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I HIV AND COVID-19

A. One study finds that HIV suppression is less common in the era of COVID-19

Potent combination HIV treatment (ART) has two main benefits—improving a person's health and preventing the spread of HIV. When a person with HIV initiates and then continues to take ART as prescribed, the amount of HIV in the blood eventually falls to very low levels. These low levels (usually less than 40 or 50 copies/mL of blood) are commonly called "undetectable." Studies have found that maintaining the use of ART so that HIV is suppressed generally results in better clinical and laboratory measures of health. These effects of ART are so profound that scientists increasingly expect many ART users to have near-normal life expectancy. Also, studies have found that HIV-positive people who maintain an undetectable viral load (thanks to ART) do not pass on HIV to their sexual partners.

Thus, HIV testing, initiation of ART, and viral load suppression and monitoring are key metrics in personal and public health efforts to gain control of the HIV epidemic.

A new pandemic

In late 2019, a new virus called SARS-CoV-2 emerged in East Asia and quickly spread around the world. This virus belongs to the family of viruses called coronaviruses. Infection with SARS-CoV-2 causes symptoms and complications collectively called COVID-19.

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The coronavirus pandemic has caused widespread social and economic disruption brought about by the need to curtail the spread of the virus with measures such as physical distancing and isolation. Access to and delivery of routine healthcare services has also been affected by the pandemic.

In San Francisco

A team of researchers in San Francisco analysed healthcare data collected from an HIV clinic (called "Ward 86") that provides services to people affected by what researchers termed "a high prevalence of mental illness, substance use and unstable housing."

As the first wave of the pandemic hit the state of California in the spring of 2020, clinic staff shifted many in-person visits to telephone appointments where possible. They stated that they also "facilitated viral load testing via rapid laboratory visits, with at least quarterly monitoring."

Researchers compared clinic data collected in two periods:

- December 1, 2019 – February 29, 2020
- April 1, 2020 – April 30, 2020

Results

In 2019, the clinic had about 1,836 in-person visits each month from patients. Researchers found that, on average, about 19% of people had an unsuppressed viral load at least once. About 16% of patients were homeless.

In April 2020, 54% of appointments were conducted over the telephone. The researchers stated that "homeless individuals were offered telehealth for only 32% of visits." They also stated that homeless people were more likely to keep telephone appointments during the pandemic compared to the pre-pandemic era.

Changes to viral load

In April 2020, researchers found that about 31% of patients had a detectable viral load.

Factors linked to an increased risk for a detectable viral load were as follows:

- being younger than 35 years old
- being homeless
- being black

According to the researchers, part of the reason for the increase in detectable viral loads might have been because "telehealth visits, while offering greater patient convenience, may lead to less access to clinic-based social support services essential to achieving viral suppression among vulnerable groups." They also stated that "homeless individuals at [our clinic] had higher odds of unsuppressed viral loads [during the pandemic] despite higher visit attendance."

Bear in mind

The present study is a good start at documenting the changes that are happening among HIV-positive people in the coronavirus pandemic. The loss of viral suppression will likely have an impact on individual health in the medium- and long-term and on the spread of HIV. Indeed, San Francisco's public health department has stated that there has been an increase in new infections. The research team issued a call to action, stating that "measures to counteract the effect of COVID-19 on HIV care outcomes are urgently needed."

REFERENCE:

Spinelli MA, Hickey MD, Glidden DV, et al. Viral suppression rates in a safety-net HIV clinic in San Francisco destabilized during COVID-19. *AIDS*. 2020; *in press*.

B. Health outcomes in HIV-positive people in San Francisco with COVID-19

Another team of researchers in San Francisco analysed health-related and limited socio-economic information on HIV-positive people who were diagnosed with COVID-19 between March and September 2020.

Out of 4,252 COVID-19 tests done by HIV-positive people during this time, 194 (almost 5%) were positive for the coronavirus. Among 272,555 HIV-

negative people who had COVID-19 tests, about 4% were positive for the coronavirus.

