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Contents

I. POLICY

A. A catastrophe unfolds

Within a few years after the recognition of a new syndrome in 1981, later called AIDS, researchers began to realize that the virus would spread to many people. By 1994, projections were that 40 million people had become HIV positive. At that time, there was no effective treatment, and turning the tide against the spread of HIV as well as the illness and death caused by this virus seemed an impossible task.

However, in 1996 effective treatment was demonstrated in clinical trials and became available in high-income countries—and lives began to be saved. This progress was made possible by a vast research enterprise that was funded by the U.S. government through its National Institutes of Health (NIH).

In the early 2000s, President George W. Bush funded a program called the President's Emergency Plan for AIDS Relief (PEPFAR). This funded HIV treatment for people in low- and middle-income countries. Later, funds from PEPFAR were used to help expand opportunities for HIV testing, referral

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555 Richmond Street West, Suite 505
Box 1104
Toronto, Ontario M5V 3B1 Canada
www.catie.ca
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for care and HIV treatment. Funds from the U.S. have helped to provide HIV treatment to more than 20 million people, and at least 84 million people have undergone HIV testing as a result of such funding. What's more, it seemed as if the world was on track to significantly reduce the spread of HIV thanks to the rollout of testing, treatment and pre-exposure prophylaxis (PrEP).

However, the current government in the U.S. has largely ended progress on HIV by cutting many programs and giving chaotic directions about funding. Thousands of people in the U.S. who monitor international aid and HIV programs have lost their jobs. An estimated 270,000 people once employed by PEPFAR in low- and middle-income countries who played a crucial role in managing the HIV pandemic have also lost their jobs.

As a result of this abandonment of vulnerable populations at high risk for HIV, progress against HIV will be lost at the global level. The projections are stark. One study estimates that by 2040 there would be 15 million deaths from HIV-related complications that otherwise would not have happened. Many of those deaths will occur in sub-Saharan Africa. Another estimate is that by 2040 there will be 14 million children who will become orphans. The evisceration of PEPFAR will mean that 26 million people will become HIV positive.

It is likely that much damage to progress has already occurred and will occur in the short and medium term. For instance, one study projects that the cuts to funding could result in between four and 11 million new HIV infections between 2025 and 2030. In the same period, the study estimates that there could be three million excess deaths among people with HIV.

These numbers are huge and hard to comprehend, but they portend a catastrophe for individuals, communities and countries. Many countries can't afford to spend the billions that the U.S. used to pour into international aid programs. People who were once taking HIV treatment and who no longer have access to it or who only have intermittent access can inadvertently develop strains of HIV that are resistant to treatment. As these strains spread in a city, country or region, it becomes difficult to help people stay healthy and stop the spread of HIV.

HIV is not the only sector that has been hit. There are important efforts underway to control tuberculosis (TB), malaria and other diseases, all of which will be affected. At best, these cuts are shortsighted. As the history of HIV, Mpox and COVID-19 shows, infectious diseases never stay in one place.

Science is at risk too

The administration has also enacted massive cuts to domestic and international research projects. Many of these projects are designed to help vulnerable populations at risk for HIV and other infections. These cuts will likely ultimately help the spread of infectious diseases in the U.S.

The cuts to scientific funding will likely affect ongoing and future research on efforts to cure HIV and treat many other infections, and likely other health conditions.

These cuts are accompanied by animus against the 2SLGBTQIA+ community, people of colour and their health and research needs. Accompanying the cuts is a fountain of irrationality about vaccines and other interventions proven to reduce the risk of disease and save lives. In a way, it seems that attitudes that were once consigned to medieval times have come roaring back to life. Public health measures are being ignored, seemingly fueled by disinformation campaigns on social media.

The architects of the funding cuts don't seem to care that vulnerable communities are hurt. But, as we mentioned earlier, infectious diseases seldom stay in one place. It is likely that in the future old diseases will resurge and new diseases will appear in the U.S. and elsewhere. This will cause much suffering and could easily have been preventable. It is time for other high-income countries and regions such as Canada, China, Japan Australia, the UK and the EU to step up and revitalize international AIDS efforts.

The world is and will be going through a difficult time—there's no doubt about that. Tensions between countries and ongoing wars will cause money to be diverted from the civilian economy to the military. As the U.S. devolves, it should be a lesson for people in Canada and other countries to realize that representative democracy is extremely fragile and needs nurturing. People should get in touch with their elected representatives at the local, provincial and national levels to let them

know that they care about science-based policy, healthcare and our common humanity.

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II HIV PREVENTION

A. Lenacapavir approved in the U.S. for HIV prevention

In mid-June 2025, the U.S. Food and Drug Administration (FDA) approved the use of lenacapavir for the prevention of HIV. The drug will be sold under the brand name Yeztugo.

