# Are People With HIV at Greater Risk for Long COVID?

HIV-positive people have a number of risk factors, including chronic inflammation and comorbidities, that increase the likelihood of long-term symptoms.

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People living with HIV may be more prone to develop long COVID, the wide range of symptoms that can last for months or years after SARS-CoV-2 infection, according to a growing body of evidence. While HIV-positive people have several risk factors that may make them more susceptible to long-term problems after a bout of COVID-19, much remains to be learned.

Since early in the pandemic, some people have reported persistent symptoms that arise after acute COVID, including relentless fatigue, cognitive impairment ("brain fog"), shortness of breath, post-exertional malaise (inability to recover after exercise) and postural orthostatic tachycardia syndrome (POTS). More severe acute COVID and various comorbidities raise the risk for prolonged symptoms, while vaccines are protective. However, some formerly healthy fully vaccinated people who had mild acute SARS-CoV-2 infection nonetheless develop long COVID.

The causes of long COVID—also known as post-acute sequelae of SARS-CoV-2, or PASC—are still unclear, but they may include persistent SARS-CoV-2 infection, reactivation of existing pathogens, immune responses that don't return to normal after acute infection, a leaky gut, abnormal blood clotting and autoimmunity.

People with HIV may be at greater risk due to underlying systemic inflammation and immune dysregulation as well as a higher comorbidity burden, according to a 2022 overview of COVID and HIV by Matthew Spinelli, MD, medical student Benjamin Jones, and Monica Gandhi, MD, MPH, of the University of California San Francisco (USCF). Indeed, a retrospective analysis of people in New York City who required emergency department care or hospitalization for COVID during the early months of the pandemic found that people with HIV were significantly more likely to report persistent symptoms a year later.

## HIV and Long COVID

HIV experts have been at the forefront of long COVID research. Michael Peluso, MD, Timothy Henrich, MD, longtime HIV cure researcher Steven Deeks, MD, and colleagues at UCSF are running a cohort study dubbed LIINC (Long-term Impact of Infection with Novel Coronavirus) that leverages

the infrastructure of UCSF's long-running SCOPE cohort of people living with HIV.

Two years ago, Peluso and colleagues reported results from a small study showing that although unvaccinated HIV-negative people and HIV-positive people on antiretroviral treatment had "broadly similar" SARS-CoV-2-specific antibody and T-cell responses, people with HIV were about four times more likely to develop long COVID symptoms. Several of the most common symptoms were at least twice as frequent in HIV-positive people. Those with HIV had lower levels of memory CD8 T cells targeting SARS-CoV-2 and higher levels of SARS-CoV-2-specific CD4 T cells expressing PD-1, a marker of immune cell exhaustion. Levels of certain inflammatory biomarkers were associated with persistent symptoms. "HIV status strongly predicted the presence of PASC," the researchers concluded. "There are lots of reasons why this might be the case based on what we know about the effects of HIV on health," Peluso told POZ.

A larger study by the same group looked at links between long COVID symptoms and medical history—including HIV status and prior infection with Epstein-Barr virus (EBV) and cytomegalovirus (CMV)—in 280 adults with prior SARS-CoV-2 infection, 54 of whom had HIV. They found that some long COVID symptoms, such as fatigue and cognitive dysfunction, were independently associated with recent EBV reactivation or high EBV IgG antibody levels but not with ongoing EBV viremia. People with HIV were more than twice as likely to have persistent neurocognitive symptoms. On the other hand, people with evidence of prior CMV infection were less likely to develop neurocognitive impairment.

As reported at the 2023 Conference on Retroviruses and Opportunistic Infections (CROI) and in a Lancet preprint, George Yendewa, MD, MPH, and Grace McComsey, MD, of Case Western Reserve University, and colleagues analyzed more than 3 million people in the TriNetX health research database, including 28,904 people with HIV, who had confirmed SARS-CoV-2 infection between January 2020 and September 2022. They found that HIV-positive people were more likely to experience persistent symptoms and had increased odds of developing new health conditions, including diabetes, heart disease and cancer, after a bout of COVID, but vaccination lowered the risk. The likelihood of long COVID did not differ based on HIV viral load, CD4 count or use of antiretroviral therapy.

