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## I COVID-19

### A. The importance of antiviral drugs for COVID-19

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The numbers of people affected by COVID-19 will repeatedly fluctuate over the coming months. However, as more of the population gets vaccines that reduce the risk of developing COVID-19, the virus has fewer and fewer people to infect. Thus, mass vaccination is very important because it carries the potential of making the pandemic a thing of the past. In the years ahead, new vaccines will likely be needed and possibly regular booster shots or regular vaccinations, as is done annually with the flu vaccine.

Until the day that COVID-19 disappears, in the short and medium term it will remain an issue for at least the following reasons:

**The rise of mutants**
Like all viruses, SARS-CoV-2 can and does mutate—change its shape or structure. The virus does this because, from time to time, small errors occur in the production of copies of SARS-CoV-2. Some of these errors lead to the creation of defective viruses. Other errors inadvertently lead to the creation of mutations that confer an advantage to the virus.

Possible advantages to the virus conferred by mutations can include the following:

- it is more easily spread
- it has the potential to cause more severe COVID-19

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- it may be able to escape from natural immunity; that is, people who have previously been infected with the virus and recovered may become infected in the future
- it may be able to escape from vaccine-induced immunity

Strains of SARS-CoV-2 that have mutated and become more troublesome in some way (as outlined above) are referred to by scientists as "variants of concern" (VOC).

**Variants of concern**
It is plausible that a year or two from now some VOC that can partially evade the protective effect of vaccines could become more numerous. It is therefore crucial that pharmaceutical companies develop second-generation vaccines that can provide a high degree of persistent protection from VOC currently in circulation as well as ones that are increasing in circulation.

These second-generation vaccines need to be developed, tested and manufactured quickly. Despite the challenges of large-scale vaccine manufacturing and distribution, it is possible that some second-generation vaccines could begin to be rolled out late in 2021 and early 2022.

## Elements of a strategy to help reduce hospitalization

In the meantime, we need to vaccinate as many people as possible with currently available vaccines in order to reduce the risk of people becoming ill and hospitalized due to COVID-19-related complications. In addition to public health measures and currently available testing and vaccination deployment, here are three potential elements related to biomedicine that can be part of a larger strategy to help reduce hospitalizations from COVID-19:

**Easier access to testing**
To further reduce hospitalizations, governments need to make testing for SARS-CoV-2 more accessible, particularly in communities and sectors hit hard by COVID-19. Easier access to SARS-CoV-2 testing could help speed up the diagnosis of infected people. People who test positive could be fast-tracked to be screened by a healthcare professional about their exposure to SARS-CoV-2 and the presence of symptoms. The next step could be that they are advised of public health measures to limit the further spread of SARS-CoV-2. However, interventions are needed, particularly for people who are at high risk for developing severe COVID-19.

**Stockpile treatments**
A key part of a strategy to reduce hospitalizations is to consider the antiviral drugs that are highly effective in COVID-19 clinical trials and that are likely to be approved in the months ahead. Governments can create modest stockpiles of these drugs with bulk purchasing once they are approved. Depending on their performance in clinical trials and on their regulatory approval, these antiviral drugs may include molnupiravir, antibodies such as Regen-CoV and VIR-7831, interferon, and so on.

**Selective deployment of treatment and biomedical prevention of SARS-CoV-2**
These drugs could be prescribed by doctors who have some expertise in COVID-19, either diagnosing or caring for patients. The patients that could be fast-tracked for access to these drugs would be the ones who tested positive and who are early in the course of COVID-19 and who, in the opinion of a physician, are at high risk for developing COVID-19.

**The need for treatment guidelines**
Antiviral drugs for COVID-19 treatment and prevention are new, and at this time many physicians do not have experience using them. Once these drugs are approved, ministries of health could bring together a panel of physicians to help craft guidelines for the use of antiviral drugs for selected people who have been diagnosed with SARS-CoV-2 infection.

**Further research**
Governments could partner with the pharmaceutical industry to launch what scientists call open label clinical trials (where everyone gets an antiviral drug), so that physicians get more experience using these novel drugs. Such trials could be used to compare the effects of different antiviral drugs by randomly assigning people to different drugs. Large open label clinical trials have been used to explore the potential efficacy of repurposed antiviral drugs during the first wave of COVID-19. One such trial found the use of the steroid dexamethasone to be highly useful.

