Tenofovir and COVID: The Jury Is Still Out

Research on the links between tenofovir and other antiretrovirals, SARS-CoV-2 infection and COVID severity has produced mixed results.

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Recent studies continue to yield conflicting evidence about whether tenofovir reduces the risk of SARS-CoV-2 infection or severe COVID-19. What's more, some patients have anecdotally reported that tenofovir improved their long COVID symptoms, but here, too, reports are mixed.

The latest study, from researchers in the Netherlands, found that tenofovir disoproxil fumarate (TDF, or Viread) did not reduce the likelihood of acquiring SARS-CoV-2 or developing severe illness. As reported in the journal AIDS, this was also the case for two HIV integrase inhibitors and the non-nucleoside reverse transcriptase inhibitor etravirine (Intelence).

HIV Meds and COVID

Over the course of the pandemic, numerous HIV medications have been suggested as potential treatments for SARS-CoV-2. Repurposing existing drugs could speed up the development of treatments for acute COVID and long-term symptoms. Several antivirals have demonstrated activity against the coronavirus in laboratory studies, but to date none have been proved effective for COVID prevention or treatment in randomized clinical trials.

TDF and a newer formulation, tenofovir alafenamide (TAF, or Vemlidy), are widely used for HIV treatment and pre-exposure prophylaxis (PrEP) as well as for hepatitis B treatment. Tenofovir is a nucleotide analog drug that acts as a defective genetic building block, interfering with the activity of viral polymerase enzymes as they attempt to copy RNA or DNA during replication. Laboratory and animal studies have shown that tenofovir is active against the SARS-CoV-2 RNA-dependent RNA polymerase and inhibits viral replication. Some research suggests it may also directly interact with the SARS-CoV-2 spike protein and block cell entry. What's more, tenofovir is active against Epstein-Barr virus (EBV), which is reactivated in some people with long COVID.

Several other medications for HIV, hepatitis B and hepatitis C are also nucleoside or nucleotide analogs—as are remdesivir (Veklury) and molnupiravir (Lagevrio), two of the three antivirals approved for COVID—but these drugs are not necessarily interchangeable across viruses.

Non-nucleoside reverse transcriptase inhibitors like etravirine interfere with the activity of HIV's

RNA-dependent DNA polymerase (better known as reverse transcriptase) in a different way than nucleoside/nucleotide analogs. Integrase inhibitors play a unique role by preventing HIV from inserting its genetic material into host cell chromosomes. Only retroviruses do this, but these drugs could potentially interfere with SARS-CoV-2 in other ways.

Protease enzymes cut up large precursor proteins so that the pieces can be used to assemble new virus particles. Most viruses employ protease enzymes, but protease inhibitors are also not interchangeable. For example, an early study showed that the HIV protease inhibitor lopinavir/ritonavir (Kaletra) is not an effective treatment for COVID. In contrast, nirmatrelvir/ritonavir (Paxlovid) is a highly active SARS-CoV-2 protease inhibitor. Maraviroc (Selzentry) is a special case. It works against HIV by blocking the CCR5 receptor the virus uses to enter cells, but it also has anti-inflammatory properties, and it is being studied as a treatment for long COVID.

Click here to learn more about the HIV life cycle and how antiretroviral drugs work.

Prior Tenofovir COVID Research

Whether tenofovir is effective against COVID in the real-world remains subject to debate. 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 to speculate about whether antiretroviral drugs might be protective.

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 plus emtricitabine (TDF/FTC, or Truvada) were at lower risk for COVID and less likely to be hospitalized than those using other antiretrovirals.

At the 2022 Conference on Retroviruses and Opportunistic Infections, the researchers reported results from a larger analysis, showing that people taking TDF/FTC for HIV treatment had a lower risk for COVID hospitalization, intensive care unit admission or death than those using other antiretrovirals—including TAF/FTC (Descovy) or abacavir/lamivudine (Epzicom)—though the effect was limited to people ages 50 and older; these findings were later published in AIDS. As a follow-up, 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—perhaps because they were more exposed to the coronavirus. But TDF/FTC users were less likely to develop symptomatic COVID and had a shorter duration of illness, though the difference was not significant. Yet another Spanish team found that people taking TDF to treat hepatitis B were significantly less likely to have severe COVID and less likely to die than those taking entecavir (Baraclude), another hepatitis B antiviral.

An analysis of more than 20,000 participants in the U.S. Veterans Aging Cohort Study, published in AIDS last October, found that people taking TDF/FTC as part of their HIV treatment regimen had a lower likelihood of SARS-CoV-2 infection and COVID-related hospitalization than those taking TAF/FTC—even though the latter group had more kidney comorbidities—or abacavir/lamivudine or other antiretrovirals.

Likewise, researchers with Kaiser Permanente Northern California compared outcomes among more than 191,000 adults in six U.S. cohorts who tested positive for SARS-CoV-2 between March and November 2020. Of these, 1,785 had HIV—a majority with viral suppression and a high CD4 count—and within this group, 1,139 were prescribed tenofovir (mostly TAF). In the HIV-negative group, 459 were taking tenofovir for PrEP.

As described in the May 2, 2023, issue of Clinical Infectious Diseases, people with HIV were at greater risk for hospitalization, mechanical ventilation or death compared with HIV-negative people. However, tenofovir use was associated with reduced hospitalization for both HIV-positive people taking it for treatment (19% reduction) and HIV-negative people taking it for PrEP (29% reduction), and the likelihood of mechanical ventilation or death fell by half in the HIV-positive group.

