# New Concerns About Coronavirus Evolution in Immunosuppressed Patients

Experts call for heightened precautions and better, more intensive therapies for COVID-19 patients with weakened immune systems.

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In the wake of findings that COVID-19 virus variants are more likely to spring from patients with weakened immune systems, leading medical experts are calling for heightened precautions in the treatment of such individuals and better, more intensive therapies to help them fully recover from their disease.

Renowned virologist Dr. Larry Corey of Seattle's Fred Hutchinson Cancer Research Center and five colleagues in the field raised their concerns in commentary published Wednesday by the New England Journal of Medicine.

"I'm very disappointed in the pace of research on what's going on with COVID-19 in immunosuppressed persons, and you know, we deserve better," Corey said in an interview prior to release of the paper.

The report, whose co-authors include Hutch computational biologist Dr. Trevor Bedford, references several studies of immune compromised patients whose COVID-19 infections lingered for months and in which the SARS-CoV-2 virus underwent large numbers of mutations.

**A multimutational evolutionary jump**

They include patients with immune system disorders, solid organ transplant patients, cancer patients undergoing long-term chemotherapy or radiation, people with blood cancers who have had CAR T-cell therapy, and people living with HIV not controlled by antiviral drug regimens. What they have in common is long term, persistent infection, which can allow the constantly replicating virus to pile up lots of mutations. Some of those mutations can lead to marked shifts in the genome of SARS-CoV-2, and if they give the virus a survival advantage, that may result in the emergence of a threatening new variant.

These rapidly emerging, multimutational variants are unusual. Biologists call them examples of

"saltational evolution."

"It's not the way Darwin taught us the evolution occurred," Corey said. "Saltational evolution is sort of an evolutionary jump that is not common. It's as if you all-of-the-sudden go from walking to flying, with nothing in between."

Among the cases cited was that of a patient with an autoimmune condition called antiphospholipid syndrome. Researchers identified in viruses from this person 31 substitutions of letters in SARS-CoV-2 genome sequences, as well as three deletions — unreplaced dropouts of letters or phrases in the genetic code.

Corey's Hutch colleague and coauthor Bedford is an expert in evolutionary biology and has been tracking the family trees of SARS-CoV-2 since the earliest days of the pandemic. He notes that the multiple mutations that have created most of the alarming "variants of interest" and "variants of concern," now designated by Greek letters such as beta and gamma, appear to have emerged in a kind of normal, stepwise accumulation of mutations. But the so-called alpha variant, which popped up in the United Kingdom, is different.

"Basically, the entire suite of mutations associated with the alpha variant appears at the same time. While it's possible that a transmission chain percolated along and gathered multiple mutations before taking off, this pattern is consistent with emergence from a single persistent infection," Bedford said.

The precise origins in India of the delta variant, the most worrisome to date, have yet to be determined. But the authors note that it is characterized by "a constellation of mutations that were identified in previous variants of concern or interest." This mashup of nasty traits has emerged rapidly with an evolutionary advantage of higher transmissibility and is quickly out-competing other variants. It is now dominant in the U.S. and worldwide.

**Changes needed to address concerns**

In the New England Journal of Medicine article, the authors call for steps to address their concerns about saltational evolution of SARS-CoV-2 in immunosuppressed patients. They include tightening the precautions taken within medical settings to reduce the risk of such patients transmitting the virus to staff, family or other patients.

Immunosuppressed patients should also be informed about the need to self-isolate until testing shows they are no longer shedding virus, and about the need for their household contacts to be vaccinated.

One step would be to prioritize those patients for immunizations, and to carry out studies of antibody and T-cell responses in such patients who are vaccinated. There are strong indications in recent studies that a third mRNA vaccination (such as the Moderna vaccine) may be beneficial to people who have difficulties generating an immune response to the first two.

The authors also recommend that nursing homes, where vaccination rates are high, provide monoclonal antibody infusions to patients who show low antibody responses to vaccines, as well as to their family members. Co-author Dr. Myron Cohen, of the University of North Carolina, helped design and run a study supporting that approach. He is a longtime collaborator with Corey, and both are co-principal investigators of the COVID-19 Prevention Network, which manages trials of vaccines and monoclonal antibody drugs to prevent the disease.

Given that some variants have begun to show resistance to currently available monoclonal antibody drugs, the authors note that new COVID-19 antiviral drugs in development, such as Merck's molnupiravir — now in large-scale testing — do not target the rapidly evolving spike proteins that endow new variants with possible evolutionary advantages. Instead, these drugs — which interfere with the virus's ability to copy itself — provide "an alternative mechanism of protection that should be unaffected by mutations that compromise monoclonal antibodies."

Finally, the authors call for development of rapid tests to identify variants with potential to escape vaccines and therapies. Together, these steps may improve the care of immunosuppressed patients who are struggling with COVID-19 and protect public health by helping to head off the rise of future variants of concern.

In his long career as a virologist at the heart of the struggle to develop drugs and vaccines for HIV, Corey has been a leading voice on the need to combat stigma against people living with that virus. He recognizes that acknowledging that SARS-CoV-2 variants may evolve more quickly in immunosuppressed people could be used to stigmatize that population.

It is a surprisingly large number of people. In the U.S. alone, a study published in 2016 estimated that about 3% of the adult population — about 6 million people — is immunosuppressed.

But Corey said stigmatization is best prevented by relying on data.

"You want to have data to take care of these patients and prevent transmission, and also recognize that the frequency of saltational evolution is not high," Corey said. "The way to handle all stigma is with truth and facts. There are many people who generate variants. It's not just the immune-compromised persons."

But Corey said much more effort is needed, immediately, to gather useful data on this intersection COVID-19 and the immunocompromised patient. That includes committing to research on the how the immune systems of immunosuppressed people respond to vaccines and treatments.

"We need to develop better data and better guidelines on how to take care of these people," he said. "We owe them… Let's move on here and start doing those studies."

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