Lenacapavir's approval is a major milestone, as the drug is given in two abdominal injections every six months. Lenacapavir is injected subcutaneously (just under the skin) by a healthcare provider.

The manufacturer of lenacapavir, Gilead Sciences, has submitted a dossier on the drug to Health Canada. Gilead hopes that lenacapavir will also be approved for HIV prevention in Canada by June 2026.

Most people who use HIV prophylaxis currently take pills (tenofovir + FTC), usually daily. There is also an injectable drug called cabotegravir (Apretude) that is taken ultimately every two months. However, cabotegravir must be injected deep into the buttocks by a healthcare provider. Such intramuscular injections can be painful.

Lenacapavir's advantage for prevention is that it only needs to be injected every six months (also by a healthcare provider). This can reduce the burden on people having to remember to take pills daily.

Getting injections of a potent HIV prevention drug every six months has the power to interest more people in HIV prevention, particularly some who could not or did not want to take daily pills.

Lenacapavir could become a major option for many people who are interested in HIV prevention. It will be interesting to see how it is deployed in the U.S., as there may be lessons Canada and other countries can learn from this once the drug is approved here.

REFERENCE:

Gilead Sciences. Yeztugo (Lenacapavir) Is Now the First and Only FDA-Approved HIV Prevention Option Offering 6 Months of Protection. *Press Release.* 18 June, 2025.

B. The promise of once-yearly lenacapavir

Clinical trials have found that lenacapavir, when used every six months (given by subcutaneous injection into the belly), reduces the risk of HIV infection between 96% and 100%, depending on the study. In these trials, an oral formulation of lenacapavir is initially taken in the first two days of therapy to quickly raise levels of the drug in the blood so that protection is obtained.

Lenacapavir for the prevention of HIV is now approved in the U.S. and will hopefully be approved in Canada in mid-2026.

Lenacapavir as part of combination therapy for HIV is already approved in Canada and many countries. This use of lenacapavir is meant for people living with HIV who have few treatment options. However, only a very small number of people with HIV in Canada use it for this purpose.

Once yearly

Gilead Sciences is the developer of lenacapavir. Scientists with the pharmaceutical company have developed new liquid formulations of lenacapavir that are long lasting. These new formulations are

meant for clinical trials where the drug is injected deep into the muscles on the sides of the hip.

A relatively small clinical trial designed to assess the safety of lenacapavir and monitor the levels of lenacapavir in the blood up to a year after one intramuscular dose has been completed.

This trial found that lenacapavir levels were, for the most part, higher with the once-yearly dose than seen in historical data with the twice-yearly dose. Overall, the drug was safe, and participants reported temporary pain at the injection site.

Study details

Researchers randomly assigned 40 participants to receive one of the following formulations of lenacapavir:

- formulation 1 – lenacapavir 5,000 mg containing 5% ethanol
- formulation 2 – lenacapavir 5,000 mg containing 10% ethanol

Participants were in their mid-30s and did not have HIV; 65% were assigned male at birth and 35% were assigned female at birth. On average, their body mass index (BMI) was 27 $kg/m^{2.}$

The formulations were administered by healthcare providers deep into muscles at the sides of the hips in two injections containing 5 mL of fluid each. Half of the participants who received formulation 2 had an ice pack placed on the side of their hip 10 minutes prior to the lenacapavir injections.

Over the course of the study, study personnel collected blood samples and conducted physical examinations from time to time, and participants completed surveys.

Results

In general, the level of lenacapavir in the blood of participants was higher than has been reported in past studies (where the drug was given subcutaneously rather than via intra-muscular injection). Furthermore, in the present study, high levels of lenacapavir in the blood were maintained for one year after injection.

Participants given intramuscular injections took longer to achieve high levels of lenacapavir in the blood (compared to people who got subcutaneous injections in past studies). However, people who took lenacapavir via subcutaneous injection in past studies also received a loading dose of an oral formulation of lenacapavir for the first two days when the drug was initiated. This rapidly raised levels of lenacapavir in the blood to protective levels.

Side effects

Intramuscular injections are used to administer many medications and cause temporary discomfort and pain.

About 80% of people who received formulation 1 of lenacapavir and 75% who received formulation 2 reported pain at the injection site. This was generally mild to moderate in intensity. Injection site pain persisted between three and four days.

Four people who received formulation 2 had temporary difficulty walking because of pain in their hip muscle.

Four people who received formulation 1 reported swelling at the injection site; this was not a problem in people who received the formulation 2.

According to Gilead, pre-treating the injection site with an ice pack for 10 minutes prior to the injections reduced the intensity of pain.