Co-infection with SARS-CoV-2

The average profile of HIV-positive people co-infected with SARS-CoV-2 was as follows:

- age – 45 years
- major ethno-racial groups: white – 39%; Hispanic – 38%; black – 12%; Asian – 7%
- gender – 91% men, 6% women, 3% transgender women
- 64% had been HIV positive for at least a decade
- 44% had an undetectable viral load at their last laboratory visit
- the distribution of CD4+ cell counts was as follows: 63% had more than 500 cells/mm^3; 31% had between 200 and 500 cells/mm^3; 6% had less than 200 cells/mm^3

Interviews

Healthcare personnel were able to interview most (95%) of the HIV-positive people who were diagnosed with COVID-19. The researchers found that only 55% of them had stable housing.

Nearly 25% of participants disclosed that they had contact with someone diagnosed with COVID-19. This is not surprising, as early in the pandemic there was an outbreak of the coronavirus at a homeless shelter in San Francisco.

A large proportion of participants (43%) disclosed that they had underlying conditions, most of which are associated with more severe manifestations of COVID-19:

- cardiovascular disease
- diabetes
- chronic liver disease
- chronic lung disease

The researchers found that 9% of patients currently smoked tobacco and 11% were former smokers.

Symptoms

Common symptoms of COVID-19 were as follows:

- cough
- fever
- runny nose
- muscle pain
- headache
- chills
- breathing problems
- sore throat
- loss of smell and/or taste

About 8% of co-infected people required hospitalization and two people needed to be admitted to an intensive care unit. No one died.

Bear in mind

The researchers stated that data from this analysis are similar to those reported from large European and U.S. studies "suggesting that HIV does not seem to predispose people to more severe COVID-19 outcomes."

The San Francisco study also suggests that HIV-positive people are at increased risk for SARS-CoV-2 co-infection. The researchers stated that this increased risk arises because many HIV-positive people in this study lived in crowded places such as "single residency hotels, homeless shelters and long-term care facilities." Also, they stated that "shared bathrooms and crowded spaces make social distancing challenging."

The coronavirus pandemic has had a disruptive impact on the health of many people and their ability to gain routine access to the full range of health services usually available. Furthermore, according to the San Francisco Department of Public Health, new cases of HIV have increased as the pandemic has intensified.

What is to be done?

The researchers noted that the city has taken steps to reduce the spread of coronavirus among vulnerable populations, including those with HIV. However, they stated, "more efforts are needed citywide to house those who are homeless as a public health measure." They added that "medical care of homeless individuals with and without HIV is paramount during a pandemic. Housing

assistance, continuation of antiretroviral therapy (ART), and continuation of care are required as we try to protect people living with HIV from SARS-CoV-2 infection worldwide."

REFERENCE:

Sachdev D, Mara E, Hsu L, et al. COVID-19 susceptibility and outcomes among people living with HIV in San Francisco. *JAIDS*. 2020; *in press*.

C. A Spanish study on HIV and COVID-19

Doctors at 60 HIV clinics in Spain pooled their data, collected between February and April 2020, to better understand the impact of the coronavirus on the health of people taking antiretroviral therapy (ART).

Out of 77,590 HIV-positive people in these clinics who were taking ART, 236 were diagnosed with COVID-19. Of these 236 people, 151 (64%) were hospitalized, 15 (6%) were admitted to an intensive care unit (ICU) and 20 (8%) died.

Comparisons

The researchers compared health-related information from HIV-positive and HIV-negative people with COVID-19 in Spain and drew the following conclusions:

Risk for a diagnosis of COVID-19
- HIV-positive people – 30 cases per 10,000 people
- HIV-negative people – 42 cases per 10,000 people

Risk of death with COVID-19
- HIV-positive people – 4 cases per 10,000 people
- HIV-negative people – 2 cases per 10,000 people

All cases of COVID-19 were diagnosed with PCR (polymerase chain reaction).