## Putting it all together

If deployed early in the course of COVID-19, these antiviral drugs would probably be very useful. In the months ahead, as more people are vaccinated, there will hopefully be less need for these drugs.

Some of the antiviral drugs being developed have activity against SARS-CoV-2 and other coronaviruses as well, at least in laboratory experiments with cells. Therefore, a modest stockpile of antiviral drugs could also be useful in this worst-case scenario: another wave of illness that occurs in the future that is driven by an entirely new coronavirus not previously encountered by humanity. Over the past 18 years humanity has been threatened by three coronaviruses:

- SARS-CoV-1 – 2002 to 2004
- MERS-CoV (Middle East Respiratory Syndrome Coronavirus) – 2012
- SARS-CoV-2 – beginning in late 2019

It is possible that we could again be faced by a coronavirus that is new and causes serious illness in some people.

Between intensified mass vaccination campaigns, continued use of public health measures to restrict the spread of SARS-CoV-2, and the selective deployment of antiviral drugs (once they have been approved), it should be possible to bring the current pandemic under control either later this year or in early 2022.

## Resource

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# B. Some variants of concern

SARS-CoV-2 infects cells and forces them to produce copies of this virus. Small errors, or mutations, in the production of copies of SARS-CoV-2 occur from time to time. These mutations result in a slightly altered shape or structure of the virus. Over many cycles of infection, as the virus passes from one person to another, mutations accumulate. Mutations that confer an advantage to the virus tend to be carried forward in future copies of the virus. Mutant viruses that can increase harm in some way—such as causing infection more easily, evading the immune system's defences, and so on—are called variants of concern (VOC) by scientists.

Variants of concern tend to have at least one of the following issues:

- they are more easily spread
- they have the potential to cause more severe COVID-19
- they may be able to escape from natural immunity; that is, people who have previously been infected with the virus and recovered may become infected in the future
- they may be able to escape from vaccine-induced immunity or antibody-based treatments

## Selected variants of concern

Information on variants of concern is constantly evolving. For the most recent information about variants of concern in your region, speak to your local public health authorities.

Also, the U.S. Centers for Disease and Control (CDC) has some information on variants of concern at the link below:

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

In the case of the following variants of concern, comparisons are made to the original variant of SARS-CoV-2 that appeared in late 2019. These comparisons are largely based on test-tube studies:

- B.1.1.7 – this variant has 23 mutations and was first identified in the UK in December 2020. It is about 50% more transmissible and may have caused more severe COVID-19 in some people. According to the CDC, it likely has a "minimal" impact on the effectiveness of antibodies generated by vaccination and on antibody-based therapies.
- B.1.351 – this variant has 23 mutations and was initially reported in South Africa in December 2020. It is about 50% more easily spread and, according to the CDC, it has "modest" impact on most vaccines and some antibody-based therapies. However, data from South Africa suggests that it can have a significant impact on protection from the AstraZeneca vaccine, reducing its effectiveness.
- P1 – this variant has 35 mutations and was initially reported in Brazil in January 2021. According to the CDC, it has a "moderate" impact on some antibody therapies and on antibodies generated by the Pfizer-BioNTech and Moderna vaccines.

These variants are spreading and have been reported in many countries, including Canada.

Other VOC include the following:

- B.1.427 and B.1.429 – these variants that were first isolated in California are estimated by the CDC to be about 20% more transmissible than the original strain of SARS-CoV-2. Furthermore, they can significantly reduce the effectiveness of some antibody-based therapies and "modestly" reduce the effectiveness of vaccines.

Over time, it is likely that other VOC will appear around the world.

## Cellular immunity

Note that the previous assessments about vaccines and variants are based largely on antibodies. The minimal level of antibodies needed in the body for protection against SARS-CoV-2 (and variants) after vaccination is not known.

