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I COVID-19

A. Evusheld – dual antibodies for reducing the risk of SARS-CoV-2 infection

The first generation of mRNA vaccines that were developed against SARS-CoV-2 were designed to reduce the risk of people becoming seriously ill, requiring hospitalization or dying from complications related to COVID-19. The vaccines were developed against the original strain of SARS-CoV-2, which became widespread in the first half of 2020.

Since that time, SARS-CoV-2 has mutated into different strains, or variants. The mRNA vaccines still continue to provide a high degree of protection from serious complications, hospitalizations and death. Getting booster shots as recommended by local public health authorities is a very good idea. However, the effectiveness of these vaccines appears to be gradually diminishing as SARS-CoV-2 continues to mutate.

Another route of potential protection from SARS-CoV-2 is the use of an antiviral treatment such as Paxlovid (a combination of the drugs nirmatrelvir and ritonavir) in people who have been recently infected with SARS-CoV-2 and who are at high risk for developing serious symptoms of COVID-19.

Monoclonal antibodies

In addition to vaccines and Paxlovid, clinical trials have found that another way to reduce the risk for developing serious symptoms of COVID-19 is

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to receive injections of antibodies that have been designed to attack SARS-CoV-2. These injections are developed from antibodies found in the blood of people who have survived coronavirus infection—either by the virus that caused an outbreak of SARS (severe acute respiratory syndrome) in 2003 or the more recent virus responsible for the present pandemic (SARS-CoV-2), as both viruses are related. Scientists have modified the antibodies to make them remain in the circulatory system at high levels for much longer than normal (likely for months).

Antibodies that are created in a lab (from clones of B-cells) in large quantities for the treatment of viral infections, cancer and other conditions are called monoclonal antibodies.

Enter Evusheld

The latest monoclonal antibody product approved in Canada is Evusheld. This is the brand name of two antibodies (tixagevimab and cilgavimab) that are used together. The antibodies in Evusheld were tested in a randomized placebo-controlled clinical trial called Provent with more than 5,000 participants at risk for developing serious symptoms of COVID-19. Researchers found that a single dose of both antibodies was able to significantly reduce the risk of developing symptomatic COVID-19.

Study details

Researchers recruited participants between November 2020 and March 2021. The average profile of participants upon entering the study was as follows:

- 54% men, 46% women
- age – 43% were 60 years and older, 24% were 65 and older, and 4% were 75 and older
- major ethno-racial groups: White – 73%; Black – 17%; Asian – 3%
- body mass index (BMI) – 29 kg/m^2

About 75% of all participants had at least one underlying factor that increased their risk for severe COVID-19, including the following:

- obesity – 42%
- high blood pressure – 36%
- smoking – 21%
- diabetes – 14%
- asthma – 11%
- cardiovascular disease (other than high blood pressure) – 8%
- cancer – 7%
- chronic obstructive pulmonary disease (COPD) – 5%
- chronic kidney disease – 5%
- chronic liver disease – 5%
- using therapies that weakened the immune system – 3%

Participants were randomly assigned to receive (in a 2-to-1 ratio) either antibodies or placebo. After being injected by a healthcare practitioner, participants were monitored for one to four hours for any signs of side effects.

Participants who were assigned to receive antibodies were given two injections of 1.5 mL of antibodies into muscle (in their buttocks). One injection contained tixagevimab and the other cilgavimab.

People who tested positive for SARS-CoV-2 while being screened for potential recruitment for the study were not allowed into the study.

At the point of study entry, none of the participants enrolled in Provent were vaccinated against COVID-19.

Once people enrolled in the study, nurses contacted them weekly to assess symptoms for possible COVID-19 infection. People with symptoms suggestive of COVID-19 underwent testing for this virus and other assessments. Participants were monitored for at least 83 days and in many cases for up to six months after entering the study.

Results – safety

The term *adverse events* is used to describe unfortunate events that can occur during a clinical trial. Some of these events are due to side effects of the treatment or drug(s) being used. In other cases, adverse events may occur because of the underlying disease process. Some adverse events may also be caused by issues unrelated to the study, such as accidents.

According to the Provent researchers, "most adverse events were mild or moderate in intensity." The overall distribution of adverse events was as follows:

People who received Evusheld
- any adverse event – 35%
- mild adverse events – 22%
- moderate adverse events – 11%
- severe adverse events – 2%

People who received placebo
- any adverse event – 35%
- mild adverse events – 21%
- moderate adverse events – 11%
- severe adverse events – 2%

Injection site reactions

Injection site reactions—redness, swelling, itchy skin—occurred in 2% of people who received antibodies and 2% of people who received placebo.

Anaphylaxis

Historically, a very small proportion of people who have received monoclonal antibodies for a range of conditions have developed a severe allergic reaction called anaphylaxis. One person developed severe chest pain shortly after being injected with Evusheld. At first, researchers thought that he had anaphylaxis, but investigation and his subsequent course suggested that the chest pain was a manifestation of cardiovascular disease.

There was a total of eight deaths, distributed as follows:

People who received Evusheld
- two people died from lung complications arising from COVID-19
- two people died from drug overdoses
- one person died from heart attack
- one person died from kidney failure

People who received placebo
- two people died from drug overdoses

All deaths were investigated and were not caused by the antibodies or the placebo.