Focus on HIV

Among HIV-positive people, researchers found that those over the age of 70 and men were at greatest risk for COVID-19 diagnosis and hospitalization.

In general, the time spent in hospital increased with a person's age. For instance, people aged 20 to 39 years spent about four days in the hospital, while people aged 70 to 79 years were hospitalized for about nine days.

HIV medicines

The drugs tenofovir DF (TDF) and FTC are combined in a pill and sold under the brand name Truvada and in generic formulations. A newer formulation of tenofovir, called TAF, is also combined in a pill with FTC and sold under the brand name Descovy.

The Spanish researchers found that the risk for certain outcomes was lower among people who took TDF + FTC. For instance, people taking those drugs had a 57% reduced risk of being diagnosed with COVID-19 and a 47% reduced risk of being hospitalized.

Bear in mind

The researchers urge caution when interpreting the finding that there appears to be a greater risk of death among HIV-positive people who were hospitalized with COVID-19. This trend needs to be explored with a much larger number of people and done over a longer period of time.

The findings concerning the potential impact of HIV treatment are interesting. However, the study's conclusions are clouded by the possibility of being skewed by unmeasured factors. The number of HIV-positive people was relatively small and the study design was observational. We do not know why some people were prescribed TDF + FTC and others were not. It is plausible that people who were prescribed TDF + FTC were healthier than people who did not take these drugs. It would have been helpful to have more data about the health of the HIV-positive people who were diagnosed with COVID-19 and who required hospitalization. For instance, factors such as CD4+ cell counts, the lowest-ever ("nadir") CD4+ cell count, the ratio of CD4 to CD8 cells, duration of viral suppression, and so on perhaps could have

contributed more to an analysis of risk. Note that the first wave of the pandemic was particularly bad in Spain and researchers had to scramble to assemble data on what was happening in their HIV-positive population.

Other studies from France and Spain (reported later in this issue of *TreatmentUpdate*) have not found any conclusive link between the use of tenofovir-containing regimens and a reduced risk for infection with SARS-CoV-2 or other outcomes.

A large randomized clinical trial is underway in Spain to assess the impact of TDF + FTC in preventing infection with SARS-CoV-2.

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1. Del Amo J, Polo R, Moreno S, et al. The Spanish HIV/COVID-19 Collaboration. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Annals of Internal Medicine*. 2020 Oct 6;173(7): 536-541.

2. Charre C, Icard V, Pradat P, et al. Coronavirus disease 2019 attack rate in HIV-infected patients and in preexposure prophylaxis users. *AIDS*. 2020 Oct 1;34(12):1765-1770.

3. Ayerdi O, Puerta T, Clavo P, et al. Preventive efficacy of tenofovir/emtricitabine against SARS-CoV-2 among PrEP users. *Open Forum Infectious Diseases*. 2020; *in press*.

D. A multi-clinic study of HIV and COVID-19 in the U.S.

A team of researchers, with the help of a computer network, analysed the medical records of 50 million people in the United States. The team focused on 50,167 people with COVID-19, 404 of whom were co-infected with HIV.

A summary of key features of the HIV-positive population was as follows:

- 71% men, 29% women
- age – 48 years
- major ethno-racial groups: black – 50%; white – 34%; Hispanic – 13%; Asian – 2%

The overall distribution of major underlying health conditions was as follows:

Higher-than-normal blood pressure
- HIV-positive people – 46%
- HIV-negative people – 28%

Chronic lung disease
- HIV-positive people – 25%
- HIV-negative people – 16%

Chronic kidney disease
- HIV-positive people – 17%
- HIV-negative people – 7%

History of nicotine dependence
- HIV-positive people – 14%
- HIV-negative people – 7%

Obesity
- HIV-positive people – 26%
- HIV-negative people – 21%

Type 2 diabetes
- HIV-positive people – 22%
- HIV-negative people – 15%

Coronary artery disease
- HIV-positive people – 14%
- HIV-negative people – 8%

Clinical outcomes – 28 days later

Twenty-eight days after COVID-19 diagnosis, researchers compared the proportions of people who died. At first, it seemed that HIV-positive people were more likely to die than HIV-negative people. However, after researchers matched each HIV-positive person with an HIV-negative person of the same age and gender, there were no statistically significant differences in survival between the two groups. Among HIV-positive people, there was no increased risk of death whether or not people were on ART.