Most vaccines stimulate B-cells to produce antibodies that attack a target – in this case, part of SARS-CoV-2 or a cell infected with this virus. However, vaccines also stimulate T-cells (and likely other cells of the immune system, such as natural killer cells) to recognize virus-infected cells and, as a consequence, release antiviral substances as they attack and destroy these cells. This is called cellular immunity. This type of immunity can also be helpful against SARS-CoV-2. Cellular immunity arising from vaccination has generally not been thoroughly assessed against many VOC at the time this publication went to press. At any rate, the rise and spread of VOC means that it is crucial for pharmaceutical companies to develop vaccines that are effective against a broad range of variants. Such research is now underway.

## Resources

*Government of Canada* – https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html#VOC

*U.S. Centers for Disease Control and Prevention* – https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

*British Columbia Centres for Disease Control* – http://www.bccdc.ca/health-info/diseases-conditions/covid-19/about-covid-19/variants

*Institut national de santé publique du Québec* – https://www.inspq.qc.ca/covid-19/labo/variants ; https://www.inspq.qc.ca/nouvelles/variants-du-sras-cov-2-pourquoi-s-en-preoccuper ; https://www.inspq.qc.ca/covid-19/donnees/variants

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## C. VIR-7831 (sotrovimab) – preventing hospitalization and death in COVID-19

There are many potential medicines in development for the prevention and treatment of COVID-19. One group of potential therapies is called monoclonal antibodies.

### About antibodies

Antibodies are proteins made by the immune system. These proteins help the immune system recognize a particular germ and mark it for destruction by the immune system.

Monoclonal antibodies are made in the lab. These antibodies are designed by scientists to attack a specific germ—in this case, SARS-CoV-2.

About a year ago, two companies—Vir Biotechnology and GlaxoSmithKline (GSK)—began cooperating on the development of potential interventions to prevent and treat COVID-19.

The companies have developed the following antibodies

- VIR-7831, also known as GSK-4182136
- VIR-7832, also known as GSK-4182137

Preliminary results from a placebo-controlled trial of VIR-7831 have found that this antibody is highly effective (85%) at reducing the risk of hospitalization or death from COVID-19.

### The Comet-Ice study

In a study called Comet-Ice, researchers recruited adults with mild or moderate COVID-19 who were at high risk for hospitalization and randomly assigned them to receive one of the following intravenous interventions:

- 500 mg of VIR-7831
- placebo

An interim analysis from 583 participants (291 who received the antibody and 292 who received placebo) found that there was an 85% reduction in the risk of hospitalization or death in people who received the antibody. Due to this effect of the antibody, the independent data monitoring committee that oversaw the study recommended that enrollment be halted. The trial will continue to monitor participants for an additional 24 weeks.

VIR-7831 has been found to be generally safe in the Comet-Ice study. Further details from this study will be released in the future.

Vir and GSK plan to test other formulations of VIR-7831 by giving it as an intramuscular injection.

Large clinical trials are also planned to confirm the findings from Comet-Ice.

## Some variants of concern

As mentioned previously in this issue of *TreatmentUpdate*, SARS-CoV-2 infects cells and forces them to produce copies of this virus. Small errors, or mutations, in the production of copies of SARS-CoV-2 occur from time to time. These mutations result in a slightly altered shape or structure of the virus. Over many cycles of infection, as the virus passes from one person to another, mutations accumulate. Mutations that confer an advantage to the virus tend to be carried forward in future copies of the virus. Mutant viruses that can increase harm in some way—such as causing infection more easily, evading vaccine-induced protection and antibody-based therapies—are called variants of concern (VOC).

Some VOC include the following:

- B.1.1.7 – first identified in the UK in December 2020
- B.1.351 – initially reported in South Africa in December 2020
- P1 – has 35 mutations and was initially reported in Brazil in January 2021

These variants, particularly B.1.1.7, are spreading and have been reported in many countries including Canada.

Lab experiments with VIR-7831 and VIR-7832 and cells infected with variants of concern have found that these antibodies are highly effective against variants of concern B.1.1.7, B.1.351 and P.1. Not only do they stop the virus from spreading in cultures of cells in the lab, they also attract cells of the immune system to help capture and destroy SARS-CoV-2-infected cells. These properties of the VIR antibodies should not be surprising. They were developed based on an antibody that was highly effective against SARS-CoV-1, the virus that caused an outbreak of SARS in 2002. As SARS-CoV-1 is closely related in shape to SARS-CoV-2, the VIR antibodies have the ability to neutralize key variants of concern. VIR-7831 has also been optimized to remain in circulation longer than most antibodies. As well, it is supposed to accumulate in the lungs and airways—places that SARS-CoV-2 tends to infect.