Effectiveness

The distribution of people in the study who became infected with SARS-CoV-2, confirmed with polymerase chain reaction (PCR) testing, and who developed COVID-19 was as follows:

- Evusheld – 0.2%
- placebo – 1%

Statistical analysis found that people who received Evusheld had a 77% relative reduction in the risk of developing COVID-19. This difference was statistically significant. That is, not likely due to chance alone.

The protective effect of Evusheld was similar among many subgroups of participants regardless of gender, age, ethno-racial background and so on.

Antibody levels

After injection, muscles tend to slowly release a drug or antibody into circulation in the body. In the Provent study, antibody levels reached their peak one month after injection and then gradually declined over the next five months.

Bear in mind

The results from the Provent study suggest that Evusheld can significantly reduce the risk of developing COVID-19. There are additional issues to consider about the deployment of Evusheld, and these are raised in the next report.

REFERENCE:

Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for prevention of COVID-19. *New England Journal of Medicine*. 2022 Jun 9; 386(23):2188-2200.

B. Evusheld – issues to consider

As mentioned earlier in this issue of *TreatmentUpdate*, a combination of two antibodies designed to attack SARS-CoV-2, sold under the brand name Evusheld, has been approved in Canada and the U.S. In a large clinical trial called Provent, Evusheld significantly reduced the risk of unvaccinated people developing COVID-19. How should Evusheld be deployed? It may be worth

considering the following issues in order to reflect on that question.

Immune suppression

The main clinical trial that tested Evusheld enrolled people who were likely to have a poor immunological response to infection with SARS-CoV-2 or to vaccines for this infection. According to AstraZeneca, the manufacturer of Evusheld, such people are likely from the following populations or have the risk factors listed below:

- age 60 and older
- obesity
- immune suppressed (we will return to this point later)
- have a history of adverse reactions to vaccines (in general)
- have congestive heart failure
- have chronic obstructive pulmonary disorder (COPD)
- have chronic kidney disease
- have chronic liver disease

In Canada, Evusheld is meant to be used in adults and adolescents (age 12 and older). In order for Evusheld to reduce the risk of SARS-CoV-2 infection and the subsequent development of COVID-19, the product monograph notes that potential users should not have been recently exposed to people infected with this virus. According to AstraZeneca, a potential user should fulfill the following categories:

- "be immune compromised and unlikely to mount an adequate immune response to COVID-19 vaccines"
- be someone "for whom COVID-19 vaccination is not recommended"

In practice, doctors are likely to restrict the use of Evusheld to people who are immune suppressed. Generally, these are people who are taking medicines to weaken their immune systems, such as the following:

- people who have a transplanted organ
- some people who are being treated for rheumatoid arthritis, Crohn's and colitis, severe psoriasis and other inflammatory conditions

HIV

Evusheld was not tested in people with HIV. At any rate, research from Canada and other high-income countries with universal health care systems, has found that people with HIV who are taking potent HIV treatment (ART) and who have a suppressed viral load and at least modestly elevated CD4+ cell counts generally respond well to COVID-19 vaccines. Such people do not appear to be at high risk for severe illness, hospitalization or death arising from COVID-19.

Potential side effects

There was a very small imbalance in adverse events relating to cardiovascular issues in the Provent study. The distribution of such events was as follows:

- Evusheld – 0.7% (23 people)
- placebo – 0.3% (5 people)

Note that twice as many people received Euvsheld as did placebo in that study.

Cardiovascular events that occurred in the study included the following:

- abnormal heart rhythms
- heart attack
- heart pain
- coronary artery disease (note that this takes many years to develop and is extremely unlikely to have occurred because of exposure to Evusheld)

There was also a slight excess of neurological issues, some of which appear to be related to cardiovascular disease (such as stroke), that occurred. Overall, less than 1% of people who received Evusheld developed such issues.

All of the participants in the study who developed cardiovascular or neuro-vascular-related adverse events either had a history of such events or risk factors for them when they entered the study.

Another study (as yet unpublished) called Storm Chaser also tested Evusheld. During this study no one developed cardiovascular adverse events. However, participants in Storm Chaser were younger than those in Provent and tended to have fewer cardiovascular risk factors.

According to Camille Kotton, MD, of Harvard University Medical School, who reviewed the findings from Provent, "Overall, the benefit of additional protection for immunocompromised patients seems to outweigh the potential risk for cardiac events."

It may also be useful for doctors to weigh the risks and benefits of Evusheld on a case-by-case basis with their patients who have cardiovascular disease risk factors.

The issue of variants

SARS-CoV-2 continues to infect many people and produce new variants. These variants have changes to their genetic makeup (called mutations) and subtle changes to the structure of the virus. Altogether these changes can help some variants better evade antibodies and other measures taken by the immune system to contain the virus. They can also help the virus evade the monoclonal antibodies that are used to help prevent COVID-19.

In late February 2022, the U.S. Food and Drug Administration (FDA) recommended that the dose of Evusheld be doubled in cases where doctors were trying to prevent infections with the SARS-CoV-2 variants BA.1 and BA.1.1, which are part of the Omicron variant family.