But other studies looking at links between tenofovir, SARS-CoV-2 infection and COVID severity have not seen similar results. For example, an analysis of nearly 15,000 people in the Spanish PISCIS cohort, published in June 2022, found that use of TDF/FTC or TAF/FTC for HIV treatment was not associated with reduced SARS-CoV-2 infection or hospitalization after adjusting for other factors.

The COVIDARE Study Team in Argentina looked at outcomes among 1,155 HIV-positive people with COVID enrolled between September 2020 and June 2022, stratified by tenofovir use (79% TDF, 21% TAF) or nonuse. They recently reported that the risk for symptomatic COVID, hospitalization or death did not differ between tenofovir users and nonusers, though people using tenofovir were less likely to need oxygen therapy.

The Spanish PANCOVID Study Group conducted a randomized clinical trial to evaluate whether HIV-negative people at high risk for severe COVID would benefit from treatment with TDF/FTC followed by the immune-modulating drug baricitinib (Olumiant). The analysis included 355 mostly hospitalized patients who were either 60 or older or had two or more comorbidities. As recently reported, the study was halted early due to a decrease in the number of cases and a low mortality. “Our results do not suggest a beneficial effect of TDF/FTC,” the study authors concluded.

New Study Findings

In the latest study, Myrthe Verburgh, MD, of the Amsterdam University Medical Center, and colleagues explored associations between antiretroviral use and SARS-CoV-2 infection, COVID-associated hospitalization and death in two Dutch observational cohorts of people with HIV.

In addition to TDF, etravirine and two integrase inhibitors—dolutegravir (Tivicay) and raltegravir

(Isentress)—were chosen because a screening study of 65 approved antivirals suggested they might interact with SARS-CoV-2 protease or polymerase enzymes. That analysis also suggested that the HIV protease inhibitors indinavir (Crixivan) and tipranavir (Aptivus) and several hepatitis C antivirals might work against the coronavirus. Other preclinical research suggested etravirine and dolutegravir might prevent SARS-CoV-2 from entering cells.

First, the researchers looked at data from a COVID-19 sub-study of the AGEhIV cohort collected between September 2020 and April 2021. This analysis included 239 HIV-positive people on antiretroviral therapy. More than 90% were men, and the median age was 62 years. All but one had viral suppression, and the CD4 count was high. During follow-up, 29 had a new SARS-CoV-2 infection. Antiretroviral regimens did not differ significantly between people who did and did not acquire the coronavirus after controlling for age, sex, race/ethnicity, HIV viral load, CD4 count and comorbidities.

Next, they used data from ATHENA, the Dutch national observational HIV cohort, which includes more than 95% of people receiving care at HIV treatment centers in the Netherlands. This analysis included 2,189 people who were on antiretrovirals when diagnosed with COVID. More than 80% were men, the median age was 50, almost all had viral suppression and, again, the CD4 count was high.

Over the course of the study, 158 ATHENA participants had severe COVID: 149 were hospitalized, and 29 died (including nine who were never hospitalized). As expected, people with severe COVID were older, had been living with HIV longer, were more often people of color, had more comorbidities and had lower current and nadir (lowest-ever) CD4 counts. People with severe COVID were more often on protease inhibitor regimens (reflecting more advanced HIV disease), but otherwise antiretrovirals did not differ significantly between those with and without severe illness.

“[T]he use of TDF, ETR or [integrase inhibitors] was not independently associated with either the risk of incident SARS-CoV-2 infection or severe COVID-19 outcomes, as was suggested by previous observational and molecular docking studies,” the researchers concluded. “Our findings do not support a strategy of modifying antiretroviral therapy to include these agents to protect against SARS-CoV-2 infection and severe COVID-19 outcomes.”

However, this and other research clearly shows that HIV-positive people who are on any antiretroviral regimen that suppresses the virus and enables CD4 cell recovery—as opposed to remaining untreated—have better COVID outcomes.

Observational studies, which compare what happens in different groups 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, while those taking TAF are more likely to gain weight and have elevated cholesterol—all risk factors for severe COVID.

“Our analyses in two cohorts of [people with HIV] support previous findings that TDF does not

protect against SARS-CoV-2 infection or severe COVID-19 outcomes. Similar to our analyses, these studies adjusted their outcome for baseline participant characteristics, such as country of origin, socioeconomic status, current CD4 cell count and CD4/CD8 ratio, years on ART [antiretroviral therapy], presence of diabetes, chronic kidney disease and metabolic disease," the study authors wrote.

"Importantly, studies suggesting a protective effect of TDF in [people with HIV] did not adjust for these participant characteristics," they continued. "It is likely that the presence of risk factors such as higher age and comorbidities influence the choice of ART regimen, which may confound the association between ART use and COVID-19 outcomes, thereby explaining the difference in study findings."

Also of note, most of these studies were done earlier in the pandemic, before most participants were vaccinated, before Paxlovid treatment was widely available and before the emergence of SARS-CoV-2 omicron variants.

Given the conflicting evidence from research to date, the effect of tenofovir and other antiretrovirals on SARS-CoV-2 infection and COVID outcomes—including long COVID—remains an open question that will need to be answered by adequately sized randomized controlled trials.

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