Long COVID among people living with HIV is also a concern in lower- and middle-income countries. An observational study in India, published in 2021, found that 11% of unvaccinated people with generally well-controlled HIV, most of whom had had mild acute COVID, had persistent symptoms four months later. In a study presented at last year's International AIDS Society Conference on HIV Science, Ever Arturo Corral-Herrera, MD, of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City, and colleagues found that more than a third of people seen at their HIV clinic had symptoms of long COVID three months after acute infection, most commonly fatigue. Women, people with overweight or obesity and those with three or more comorbidities were more likely to have persistent symptoms. People with and without long COVID were about equally likely—over 90%—to have received three vaccine doses.

In addition to other risk factors, people with HIV may be more prone to SARS-CoV-2 reinfection.

The risk of long COVID does not appear to be greater with a subsequent infection—in fact, it is likely to be lower as people develop stronger immunity—but the cumulative risk adds up with more infections over time.

As reported in Emerging Infectious Diseases, researchers from the Centers for Disease Control and Prevention and the Chicago Department of Public Health longitudinally followed more than 453,000 adults from their first reported SARS-CoV-2 infection until May 2022. About 70% were first infected prior to vaccination. Of these, 2,886 had diagnosed HIV. Most were on antiretroviral treatment with viral suppression, and a majority had a current CD4 count of 500 or higher, but nearly half previously met the criteria for AIDS.

The study authors found that 6.7% of HIV-positive people had a subsequent SARS-CoV-2 infection, compared with 5.2% of their HIV-negative counterparts, even though more people in the HIV-positive group had completed their primary COVID vaccine series. People with HIV still had a higher reinfection rate after controlling for sociodemographic and other factors. This was the case irrespective of viral load or CD4 count, suggesting that even people with well-controlled HIV might have a higher risk for SARS-CoV-2 reinfection. However, those with a viral load above 200, a CD4 count below 200 or a history of AIDS had more cumulative reinfections over time. Based on these findings, the researchers urged people living with HIV to stay up to date with recommended COVID vaccines.

Long COVID Risk Factors
In a review of long COVID in people living with HIV, published in Current Opinion in HIV and AIDS, Peluso and Annukka Antar, MD, PhD, of Johns Hopkins University Medical School, suggested several reasons why HIV-positive people might be more prone to long COVID.

- People with HIV—in particular those with low CD4 counts or comorbidities—are more likely to have severe acute COVID, which raises the risk for long COVID.
- Chronic HIV infection can cause ongoing systemic inflammation, even in people on suppressive antiretroviral therapy.
- HIV damages the gut lining, and a leaky gut that allows bacteria and their toxins to escape (known as microbial translocation) can also trigger chronic inflammation.
- Due to immune suppression, HIV-positive people may be more likely to have persistent SARS-CoV-2 infection if the immune system cannot completely clear the virus.
- People with HIV are more likely to carry and experience reactivation of EBV, CMV and other latent pathogens.
- People with HIV have higher rates of endothelial (blood vessel) dysfunction, hypertension and

other risk factors for cardiovascular disease, which could worsen COVID-related clotting and heart problems.

- Even people with well-controlled HIV may experience neurocognitive impairment, which may exacerbate SARS-CoV-2 cognitive symptoms.
- Finally, people with HIV have higher rates of comorbidities and socioeconomic factors that are associated with increased risk for long COVID.

These and other studies underscore the importance of prompt antiretroviral treatment, which preserves immune function and reduces chronic inflammation. Beyond that, scientists and patients themselves are exploring a wide variety of therapies to prevent and treat long COVID. Some studies have shown that COVID vaccines, the antiviral drug Paxlovid and the diabetes drug metformin may lower the risk of long COVID, but data are mixed. Some research shows that various antiretrovirals used to treat HIV also have activity against SARS-CoV-2—and anecdotal reports suggest that some may improve long COVID symptoms—but here, too, there is conflicting evidence.

Peluso and Antar stress that HIV-positive people must be included in this research.

“More research examining the epidemiology of long COVID in people living with HIV, in particular whether people living with HIV are at higher risk for developing long COVID and whether the clinical manifestations or natural history differ between HIV-seropositive and HIV-seronegative people [is] needed,” they wrote. “As the mechanisms of long COVID in the general population are further delineated, these need to be examined in people living with HIV, and attention needs to be paid to contributors that might be unique or more important in driving long COVID among people living with HIV. And critically, efforts must be made to ensure that people living with HIV experiencing long COVID are not systematically excluded from the nascent clinical trials that will soon be implemented to determine how best to manage long COVID symptoms.”

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