The Omicron variant has also spawned a number of other subvariants, such as BA.2, 3, 4 and 5 (there are others). It is possible that in the coming months new subvariants or entirely new variants may form and spread.

Scientists at the Institut Pasteur in Paris and other research centres in France have been monitoring antibodies in blood samples from people who received Evusheld and other treatments. They have extracted these antibodies from blood samples and tested them against variants of SARS-CoV-2.

They found that Evusheld antibodies in those blood samples were able to attack the variant BA.1. in 19 out of 29 people and the variant BA.2 in 29 out of 29 people.

Participants had previously been vaccinated with at least three doses of an mRNA vaccine (usually from Pfizer-BioNTech). All participants either had disorders in which their immune systems attacked parts of the body or had received organ transplants. As a result, all participants were receiving medication to partially weaken their immune systems.

Four out of the 29 Evusheld recipients developed COVID-19. In three of these cases, the infection was caused by the Omicron variant and symptoms were mild. These cases occurred between 15 and 21 days after Evusheld injections.

A fourth person was infected with the subvariant BA.1 and developed severe symptoms of COVID-19 three weeks after receiving Evusheld. This person was hospitalized.

Researchers did not provide circumstances as to how participants became infected and this was not a randomized clinical trial, so the results have to be interpreted cautiously. Nevertheless, the report by the Institut Pasteur scientists suggests that 25 out of 29 people who received Evusheld subsequently had a reduced risk for developing COVID-19.

Extending Evusheld's potential

In the Provent study, Evusheld was used as a form of pre-exposure prophylaxis (PrEP) against SARS-CoV-2. Interim results from another study called Tackle suggest that doubling the dose of Evusheld, from 300 mg to 600 mg, can reduce the risk of progression to severe illness in people who are treated early in the course of SARS-CoV-2 infection. It is possible that AstraZeneca may seek approval from regulatory agencies to use Evusheld in this way.

For the future

The study from the Institut Pasteur underscores the complexity of the current pandemic. Scientists can develop vaccines, drugs and monoclonal antibodies against SARS-CoV-2 and to varying degrees these interventions provide protection from developing severe COVID-19 or dying. However, as the virus continues to mutate, it is likely that a broad range of second-generation interventions—better antiviral drugs, vaccines and monoclonal antibodies—will be needed.

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C. Paxlovid (nirmatrelvir + ritonavir) — key information

Paxlovid is the brand name given to a combination of two drugs:

- nirmatrelvir (formerly PF-07321332)
- ritonavir

Paxlovid is meant for the treatment of mild-to-moderate COVID-19 in adults who test positive for SARS-CoV-2 and who are at high risk for developing severe symptoms of COVID-19.

Nirmatrelvir is an antiviral drug designed to attack SARS-CoV-2. Nirmatrelvir impairs the activity of a viral enzyme called main protease. By weakening the activity of this enzyme, nirmatrelvir reduces the production of new copies of SARS-CoV-2.

A low dose of the drug ritonavir is taken with each dose of nirmatrelvir. The purpose of this low dose of ritonavir is to slow the breakdown of nirmatrelvir in the body. Ritonavir has no antiviral activity against SARS-CoV-2.

Pfizer, the developer of Paxlovid, recommends the following dose and schedule:

- nirmatrelvir 300 mg (two 150-mg tablets)
- ritonavir 100 mg (one 100-mg tablet)

A total of three tablets (as above) are taken twice daily for five consecutive days.

Paxlovid is not approved for the following:

- treating people with COVID-19 who require hospitalization
- pre-exposure prophylaxis (PrEP; that is, taking Paxlovid prior to exposure to SARS-CoV-2)
- to be taken for more than five consecutive days

Pfizer advises that there are many factors that can increase the risk for developing severe symptoms of COVID-19 in people who have been infected with SARS-CoV-2, such as the following:

- age 60 and older
- being overweight or obese
- smoking
- chronic kidney disease
- diabetes
- having a condition that weakens the immune system
- taking medicines that weaken the immune system
- cardiovascular disease
- chronic lung disease
- the presence of cancer
- sickle cell disease
- cerebral palsy and Down's syndrome

Kidney injury or dysfunction

The estimated glomerular filtration rate (eGFR) is used to assess the health of the kidneys. Pfizer advises that in people with a moderate degree of kidney injury or dysfunction—an eGFR of 31 or from 31 to less than 60 mL/min—the dose of Paxlovid be reduced as follows:

- nirmatrelvir 150 mg (one tablet)
- ritonavir 100 mg (one tablet)

These two tablets are taken every 12 hours for five consecutive days.

Pfizer further advises that Paxlovid should not be used in people who have an eGFR less than 30 mL/min.

Liver health

Pfizer advises that no dose adjustments are needed in people with the following degrees of liver impairment:

- mild liver impairment (graded as Child-Pugh class A)
- moderate liver impairment (graded as Child-Pugh class B)

There is no safety data about Paxlovid in people with severe liver impairment (graded as Child-Pugh class C).

