

The critical role of antivirals in the management of COVID-19 and Long COVID

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Long COVID

Post-COVID-19 syndrome or 'long COVID' is generally described as symptoms extending beyond 12 weeks from initial COVID-19 symptom onset, although the World Health Organization more specifically defines the syndrome as one that "occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis". Both definitions appear vague and cover a gamut of symptoms which has caused difficulties in study design and comparison between studies.

Symptoms of long COVID are also often diversely defined between individuals and studies but range from fatigue and difficulty concentrating, to neurological and neuropsychiatric symptoms, respiratory and cardiovascular problems, and metabolic disease. Long COVID can be very mild to severely debilitating and can include evidence of organ damage. Evidently the syndrome is complex and studies can not only be complicated by the definitional issues but also by the impact of other underlying conditions and, for example, recovery from post-intensive care unit syndrome. The underlying pathophysiological mechanisms are poorly understood at present.

Several large studies have shown correlations between the severity of the initial disease and the impact of post-COVID-19 syndrome. However, people experiencing mild illness may also report long COVID symptoms. For example one study documented long COVID in almost 60% of 16-30 year old patients without correlation to primary illness severity (Mehandru, S., Merad, M. Pathological sequelae of long-haul COVID. *Nat Immunol* 23, 194–202 (2022). <https://doi.org/10.1038/s41590-021-01104-y>). Current hypotheses of the underlying mechanisms contributing to long COVID are outlined in Figure 1 and include ongoing viral replication (including associated pro-inflammatory responses), viral and/or immune mediated tissue damage, a severe inflammatory response coupled with a delayed or defective resolution of inflammation, persistent immunological abnormalities and altered homeostatic processes amongst others.

There are reports of isolation of viral RNA and antigens in, for example stool specimens, for up to 7 months after acute illness but it is unclear if this represents ongoing viral replication. Others have described patients that shed "live" virus from the respiratory tract for over 100 days (Ma, MJ., Qiu, SF., Cui, XM. et al. Persistent SARS-CoV-2 infection in asymptomatic young adults. *Sig Transduct Target Ther* 7, 77 (2022). <https://doi.org/10.1038/s41392-022-00931-1>). Taken together numerous studies suggest that replicating virus is able to persist in various tissues and/or is inadequately cleared over an extended time period (Proal and VanElzakker. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Front. Microbiol.*, 23 June 2021 | <https://doi.org/10.3389/fmicb.2021.698169>). These data are consistent with a role for antivirals in the treatment of long COVID.

The role of antivirals

Reports of improved clinical symptoms on administration of anti-SARS-CoV-2 vaccines in patients with post-COVID syndrome are consistent with a role for a persistent "pool" of replicating SARS-CoV-2 and suggest that interventions, such as antivirals, that may eradicate these pools could assist in the treatment of long COVID. Indeed, recent anecdotal data from studies involving small numbers of long COVID patients treated with the antiviral Paxlovid indicate that antiviral treatment can have a positive impact on long COVID symptoms.

