The origin of SARS-CoV-2 variants of concern

A narrative propagated by the media of SARS-CoV-2 variants of concern arising in people living with HIV does not tell the whole story. Talha Burki reports.

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The omicron variant (B.1.1.529) of SARS-CoV-2 did not come out of nowhere. But nor did it emerge from the dominant variants in circulation last year. Omicron is most closely related to the strains of SARS-CoV-2 that were sequenced in mid-2020. What happened between then and November, 2021, when the new variant was first detected?

There are three main theories. The first holds that omicron simmered for months in a population where sequencing was scarce and travel highly restricted. This seems implausible, given the interconnectedness of the world and the extraordinary transmissibility of the variant. The second theory is that an animal population became infected, the virus mutated, and it was then spread back into humans. In March, 2020, a tiger at Bronx Zoo in New York City (NY, USA) started coughing. She subsequently tested positive for SARS-CoV-2, as did three other tigers and three lions. Human-to-mink and mink-to-human transmission of SARS-CoV-2 have been documented.

"Many animals get infected by this coronavirus, so it is very difficult to tell how common back-and-forth transmission between animals and humans might be; the potential for the emergence of variants is certainly there, though I think that it is not very likely", said Salim Abdool Karim, director of the Centre for the AIDS Program of Research in South Africa (Durban, South Africa). Very few places track diseases in animal populations, and mid-pandemic is not an easy time to start.

The theory that has gained the most traction involves a persistent infection with SARS-CoV-2 in an individual whose immune system is compromised. The mechanism is straightforward. If your immune system is unimpaired, it typically takes 10–14 days to clear an infection with SARS-CoV-2. But people with immunosuppression struggle to generate a sufficiently powerful immune response to do this. In which case, it is possible for the virus to linger, perhaps for several months, neither killing the host nor being destroyed by the neutralising antibodies. "The immune system would be doing enough to prevent the virus from overwhelming the host, but the virus can still hang around and mutate; the immune system continues trying to clear the virus, and the virus keeps replicating", said Linda-Gail Bekker, director of the Desmond Tutu HIV Centre at the University of Cape Town (Cape Town, South Africa).

"If a virus is going through an evolutionary process inside the host, then it is quite likely that it would be adapting to be better at entering the cells and evading the immune response; this could lead to a variant with enhanced transmissibility, and enhanced immune evasion", added Richard Lessells of the School of Laboratory Medicine & Medical Sciences at the University of KwaZulu-Natal (Durban, South Africa).

Lessells is co-author of a preprint that describes the case of a 36-year-old woman with HIV who was not being effectively treated. "She had been prescribed antiretroviral therapy but the fact that it was not suppressing the HIV was not initially picked up and acted upon", said Lessells. The patient was infected with SARS-CoV-2 before the emergence of the beta variant (B.1.351). The virus remained detectable for 216 days, during which time it evolved from something resembling the ancestral virus into a strain similar to beta, with indications that it had the capacity for partial vaccine escape. The variants that emerged within the patient were never detected by the wider genomic surveillance system, indicating that they did not successfully spread into the general population. The woman overcame the SARS-CoV-2 infection soon after she started effective antiretroviral therapy (ART).

There are precedents for prolonged infections in patients with HIV. "We are seeing an epidemic of cervical carcinoma in women who are living with HIV, because human papillomavirus infection is persisting in a way that it would not in someone with full immunity", said Bekker. Omicron was first identified in South Africa, where there are 7·8 million people living with HIV, one-third of whom are not virally suppressed. The country reported the presence of omicron to WHO on Nov 24, 2021. Still, South Africa is one of a minority of nations worldwide to do substantial genomic sequencing of SARS-CoV-2. Omicron was also found in samples taken from patients in Botswana on Nov 11. Within days of the South African announcement, it became clear that the new variant was in several countries around the world.

"We can allow for the possibility that omicron developed in a South African patient with uncontrolled HIV, but that does not mean we should regard people living with HIV as the major source of SARS-CoV-2 variants. A lot of media reports are failing to make this clear", commented Bekker. "Anyone who is severely immunocompromised can develop persistent infection with SARS-CoV-2. It could be someone with cancer, the recipient of an organ transplant, or an individual living with untreated diabetes."

Bekker worries that discussions implicating immunosuppression in variants of concern are coming to be dominated by HIV, further stigmatising a community that already faces plenty of prejudice. Moreover, exacerbating stigma might discourage people with HIV, diagnosed or otherwise, from seeking health care, reducing the possibility of viral suppression, and heightening the chances of the emergence of a variant of concern. Around 8 million of the estimated 25·3 million people living with HIV in sub-Saharan Africa are not virally suppressed.

Karim points out that the five variants of concern have come from four different continents. Indeed, the alpha variant (B.1.1.7) is thought to have arisen as the result of a persistent infection in the UK. "Variants are occurring in all kinds of settings; people with immunosuppression can be found all over the world. I am dismayed to see undue attention focused on HIV—why not point the finger at cancer or other causes of immunosuppression? You cannot help but wonder whether it is because HIV is most common in Africa", Karim told *The Lancet Infectious Diseases*. "The issue here is immunosuppression, and that is a phenomenon that is far broader than HIV", agreed Lessells. "We certainly should not be pinning all this on HIV specifically."

Ensuring that patients with HIV are placed on effective treatment would help minimise the risk of lingering SARS-CoV-2 infection, which would in turn reduce the chances of a variant spilling into the general population. But advancing this argument as a primary reason for rolling out ART implies that HIV matters because of the hazards it presents to those who are not infected.

"Of course we need to step up antiretroviral therapy for its HIV therapeutic and prevention benefits, but we do not need to use the threat of variants for why people with HIV should be on treatment", stressed Karim. "We should not be creating a narrative that people who do not know that they are HIV positive or who are not on antiretroviral therapy are a COVID-19 threat to the rest of the world." Measuring antibody response after vaccination against COVID-19 in anyone with suspected immunosuppression, and providing additional doses of the vaccine for individuals whose response is suboptimal, would help slow the spread of any variant. "If it is true that immunosuppressed people are the main source of variants, then we should be putting a lot more effort into ensuring these individuals, regardless of the cause of their immunosuppression, have effective immunity through vaccination", concluded Karim.

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