Drug interactions

The drugs nirmatrelvir and ritonavir interfere with enzymes in the liver that break them down. These enzymes include the following: CYP3A, CYP3A4 and CYP2D6. Many other medicines are affected by the liver enzymes CYP3A and CYP3A4. As a result, there is the potential for ritonavir, and to a lesser extent, nirmatrelvir, to raise or in some cases lower levels of other medicines in the body or vice versa. These interactions can potentially have the following effects:

- enhance pre-existing side effects (from other medicines)
- cause new side effects
- decrease the benefit of other medicines
- decrease the benefit of Paxlovid

Therefore, before taking Paxlovid, always discuss with a pharmacist any other medicines that you may be taking, both prescription and over the counter, as well as any supplements and herbs that you may be taking. Your pharmacist can provide advice about potential drug interactions and how to avoid or minimize them.

Common side effects

In clinical trials, common side effects with Paxlovid included the following:

- altered sense of taste
- diarrhea

This article is just a summary of some information on Paxlovid. Your pharmacist will have more information.

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D. Paxlovid (nirmatrelvir + ritonavir) for early treatment of COVID-19

Paxlovid is the brand name of two medicines (nirmatrelvir + ritonavir). Nirmatrelvir is an antiviral drug that reduces the production of new copies of SARS-CoV-2, the virus that causes COVID-19. Ritonavir is used to slow the breakdown of nirmatrelvir in the body.

Nirmatrelvir was designed to interfere with an enzyme used by SARS-CoV-2. This enzyme is called main protease.

In a clinical trial called Epic-HR, researchers randomly assigned 2,246 people who had recently been infected with SARS-CoV-2 to receive one of the following interventions every 12 hours for five consecutive days:

- nirmatrelvir 300 mg + ritonavir 100 mg
- placebo

At the start of the study, participants had recently developed symptoms of COVID-19 and did not require hospitalization. However, they were considered to be at heightened risk for hospitalization or dying from COVID-19. Furthermore, they had not been vaccinated against SARS-CoV-2.

Twenty-eight days after entering the study, the risk of developing severe COVID-19, hospitalization and death was 6% less in people who received Paxlovid compared to people who received placebo. Statistical analysis revealed that the use of Paxlovid resulted in an 89% reduction in the risk of severe disease, hospitalization or death.

Nine people died during the study—all deaths occurred in people who received placebo.

Study details

The average profile of the 2,246 participants was as follows:

- 51% men, 49% women
- age – 46 years
- major ethno-racial groups: White – 72%; Asian – 14%; Indigenous – 9%; Black – 5%

A majority of people had symptoms consistent with COVID-19 for three days or less. All tested positive for SARS-CoV-2.

Participants were enrolled between July 16 and December 9, 2021, at 343 clinics around the world.

At the start of the study, the most common underlying conditions associated with an increased risk for worsening COVID-19 were as follows:

- a body mass index (BMI) greater than 25 kg/m^2 – 81%
- smoking tobacco – 39%
- having high blood pressure – 33%

Overall, 61% of participants had two or more of the above characteristics.

Results – effectiveness

The researchers found that the following proportions of people were hospitalized and/or died:

- Paxlovid – 0.72% (five people were hospitalized and none died)
- placebo – 6.45% (35 people were hospitalized and nine died)

This difference was statistically significant; that is, not likely due to chance alone. Further analysis indicated that Paxlovid reduced the likelihood of serious issues developing (hospitalization and deaths) by 89% compared to placebo.

Paxlovid had a significant benefit regardless of the following factors:

- age, BMI, gender, ethno-racial group, underlying conditions, the amount of SARS-CoV-2 produced (viral load)

Paxlovid reduced the average amount of SARS-CoV-2 produced by participants by 10-fold.

Safety

Overall, the proportions of people reporting any adverse event were similar—23% in people on Paxlovid and 24% in people on placebo. Note that the term *adverse event* refers to a range of unfortunate events that can occur during a clinical trial. These include drug side effects, issues caused by the underlying disease process and things that have nothing to do with the study drugs (such as accidents).

In general, people who received Paxlovid reported fewer serious or life-threatening adverse events (4%) than people on placebo (8%). This difference arose because more people on placebo developed adverse events related to COVID-19 (such as pneumonia).

More people who used Paxlovid reported or developed certain side effects as follows:

Altered sense of taste
- Paxlovid – 6%
- placebo – 0.3%

Diarrhea
- Paxlovid – 3%
- placebo – 2%

Vomiting
- Paxlovid – 1%
- placebo – 0.8%

According to the researchers, these side effects were mostly mild to moderate and resolved after treatment ended.

Managing potential drug interactions

Many people at high risk for severe COVID-19 symptoms will likely be taking medications to treat underlying conditions (high blood pressure, high cholesterol and so on). Paxlovid contains nirmatrelvir and ritonavir, both of which can affect the body's ability to break down other drugs. This effect of one drug on another is called a drug interaction. Ritonavir is notorious for its potential to cause drug interactions. Aware of this issue, the researchers suggested that healthcare providers who are concerned about potential

drug interactions could do any of the following as clinically appropriate:

- reduce the dose of the other medicine(s)
- use a different medicine for the underlying condition
- increase monitoring for potential side effects
- have a lab assess blood samples from Paxlovid users to check the level of medications in the blood
- temporarily discontinue use of the medicine(s) for the underlying condition

REFERENCE:

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, non-hospitalized adults with COVID-19. *New England Journal of Medicine*. 2022 Apr 14; 386(15):1397-1408.