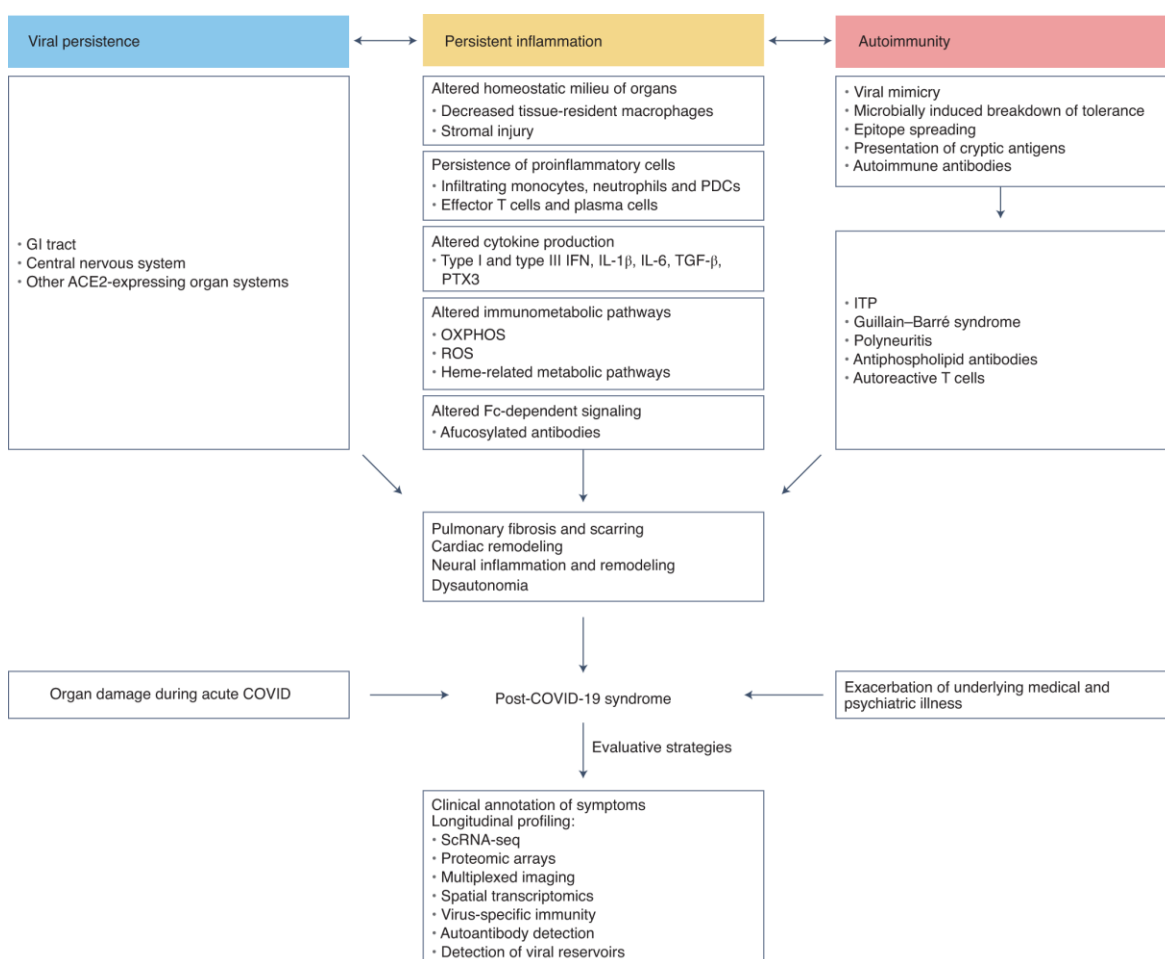
There is also emerging evidence that the use of antiviral medications during the acute phase could reduce a person's risk of developing long COVID. These observations are consistent with studies linking disease severity and high viral load during the acute phase with the risk of developing long COVID.

Further studies are warranted, but at this stage it appears antivirals may have a twofold role in the management of long COVID:

1. Early treatment during the acute phase to reduce viral replication and the development of more severe disease which may increase the risk of developing long COVID
2. Eradication of persistent viral replication in long COVID patients

Fig. 1: Putative mechanisms and diagnostic strategies for patients with post-COVID-19 syndromes.

From: Mehandru, S., Merad, M. Pathological sequelae of long-haul COVID. Nat Immunol 23, 194–202 (2022)

