

Superinfection: Second HIV infections happen as often as first ones

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Two studies of people with HIV in Rakai, Uganda, and Mombasa, Kenya, presented at the 19th Conference on Retroviruses and Opportunistic Infections, show that the rate at which the patients acquired second, subsequent strains of HIV was about the same as the HIV incidence rate in the general population.

This is called superinfection. It needs to be distinguished from dual infection, where a person acquires two different strains of HIV at the same time (this is quite common) and viral divergence, which is when a person acquires one strain of HIV but it diversifies into different strains during chronic infection because of 'copying mistakes' during replication, which happens in all untreated chronic infections.

Superinfection is of particular interest to vaccine studies because it shows that HIV infection does not confer any general immune protection to infection with other HIV viruses, although some studies have shown that some people develop a degree of immunity to their partner's specific virus.

There has been little consensus on how often superinfection happens and, if it does, whether it has any consequences for the health of people living with HIV.

The first cases of superinfection were detected because in individual cases something clinical *did* happen, usually a jump in viral load or drug failure because the second virus was a drug-resistant strain, and for a while such cases were used as a warning to HIV-positive people not to stop using condoms with HIV-positive partners.

Until recently, however, we have not had the genetic equipment to show how common superinfection is, and therefore how common adverse consequences are.

Superinfections in Rakai

Andrew Redd of the National Institute of Allergies and Infectious Diseases collaborated with the researchers conducting the well-studied Rakai Cohort in Uganda to perform so-called ultra-deep sequencing, next-generation genetic tests on blood samples collected at different times from people with HIV.

They were looking for evidence that the HIV in some people's blood tended to cluster into two or more different strains that were dissimilar to each other and that only one strain had initially been there. Only if both of these requirements were satisfied could the person be considered to have had a superinfection. The tests detected differences in the p24 core and the gp41 envelope proteins of HIV and could detect a virus that formed as little as 1% of the total viruses circulating in a person's blood if they came from totally different viral subtypes, or 7% if they came from the same subtype but were genetically distinct.

They tested blood samples from two different periods: one taken at diagnosis between 1997 and 2002, and then one taken at least 2 years later, before the people started antiretroviral therapy. These samples were taken between 2 and 11 years later.

The researchers initially did the tests on 11 couples where both partners had HIV but had been infected with different subtypes, and found 2 cases of superinfection.

They then performed the test on samples from 109 people and found 7 cases of superinfection. This was equivalent to a second-infection incidence of 1.44 superinfections per 100 people a year.

They then performed the test on samples from 149 people and found 7 cases of superinfection. In 4 cases both the initial and the second infections were of HIV subtype D, which is the most common one in the area, and 3 were of different HIV subtypes.

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people a year, which is not significantly different to the current annual infection rate in the Rakai cohort, which is 1.15% a year. However, HIV-positive people in the Rakai cohort tend to have higher risk factors on average than others (by definition, since they acquired HIV). Adjusting for risk factors, the present-day annual HIV incidence in this group of people would be 2.51%, or just under twice the superinfection rate.

Superinfections in Kenyan women

The study of superinfection in Kenya is an ongoing project in the Mombasa female sex worker cohort, a group of initially HIV-negative women who have been studied since 1993 – one of the longest cohort studies in Africa. In this cohort of 2 759 women there have been 311 cases of HIV infection within a median follow-up time of 5 years.

This study compared samples from within 6 months of infection in HIV-positive women in the cohort, with samples from more than 2 years after infection. The method looked at genetic differences between the samples in 3 areas of the HIV genome – the *gag*, *pol* and *env* genes – and used a mathematical method to calculate the likelihood that different sequences in an individual were due to viral diversification, or came from 2 viruses.

In 56 women previously examined they found 12 cases of superinfection. They have now screened another 54 women and found 7 new cases of superinfection, totalling 19 in 110 women screened so far.

AIDS brief

They calculated that the annual incidence of superinfection in the women was 3.06%. This is similar to the HIV incidence, which is currently 3.25% a year.

The majority of the superinfections found happened in the first 4 years after infection, and 8 of the 19 within the first 2 years, with another 4 in the first 3 years. Of the 7 others, 3 happened at an indeterminate time within the first 4 years, one happened between years 3 and 4, but 3 happened after 5 years of infection. This is relevant because most cases of superinfection tend to happen in

the first few years after infection, which may indicate a reduction in risk behaviour but may indicate a broadening of the immune response to HIV over time.

Researcher Keshet Ronen of the Red Hutchinson Cancer Research Institute in Seattle commented: 'We don't know yet whether the clinical outcome for superinfected women is different, or whether incidence differs between subtypes.' The researchers will now compare the immune responses in women who were and were not superinfected

to determine if the latter have broader protective immune responses.

Redd A, et al. Next-generation deep sequencing reveals that the rate of HIV superinfection is the same as HIV incidence in heterosexuals in Africa. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 58, 2012. The abstract is available on the official conference website.

Ronen K, et al. Detection of frequent superinfection among Kenyan women using ultra-deep pyrosequencing. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, abstract 59LB, 2012. The abstract is available on the official conference website.

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