E. Paxlovid – CDC issues advisory on possible rebound of COVID-19

The U.S. Centers for Disease Control and Prevention (CDC) has issued an advisory about Paxlovid to healthcare providers in that country. The CDC notes that since the treatment was approved there have been reports of a rebound of COVID-19 in some Paxlovid users.

In its advisory, the CDC first provided the following reassurance:

> "Paxlovid continues to be recommended for early-stage treatment of mild-to-moderate COVID-19 among persons at high risk for progression to severe disease. Paxlovid treatment helps prevent hospitalization and death due to COVID-19."

Second, the CDC made the following statement about possible rebound in some uses of Paxlovid:

> "COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. A brief return of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status. Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected."

The CDC provides the following advice for healthcare providers whose patients experience COVID-19 rebound after completion of Paxlovid treatment:

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of Paxlovid.
- Advise people with COVID-19 rebound to follow the CDC's guidance on isolation and take precautions to prevent further transmission. Patients should re-isolate for at least five days. Per CDC guidance, they can end their re-isolation period after five full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started.
- Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.

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II HIV

A. Lenacapavir moves forward

Lenacapavir is an experimental drug being developed for at least the following uses:

- combination therapy for people who have multidrug-resistant HIV
- to reduce the risk of acquiring HIV

About lenacapavir

Lenacapavir is different from all other approved anti-HIV drugs. It belongs to a new class of drugs called capsid inhibitors. This class of drugs target capsid proteins.

Here is the role of capsid proteins in HIV infection:

When HIV enters a cell, the capsid protein acts as a shell protecting HIV's genetic information from the cell's viral sensors and defence system. The capsid also helps to transport the virus' genetic information to the cell's control centre, or nucleus. As it nears the nucleus, the capsid releases HIV's genetic information so that it can insert itself into the cell's genetic information. Once this has happened, HIV usually takes over the cell, forcing it to become a mini-virus factory. The infected cell produces new copies of HIV.

If the capsid protein is absent or defective, HIV cannot infect a target cell.

Enter lenacapavir

Lenacapavir (formerly GS-6207) is the first capsid inhibitor that is being developed for use against HIV. It is currently in phase III clinical trials, where it is being tested as part of a treatment for people with multidrug-resistant HIV. It is also being tested in other clinical trials as a form of HIV prevention.

Lenacapavir comes in two formulations—tablets and a liquid. People initiating lenacapavir first take the tablet formulation. This raises concentrations of lenacapavir in the blood. After a couple of weeks, people can then decide whether they want to continue taking oral lenacapavir or switch to the liquid formulation, which is injected just under the skin (subcutaneous injection). If they continue with the tablets, they can do so at a reduced frequency of once weekly, as the drug levels have built up. With the liquid formulation, once lenacapavir has been injected, it is gradually released into circulation. Lenacapavir has been designed to break down slowly. All of these properties—gradual release from subcutaneous tissue and its slow breakdown—mean that lenacapavir need only be injected once every six months.

A temporary stop

In December 2021, trials of injectable lenacapavir were halted because of an issue with the glass vials that were used to package the liquid. It appeared that in some cases tiny particles of glass entered the lenacapavir solution.

Gilead has investigated the issue and changed the formulation of the vials. The U.S. Food and Drug Administration (FDA) has since allowed trials of injectable lenacapavir to resume.

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B. Lenacapavir and multidrug-resistant HIV

Lenacapavir is an experimental drug undergoing clinical trials in different populations, including the following:

- people who have HIV that is partially or wholly resistant to other treatments
- people without HIV who are using it to reduce their risk of getting HIV

Lenacapavir belongs to a new class of anti-HIV drugs called capsid inhibitors. For use in clinical trials, lenacapavir is available as tablets taken orally or as a liquid for injection just under the skin (subcutaneous injection). When a person initiates the use of lenacapavir, they begin with several

doses of the oral formulation over the course of two weeks. After this time, they can switch to the injectable formulation. Lenacapavir is designed to be slowly broken down, so injections are required only every six months.

Limited treatment options

Researchers in the U.S. and other countries conducted a short placebo-controlled study of lenacapavir in 36 people whose HIV treatment regimens were failing. After 14 days, people who were on placebo and their failing regimen switched to lenacapavir and an optimized background regimen (their regimens were adjusted based on HIV resistance testing to try to maximize the antiviral activity of their treatments). At the end of the initial 14-day period, participants switched from oral to injectable lenacapavir. The remaining participants who initiated the study with oral lenacapavir and their failing regimen were also switched after 14 days to injectable lenacapavir and an optimized background regimen.

Researchers subsequently recruited 36 other people whose regimens were also failing and gave them a combination of oral lenacapavir and an optimized background regimen for two weeks. After this time, these people switched from oral to injectable lenacapavir.

Participants were monitored for one year.