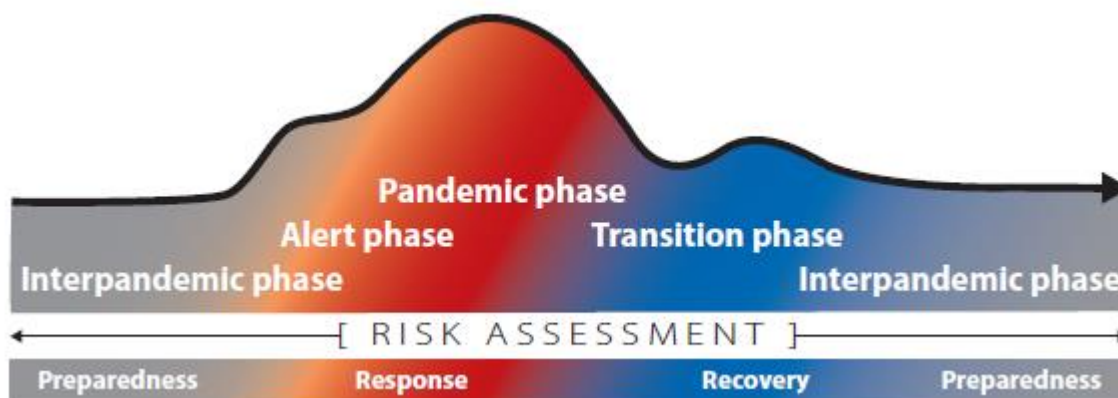


Delayed resolution of inflammation, autoimmunity and viral persistence represents overlapping mechanisms that may contribute to the pathogenesis of post-COVID-19 syndromes. Strategies to better characterize patients with post-COVID-19 syndromes are indicated. ITP, idiopathic thrombocytopenic purpura; OXPHOS, oxidative phosphorylation; PDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; TGF- β , transforming growth factor- β .

The future of the COVID-19 pandemic

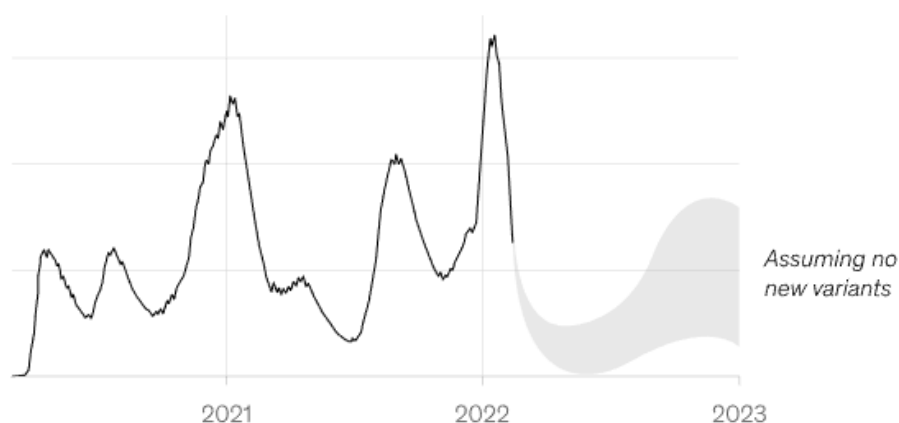
A pandemic is defined as “an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people”. COVID-19 is the most recent pandemic but by this definition there were at least 5 in the last roughly 100 years: 4 influenza and 1 HIV/AIDS. Typically viral diseases are not eradicated post pandemic (in fact only one human viral disease has ever been eradicated: smallpox) but remain in the population and continue to cause disease, albeit at a less globally significant level. For example, the virus which caused the most recent pandemic before COVID-19 (influenza 2009 H1N1) remains in circulation today. Influenza was and remains a significant pathogen responsible for a large number of illnesses and deaths worldwide.

The stages of a pandemic are as follows (reproduced from the US CDC):



The COVID-19 pandemic phase is still ongoing and it is not yet clear if the world is moving into the transition phase.

Dr. Fauci, director of the USA National Institute for Allergy and Infectious Diseases has noted that eradication of SARS-CoV-2 is “not going to happen with this virus”, so the key question is will COVID-19 become an endemic disease much like influenza (although potentially significantly worse) or will new variants emerge? Modelling of US hospitalisation data by McKinsey & Company suggests a further wave comparable to the above transition phase in late 2022/early 2023 *if no new variants emerge*:



Notably, community based disease is likely to be significantly greater than that predicted by the hospitalisation wave.

The WHO currently lists 4 circulating variants of concern and one variant of interest, all of the Omicron lineage. It is not possible to predict the timing of the next variant or if/when it might emerge, but the ongoing high levels of infection, even in highly vaccinated countries like Australia and the mixed worldwide vaccination status provide a fertile ground for such an emergence.

We also know that like influenza, immunity to SARS-CoV-2 wanes over time, so like influenza it is likely to become endemic and cause periodic epidemics, perhaps during the winter months. **In short it is here to stay and antivirals will have an ongoing role whether in dealing with global disease caused by emergent variants or national outbreaks as a result of waning immunity and/or novel variants.**