## Harmful antibodies

In the case of infection with certain viruses (such as Dengue virus, HIV and Zika virus), the immune system produces antibodies that quickly lose their potency and/or are generally unhelpful in containing infection. In some cases, antibodies produced by the immune system against these viruses may even help the viruses infect cells. However, VIR-7831 and VIR-7832 do not cause this problem in laboratory experiments.

## Hamsters

The Middle Eastern hamster (also called the golden or Syrian hamster) is an important animal model to study SARS-CoV-2 infection. These animals tend to experience severe disease when they are infected with SARS-CoV-2. Experiments with these hamsters confirm that VIR-7831 (no data was made available about the other antibody) was able to reduce levels of SARS-CoV-2.

## For the future

In the months ahead, Vir and GSK are seeking approval for VIR-7831 from regulatory authorities in the U.S., Canada and Europe while continuing to conduct further studies.

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## D. Regen-CoV for preventing hospitalization and death in COVID-19

Scientists at Regeneron Pharmaceuticals have developed two antibodies that attack different parts of SARS-CoV-2. The combination of antibodies is called Regen-CoV. It is important that they are used in combination, as this minimizes the chance of SARS-CoV-2 developing the ability to resist their effects. Modifications have been made to the Regen-CoV antibodies so that they persist in circulation when infused. The antibodies are:

- casirivimab
- imdevimab

In experiments with hamsters and monkeys, Regen-CoV can significantly reduce the amount of SARS-CoV-2 in the lungs of infected animals. The antibodies also reduce complications from this viral infection. They are effective against the ancestral strain of SARS-CoV-2 that first appeared in 2019 as well as key variants of concern.

### In people

Regen-CoV has been tested in a placebo-controlled study with 4,567 people who were diagnosed with COVID-19. All participants were not sufficiently ill to be hospitalized but were considered at high risk for becoming severely ill with COVID-19. Treatment consisted of a single dose of each antibody given intravenously on the same day. The study assessed the effect of a combined dose of 1,200 mg (600 mg of each antibody) vs. a combined dose of 2,400 mg (1,200 mg of each antibody) vs. placebo. The antibody combination reduced the risk of hospitalization and death by about 70%, regardless of which dose was used.

All participants in the study had at least one risk factor associated with an increased risk of severe COVID-19. These risk factors included the following:

- obesity – 58%
- age greater than 50 years – 51%
- cardiovascular disease – 36%

### Results

Regardless of the dose used, the antibodies reduced the time to resolution of symptoms by four days vs. placebo. The total duration of symptoms was as follows:

- Regen-CoV – 10 days
- placebo – 14 days

There were seven deaths in the study, distributed as follows:

- 1,200-mg dose group – one person
- 2,400-mg dose group – one person
- placebo group – five people

Regeneron has not released detailed information about the safety of the antibodies used in this study but stated that "serious adverse events were largely related to COVID-19" and were distributed as follows:

- 1,200-mg dose group – 1.1%
- 2,400-mg dose group – 1.3%
- placebo group – 4%

In a different study of Regen-CoV, doctors tested the effects of different doses and formulation of the antibodies in about 800 non-hospitalized people with COVID-19:

- intravenous doses – 2,400 mg, 1,200 mg, 600 mg, 300 mg, placebo
- injection just under the skin (subcutaneous injection) – 1,200 mg, 600 mg, placebo

The company stated that all doses of the antibody reduced the amount of SARS-CoV-2 in participants compared to placebo.

Subcutaneous doses are easier to administer than intravenous doses. Regeneron plans to discuss the effects of this study with regulatory authorities to find out if they will approve the subcutaneous dosing of the antibodies.

Other trials of Regen-CoV testing the antibodies in people hospitalized with COVID-19 are underway.