However, the researchers did find that more HIV-positive people (19%) required hospitalization than HIV-negative people (11%).

Lab tests

Lab test results on blood samples for proteins that are elevated during inflammatory conditions were not different between HIV-positive and HIV-negative people with COVID-19. These blood tests assessed levels of the following proteins:

- C-reactive protein (CRP)
- ferritin

- ESR (erythrocyte sedimentation rate)
- lactate dehydrogenase

Bear in mind

This is one of the largest formal comparative studies of COVID-19 in HIV-positive and HIV-negative people from a high-income country published so far. Although it found that comorbidities (underlying health conditions) are relatively common among HIV-positive people, which has been reported in smaller studies, a greater prevalence of comorbidities did not lead to an increased risk of death.

Like many other studies reported in this issue of *TreatmentUpdate*, these findings should be treated as exploratory until results from a much larger group of HIV-positive people with COVID-19 can be obtained. The present study is based on limited analysis from a database that appeared to lack detailed immunological and virological data related to HIV care. Despite these caveats, the study is a useful and necessary step in understanding the impact of COVID-19 on the health of HIV-positive people. As well, it shows that research can be done in the face of a major pandemic.

REFERENCE:

Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. *AIDS*. 2020 Nov 1;34(13):F3-F8.

E. HIV and COVID-19 – an international registry

In an attempt to assess the impact of COVID-19 on HIV-positive people, a team of researchers in the U.S., Spain and Singapore pooled health-related information. A total of 286 people with both HIV and COVID-19 were found in the researchers' databases. About 94% were on antiretroviral therapy (ART) at the time COVID-19 was diagnosed. Out of 286 people, nearly 60% were hospitalized within 30 days of being diagnosed with COVID-19; about 9% subsequently died. These figures seem large, but they should be treated with caution. That is, readers should not assume that such a large proportion of HIV-positive people who have a diagnosis of COVID-19 will be hospitalized and die in other settings. Indeed, other studies from the U.S. and other countries do not reveal such a high rate of hospitalization and death among HIV-positive people who have COVID-19.

Study details

Participants were recruited between April 1 and July 1, 2020, from three high-income countries. The average profile of participants at the time they entered the study was as follows:

- age – 51 years
- 75% men, 25% women
- major ethno-racial groups: black – 48%; Hispanic – 28%; white – 17%, Asian/other – 8% (figures do not total 100 due to rounding)
- most people had been HIV positive for more than five years
- CD4+ count – 531 cells/mm^3
- proportion with a suppressed viral load – 89%
- most people on ART (61%) were taking a regimen anchored by an integrase inhibitor together with two nucleoside analogues; other people were taking regimens anchored by a non-nuke (NNRTI) or protease inhibitor
- a majority of people (90%) were from the U.S.

Many people had underlying health conditions, or comorbidities:

- obesity – 32%
- diabetes – 21%
- chronic lung disease (including asthma and chronic obstructive pulmonary disease) – 17%
- chronic kidney disease – 17%
- cardiovascular disease – 11%
- chronic liver disease – 10%
- active cancer – 5%

About 38% of participants smoked tobacco.

Only 14% of participants had no comorbidity.