Four people with pre-existing high levels of LDL-C (so-called bad cholesterol) had levels of this protein increase further, peaking more than six months after injection in three of the four people. However, after this time, their LDL-C levels gradually returned to their pre-study level.

For the future

Gilead scientists need to refine their intramuscular formulations; perhaps the high dose used in the current study is necessary. Initially, oral doses of lenacapavir will be needed to ensure that levels of the drug rise rapidly once it is initiated.

Although no one became HIV positive during the study, participants were at low risk for HIV infection, according to the researchers.

Future studies will be needed with populations that reflect people who might use lenacapavir once yearly in the future. This will mean recruiting people who are age- and gender-diverse. As well, participants from the present study were from the U.S. A future study of intramuscular lenacapavir should include people from different regions of the world.

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III ANTI-HIV AGENTS

A. Doravirine + low-dose islatravir in a single pill

Doravirine (Pifeltro) is an anti-HIV drug that is approved for combination HIV treatment. Doravirine is available in pill form and is taken once daily in the following medication:

- Delstrigo (containing doravirine + TDF + 3TC)

The pharmaceutical company Merck (also known as MSD in some countries) is developing a new doravirine-based medicine that contains two drugs: doravirine + islatravir (nick-named "dora-isla" by some researchers).

Doravirine belongs to a class of HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs or non-nukes).

Islatravir belongs to a new class of HIV medicines called translocation inhibitors. It interferes with HIV-infected cells at several points in the viral life cycle. In particular, islatravir interferes with HIV's ability to use a viral enzyme called reverse transcriptase.

In previous clinical trials with relatively high doses (0.75 mg/day) of islatravir, this drug was found to depress levels of lymphocytes (T and B cells) in the blood as well as CD4+ cells in people with and without HIV. However, subsequent studies with lower doses of islatravir have found it to be safe. We will now focus on the lower doses (0.25 mg/day) of islatravir.

When islatravir is combined with doravirine, the combination has powerful anti-HIV activity in lab experiments with cells and HIV.

Two recent clinical trials of doravirine (100 mg/day) and islatravir (0.25 mg/day) have been completed in people with HIV. In one of these studies, participants who had been virally suppressed with daily Biktarvy (bictegravir + TAF + FTC) were randomly assigned to receive either continued Biktarvy or once-daily doravirine-islatravir. In this trial, the combination was safe and highly effective. We will mention details about the other trial later.

Study details

Researchers enrolled 513 participants with HIV who were randomly assigned in a 2:1 ratio to receive doravirine-islatravir or Biktarvy for 48 weeks.

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

- age – 47 years
- 78% assigned male at birth; 22% assigned female at birth
- main ethno-racial groups – White – 61%; Black – 31%; Asian – 6%
- time since HIV diagnosis – 11 years
- CD4+ count – 700 cells/mm^3
- all participants had a viral load less than 50 copies/mL

Results

After 48 weeks, the proportion of participants who continued to have a suppressed viral load was distributed as follows:

- doravirine-islatravir – 92%
- Biktarvy – 94%

This difference was not statistically significant.

Five people on doravirine-islatravir and one on Biktarvy had a viral load of 50 copies/mL or greater.

In two of these people, viral loads were 200 copies/mL or greater. No resistance by HIV to doravirine or islatravir was detected in blood samples from these two people.

No data were available on the remaining participants.

Lab and other tests

Throughout the study, lymphocyte levels continued to rise modestly in participants regardless of which regimen they were taking. On average, CD4+ cell counts rose in participants regardless of study regimen.

One participant taking doravirine-islatravir had a significant decrease in the level of platelets in their blood (needed for clotting). They were withdrawn from the study as a precaution.

Neither doravirine-islatravir nor Biktarvy appeared to cause noticeable and significant side effects. A small proportion of participants on both study medicines had mild and temporary bone pain and fatigue. It is not clear if these were caused by the study medicines or COVID-19.

People who used doravirine-islatravir had, on average, virtually no change in weight or a slight decrease. People who used Biktarvy had a slight increase in weight. This difference between regimens was not meaningful.

Focus on hepatitis B virus

Some people with HIV are also chronically coinfected with hepatitis B virus (HBV). In many such cases, doctors prescribe regimens containing drugs that have activity against HIV and HBV to keep both viruses suppressed. Examples of such drugs include:

- TAF + FTC
- TDF + FTC
- TDF + 3TC

Doravirine and islatravir do not have anti-HBV activity; they are only active against HIV. Nevertheless, researchers found that none of the study participants with HIV and HBV who used doravirine-islatravir had their HBV reactivate and cause symptoms of HBV-related illness.