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## E. Regen-CoV for preventing the further spread of COVID-19

Regen-CoV is the brand name of a combination of two antibodies that attack SARS-CoV-2. The antibodies are as follows:

- casirivimab
- imdevimab

Regeneron Pharmaceuticals, the developer of the antibodies, has conducted a placebo-controlled study in 409 adults without COVID-19 who were living with someone who had been diagnosed with COVID-19. The purpose of the study was to find out if Regen-CoV could reduce the risk of the virus infecting other people in the household.

The antibodies were given via injection just under the skin (subcutaneous injection) at a dose of 600 mg each (for a combined total dose of 1,200 mg) within 96 hours of a household member testing positive by PCR (polymerase chain reaction) for SARS-CoV-2. Participants had nasal swabs done at the start of the study and weekly to collect samples for SARS-CoV-2 testing.

The average profile of participants at the start of the study was as follows:

- age – mid-50s
- 54% women, 46% men
- major ethno-racial groups – 78% white, 50% Hispanic, 13% Black, 3% Asian (due to the overlap of ethno-racial categories, the total proportion does not equal 100%)
- body mass index (BMI) – 29

### Results

The distribution of initially negative household contacts with a subsequent positive test for SARS-CoV-2 was as follows:

- placebo – 10%
- Regen-CoV – 5%

Among people who tested positive for SARS-CoV-2, the duration of infection was generally shorter for those who received Regen-CoV vs. placebo. Also, people who received Regen-CoV subsequently had significantly less SARS-CoV-2 in their blood than people on placebo.

### Side effects

Monitoring skin reactions at the site of injection is important in studies of injectable medicines. The distribution of injection site reactions in this study was as follows:

- Regen-CoV – 3%
- placebo – 1%

The proportions of participants with at least one serious adverse event were as follows:

- placebo – 1%
- Regen-CoV- 1%

Details were not provided on the serious adverse events. No hypersensitive reactions or seizures occurred.

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## F. Regen-CoV for early treatment in people recently infected with SARS-CoV-2

Regen-CoV is the brand name of a combination of two antibodies that attack SARS-CoV-2. The antibodies are as follows:

- casirivimab
- imdevimab

Regeneron Pharmaceuticals, the developer of the antibodies, has conducted a placebo-controlled study in 204 adults who were diagnosed with SARS-CoV-2 infection but who had not yet developed symptoms.

Researchers divided participants into two groups, as follows:

- Regen-CoV at a single dose of 1,200 mg (600 mg of each antibody) administered as four injections just under the skin – 100 people
- injections of placebo just under the skin – 104 people

According to the company, at the start of the study, 32% of participants had "at least one known factor that put them at high risk of suffering severe consequences from COVID-19," including obesity and older age.

### Results

The proportion of participants who developed symptoms of COVID-19 three days after injections were distributed as follows:

- Regen-CoV – 29%
- placebo – 42%

These results suggest that Regen-CoV can reduce the risk of developing COVID-19 by 31% vs. placebo. This difference favouring Regen-CoV was statistically significant.

For participants who developed symptoms, Regen-CoV reduced the duration of symptoms by 45%.

Although the study was not designed to assess the risk of hospitalization, it is noteworthy that the distribution of participants who visited a hospital emergency department or were hospitalized after injections because of COVID-19 was as follows:

- Regen-CoV – 0 people
- placebo – 6 people

Hopefully Regeneron will release detailed results from this and other studies in the future to help regulatory agencies decide on the scope of its use.

Given the totality of clinical data with Regen-CoV, it is likely that this antibody will be in the news in the future.

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## G. AT-527 enters clinical trials for COVID-19 treatment

AT-527 is a nucleoside analogue that is being developed as a potential treatment for COVID-19. The drug is taken orally. This drug is an analogue of a naturally occurring substance called guanosine. In cells, guanosine is used to make RNA and DNA.

Experiments with cells in the lab have found that AT-527 has potent antiviral activity against SARS-CoV-2. The drug works by interfering with an enzyme needed by the virus called RNA polymerase. This enzyme is also used by other coronaviruses and potentially AT-527 could be used against them as well.

Experiments in monkeys and people have found that AT-527 is well absorbed and, according to the developer, Atea Pharmaceuticals, "well tolerated." When taken at a dose of 550 mg twice daily, levels of AT-527 in the lungs are high.

