

Learning from the elite

Researchers hope to unlock the secrets of the select few who rein in, or even resist, HIV infection, says **Bijal Trivedi**.

Bob Hoff has been HIV-positive since 1984. He has never taken antiviral drugs, yet his immune cells are numerous and healthy, and the virus is undetectable in his blood.

Hoff is an 'elite controller' who can do what big pharma and vaccine developers cannot: hold HIV in check and keep AIDS at bay without medications.

More than 33 million individuals are infected with HIV, and about 2.7 million join those ranks each year. However, it is estimated that 1 in every 200 people infected never succumbs to the virus¹, whereas another 6 or so 'long-term non-progressors' (LTNPs) control HIV, albeit with a higher viral load, and remain symptom-free for at least seven years.

Figuring out how these people control HIV could inspire vaccines and therapies that mimic their immune systems. "[When] you meet someone who's been infected for 25 years, looks entirely healthy and has never taken any medications, you just feel like the answer is standing there for us to just fish out," says Bruce Walker, director of the Ragon Institute in Charlestown, Massachusetts.

Since 2003, the International HIV Controllers Study has examined the factors that keep elite controllers and LTNPs healthy. Other research groups are studying the few people with natural immunity to HIV, who resist infection even after multiple exposures.

An infected individual carries, on average, about 30,000 copies of HIV RNA per millilitre of blood. Those with AIDS have more than 100,000 copies, LTNPs have between 50 and 2,000, and elite controllers have fewer than 50, which is well below the detection limit of most conventional tests.

Last year, Walker showed that the immune system in elite controllers cripples the virus,



Some Kenyan sex workers, like Dorothy Mumbo (above), resist HIV infection even after being exposed hundreds of times to HIV-positive men.

forcing it to mutate and evolve in a way that renders it less fit². "These people didn't get infected with a wimpy virus — they made their viruses wimpy," he says.

Hints from the genome

Together with researchers at the Broad Institute in Cambridge, Massachusetts, Walker also led a genome-wide association study including about 1,000 elite controllers. Earlier this year his team announced, at a conference in Banff, Canada, that 350 single-nucleotide polymorphisms (SNPs) clustered in the major histocompatibility complex (MHC) — a region on chromosome 6 rich with immune-response genes — seem to protect elite controllers from the effects of the virus.

One clue to the role of these SNPs comes from a study published in *Nature* in May this year³. Walker and colleagues reported that a variant of the human leukocyte antigen B (*HLA-B*) gene located in the MHC boosts the immune response by producing powerful killer T cells, which recognize and destroy infected cells. T cells from those who carry the *HLA-B57* variant recognize many parts of the HIV virus and more HIV mutants than do T cells from controls.

About 65% of elite controllers carry the *HLA-B57* allele, says Mark Connors, chief of the HIV-Specific Immunity Section at the US National Institute of Allergy and Infectious Diseases. The link between the allele and T-cell function is "an attractive idea," but the computer models need to be backed up experimentally, Connors notes.

Quiescent systems

Rare individuals with natural immunity to HIV could also yield game-changing discoveries. These people — including sex workers, haemophiliacs who have received contaminated blood, and individuals with an infected

partner — are repeatedly exposed to the virus, but never get infected.

"Some women we've been studying for years have been exposed hundreds of times to men we know are HIV-positive. They weren't using a condom, despite counselling, and still they weren't infected," says microbiologist Keith Fowke of the University of Manitoba who has been studying a cohort of commercial sex workers in Nairobi for more than 20 years. "That's well beyond the realm of luck — it's something really biological," he says.

HIV-resistant women appear to have 'quiescent' or resting immune systems, Fowke says. They show lower levels of cytokines, which are signalling proteins that ramp up the immune response, and the activity of many non-immune genes is also lower than in controls.

The women have more regulatory T cells, which calm the immune system, and fewer activated CD4 immune cells. However, their ability to fight other infections and viruses is not compromised.

HIV infects and replicates better in activated cells. Fewer targets allow greater opportunity for the evolution of immune responses that would eliminate the virus, says Frank Plummer, scientific director general of the National Microbiology Laboratory at the Public Health Agency of Canada. The idea that a quiet immune system could be the key is "potentially paradigm shifting," Plummer adds.

Some reported data contradict this hypothesis. Plummer has proposed launching a global consortium to study individuals with natural immunity. He and others are also trying to identify the genes that endow the Kenyan women with resistance to HIV. ■

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1. Okulicz, J. F. et al. *J. Infect. Dis.* **200**, 1714-1723 (2009).
2. Miura, T. et al. *J. Virol.* **83**, 2743-2755 (2009).
3. Košmrlj, A. et al. *Nature* **465**, 350-354 (2010).