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The genetics of coping with HIV

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We respond to infections in two fundamental ways. One, which has been the subject of intensive research over the years, is "resistance," where the body attacks the invading pathogen and reduces its numbers. Another, which is much less well understood, is "tolerance," where the body tries to minimise the damage done by the pathogen. Now an elegant study using data from a large Swiss cohort of HIV-infected individuals gives us a tantalising glimpse into why some people cope with HIV better than others.

The authors find that tolerance varies substantially between individuals, that it's determined at least partly by the genes that one inherits, and that the genes that influence tolerance of HIV are distinct from those that influence resistance. The team, led by Roland Regoes at ETH Zurich, publishes their work on 16th September in the open access journal *PLOS Biology*.

HIV offers a unique opportunity to tease apart the way that the human body handles disease. After the initial infection event, the virus takes up residence in a population of white blood cells called CD4+ T cells. The number of viruses a few months after infection, called the "set-point viral load," can be used to measure resistance – how well a person is fighting the virus. However, HIV infection also offers a ready measure of tolerance – the slower you lose your CD4+ T cells, the better you are tolerating the infection. This situation of cohabitation between human and virus can last many years, but when the number of CD4+ T cells falls below a critical level (fewer than 200 cells per microliter of blood) then the immune system is compromised and the HIV carrier becomes

an AIDS patient, with potentially fatal consequences, if not treated.

The key to the study is the existence of the Swiss HIV Cohort Study, started in 1988, – this provided the authors with more than 3000 HIV-infected people in whom they could measure both set-point viral load and the rate of CD4+ T cell loss. These two values could be used to simultaneously assess both resistance and tolerance, and combining these with a wealth of demographic and genetic data on the same individuals allowed the authors to start to explore the workings of tolerance.

The first question they asked was whether age and sex matter. On average, they found, men and women tolerated HIV equally well, but older people had a lower tolerance, with the disease progressing almost twice as fast in a 60-year old as in a 20-year old.

The authors then looked at hereditary factors that influence tolerance of HIV. They looked at genetic differences that are known to be associated with resistance to HIV and asked whether these were also associated with tolerance. The answer was an overwhelming "no," confirming the expectation that resistance and tolerance are biologically distinct phenomena.

However, one gene that is involved in resistance also seemed to be involved in tolerance. The HLA-B gene, which encodes a protein involved in recognition of pathogens by the immune system, varies considerably between individuals. Although some of these variants are known to influence a person's resistance to HIV, the authors found that other variants of the same gene correlated with tolerance. So this key player in the immune system seems to influence both tolerance and resistance, but in distinct ways.

Surprisingly, there seemed to be no trade-off between tolerance and resistance – this had been expected from other studies, but it seemed that

in this cohort of HIV carriers, tolerance and resistance could be independent or go hand-in-hand.

The authors claim that "these findings add to our understanding of how hosts tolerate infections and could open new avenues for treating infections." The exciting thing about tolerance is that – unlike resistance – it's expected to be "evolution-proof." One of the issues with achieving resistance to a virus, whether naturally or with the use of drugs is that it is in the virus's interest to develop evasive tactics that get round the resistance mechanism. However, tolerance of the virus is as much in the virus's interest as it is in the human host's, so viral evolution should not be an issue.

The work described here represents an early step in exploring the mechanism of tolerance in humans, and once we understand how tolerance works, we may then be in a position to manipulate it and help people to live with HIV more comfortably and for longer

More information: Regoes RR, McLaren PJ, Battegay M, Bernasconi E, Calmy A, et al. (2014) Disentangling Human Tolerance and Resistance Against HIV. *PLoS Biol* 12(9): e1001951. DOI: 10.1371/journal.pbio.1001951

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