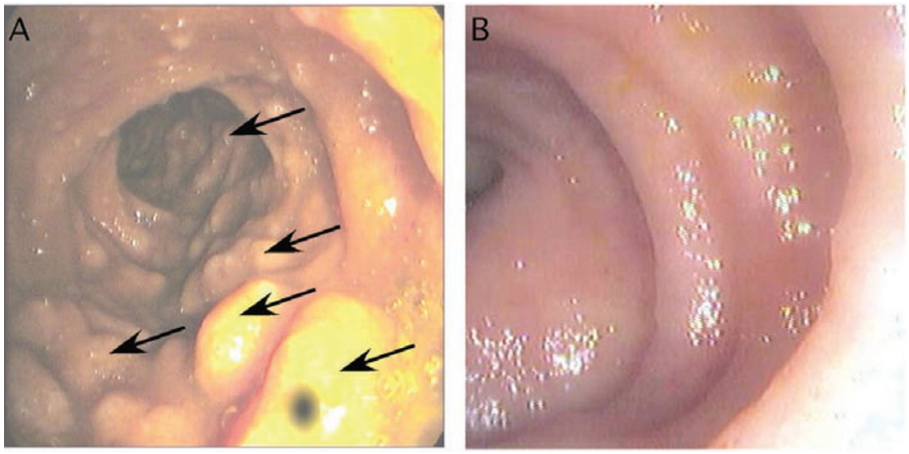
What causes immune activation? Most obviously, it is the virus. Like any invader, it causes immune cells to wake up and gird their loins for battle. It is not clear, however, why the state of activation should persist for decades.

It might be that the kind of cells that are infected are so important to the immune system that the host has no choice but to try to get rid of every last bit of the virus, suggests Guido Silvestri, a pathologist at the Hospital of the University of Pennsylvania in Philadelphia.

In particular, the presence of virus in lymph nodes, where 'central memory' CD4 cells live, could keep the immune system engaged in fighting the virus, Silvestri suggests. These cells specialize in retaining information about a pathogen's identity and creating armies of rank-and-file 'effector' memory cells for when the host re-encounters the threat. Tellingly, sooty mangabeys and African green monkeys do not lose as many central memory cells or show chronic immune activation.

"It doesn't really matter how much virus you produce in the body, but what kind of cells are killed," says Silvestri. "Not all CD4 cells are created equal. Some are really quite expendable."

Evidence in the past seven years of a great decline of CD4 cells in the gut has prompted two more theories about how HIV causes chronic immune activation.



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In the acute phase of infection, HIV depletes the gut's CD4 immune cells (seen in the bumps on left), and their numbers never bounce back (right).

In the acute phase, the virus depletes CD4 cells in the mucosal tissue of the gut, and their numbers never bounce back[5,6]. In the process, the virus also destroys the gut mucosa's structural cells. "The gut has holes, it is leaky," says Douek.

Damage to the gut's immune system allows other pathogens to make their way to lymph nodes and penetrate the body, where the rest of the immune system must wake up and fend them off, says Satya Dandekar, a microbiologist at the University of California, Davis.

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This immune activation persists even when drugs knock the virus down to undetectable levels because the gut has lost its ability to repair itself. Early treatment might prevent this damage, Dandekar says. "A lot of benefit that one sees in early treatment may really stem from repair of the mucosal sites."

Another, potentially complementary, theory suggests that the weakened gut defence allows pieces of the omnipresent — and generally benign — gut bacteria to enter the bloodstream, where they activate the immune system[7].

This 'microbial translocation' has been shown in HIV-infected people in several studies, mostly in the later stages of disease. In May 2010, Douek, Brenchley and colleagues reported in *Science Translational Medicine* that HIV infection increases the numbers of regulatory T cells — a subtype of CD4 cells that modifies the immune response — and lowers the numbers of another immune cell that helps defend the gut mucosa[8]. The resulting imbalance might lead to a leaky gut and a dysfunctional immune system, the researchers suggest.

Some researchers argue that microbial translocation is the consequence, not cause, of immune activation, but Douek dismisses the criticism. "It's a circle — immune activation causes leaky gut which causes immune activation which causes leaky gut," he says. "In a sense it doesn't matter [which came first]."

Given that immune activation is intricately tied to disease progression, measuring viral load or even the number of CD4 cells might not be the best way to chart the disease, Douek adds. Doctors could instead count central memory CD4 cells or markers of immune activation and inflammation, and combine several measurements into a standardized algorithm that predicts the course of infection.

Meanwhile, some groups are trying to calm the chronically alert immune system by adapting therapies for other inflammatory conditions — some as basic as aspirin or vitamin D — and designing drugs to stop microbial translocation.

"Now that we are able, we believe, to suppress virus for many, many years with antiretroviral drugs," says Douek, "immune activation and inflammation in treated individuals may become the greatest obstacle to long-term health." ■

Emma Marris writes for *Nature* from Columbia, Missouri.

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