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Tenofovir-based PrEP for COVID-19: an untapped opportunity?

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Early in the pandemic, when the Centers for Disease Control (CDC) identified possible risk factors for COVID-19, it was rational to include HIV due to concerns that an impaired immune response could lead to severe infection.

As the data bore out over time, however, there was little evidence that HIV increased COVID-19 risk in settings with good access to antiretroviral therapy (ART).[1] Furthermore, observational studies of people with HIV (PWH) and *in vitro* studies yielded intriguing results around the potential activity of tenofovir disoproxil fumarate (TDF) against COVID-19. TDF in combination with emtricitabine, TDF/FTC (Truvada®), is used worldwide for HIV treatment and pre-exposure prophylaxis (PrEP).

The first signal came in June, with publication of a Spanish cohort study of 77,590 PWH taking ART.[1] The incidence per 10,000 persons of COVID-19 diagnosis among people taking TDF/FTC was 16.9 (95% CI, 10.5–25.9), compared to 28.3–39.1 for those on other antiviral regimens and 41.7 in the general population. Risks of hospital admission and death from COVID-19 were both similarly reduced, although channeling bias (with healthier patients prescribed TDF/FTC) could not be ruled out. Participants taking a formulation of tenofovir that is safer in renal disease—tenofovir alafenamide (TAF)—fared no better than the general population, supporting the possibility of confounding. However, TDF also leads to approximately 10-fold higher extracellular tenofovir concentrations than TAF, corresponding to greater penetration into some mucosal tissues[2] and possibly stronger immunomodulatory effects.[1,3]

While this finding was provocative, it was the pattern that emerged from other cohort studies that caught the interest of the HIV research community. In a cohort of 3.5 million people (16% HIV positive) in the Western Cape, South Africa, PWH taking TDF/FTC who contracted SARS-CoV-2 experienced 59% lower mortality from COVID-19 than those taking abacavir or zidovudine (aHR, 0.41; 95% CI, 0.21–0.78).[4] In this case, without TAF/FTC availability, channeling bias was likely not a factor.

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A third cohort of 750 men who have sex with men and transgender women found that PrEP users who tested positive for SARS-CoV-2 antibodies showed higher rates of asymptomatic infection (42.7% of PrEP users vs. 21.7% of non-PrEP users; p=0.07).[5] This mild outcome occurred despite PrEP users having a higher seroprevalence of SARS-CoV-2 than those not on PrEP (15.0% vs. 9.2%); this might be due to greater social contact among people using PrEP during the pandemic.

What could explain these observations? In vitro and molecular docking studies suggest that tenofovir inhibits RNA-dependent RNA polymerase of SARS-CoV-2, although with weaker binding than remdesivir, which did not improve clinical outcomes in the World Health Organization (WHO) SOLIDARITY trial, and showed faster time to recovery, but not improved survival in ACTT-1.[6–9] TDF also has immunomodulatory effects, including decreased production of IL-8 and IL-10.[3] Both IL-8 and IL-10 have been shown to predict COVID-19 severity,[10] and IL-10 may play a detrimental role in the pathogenesis of severe COVID-19.[11] Other drugs targeting IL-8, such as colchicine, are under investigation for COVID-19, with one trial of outpatient colchicine demonstrating reduced rates of death or hospitalization in the group with PCR-confirmed COVID-19.[12,13]

Although TAF did not show activity against COVID-19 in a cell model,[14] TDF was not examined in that study, and there is other promising data for TDF *in vitro* and in a pre-clinical animal model. Among ferrets, SARS-CoV-2 viral loads decreased in nasal swabs with the administration of TDF-emtricitabine, whereas lopinavir-ritonavir and hydroxychloroquine (both now shown to be ineffective for COVID-19 in clinical trials) had no effect on the animals' nasal viral titers.[15]

While subject to confounding, these observational and animal model studies are compelling enough to warrant further evaluation of TDF in randomized controlled trials for COVID-19 prevention and treatment. Such trials, however, have been few. For instance, a trial to examine TDF/FTC versus placebo for COVID-19 prophylaxis in Spain has been recruiting healthcare workers since April, but the trial coincided with the introduction of non-pharmaceutical interventions, such as universal masking, and has not met its endpoints. Other sizable trials of TDF or TAF are planned or recruiting in Colombia, Argentina, and France, but no trials of tenofovir for COVID-19 are registered in the U.S. or U.K. SOLIDARITY—the WHO's ongoing adaptive trial—recently reported that remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a all lacked benefit among patients hospitalized with COVID-19, but has not yet examined tenofovir.[8]

It is notable that costly or scarce drugs—including remdesivir, a drug designed for Ebola but found to be ineffective; baricitinib, a janus kinase inhibitor for rheumatoid arthritis; and interferon beta-1a, a multiple sclerosis drug costing over $7,000 per month—were chosen for ACTT-2 and SOLIDARITY over an inexpensive and widely-available ART agent with promising *in vitro* activity against SARS-CoV-2. Given our 30 years of experience treating HIV and a deep bench of available therapies, why not examine more ART agents—particularly TDF—in early adaptive trials?

One possible explanation is that TDF is generic, meaning that it lacks a commercial sponsor and has fewer available pathways for investigation. Whereas patented drugs can be efficiently investigated by their manufacturer, generics rely on public agencies, who must choose between many therapeutic candidates and still often rely on industry for drug donations and trial support.[16] Many publicly funded trials opted to investigate hydroxychloroquine, in the context of overwhelming public interest, which unfortunately proved ineffective. Agents with stale patents or limited generic entry—still costly to purchase and study, but without financial incentives for the manufacturer to support trials—are potentially the ones least studied.

Drug manufacturers have shown a strong public commitment in COVID-19, releasing patented drugs at fair prices and donating large supplies of experimental COVID-19 therapies. Nevertheless, they are for-profit companies and are primarily incentivized to investigate brand-name drugs for COVID-19. Gilead, which manufactures TDF, TAF, and remdesivir, is unlikely to fund trials of generic TDF, and alternative funding mechanisms are needed.[16] Importantly, even if tenofovir has lower efficacy than other experimental agents against COVID-19, its wide availability and low cost might still enable a greater public health impact. Indeed, due to its cost of roughly $3,000 per course and lack of clinical benefit in the SOLIDARITY trial,[8] the WHO did not recommend remdesivir for worldwide use against COVID-19.

Operation Warp Speed showcased the potential of public-private partnerships to overcome traditional market forces and accelerate discovery of COVID-19 interventions. We advocate that TDF/FTC or TDF be added as an arm to ongoing adaptive trials, such as ACTIV-2 or SOLIDARITY, or examined in investigator-led trials with support from Gilead. Supplies should be donated by Gilead to support its study in the U.S. and Europe, or purchased from generic manufacturers abroad.

The swift arrival of a vaccine for COVID-19 is heartening, but vaccines will not be available in low-resource settings for some time. Some will not respond to vaccines, and others may decline vaccination. Availability of more than one prevention option is likely to increase uptake, as we have seen for birth control and, increasingly, for HIV PrEP.

As we learned from hydroxychloroquine, promoting untested drugs for COVID-19 can cause harm, both through adverse drug reactions and by constraining supply to those who rely on the drug for other conditions. In the case of tenofovir, there are also risks of HIV resistance if TDF becomes an experimental therapy for COVID-19. We do not advocate experimental use of tenofovir outside of trials, but rather, urge WHO and NIH to consider inclusion of tenofovir and other generic antiviral therapies in multi-armed therapeutic trials. We are urgently in need of COVID-19 therapies, especially for outpatients, that are both effective and accessible in low-resource settings around the world.

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