COVID-19 symptoms

Common symptoms associated within 72 hours of testing positive for COVID-19 were as follows:

- cough
- fever
- fatigue

People who were not hospitalized tended to have the following symptoms:

- sore throat
- stuffy nose
- headache

About 60% of people were hospitalized and researchers stated that those people were more likely to have the following symptoms:

- fever
- fatigue
- difficulty breathing
- gastrointestinal symptoms
- "altered mental status"

Most hospitalized people had abnormalities on their chest X-ray or CT scan.

Focus on hospitalization

Overall, 164 people were hospitalized, 29% of whom required admission to an intensive care unit (ICU). Once in the ICU, 23% of people needed mechanical ventilation. A total of 27 hospitalized people (17%) died within eight to 24 days after testing positive for SARS-CoV-2.

Taking many factors into account, people with one or more of the following were more likely to be hospitalized:

- older age
- lower CD4+ count
- chronic kidney disease
- chronic lung disease

Severe outcomes

The doctors defined "severe outcomes" as any of the following—admission to an ICU, the need for invasive mechanical ventilation, or death.

In total, 18% of all participants had such an outcome. Also, severe outcomes were more common among hospitalized people (31%).

Researchers found that having one or more of the following factors was significantly associated with a severe outcome:

- older age
- lower CD4+ count
- chronic lung disease
- higher-than-normal blood pressure
- having more than one comorbidity

Survival

Based on data from 47 people admitted to ICU and 27 people who died in this study, researchers suggested that the CD4+ count may have had an impact on major outcomes—admission to an ICU and survival. Intuitively this makes sense, as, in general, HIV-positive people with higher CD4+ cell counts are usually in better overall health than people with lower cell counts. Analysis found that people with less than 200 CD4+ cells were more likely to require admission to an ICU or subsequently die compared to people with more than 500 CD4+ cells.

Bear in mind

The study found that COVID-19 symptoms in HIV-positive people are similar to what has been reported in HIV-negative people.

The researchers stated that people of colour, particularly black and Hispanic people, were at heightened risk for severe symptoms of COVID-19. However, race/ethnicity was not a factor associated with worse outcomes in this study.

HIV-positive people with COVID-19 seem to have a relatively high rate of underlying conditions. These underlying conditions are a risk factor for hospitalization in both HIV-positive and HIV-negative people.

"Based on our analyses, rates of ICU admission, mechanical ventilation use, and death among [HIV-positive people with COVID-19] were consistent with general U.S. data," according to the researchers.

Untreated HIV infection was not a risk factor for severe symptoms of COVID-19. The researchers stated that this was likely because the proportion of untreated people was relatively small and not statistically meaningful.

The present study found that having a low CD4+ count (less than 200 cells) was a risk factor for poor outcomes. Although there were some deaths in people with more than 200 CD4+ cells/mm^3, most deaths occurred in people with less than 200 CD4+ cells.

Like nearly every study done in the midst of the coronavirus pandemic, there are missing data. For instance, it might have been useful to assess the lowest-ever ("nadir") CD4+ cell count. This could be used to estimate past immunological injury. It also might have been useful to have patients' CD4 to CD8 ratios. A normal ratio is at least 1.0. A smaller ratio, which is relatively common even among some ART users, is suggestive of immunological weakness. These missing data could have allowed researchers to better understand the immunological underpinnings of COVID-19 in people with HIV.

Other missing pieces of information concerned the following:

- the exact cause of death
- socio-economic information
- any formal comparison to HIV-negative people with COVID-19

Despite these caveats, the present study provides a picture of what has happened to some people with HIV who have been hospitalized with COVID-19, mostly in the U.S. It will be interesting to see the results of larger data sets as the pandemic continues.

REFERENCE:

Dandachi D, Geiger G, Montgomery MW, et al; HIV-COVID-19 consortium. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19. *Clinical Infectious Diseases*. 2020; *in press*.

F. Comparisons between hospitalized people in the UK

A study called ISARIC compared health-related information from HIV-positive and HIV-negative people, all of whom were hospitalized due to COVID-19. Researchers with ISARIC found that, in general, HIV-positive people tended to be younger, were more likely to be obese, and had higher levels of inflammation and more symptoms of COVID-19 than HIV-negative people. Overall, HIV-positive people hospitalized with COVID-19 had a 47% increased risk of death compared to HIV-negative people who were also hospitalized for COVID-19.