AT-527 is currently in a clinical trial with people diagnosed with COVID-19. Preliminary findings from a study of 30 people suggest that the drug is

safe. The drug's impact on the course of COVID-19 will hopefully be known in the months ahead.

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## H. How adenovirus vaccines work

Adenoviruses are a large family of viruses that can cause a range of illness in people and animals. In people, these viruses can cause relatively mild illness such as colds and pink eye or more serious issues such as diarrhea and pneumonia.

For decades, scientists have been experimenting with adenoviruses and turning them into vehicles or vectors to send information to cells in the body so that the cells can help the immune system recognize certain germs (other than adenoviruses) and attack them. In effect, these efforts with modified adenoviruses have turned them into vaccines.

To do this, scientists first remove the part of the adenovirus' genetic information that causes harm. They then insert instructions for making viral proteins of the germ they will need to vaccinate against. A dose of vaccine using adenoviruses usually contains many millions or even billions of modified adenoviruses. The vaccine is injected into the muscles of the upper arm. After injection, the modified adenovirus reaches muscle cells and enters them, where it releases its cargo. This cargo consists of instructions for making viral proteins chosen by scientists.

The cells' machinery "reads" the instructions carried by the adenovirus. As a result, the cells begin to produce the proteins mentioned in the instructions. In this case, the proteins are tiny pieces of SARS-CoV-2.

The muscle cells release the proteins into circulation, where cells of the immune system encounter the proteins. The cells of the immune system recognize the proteins as foreign and a process that we describe next is then triggered.

The cells of the immune system capture the proteins and migrate to nearby lymph nodes. Once inside the lymph nodes, the cells that have captured the viral proteins teach other cells of the immune system to recognize the proteins as foreign and to respond in different ways when they encounter the proteins in the future. For instance, a group of the immune system's cells called B-cells begins to make antibodies against the viral proteins.

Another group of the immune system's cells called T-cells learns to attack and destroy the virus and cells that it has infected.

B- and T-cells that have been stimulated by vaccination make many millions, perhaps billions, of copies of themselves and leave the lymph nodes to circulate in the body. Over time, the levels of B- and T-cells in circulation that can recognize the virus fall to low levels. However, a small portion of these cells transform into memory B- and T-cells. These memory cells can live many years and retain the memory of how to defend the body from SARS-CoV-2. These cells reside in lymph nodes and organs of the immune system such as the spleen. Should infection with SARS-CoV-2 occur in the future, once these cells encounter the virus, they become activated and spring into action, making millions of copies of themselves, and contain the virus.

The immunological events described above are a simplified and idealized scenario. SARS-CoV-2 is new to science and it is plausible that sometime after vaccination—perhaps a year or two later—a booster shot may be needed to help people maintain high levels of immunity to SARS-CoV-2.

It is also possible, likely even, that entirely different vaccines may be needed in the future, as SARS-CoV-2 is mutating.

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## I. The Janssen COVID-19 vaccine

Clinical trials of the Janssen COVID-19 vaccine (in some parts of the world this is called the Johnson & Johnson COVID-19 vaccine) have found that it is generally safe. Common side effects included pain at the injection site, headache, fatigue and muscle soreness. These side effects were generally mild and temporary. Furthermore, they suggest that the immune system is responding to the vaccine. The vaccine was 66% effective at reducing the risk of developing COVID-19 after one injection. Leading scientists and public health officials in Canada, the European Union and the U.S. have noted the following:

Although there may be a risk of developing blood clots with this and other COVID-19 vaccines, the risk is generally very small compared to the much greater risk of developing COVID-19 and requiring hospitalization if one is not vaccinated.

The Janssen vaccine is based on a modified adenovirus. For further information about how adenoviruses are used as vaccines, please see the previous article about adenoviruses in this issue of *TreatmentUpdate*.