In the placebo-controlled portion of the study, after two weeks HIV viral load fell by at least two thirds (half a log) in 88% of people on lenacapavir vs. 17% of people on placebo.

After six months, about 82% of all 72 participants had a suppressed viral load (less than 50 copies/mL) and CD4+ cell counts had increased by 75 to 104 cells/mm^3.

Side effects during the first six months were usually mild to moderate and were resolved.

Results after one year are presented later in this report.

Study details

Researchers recruited 72 participants primarily from the U.S. and also Europe and Asia. Their average profile at the start of the study was as follows:

- age – 52 years (ranging between 23 to 78 years)
- 75% men, 25% women
- major ethno-racial groups: White – 41%; Black – 38%; Asian – 21%
- viral load – 15,000 copies/mL; 14 people had a viral load greater than 100,000 copies/mL
- CD4+ count – 150 cells/mm^3; 16 people had a CD4+ count below the 50 cell/mm^3 mark, indicating severe immune deficiency

The four classes of drugs commonly used in background regimens were as follows:

- nucleoside reverse transcriptase inhibitors (nukes)
- non-nucleosides (non-nukes)
- protease inhibitors
- integrase inhibitors

The proportions of people with HIV that was resistant to two or more drugs in each class were as follows:

- nukes – 99%
- non-nukes – 97%
- protease inhibitors – 81%
- integrase inhibitors – 69%

A total of 33 people (46%) had HIV that was resistant to at least two drugs in all four classes. Indeed, the researchers stated that "many [participants] had exhausted both the integrase (54%) and protease inhibitor (42%) classes."

The dosing of lenacapavir in this clinical trial was as follows:

- day one – 600 mg orally (two 300-mg tablets)
- day two – 600 mg orally
- day eight – 300 mg orally
- day 15 – two subcutaneous injections into the abdomen of 1.5 mL of the liquid formulation, for a total injected dose of 927 mg

Results – the first six months

Six months after entering the study, whether participants immediately initiated lenacapavir or placebo, the proportion that ultimately achieved a suppressed viral load was similar, about 82%. Also,

after six months, CD4+ cell counts increased by at least 75 cells/mm^3.

Focus on lenacapavir resistance

Blood samples from 19 participants were subsequently analysed for the presence of HIV that may have become resistant to lenacapavir. The reason for this was that not all participants achieved or maintained viral suppression and researchers wanted to better understand how lenacapavir fared in such circumstances, as it is a new drug. Eight of the 19 people developed HIV that was partially resistant to lenacapavir. Despite this finding, four of these eight people were able to suppress their viral load once again while continuing to use lenacapavir.

Among the four other people (out of the eight who developed partial resistance to lenacapavir), two remained in the study with detectable HIV. One person died at week 10 of the study (explained later) and the other person left the study at week four.

Among all eight participants with HIV that was partially resistant to lenacapavir, researchers found that the level of this drug in their blood was within the acceptable range. This finding suggested that lenacapavir was being released at expected rates from subcutaneous tissue.

The researchers noted that four of these eight people "had poor adherence to their background therapy." This likely explained why their viral load became detectable during the study.

Among the remaining 11 participants whose blood samples were analysed—none of whom had any resistance to lenacapavir—seven were able to re-suppress their viral load while they continued in the study (and remained on lenacapavir).

Safety

Readers should note that people with relatively low CD4+ cell counts and detectable viral loads—which would have been the majority of participants when they entered the study—tend to have immune deficiency and high levels of inflammation and exposure to proteins from HIV in their blood. As a result, they are more susceptible to developing drug side effects, fatigue, low-level and even serious infections and, in some cases, cancer.

Some general adverse events experienced by participants over the course of the study were as follows:

- nausea – 13%
- constipation – 11%
- diarrhea – 11%

Investigation suggested that these symptoms were unrelated to lenacapavir. Furthermore, such symptoms were mostly mild.

The person who died (as mentioned earlier) entered the study with an extreme degree of immune deficiency—a CD4+ count of just 7 cells/mm^3. This person would likely have been physically weak. They had a history of non-Hodgkin's lymphoma and died from complications related to an unspecified cancer in the 10th week of the study.

Injection site reactions

As is usual with injectable therapies, a majority of participants (63%) had some injection-site side effects, including the following:

- pain – 31%
- swelling – 31%
- redness – 25%
- formation of a nodule – 24%

Most of these reactions were mild and resolved in a few days.

One person left the study because a nodule formed 10 weeks after they received their second injection of lenacapavir.

Abnormal lab test results

In 28% of participants, lab analysis of blood and/or urine samples revealed serious abnormalities. However, these particularly abnormal measures of kidney health were temporary and, in most cases, quickly normalized without further intervention.

Some people also developed elevated levels of sugar in their blood and urine. These were usually temporary or linked to pre-existing diabetes.

Results – one year later

Researchers provided some results after one year for 35 people initially randomized to placebo or lenacapavir add-on therapy for 14 days at the start of the study. Safety data were provided for about 70 people.