In two people with HBV coinfection who were taking doravirine-islatravir, researchers detected low levels of HBV-infected cells in their blood but no HBV-related proteins or increases in liver enzymes (suggestive of liver inflammation caused by HBV).

Two other people on the same combination who did not have HBV coinfection at the start of the study subsequently developed HBV coinfection.

No participants on Biktarvy developed low-level HBV coinfection or new HBV co-infection. This is not surprising, as Biktarvy contains TAF + FTC, which have activity against both HIV and HBV.

Bear in mind

The present study found that the combination of doravirine-islatravir was safe and effective for people who were virally suppressed on a regimen of Biktarvy and who were switched to doravirine-islatravir.

There were only two cases of reactivated HBV, which is reassuring. However, the study underscores the need for physicians to screen potential users of doravirine-islatravir to be sure that they do not have active HBV.

The study also raises the issue of the future role of doravirine-islatravir. While the combination is generally safe and effective, what do doctors do for patients at risk of HBV?

This is a question that will become increasingly important in the future as more people and their healthcare providers contemplate the use of two-drug regimens for HIV treatment.

A pill containing doravirine-islatravir meant for once-daily use will hopefully be approved in Canada in 2026. It will provide another treatment option. However, the ideal population that could benefit from doravirine-islatravir is not yet clear.

A second study

In another study, researchers randomly assigned 551 participants on an oral ART regimen in a 2:1 ratio to receive doravirine-islatravir (at the same once-daily dose previously mentioned). After one year, results were broadly similar to the trial discussed

in this article. That is, 96% of people on doravirine-islatravir and 92% of those continuing their pre-study regimen had a suppressed viral load. This difference was not statistically significant.

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Orkin C, Mngqibisa R, Diego Velez J, et al. Switch to doravirine/islatravir (100 mg/0.25 mg) once daily from oral ART: an open label phase 3 study in adults with HIV-1. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections*, March 9-12, 2025, San Francisco. Abstract 204B.

B. Oral lenacapavir + islatravir once weekly as treatment

The combination of oral lenacapavir + oral islatravir is being investigated as a potential treatment.

Lenacapavir interferes with an HIV protein called the capsid. Islatravir interferes with HIV's ability to use a viral enzyme called reverse transcriptase. Both drugs have long-acting potential.

In a clinical trial, participants who were taking Biktarvy (bictegravir + TAF + FTC) and whose HIV was suppressed were randomly assigned to either receive the combination of lenacapavir + islatravir taken in pill form once weekly or to continue with daily Biktarvy.

Interim data from that study suggests that the combination of lenacapavir 300 mg + islatravir 2 mg was able to keep HIV suppressed in 94% of participants (vs. 92% on Biktarvy).

After 48 weeks, participants who remained virally suppressed on Biktarvy could opt to switch to once-weekly lenacapavir + islatravir. This trial is ongoing.

Analysis of blood samples from participants taken in the first 48 weeks of the study suggest that the combination of lenacapavir + islatravir is potent, as it was able to keep HIV suppressed in a person who entered the study with partial resistance to islatravir (and the drugs 3TC/FTC).

The final stage of studies (phase III) testing the combination of lenacapavir + islatravir is underway.

REFERENCES:

Colson A, Crofoot G, Ruane PJ, et al. Efficacy and safety of weekly islatravir plus lenacapavir in PWH at 24 weeks: A phase II study. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections,* March 9-12, 2025, San Francisco. Abstract 208.

Vanderveen L, Chang S, Selzer L, et al. Resistance analysis of weekly islatravir plus lenacapavir in people with HIV at 48 weeks. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections,* March 9-12, 2025, San Francisco. Abstract 736.

C. The Rio study – powerful antibodies help give people a break from treatment

HIV treatment has advanced tremendously since 1996. Today, treatments are much safer, and an entire regimen can be taken once daily in a pill or ultimately once every two months via injection.

However, despite a good track record of safety with modern antiretroviral therapy (ART), some researchers and pharmaceutical companies are concerned that since HIV treatment is lifelong, there is the potential for patients to develop side effects after decades of exposure to ART.

Some companies, such as ViiV Healthcare, have developed regimens consisting of only two drugs, as follows:

- Dovato – a pill containing dolutegravir + 3TC
- Juluca – a pill containing dolutegravir + rilpivirine
- Cabenuva – this contains long-acting formulations of dolutegravir + rilpivirine and is ultimately injected every two months

Other two-drug regimens under development for HIV treatment include the following:

- doravirine + islatravir
- lenacapavir + islatravir

Studies of super antibodies

Scientists have developed antibodies with potent activity against HIV. The technical term for such

antibodies is broadly neutralizing antibodies (bNAbs); they are sometimes called super antibodies because of their potency against HIV.

