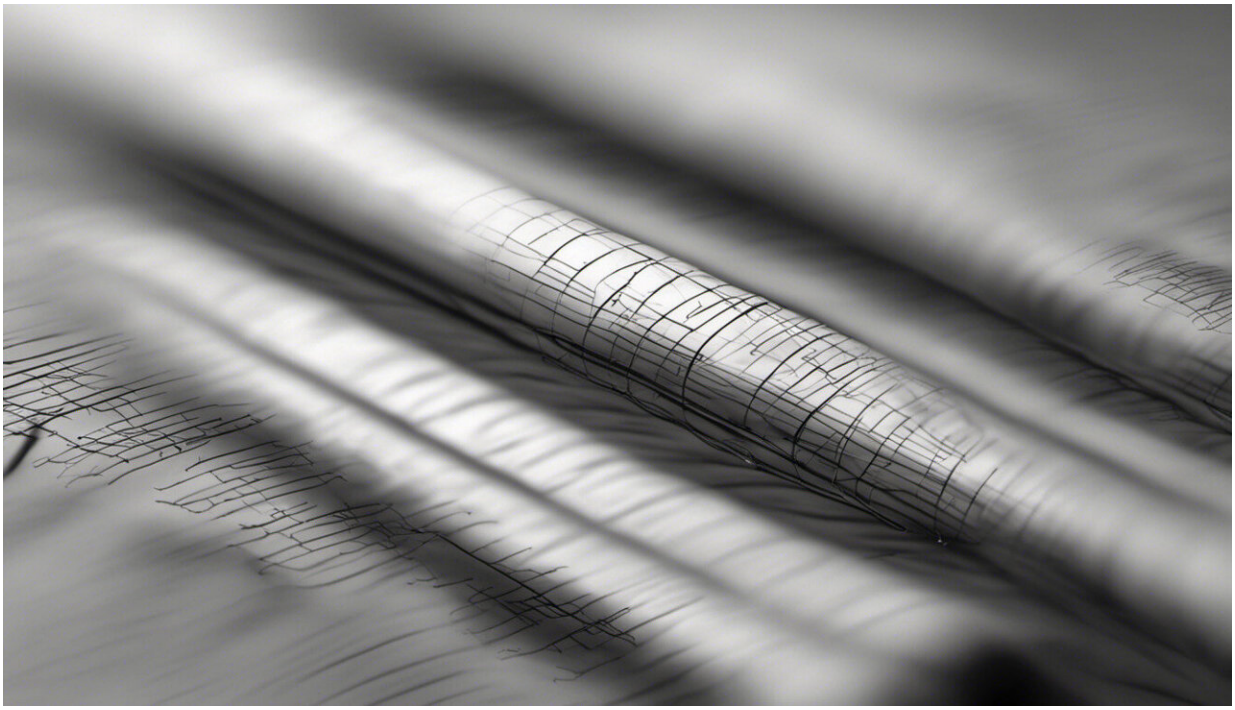
Withdrawal from the evolutionary race

September 18 2014, by Peter Rüegg



Credit: AI-generated image (disclaimer)

In some HIV sufferers, the immune system does not fight off the immune deficiency virus. Instead, the body tolerates the pathogen. A research team headed by ETH Zurich has now determined how strongly patients differ in their tolerance and upon which factors it depends.

In ecology, disease tolerance is defined as a host strategy not to fight a pathogen tooth and nail, but rather tolerate it to live (and survive) better

in the long term. One key feature of tolerance is that the disease only progresses very slowly – if at all – even if the host carries a high pathogen load.

Roland Regoes, a senior scientist at ETH Zurich's Institute of Theoretical Biology, has now transferred this approach to HIV. He set about investigating whether there are infected people who are more tolerant of the HI virus than others and if so which factors this tolerance depends upon. The paper has just been published in *PLOS Biology*.

From the mangabey to man

Regoes came up with the idea for the study during his postdoctoral stay in Atlanta, where he was working with researchers from a large primate centre. They studied sooty mangabeys (Cercocebus atys) infected with SIV, an HIV-like virus that affects primates. Although a large amount of the SI virus was found in their blood, some of the monkeys did not become ill. "The infection in this primate species is one of the best examples of disease tolerance," says the researcher. He and his co-authors – all medical doctors – are now interested in whether the concept of tolerance can also be carried over to human diseases. In order to determine which factors are linked to tolerance, the scientists evaluated the data from the Swiss HIV Cohort Study statistically.

The young tolerate HIV better than older individuals

Their analyses revealed that certain patient groups are more tolerant of HIV than others. For instance, the twenty-year-old group is more tolerant than sixty-year-olds, with the disease developing 1.7 times more rapidly in older patients than in their younger counterparts.

The same goes for the group of patients whose HLA-B genes come in

two different variants. HLA-B genes are a group of genes which facilitate immunity to the HI virus. Every person has two copies of every gene, which do not have to be identical. If they are not, this is referred to as heterozygosity. If both HLA-B variants are identical, i.e. homozygotes, the tolerance of the virus is considerably lower.

Certain HLA-B variants are known to facilitate an immune defence against the virus geared towards its destruction. These variants are not responsible for tolerance. Instead, tolerance is linked to combinations of other HLA-B variants.

Regoes and his co-authors did not find any difference in tolerance between genders. The ETH-Zurich researcher recorded roughly the same high values in women and men, although on average women exhibit lower initial viral loads than men.

Ratio of immune cells to virus decisive

For his analyses, Regoes used the number of particular immune cells, the CD4+ cells, on the one hand and the viral load during the asymptomatic phase on the other. The latter is a key quantity in HIV infection. As soon as the virus infects someone, it multiplies rapidly and heavily before the immune system reduces its number to a certain level. From then on, the immune system keeps the pathogen relatively well under control for a long time. However, the number of CD4+ cells drops continuously until it reaches a critical level. If the number of these immune cells falls below 200 per millionth of a litre of blood, AIDS breaks out. The researchers calculated the tolerance of HIV sufferers to the virus from the correlation between the rate at which the CD4+ cells decreased and the viral load during the asymptomatic phase.

Tolerance-based treatments?

Tolerance and resistance are alternative but complementary defence strategies deployed by a host to combat pathogens. In the case of tolerance, it is not the destruction of the adversary and thus the reduction of the viral load that is the priority, but rather the alleviation of the negative effects of the infection for the host. This is not tantamount to capitulation. Instead, the strategy ensures that the evolutionary race between the parties cools off. "It is heading in the direction of commensalism," says Regoes – a kind of ceasefire between two disparate partners. However, the two strategies have different evolutionary consequences: while tolerance tends to suppress the emergence of adaptations, resistance challenges the adaptability of viruses, which results in an evolutionary arms race with the adversaries.

"In the long run, one could try to use this ceasefire therapeutically," says the ETH-Zurich researcher. Tolerance-based therapeutic strategies could constitute interesting alternatives as they are not expected to lead to treatment-resistant pathogens.

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 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

Provided by ETH Zurich