Here are the virological results:

- 30 people achieved a suppressed viral load
- five people had virological failure

Analysis found a trend: the greater the number of fully active drugs (this means that HIV had no resistance to such drugs) in a background regimen at the end of the first year, the greater the likelihood that a person's viral load would be suppressed. Here is the distribution of viral suppression by the number of active drugs in a background regimen:

- no active drugs – four out of six people (67%) were undetectable
- one active drug – 11 out of 14 people (79%) were undetectable
- two or more active drugs – 15 out of 16 people (94%) were undetectable

The average CD4+ cell count stabilized by the 36th week of the study and then remained stable for the rest of the year. Participants gained an average of 83 more CD4+ cells/mm^3 by the end of the year. The impact of lenacapavir was dramatic—after one year on lenacapavir and an optimized background regimen, 60% of participants had a CD4+ count of at least 200 cells/mm^3.

Not everyone had such good results. Recall that many people entered the study with severe immune deficiency and few treatment options.

Initially there were eight people who entered the study with less than 50 CD4+ cells/mm^3. By the 16th week of the study, all eight had more than 50 CD4+ cells/mm^3. However, after one year in the study, one person's CD4+ count fell below the 50-cell mark. This probably occurred because of increasing resistance by HIV to their regimen.

Injection site reactions

By the sixth month of the study participants received their second injection of lenacapavir. Researchers could then assess reactions to the second injection. For the most part, researchers found that injection site reactions were mild to moderate after the second injection. Here is the breakdown of injection site reactions after the second dose:

- swelling – 13%; average duration – 12 days
- redness – 11%; average duration – six days
- pain – 21%; average duration – three days
- nodule – 11%; average duration – 180 days
- hardening of the skin – 10%; average duration – 118 days

Bear in mind

Lenacapavir has been shown to be very helpful for many people with few treatment options. Most people tolerated it.

For the future

If all goes well in this clinical trial, lenacapavir likely will be approved for use by people who have multidrug-resistant HIV in many high-income countries over the coming 24 months. Approval of lenacapavir for HIV prevention will take longer, as those clinical trials were interrupted because of the issue with the glass vials (mentioned in the previous report). Now that this issue has been resolved, those trials can now resume using injectable lenacapavir.

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C. Preparing patients and doctors for their next visit enhances patient satisfaction and care

The widespread availability of potent HIV treatment (ART) in Canada and other high-income countries has transformed HIV care. For many people with HIV, care is no longer focused on preventing and treating life-threating infections (AIDS). The power of ART is so tremendous that researchers project and report that many ART users will have a near-normal life expectancy.

The focus of medical appointments today for many ART users has largely turned to preventing issues arising from other chronic health conditions, many of which are associated with aging and persistent inflammation. As ART users live longer, some of them may have to grapple with issues that were not previously of primary concern, such as those related to mental health, drug dependency, violence in relationships, homelessness, persistent fatigue, frailty and so on.

Patient-reported outcomes (PROs)

To help doctors, nurses and their patients better prepare for their next appointment, some cancer treatment centres have been asking incoming patients about certain key aspects of health and well-being prior to their visit. Patients can be surveyed about a wide range of issues, including pain, general health, quality of life, mental health and more. The responses of these surveys are summarized and then sent to the medical care team just before the patient's appointment. Analysing the responses to these surveys (called patient-reported outcomes, or PROs) has been found to have a positive impact on patient satisfaction and communication between patients and their healthcare providers in the field of cancer treatment.

It would therefore be a good idea to adapt such surveys for people with HIV and to assess the impact of PROs on them and their interaction and care with their healthcare providers.

The PROgress project

A team of researchers at the University of Washington along with other researchers at clinics in Florida and Toronto cooperated in a study to design, implement and assess the capture and impact of PROs on both patients and their healthcare providers.

The survey for capturing PROs took about nine minutes to complete using electronic tablets (iPads). After completion of the survey, the data were evaluated by software and summarized in one page for the healthcare provider just prior to the patient visit. The analytic software flagged any issues for discussion based on the patient's responses to the survey.

The study team found that the use of PRO surveys achieved the following:

- improved communication between patients and their healthcare providers
- increased the number of complex health and behavioural issues identified, recorded and acted upon; such issues included anxiety and thoughts of self-harm

Overall satisfaction with the process and result of capturing and discussing issues raised by PROs was high. Furthermore, both patients (82%) and healthcare providers (82%) found that the PRO surveys improved the value of the patient-healthcare provider visit.

The Toronto site for the PROgress study was at St. Michael's Hospital. Based on the promising results, researchers are working on refining and extending the use of PROs to some other clinics in Ontario in partnership with the Ontario HIV Treatment Network.

Study details

The PROgress study was complex and involved several different phases, including preparation, setup, and testing on about 200 participants before rolling it out to a larger study population. The full details of the study are beyond the scope of this report, but here is a summary of key elements.

Staff at the HIV clinics in the study received training on how to integrate PROs into daily clinical practice by researchers from the University of Washington at Seattle who have become experts in such issues with PROs.

The surveys for the PROs enquired about many issues using previously validated and widely used questionnaires, such as the following:

- alcohol use
- drug use
- sexualized drug use ("chemsex")
- sexual behaviour
- adherence to ART
- physical symptoms
- nicotine use
- gender identity
- sexual orientation
- intimate partner violence
- housing
- nutrition
- depression
- anxiety
- current healthcare
- affordability of medication

Researchers reviewed the medical records of participants to assess the impact that PROs might have had. They also surveyed patients and healthcare providers about their thoughts on the impact of PROs.