The idea behind bNAbs is to offer them to patients whose HIV is already suppressed on ART. Potential bNAb users will be screened for HIV that is susceptible to these antibodies. People with susceptible HIV will then be switched from their pre-existing ART to a combination of two or more antibodies given every six months. Antibodies can either be given intravenously or via injection. As using antibodies to replace ART is an experimental approach, much remains to be understood (such as the best way to administer the antibodies, the duration of effectiveness, and so on).

The Rio study

A team of researchers in the UK and Denmark conducted a study called Rio. In this study, participants who were diagnosed early in HIV infection were randomly assigned to receive ART for at least 12 months to suppress their HIV. At the end of this time, they were randomly assigned to receive one of the following interventions after cessation of ART (they were not told at the time of the infusion what they were receiving):

- infusions of two antibodies (3NBC117-LS + 10-1074-LS) – 34 people
- infusions of placebo – 34 people

Participants were monitored with weekly blood tests for the first eight weeks with a focus on changes to viral load and CD4+ cell counts. After this, they had blood drawn twice monthly.

Participants who remained virally suppressed after 20 weeks could then receive another intravenous infusion (which was also blinded) and continue to be monitored.

Participants whose HIV resurged or whose CD4+ counts decreased significantly were withdrawn from the study.

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

- age – 40 years
- all were cisgender men
- body mass index (BMI) – 25 kg/m^2
- most participants (80%) were White
- CD4+ count – 800 cells/mm^3 (recall that participants were enrolled in the early stages of HIV infection)
- all were virally suppressed, as they had been on ART
- 80% of participants had HIV clade B; this is the variant, or strain, of HIV that is most common in Western Europe, North America, Australia and New Zealand

Partners of participants were offered HIV testing and free PrEP.

Results

Twenty weeks after the first infusion, the proportions of participants who remained virally suppressed were as follows:

- antibodies – 75%
- placebo – 9%

This difference was highly statistically significant; that is, not likely due to chance alone. It suggests that just one infusion of two potent antibodies can maintain viral suppression for many people with HIV for 20 consecutive weeks.

After week 20

Twenty weeks after the first infusion, most participants who remained suppressed received a second infusion of antibodies. In total, 50% of people who received a second dose of antibodies remained virally suppressed for 62 weeks. So far, 39% of these participants have remained virally suppressed at week 72 of the study.

Only two people who had received an infusion of placebo and who were still suppressed at week 20 received another infusion and remained virally suppressed at week 120.

Adverse events

One person died, but researchers stated that this was unrelated to exposure to bNAbs or time off ART (details were not provided). No one developed reactions to infusions of antibodies or placebo.

Everyone who restarted ART did so because of resurging viral loads and not because of significant CD4+ cell decreases.

On average, people who received bNAbs had a viral load of 55,000 copies/mL when restarting ART. The viral load among people who received placebo was 1 million copies/mL.

When participants restarted ART, it took on average 12 weeks of treatment for their viral load to fall below the 50 copy/mL mark. For people with very high viral loads (1 million copies or more), in some cases it could take up to 24 weeks of ART to resuppress their virus.

Why was virus suppressed off ART?

In most of the people who received antibodies, it is possible that the antibodies interacted with their immune system in some way to help them better control HIV. This effect of super antibodies is being investigated. For instance, research suggests that bNAbs decreased the pool of infected cells in the body and enhanced the immune system's ability to attack HIV-infected cells.

It is possible that the people on placebo who had sustained HIV suppression did so because they may have had pre-existing mechanisms that somehow naturally controlled HIV.

Bear in mind

The Rio data are exciting, but many challenges remain. For instance, many people will not have HIV that is susceptible to the antibodies used. Also, the frequency of viral load monitoring—initially weekly then every two weeks—can be stressful for people who worry about possibly infecting their partners or having their health deteriorate. In Rio, no partners were infected, and no one was harmed by staying off ART with controlled HIV.

Rio is an important clinical trial that will likely pave the way for many future studies of interventions (antibodies, drugs, and so on) that seek to help people's immune systems develop the ability to successfully control HIV for months so that they do not need to take ART. Enrolling in such studies is important and helps to advance the field.

Future trials need to enroll more women, people of different ethno-racial groups and those who have different strains or clades of HIV.

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Fidler S, Lee MJ, Collins S, et al. RIO: A randomised placebo-controlled study of 2 LS-bNAbs in people treated in early HIV. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections*, March 9-12, 2025, San Francisco. Abstract 107.