Comparisons

Researchers analysed information collected between January and June 2020. For the current analysis they used data from 47,592 HIV-negative people and 122 HIV-positive people, 112 of whom had a record of using HIV treatment (ART). Only one person was diagnosed with HIV upon admission to hospital. Generally, HIV-positive people were younger than HIV-negative people (56 vs. 74 years old) and had fewer comorbidities. Black people were over-represented among HIV-positive people who were hospitalized due to COVID-19—45% vs. about 26% of all HIV-positive people in the UK.

- As with the overall HIV epidemic in the UK, there were more men in the HIV-positive group.
- HIV-negative people were more likely to have two or more co-morbidities.
- HIV-positive people tended to have higher rates of obesity and moderate/severe liver disease.

Symptoms

HIV-positive people were more likely to have the following symptoms upon hospitalization:

- fever
- headache
- cough
- muscle pain
- higher-than-normal heart rate
- chest pain

Lab tests revealed that HIV-positive people were more likely to have lower total white blood cell and platelet counts but higher lymphocyte levels. The amount of C-reactive protein (CRP; indicative of inflammation) was greater in HIV-positive people than in HIV-negative people.

Critical care and survival

The chance of being admitted to a critical care unit was similar for both populations.

28 days after a diagnosis of COVID-19

Overall, 28 days after a diagnosis of COVID-19, 27% of HIV-positive people died vs. 32% of HIV-negative people. However, when researchers adjusted their analyses by age, they found a significant difference in the distribution of deaths in people under the age of 60, as follows:

- HIV-positive people – 21%
- HIV-negative people – 10%

This difference was statistically significant.

The reason(s) for these findings regarding age and survival in ISARIC is unclear.

The researchers found that HIV-positive people who died were slightly older and more likely to have diabetes and obesity than HIV-positive people who survived. Furthermore, it appears that in ISARIC, HIV-positive people who died were less likely to have a record of ART use.

Bear in mind

In ISARIC, HIV-positive people had fewer comorbidities than HIV-negative people. Researchers suspect that this difference arose because HIV-positive people were significantly younger than HIV-negative people.

Although diabetes and obesity were linked to an increased risk of death in HIV-positive people, researchers suspect that there may be other, as yet unidentified, underlying issues that played a role in their demise.

ISARIC's strength is that it was directly able to compare data from HIV-positive and HIV-negative people and take into account many factors, including age, gender, and so on. However, ISARIC also had weaknesses that seem to bedevil many published studies of HIV-positive people with COVID-19. It lacked comprehensive immunological and virological data related to HIV as well as data about the use of ART. ISARIC was also missing data about socio-economic status. This lack of data on different issues is due to the difficulty of conducting research in the midst of a pandemic caused by a novel virus that has had a tremendously disruptive impact on health systems and societies. Many hospitals in the UK and elsewhere were over-burdened with sick and dying patients and many hospital staff likely were exhausted during the time that data were collected.

In the meantime, the ISARIC team offered the following advice for healthcare providers who are caring for people with HIV or who are at high risk for HIV:

- Diagnose HIV early.
- If diagnosed with HIV, offer ART promptly.
- Engage in optimized screening for and control of comorbidities, including obesity and diabetes.

REFERENCE:

Geretti AM, Stockdale AJ, Kelly SH, et al. Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO Clinical Characterization Protocol (UK): a prospective observational study. *Clinical Infectious Diseases*. 2020; *in press*.

G. Finding treatments for COVID-19

The SARS-CoV-2 virus is responsible for a global pandemic. Some people infected with this virus will develop complications called COVID-19. As SARS-CoV-2 is new to humanity, it could take several years to develop new antiviral drugs specifically designed to attack this virus.