Results

Here are some areas that were investigated by the researchers.

Reach – people with HIV who were willing to engage with PROs

Among 1,813 eligible patients, 90% (1,632 people) agreed to participate in the study.

The reasons that some people gave for refusing or being unable to participate (among 181 people) were as follows:

- language barriers – 68 people
- felt that PROs were not needed or useful – 22 people
- literacy barriers – 21 people
- visual difficulty (including the lack of reading glasses) – 11 people

Impact of PROs on clinical practice

The researchers found that delivering the summary of PROs to healthcare practitioners with key issues flagged for attention "increased the number of complex health and behavioural issues that were identified, recorded and acted on."

They found that healthcare providers "were significantly more likely to document [whether patients had thoughts of self-harm] and anxiety and were significantly more likely to refer to mental health services for anxiety" than they were before PROs were available.

After PROs became available, healthcare providers were more likely to document the following issues:

- dissatisfaction with ART
- depression
- experiences of psychological distress that patients may have had

Views of healthcare providers

Eleven healthcare providers were surveyed about the impact of PROs. According to the researchers, "nine of them (82%) agreed or strongly agreed that the PROs helped them prioritize discussion points with patients, identified topics that otherwise might not have been brought up, led to more discussions on potentially sensitive topics, and added value to the visit overall." The researchers added that "most providers (eight of the 11 or 73%) found that the PROs made their consultation easier."

Based on the study's results, 100% of healthcare providers and clinic staff decided to keep using PROs beyond the duration of the study.

Impact of PRO collection process on the clinic workload

HIV clinics are busy places and healthcare providers tend to be cautious about introducing new processes and procedures that might increase workload. However, the researchers found that healthcare providers perceived PROs as "having a minimal and/or manageable impact upon workload and time for providers." The researchers found that other clinic staff regarded PROs as providing added value to the patient visit. Additional tasks triggered by the collection of PROs were found to add approximately four minutes to each patient visit. This additional time included explaining the procedures involved with PRO collection and analysis to patients, keeping an eye on patients to determine when they had completed the survey, and retrieving the electronic tablets and sanitizing them.

Views of patients

A subset of patients (200) was surveyed about the collection and impact of PROs. The researchers

reported that large majorities agreed or strongly agreed on the following:

- "the PRO assessment helped them consider overall health (88%)"
- "recall health concerns to raise (80%)"
- "discuss topics that might otherwise not have arisen (76%)"
- "discuss issues difficult to speak frankly about (71%)"
- help them "decide what to talk about (67%)"

Patients who completed PROs expressed high levels of satisfaction. According to the researchers, based on evaluation questionnaires "most participants enjoyed using the assessment and found it easy to use, well explained, understandable and helpful in describing their symptoms and health behaviours. They also found the amount of time taken to complete the PRO assessment to be highly acceptable."

The researchers found that 65% of patients reported "that they had discussed the burden of their HIV medication and its impact on their life."

Cost issues

The cost of implementing any intervention is important to consider. The researchers found that the cost of implementing PROs was relatively low and included the purchase of tablet computers (four in the Florida clinic and eight at St. Michael's HIV clinic in Toronto). According to the researchers, the largest costs were "human resources, including time for setup, training, monitoring and reviewing. Once the PRO program was established, the program took up about 9% of the daily time of a full-time employee (based on an average of 11 patient visits per day)."

Bear in mind

The study found that the use of PROs was helpful for both patients and healthcare providers. What's more, the researchers found that PROs were able to bring healthcare providers' attention to issues "which are known to be less observable, underreported and/or inadequately addressed in consultations."

The researchers found that PROs revealed that about 25% of patients were dissatisfied with their ART. The study took place at a time when there are several well-tolerated one-pill daily treatment options. It is possible that dissatisfaction arose because of issues such as difficulty swallowing pills, stress about adherence, and concerns about pill-taking revealing a person's HIV status. Such issues have been found in another study.

Overcoming barriers

As mentioned earlier, about 10% of people who were eligible to participate in the PROgress study declined due to different barriers such as language and visual issues. The study team noted that many of the questions incorporated into the PRO survey were taken from other well-validated and widely used surveys.

Language barriers could be overcome by implementing translated versions of the questions (which are available).

For people with visual difficulty (that cannot be resolved with reading glasses) and others who have literacy issues, it is possible to enquire about PROs using audio.

The study took place in community clinics and its applicability is probably greater than with previously published research about PRO implementation.

For the future

The research team plans to assess the impact of PROs over the long term and additional interviews with healthcare providers and patients have been done and need to be evaluated. The researchers stated that the Ontario HIV Treatment Network (OHTN) hopes to extend the collection and implementation of PROs to many of the HIV clinics with which it is affiliated.

Based on the results from the PROgress study, surveying patients about important issues prior to an appointment with their healthcare provider can help maximize the impact and value of medical visits.

For more information on the PROgress project, visit https://progresshivcare.org/

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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.

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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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