D. Lenacapavir + two antibodies

As mentioned in the previous article, some antibodies have powerful anti-HIV effects. Researchers at several research centres in Canada, the U.S. and Australia tested a combination of two antibodies: teropavimab (3BNC117-LS) and zinlirvimab (10-1074-LS). These were given in an intravenous infusion at a dose of 2,550 mg. In addition, participants received injectable lenacapavir, a long-acting anti-HIV drug, at a dose of 927 mg. Around the time the antibodies were infused, participants also received oral formulations of this drug (600 mg) for two consecutive days to rapidly raise the levels of lenacapavir in the blood.

The antibodies impair HIV's ability to attach itself to and thereby infect cells. Lenacapavir also impairs HIV's ability to infect cells.

Prior to entering the study, potential participants had been on oral ART for at least one year with a suppressed viral load and had stable CD4+ cell counts.

Potential participants had blood samples drawn to check if their HIV was susceptible to the antibodies that were going to be used. Only participants with HIV susceptible to the antibodies moved beyond this stage.

Next, participants were randomly assigned to one of two groups in a 2:1 ratio:

- cease ART and immediately begin infusions of antibodies followed by infusions (and oral doses) of lenacapavir – 53 people
- continue with oral ART – 27 people

These interventions would continue for 52 weeks.

The average profile of participants upon entering the study was as follows:

- age – 50 years
- 85% assigned male at birth; 15% assigned female at birth
- most participants were White, followed by Black people
- body mass index (BMI) – 30 kg/m^2
- CD4+ count – 700 $cells/mm^3$
- more than 70% of participants were from the U.S.

Results

Most participants, regardless of intervention, maintained viral suppression (less than 50 copies/mL), distributed as follows:

- antibodies + lenacapavir – 96%
- continued oral ART – 96%

No data were available for two people—one in each group—as they had discontinued the study due to moving or the development of cancer (unrelated to the study medicines).

One person had a detectable viral load while on antibody therapy + lenacapavir. This person had been taking Biktarvy (bictegravir + TAF + FTC) at the start of the study prior to receiving antibodies. By the 24th week, they had a viral load greater than 100,000 copies/mL. HIV in this person's blood had lost its susceptibility to zinlirvimab. They also had HIV that was resistant to lenacapavir. Analysis of blood samples from this person suggested that levels of lenacapavir in their blood began to mysteriously fall 12 weeks after they were first infused with the drug. The person left the study and was restarted on Biktarvy; within 12 weeks they once more had a suppressed viral load.

Adverse effects

Lenacapavir is known to cause injection site reactions—temporary mild-to-moderate pain, swelling and sometimes nodules (persistent small bumps) can form. Many people (62%) in the study developed injection site reactions to lenacapavir; these were mostly mild. A total of 38% of people who received lenacapavir developed nodules at the injection site. Twenty percent reported temporary pain.

No participants reported infusion site reactions to the antibodies.

Five people who received infusions developed diarrhea (vs. one person who was on continued oral ART).

Bear in mind

The present study's results are exciting in that it is possible for many people (in theory) to maintain viral suppression with a combination of infusions of antibodies and lenacapavir injections given once every six months.

A major issue is screening people for HIV that is susceptible to the antibodies used. For instance, in the present study, 241 people were screened but the assay failed in 40 people. This left the researchers with susceptibility results on 200 people, of whom only about 80 were randomized in the trial. Thus, antibody therapy will not be for every person with HIV.

REFERENCE:

Mponponsuo K, McMahon JH, Gorgos L, et al. Efficacy and safety of lenacapavir, teropavimab, and zinlirvimab: Phase II week 26 primary outcome. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections,* March 9-12, 2025, San Francisco. Abstract 151.

E. VH-184 – a new integrase inhibitor

The first approved integrase inhibitor was raltegravir (Isentress), followed by elvitegravir (in Stribild and later Genvoya).

A second generation of integrase inhibitors came with the drugs dolutegravir (in Dovato, Juluca, Tivicay and Triumeq), bictegravir (in Biktarvy) and cabotegravir (in Cabenuva).

Now, a third-generation experimental integrase inhibitor code-named VH-184 (the long-form identification number is VH-4524184) is being developed by ViiV Healthcare. This drug has long-acting potential.

In lab experiments with cells and HIV, VH-184 is active against many strains of HIV that are partially or wholly resistant to second-generation integrase inhibitors.

VH-184 in people

Researchers enrolled 22 people with HIV and gave them different doses of either VH-184 or placebo every three days. The doses of VH-184 used were 10, 50 and 300 mg. After 10 days, they were switched to approved regimens of ART.

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

- age – 32 years
- 86% assigned male at birth; 14% assigned female at birth
- major ethno-racial groups: White (68%) and Black (14%)
- CD4+ count – at least 500 cells/mm^3
- viral load – less than 100,000 copies/mL

All participants completed the study and had not used any HIV treatment prior to entry.