### Study details

Janssen conducted a phase III clinical trial of its vaccine in about 40,000 people. Participants were randomized to receive one of the following interventions:

- a single intramuscular injection of the vaccine into the upper arm
- a single intramuscular injection of placebo into the upper arm

The average profile of participants upon study entry was as follows:

- 55% men, 45% women
- age distribution: 18 to 59 years – 65% of participants; 60 and older – 35%; 65 and older – 20%; 75 and older – 4%
- major ethno-racial groups – 62% white, 45% Hispanic, 17% Black, 8% Indigenous, Asian – 4% (due to the overlap of ethno-racial categories, the total proportion does not equal 100%)
- presence of one or more underlying conditions (comorbidities) – 40%

### Focus on comorbidities

Participants had a wide range of comorbidities. The four most common were as follows:

- obesity – 29%
- high blood pressure – 3%
- HIV infection – 2%
- asthma – 1%

### Results

Before the data were analyzed, participants were monitored for about two months post-vaccination.

Cases of flu-like symptoms that occurred at least 28 days after vaccination and that tested positive for SARS-CoV-2 (via analysis of nasal swabs) were distributed as follows:

- vaccine – 66 cases of COVID-19
- placebo – 193 cases of COVID-19

According to calculations by the U.S. Food and Drug Administration (FDA), the vaccine was 66% effective in reducing the risk of moderate-to-severe COVID-19.

## Hospitalizations

Beginning 14 days after vaccination, the numbers of people hospitalized were distributed as follows:

- vaccine – 2 people
- placebo – 29 people

There were no further cases of hospitalization among people who received the vaccine. However, among people given placebo, further cases of hospitalization occurred beyond the initial 14-day analysis. No one who was vaccinated died from complications arising from COVID-19. However, seven people who received placebo and who developed COVID-19 and who were hospitalized died.

## Demographics

There was no significant impact of the following factors on the effectiveness of the vaccine:

- age
- comorbidities
- ethno-racial groups

## Adverse effects

Common side effects were as follows:

- pain at the injection site – 49%
- headache – 39%
- fatigue – 38%
- muscle ache – 33%

In general, these were more common in younger than older people.

The above-mentioned side effects were generally very mild and temporary. In most people they appeared within a day or two after vaccination and resolved within a couple of days.

## Clotting-related events

There was a slight imbalance in the distribution of excess formation of blood clots, as follows:

- vaccine – 15 clots in 14 people (0.06%)
- placebo – 10 clots in 10 people (0.05%)

Readers can see that excess clot formation normally occurs in a population but at very low rates. It is not clear how many people who received the vaccine would have developed excess blood clots had they not been vaccinated. However, clotting problems that may be associated with this vaccine are likely very rare.

These clots occurred in different parts of the body—limbs, lungs, carotid artery, hemorrhoids. Most participants affected in the vaccine group were male (12 men vs. two women). The clots were generally associated with only a modest degree of injury and everyone recovered or is recovering. The age range affected by the excess clots among vaccinated people was between 25 and 90 years. An FDA analysis suggested that many of the affected participants were at heightened risk for excess blood clots due to underlying issues. Furthermore, in all but one case of blood clots that occurred in vaccinated persons, investigators concluded that the clots were unrelated to the vaccine.

Here are details on the only case where investigators concluded that the clots were related to vaccination:

A 52-year-old male with obesity (his body mass index was 32.4 $kg/m^2$) developed pain in one of his calves 27 days following vaccination. An ultrasound scan revealed the presence of a blood clot in his calf. He was diagnosed with deep vein thrombosis. According to the FDA, investigators considered this issue "non-serious" but related to his vaccination. However, Janssen disputes any relationship with its vaccine and the subsequent development of blood clots in this man.

A future issue of *TreatmentUpdate* will explore the topic of blood clots that have occurred in very rare cases with COVID-19 vaccines.

## Hypersensitivity reactions

There was one report of a hypersensitivity reaction (a kind of allergic reaction) that occurred in a person two days after vaccination. This was not fatal and no further details were provided.

## Pregnancy

As with many large COVID-19 vaccine studies, women of childbearing potential were screened for pregnancy prior to randomization. Those

who tested positive were excluded from the study. However, once vaccinated, some women in these and other COVID-19 vaccines studies may become pregnant.

Two women in the vaccine group in the Janssen study are currently pregnant and the results of the pregnancy are not known.

Experiments with rabbits before, during and after pregnancy found no harmful effects on the pregnant rabbits or their offspring when they were given the same dose of the vaccine used in humans.