Given the catastrophic nature of the pandemic, scientists are scrambling to assess drugs approved for one condition (usually another viral infection) to find out if they can be repurposed for SARS-CoV-2 treatment and prevention.

A repurposed drug may not necessarily be the best or most powerful antiviral against SARS-CoV-2. However, until more potent treatments are approved, repurposed drugs are all that will be available.

From the computer to the lab

Some scientists have carried out computer-based simulations that mimic the interaction between antiviral drugs and a key enzyme used by SARS-CoV-2. This enzyme is called RdRp (RNA-dependent RNA polymerase).

Computer simulations of complex interactions at the molecular level are imperfect. But they are

a good first step toward identifying compounds that can be tested in coronavirus-infected cells or animals.

Repurposed drugs – caution needed

There have been immense efforts in the past 20 years to repurpose drugs (to find new uses for old drugs) for different diseases. Using computer simulations and/or traditional laboratory testing, even experiments with animals and people, these efforts have not yielded many new uses for old drugs where such new uses have been approved by regulatory authorities, at least in high-income countries.

Potentially, there are many drugs that could be tested in lab studies with cells or animal experiments to assess their effectiveness against SARS-CoV-2. Computer simulations have suggested some possible drugs to test. If the results are promising, such drugs could subsequently be tested in people. Some of these drugs have been mentioned in previous issues of *TreatmentUpdate*.

Given the crisis nature of the coronavirus pandemic, scientists and doctors have been forced to take one of the following routes:

- engage in extensive laboratory experiments with cells and then animals to find candidates worthy of being repurposed against COVID-19; such experiments take time and delay the testing of drugs in people who are sick with COVID-19
- rush already approved drugs into clinical trials in the hope that they might work against COVID-19

Observers of the massive number of studies that have been launched since the discovery of SARS-CoV-2 have noted that many of these trials were generally not well designed. It should not be surprising that several repurposed drugs have failed to yield major clinical benefit, particularly concerning the endpoint of survival after a diagnosis of COVID-19. An exception so far as been the anti-inflammatory drug dexamethasone.

Professor Aled Edwards, PhD, from the University of Toronto, reviewed the history of drug repurposing with leading scientists, doctors and members of the pharmaceutical industry and gave the following examples of repurposed drugs where a new use for an old drug has been approved by regulatory authorities in high-income countries:

- thalidomide – originally used as a sedative in pregnant women and withdrawn from sale due its ability to harm the fetus; it was reintroduced and repurposed as a treatment for multiple myeloma
- sildenafil – initially researchers tested this drug for cardiovascular disease, but it was repositioned for male erectile dysfunction
- minoxidil – originally used to treat higher-than-normal blood pressure; now most commonly used for treating hair loss

It is possible that other drugs have been discovered through mass screening of almost randomly selected compounds and granted approval by regulatory agencies for the treatment of other diseases. However, it is likely that there is not a huge number of such drugs.

For the future

In the absence of a timely and major breakthrough in COVID-19 treatment, it is likely that the pandemic caused by SARS-CoV-2 will be with us for some time, waxing and waning for reasons not fully understood. Even after the current pandemic has abated, some scientists have predicted that there may be future pandemics caused by other coronaviruses. Therefore, it may be worth launching well-funded programs to discover a range of potential anti-coronavirus drugs and quickly test them in animals and people. In parallel with this, the search for worthy candidates for assessment in repurposing against COVID-19 needs to continue in clinical trials.

Resources

TreatmentUpdate 237 – Antiviral agents for COVID-19

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1. Edwards A. What are the odds of finding a COVID-19 drug from a lab repurposing screen? *Journal of Chemical Information and Modeling*. 2020; *in press*.

2. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. *Nature Reviews Drug Discovery*. 2019 Jan;18(1):41-58.

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plasma and target site concentrations derived from their established human pharmacokinetics. *Clinical Pharmacology and Therapeutics*. 2020 Oct;108(4):775-790.