Results

The 50 mg and 300 mg doses of VH-184 every three days resulted in a 2-log decrease in viral load.

No resistance was detected by day 10.

Researchers stated that the drug was generally "well tolerated" and any side effects were generally mild. No one left the study due to side effects.

Long-acting formulations of VH-184 are being developed and plans are underway to test them for safety.

VH-184 will likely form the backbone of future long-acting HIV treatment options from ViiV.

REFERENCE:

Rogg L, Nunez SA, Mingrone MV, et al. Proof-of-concept trial of VH4524184 (VH-184), a third-generation integrase strand transfer inhibitor. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections*, March 9-12, 2025, San Francisco. Abstract 152.

F. VH-499 – a new capsid inhibitor

VH-499 (the long-form identification number is 4011499) interferes with an HIV protein called the capsid. This drug has potential to be used as part of a long-acting anti-HIV treatment.

VH-499 does not interfere with a group of enzymes used to break down many medicines.

In a clinical trial, different doses of VH-499 (25 mg to 250 mg every five days) or placebo were given to 23 people who had not previously used HIV treatment (ART). Doses were given on days 1 and 6. On day 11, participants were given approved ART.

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

- age – 31 years
- 83% assigned male at birth; 17% assigned female at birth
- body mass index (BMI) – 24 kg/m^2
- CD4+ count – 481 cells/mm^3
- viral load – 71,000 copies/mL

Participants were recruited from Canada, Argentina, France, Germany, Italy, Mexico, Spain, the UK and the U.S.

Results

The greatest decrease in viral load was seen with the 250-mg dose of VH-499. This resulted in a decline of more than 2 logs (vs. 0.18 log with placebo).

Nineteen out of 20 people given VH-499 did not have any resistance detected. One person who received the lowest dose of VH-499 (25 mg) developed HIV that could resist the drug by the sixth day of the study. This person was subsequently given dolutegravir + 3TC on day 11 and within several weeks had a viral load of 69 copies/mL. Subsequently, their viral load fell to less than 20 copies/mL.

Side effects were generally mild—mostly headache. No major changes to lab test results occurred.

For the future

ViiV is developing long-acting formulations of VH-499 and further clinical trials are planned.

REFERENCE:

Griesel R, Nunez SA, Perez Rios AM, et al. Proof-of-concept trial of oral VH4011499 (VH-499), a new HIV-1 capsid inhibitor. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections*, March 9-12, 2025, San Francisco. Abstract 153.

IV INFLAMMATION

A.Semaglutide and HIV

Semaglutide (Ozempic, Wegovy) is a long-acting compound that mimics a hormone used by the body called GLP-1 (glucagon-like peptide 1). Semaglutide belongs to a class of drugs called GLP-1 receptor agonists.

GLP-1 is released by cells in the intestine in response to food entering the intestine. Some tissues have receptors for GLP-1, such as the following:

- pancreas gland
- stomach
- kidney
- heart
- brain (in the hypothalamus)

When GLP-1 binds to its receptors, the effect is to slow the movement of food in the intestine, decreasing appetite. GLP-1 agonists were initially developed for the treatment of type 2 diabetes. Over time, researchers have found that some GLP-1 agonists (such as semaglutide) can cause weight loss in people who can tolerate them.

Note that GLP-1 agonists can cause a range of side effects, including nausea, vomiting, diarrhea and constipation. Some people also experience a decrease in muscle mass. For many people, these side effects are mild and resolve over time. However, for some people they can be bothersome or even severe. As a result, not everyone prescribed a GLP-1 agonist can tolerate it over the long term. What's more, researchers are finding that a minority of people who are treated with drugs such as semaglutide do not always respond to it. The reasons for this non-response are not known.

In addition, improvements in blood sugar and the health of the heart and other organs has been found in users of GLP-1 agonists.

The impact of GLP-1 agonists on human health is an area of intense research. As there are receptors for GLP-1 in different organs/tissues, it is possible that this class of drugs can have an impact on many conditions. One study suggests that GLP-1 agonists have potential in the following areas:

- substance use disorder
- psychotic disorders
- seizures
- neurocognitive disorders (including Alzheimer's disease and dementia)
- coagulation disorders
- cardiometabolic disorders, including liver inflammation
- infectious illnesses
- some respiratory conditions

However, these other potential uses for GLP-1 agonists (and related drugs) should be considered preliminary and require well-designed clinical trials to better understand the effects of these drugs in different conditions.

Also noteworthy is that the benefits of GLP-1 agonists quickly fade once cessation of these drugs occurs.

