New Study Sheds More Light on Tenofovir and COVID-19

Research on links between tenofovir, SARS-CoV-2 infection and COVID severity have yielded mixed results, but new study suggests the HIV drug helps.

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A new large study has found that HIV-positive men taking the older formulation of tenofovir were less likely to acquire the SARS-CoV-2 coronavirus and less likely to be hospitalized for COVID-19, according to results published in the October edition of AIDS.

In this analysis of more than 20,000 participants in the U.S. Veterans Aging Cohort Study, people taking tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada and generic equivalents) had a 35% lower likelihood of SARS-CoV-2 infection and a 57% lower risk of COVID-related hospitalization than those taking the newer tenofovir alafenamide/emtricitabine (TAF/FTC; Descovy).

The association between COVID-19 and tenofovir, an antiviral drug used for HIV and hepatitis B treatment as well as HIV pre-exposure prophylaxis (PrEP), has spurred speculation since the early days of pandemic.

Early on, small studies and anecdotal reports suggested that people living with HIV were no more likely to acquire SARS-CoV-2 or to develop severe illness, despite having a higher likelihood of immune suppression, leading some people to wonder whether antiretroviral drugs might be protective. Later research, however, produced mixed results. While some research suggests that people with HIV experience more severe COVID and have a higher mortality rate—especially if they have uncontrolled HIV or a low CD4 count—other studies have seen no difference.

Researchers and advocates have focused on TDF in particular because it is so widely used for HIV treatment and prevention. The active form of tenofovir, a nucleotide analog that stops viruses from copying their genetic material, showed activity against SARS-CoV-2 in laboratory and animal studies. TDF is processed more slowly than TAF, so it remains at higher levels in the blood. But activity in the lab doesn't mean it can prevent infection or treat COVID in the real world.

Prior Tenofovir and COVID Research

Indeed, studies over the past three years have yielded conflicting evidence. In June 2020, Julia del Amo, MD, PhD, and colleagues with the Spanish HIV/COVID-19 Collaboration first reported results

from an observational study showing that HIV-positive people who used TDF/FTC were at lower risk for COVID and less likely to be hospitalized than those using other antiretrovirals.

At this year's Conference on Retroviruses and Opportunistic Infections, the group reported that people taking TDF/FTC for HIV treatment had a lower risk of COVID hospitalization, intensive care unit admission or death than those using other antiretrovirals—including TAF or or abacavir/lamivudine (Epzicom)—though the effect appeared to be limited to people ages 50 and older. And in August, they reported findings from a randomized, controlled trial showing that TDF/FTC, hydroxychloroquine or both were associated with a slightly lower rate of symptomatic COVID in HIV-negative health care workers, but the study was too small to yield statistically significant results.

Another Spanish study found that people using either TDF/FTC or TAF/FTC for PrEP were more likely to test positive for SARS-CoV-2 antibodies. But TDF/FTC users were less likely to develop symptomatic COVID and had a shorter duration of symptoms, though the difference was not statistically significant, and a majority of those hospitalized were on PrEP. Finally, another Spanish team reported results at the 2021 International Liver Congress showing that people taking TDF to treat hepatitis B were significantly less likely to have severe COVID (6% versus 36%) and less likely to die (1.5% versus 10%) than those taking entecavir (Baraclude), another hepatitis B antiviral.

But several other studies looking at links between tenofovir, SARS-CoV-2 infection and COVID severity have not seen significant associations. For example, an analysis of participants in the French Prévenir PrEP trial found that gay and bisexual men who used TDF/FTC for PrEP and those who did not were about equally likely to have SARS-CoV-2 antibodies indicating prior infection. Another analysis of nearly 15,000 people with HIV in the Spanish PISCIS cohort found that use of TDF/FTC or TAF/FTC was not associated with reduced SARS-CoV-2 infection or COVID hospitalization after adjusting for other factors.

New Study Findings

Now, new findings from a large study in the United States suggest that TDF/FTC might indeed have a protective effect against SARS-CoV-2 infection and severe COVID, but the results come with caveats.

Katherine Guilin Li, of Harvard T.H. Chan School of Public Health, and colleagues looked at the association between antiretroviral drugs and COVID outcomes among men living with HIV in the Veterans Aging Cohort Study. Specifically, they compared outcomes for people taking TDF/FTC, TAF/FTC, abacavir/lamivudine (Epzicom) or other antiretrovirals.

The study included 20,494 men on antiretroviral therapy between February 2020 and October 2021. The mean age was 59 years, nearly half were Black and comorbidities were common. The participants had stable HIV viral suppression, never had severe immune suppression (a CD4 count below 50), had not previously been diagnosed with SARS-CoV-2 and had not received a COVID vaccine.

The treatment groups were generally similar, except those taking TDF/FTC were less likely to have kidney disease (a contraindication for TDF) or diabetes—both of which have been linked to more severe COVID. Of note, nearly two thirds were taking TAF, and only a small proportion were on TDF, which does not reflect use of the drugs outside the veterans' health care system, where lower cost favors generic versions of TDF.

People taking TDF/FTC had a 35% lower incidence of documented SARS-CoV-2 infection than those taking TAF/FTC (4.9% versus about 7.5%). What's more, those taking TDF/FTC were 57% less likely to be hospitalized than those on TAF/FTC (0.9% versus 2.0%), even though the latter group had more COVID-linked comorbidities. The likelihood of admission to an intensive care unit was also lower for people on TDF/FTC, but these estimates were imprecise due to small numbers, the study authors noted. Participants on abacavir/lamivudine or other antiretrovirals had outcomes similar to those on TAF/FTC. COVID-related mortality was low overall, and all-cause mortality was similar across all treatment groups.

"Our study suggests that, in men living with HIV, TDF/FTC may protect against COVID-19-related events," the researchers concluded. "Randomized trials are needed to investigate the effectiveness of TDF as prophylaxis for, and early treatment of, COVID-19 in the general population."

Observational studies like this one—which compare what happens in different groups over time but do not randomly allocate participants—are prone to confounding factors that could affect the results. For example, people who are prescribed TAF are older on average and more likely to have kidney problems than those taking TDF. On the other hand, many doctors are more likely to prescribe tenofovir over abacavir for people with cardiovascular problems. The authors of the PISCIS analysis noted that "TDF/FTC users had baseline characteristics intrinsically associated with more benign SARS-CoV-2 infection outcomes."

Given the conflicting evidence from this and prior studies, the effect of tenofovir on SARS-CoV-2 infection and COVID outcomes remains an open question. Adequately sized randomized trials with well-matched control groups will be needed to tease out the true impact of the drug.

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