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8. Chien M, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, Russo JJ, Kirchdoerfer RN, Ju J. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase, a key drug target for COVID-19. *Journal of Proteome Research*. 2020; *in press*.

H. Revisiting TDF + FTC as a potential preventive for COVID-19

Researchers in the U.S. and other countries have identified that a combination of two drugs—tenofovir DF (TDF) + FTC—has antiviral potential against SARS-CoV-2 in simulations and possibly in studies of coronavirus-infected cells. The combination of TDF + FTC is co-formulated into one pill and sold under the brand name Truvada; it is also available in generic formulations.

Other drugs that have been considered for repurposing against COVID-19 include the following:

- abacavir
- atazanavir + ritonavir
- azithromycin
- AZT
- chloroquine (CQ) and hydroxychloroquine (HCQ)
- d4T (stavudine)
- entecavir
- ganciclovir
- ivermectin
- lopinavir + ritonavir (in Kaletra)

On one hand, some of these drugs—particularly CQ, HCQ and lopinavir-ritonavir—have been tested in people with COVID-19. Large well-designed clinical trials have almost always found that they don't have a clinically significant impact. On the other hand, an older and commonly used corticosteroid, dexamethasone, has been associated with a reduced risk of death in people with COVID-19.

CQ and HCQ are interesting in that they have traditionally been used for malaria in some low-income countries, and HCQ has been used for the treatment of some autoimmune conditions (such as arthritis) in both high- and low-income countries.

About two decades ago, laboratory experiments suggested that CQ and/or HCQ had anti-HIV activity in lab experiments with cells and virus. However, subsequent clinical trials in people with HIV found that CQ and/or HCQ only had very modest anti-HIV activity. This is par for the course; many drugs first appear to have potential in lab experiments with cells and virus. However, when such drugs are tested in people, they can sometimes fail or have very modest effects. This is a normal part of the drug development process. Experienced scientists estimate that nine out of 10 drugs that appear useful in the test-tube or animal models of human disease subsequently do not pass over the hurdles of human experiments (clinical trials). This happens because experiments in the lab or in animals, while a good first step, cannot capture the complexity of the human body. These challenges are even more pronounced with attempts at repurposing drugs.

COVID-19 and repurposed drugs

Due to the pandemic nature of SARS-CoV-2 infection, CQ and HCQ were rushed into studies in the hope that they could help people with COVID-19 recover. Many initial studies of CQ and HCQ in COVID-19 were not well designed, and this led some scientists to erroneously conclude that these drugs, particularly HCQ, were useful against COVID-19. Interestingly, experiments with animal models (monkeys and hamsters) have found that HCQ does not prevent infection with SARS-CoV-2. Also, HCQ was not effective as a treatment in animals—a finding confirmed in well-designed clinical trials in people with SARS-CoV-2 infection.

TDF + FTC

As reported earlier in this issue of *TreatmentUpdate*, one study from Spain suggested the possibility that some HIV-positive people who were using TDF + FTC had a reduced risk of developing infection with SARS-CoV-2. These findings are from an observational study. Another study, also observational in design, has found no protective effect from TDF + FTC (or from the newer formulation of tenofovir, TAF + FTC) in HIV-negative people who used these drugs as HIV pre-exposure prophylaxis (PrEP). A French study, retrospective in design, examined the impact of TDF + FTC in people with and without HIV who were using the combination as HIV treatment or PrEP. In either case, the combination was not protective against SARS-CoV-2. All of these studies, whether observational or retrospective, cannot prove that the combination of TDF + FTC can prevent SARS-CoV-2 infection. These studies are limited by issues related to their design.

However, a large prospective, randomized, placebo-controlled study of TDF + FTC is underway in Spain. The trial is being done in healthcare personnel to see if these drugs can reduce the risk of becoming infected with SARS-CoV-2. The results are expected in late 2020 or early 2021.

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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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