In HIV

HIV causes excess levels of inflammation and immune activation. These effects are only partially normalized with the use of effective HIV treatment (ART). As a result, researchers are seeking multiple therapies to try to further reduce excess inflammation. Therefore, semaglutide and similar drugs need to be tested in clinical trials over the long-term in people with HIV.

HIV is also associated with an increased risk of neurocognitive issues. Before ART was available, severe neurocognitive issues (such as dementia) were a growing problem in people living with HIV. However, the widespread availability of ART has meant that HIV-related dementia is now rare.

In the current era, some people with HIV have developed obesity (as have many people without HIV). The cause of this excess weight gain is unclear but may be related to overall trends in society (excess intake of carbohydrates and calories, less physical activity). In some cases, exposure to HIV treatment may have played a role. Obesity is associated with an increased risk for type 2 diabetes, and sometimes this can affect the functioning of the brain.

Preliminary results from clinical trials suggest that GLP-1 agonists are generally safe in people with HIV. In one study, semaglutide resulted in weight loss (in obese people) of nearly seven kilograms per year.

What's to come

In this issue of *TreatmentUpdate*, we introduced some studies with semaglutide, a commonly used GLP-1 agonist. Currently, the availability of potent GLP-1 agonists is restricted, particularly on provincial and territorial drug subsidy programs. However, in the future, possibly sometime in 2026, a major patent on semaglutide will expire in Canada and perhaps generic competition may result in price reductions and less restrictive access.

Drugs such as semaglutide work on one protein. But newer drugs and combinations of drugs designed for treating obesity and type 2 diabetes tend to work on two or more proteins in the body. As a result, these newer drugs, such as tirzepatide (Mounjaro, Zepbound) are associated with a greater degree of weight loss than semaglutide.

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Thiara D. GLP-1 Receptor Agonists-From Breakthroughs in Cardiometabolic Treatment to Emerging Neuroprotective Potential. *JAMA Neurology.* 2025 May 1;82(5):437-438.

Melson E, Ashraf U, Papamargaritis D, et al. What is the pipeline for future medications for obesity? *International Journal of Obesity.* 2025 Mar;49(3):433-451.

Lowe D. Novo Nordisk's Canadian Mistake. *In the Pipeline.* 10 June, 2025.

B. Can semaglutide help the brain in people with HIV?

As mentioned earlier in this issue of *TreatmentUpdate*, semaglutide is being tested in different populations, including some people with HIV.

A clinical trial in Ohio randomly assigned participants with HIV who had excess belly fat to receive semaglutide or placebo.

Participants who received semaglutide followed the schedule below:

- for the first eight weeks, gradually increasing doses until 1 mg/per week
- for the subsequent 24 weeks, 1 mg/week

Semaglutide was injected subcutaneously (just under the skin) once weekly (as was placebo).

Participants underwent different assessments, including low-dose X-rays to assess body composition, blood tests and a computerized neurocognitive assessment tool called Cognivue, approved by the U.S. Food and Drug Administration (FDA).

Participants did not have diabetes or cardiovascular disease.

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

- age – 53 years
- 60% assigned male at birth; 40% assigned female at birth
- 35% were current smokers
- main ethno-racial groups: Black – 60%; White – 35%
- body mass index (BMI) – 33 kg/m^2
- CD4+ count – 810 cells/mm^3
- viral load – all participants were suppressed
- time since HIV diagnosis – 18 years

Results

Overall neurocognitive scores between people on placebo or semaglutide were not different. However, when researchers considered sex and CD4+ count, they found that people on semaglutide had improved visuospatial scores.

The researchers did additional analyses and found that this improvement in one area of neurocognitive function seemed to be related to another effect of semaglutide. People who received this drug had a decreased level of proteins associated with inflammation, such as C-reactive protein and soluble CD163.

Bear in mind

These results should be seen as preliminary and in need of confirmation. The present study was a sub-analysis of a study that was designed to assess semaglutide's impact on people with excess weight. Assessing neurocognitive function is complex and there are many aspects to brain health. It is not clear what impact of semaglutide on visuospatial processing has on long-term brain health and cognitive function.

When the data were presented, factors such as diet, exercise and depression were not apparently considered in the analysis. So, the study's findings should be considered preliminary.

The present study has provided data that could be used to design a larger, longer and complex study that examines the impact of semaglutide on HIV-related inflammation and the impact of a reduction in inflammation on many aspects of health.

REFERENCE:

Atieh O, Baissary J, Wu Q, et al, Semaglutide improves cognitive function in HIV, effect mediated by decrease in inflammation. *Program and abstracts of the 32nd Conference on Retroviruses and Opportunistic Infections*, March 9-12, 2025, San Francisco. Abstract 172.

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505-555 Richmond Street W
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