### Vulnerable populations

There were relatively small proportions of people with HIV infection—about 3%. HIV-positive participants would have been on treatment (ART) and healthy and well. No results of the vaccine in this population were released.

About 0.5% of participants were categorized as having an unspecified liver disease. It is possible that some of them had viral hepatitis, but at this time the company has not released details.

### For the future

Janssen is conducting another large study in which two injections of the vaccine are given. Results from this study are expected later in 2021. The company is also planning other studies.

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## II COVID-19 AND HIV

## A. Changes in the profile of people seeking care in London, UK

Observational studies have generally reported similar results in HIV-positive and HIV-negative people who have been hospitalized with COVID-19. Further details can be found in the links below:

https://catie.ca/en/treatmentupdate/treatmentupdate-238/hiv-and-covid-19

https://www.catie.ca/en/catienews/2021-02-23/new-york-state-assesses-impact-covid-19-hiv-positive-people

A report of a change in the profile of people seeking care at a major HIV clinic in London, UK, has recently emerged.

Doctors at Chelsea and Westminster Hospital noticed an increased number of HIV-positive people who sought care because of AIDS-related complications.

The doctors compared HIV-related hospital admissions in two periods: July to October 2019 and the same months in 2020.

### Key findings – focus on AIDS in hospitalized patients

Although there were fewer admissions in 2020 than in 2019, doctors found a large increase in the proportion of hospitalization for AIDS-related causes. Here is a comparison of the two years:

2019
27% of hospitalizations were due to AIDS-related causes such as the following:

- cancers – 48%
- life-threatening infections – 52%

2020
54% of hospitalizations were due to AIDS-related causes such as the following:

- cancers – 28%
- life-threatening infections – 72%

Laboratory testing of blood samples found a trend toward increasing immunodeficiency in hospitalized HIV-positive people in 2020 compared to 2019.

2019
- newly diagnosed HIV infections – 16%
- CD4+ cell count among newly diagnosed people – 157 cells/mm$^3$

2020
- newly diagnosed HIV infections – 16%
- CD4+ cell count among newly diagnosed people – 63 cells/mm$^3$

There was also a trend to higher viral loads among hospitalized patients in 2020 compared to 2019.

The differences in the types of life-threatening infections/complications between the two study periods is too small to draw statistical comparisons. However, it was striking that in 2019 two out of 80 HIV-positive people (3%) had severe problems with memory and thinking clearly compared to five out of 48 people (10%) who were diagnosed with HIV in 2020. It is possible that this difference in the proportion of people with severe memory and thinking problems was due to chance. Yet, in an era of widely available HIV testing and effective treatment in a high-income country, people who were seeking care clearly had HIV-related neurocognitive impairment. Such problems were common in the time before potent combination HIV treatment became available (prior to 1996).

## What is going on?

It is clear that a shift toward the development of more severe HIV-related immune deficiency has occurred among some people in London in the current era. Hospitalized patients were seriously ill. The research team stated that the shift in the profile of illness of patients is due to one or more of the following issues:

- "difficulty accessing healthcare"
- "reluctance to attend healthcare facilities during the first wave of the COVID-19 pandemic and the inevitable lockdown"

A similar trend—reluctance to access healthcare—has been reported among some HIV-negative people in different parts of the world during the initial wave of the pandemic.

The report from Chelsea and Westminster Hospital underscores the severe impact of the indirect effects of the COVID-19 pandemic on some people's access to HIV testing, care and treatment. It also shows how deaths among HIV-positive people may arise in the pandemic era—from AIDS-related causes and not from COVID-19.

## Resources

HIV and COVID-19 – *TreatmentUpdate* 232

New York State assesses the impact of COVID-19 on HIV-positive people – *CATIE News*

REFERENCE:

Bell N, Bracchi M, Dalla Pria A, et al. Indirect HIV morbidity and mortality due to COVID-19. *Clinical Infectious Diseases*. 2021; *in press*.

## Disclaimer

**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.**

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

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.

CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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***HepCInfo Updates***
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***A Practical Guide to HIV Drug Side Effects***
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

***The Positive Side* magazine**
Holistic health information and views written by and for people living with HIV.

**Fact Sheets**
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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