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Contents

I PREVENTION

A. Major change is coming – long-acting HIV pre-exposure prophylaxis

A long-acting injectable formulation of the HIV drug cabotegravir has been developed for the prevention of HIV. In well-designed clinical trials, long-acting cabotegravir (LA cab) has been found to be highly effective at reducing the risk of HIV infection. Furthermore, LA cab has been found to be superior to daily oral tenofovir DF + FTC (a combination sold as Truvada and available in generic formulations).

When HIV drugs are used prior to exposure to prevent infection, this is called pre-exposure prophylaxis (PrEP). LA cab represents the first long-acting formulation of PrEP that has been found to be highly effective. Initially people who are interested in getting LA cab injections first take the oral formulation of cabotegravir every day for several weeks (one 30 mg pill of cabotegravir daily). Doctors then switch patients to injections of LA cab once monthly for two consecutive months. Injections are given deep into the buttocks. After this initial injectable dosing, LA cab is given every two months.

Due to its infrequent dosing, LA cab has the potential to change the way PrEP is used. Some people do not wish to use daily oral PrEP, or have difficulty taking pills or remembering to take pills. In such cases, injectable long-acting PrEP in the form of LA cab could meet their HIV prevention needs.

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LA cabotegravir has been approved in the U.S. and the European Union, but it is not likely to be approved in Canada for HIV prevention until late Spring 2024.

When LA cab is approved in Canada, there will be much to learn from how it has been implemented in other countries. Due to its high rate of effectiveness in clinical trials, there is hope that if LA cab is used in populations at high risk for HIV, it has the potential, along with regular HIV testing, to help further reduce the spread of HIV. Regional and local public health authorities, clinics, healthcare providers and community organizations will have to determine in the months and years ahead how best to deploy LA cab to reduce the spread of HIV infection.

LA cabotegravir is the first long-acting formulation of PrEP. In a few years, it is likely that another long-acting formulation for PrEP will become available—long-acting lenacapavir. This other formulation requires injection just under the skin of the abdomen every six months.

In this issue of *TreatmentUpdate*, we present information on LA cab from clinical trials and an important case report. This information may be useful for clinicians and people interested in this new technology for HIV prevention.

B. Safety and effectiveness of long-acting cabotegravir for prevention in men and transgender women

Clinical trials have found that long-acting cabotegravir (LA cab) is highly effective at reducing the risk of getting HIV. Furthermore, at least one randomized double-blind clinical trial (code-named HPTN 083) found that LA cab was statistically superior to daily oral tablets of tenofovir DF + FTC (sold as Truvada and available in generic formulations; hereafter abbreviated to TDF + FTC) at preventing HIV infection. About a year and a half into HPTN 083, this trial was unblinded, as statistical analysis found that LA cab was highly effective. When this trial was unblinded, participants were told which drug(s) they were receiving. At that point, participants could choose to receive either prevention option. In the report below, we detail findings from the unblinded part of the study. Examining results from the unblinded phase is important because this phase is more likely to resemble what will occur in clinics where participants will know which drug they are getting.

A total of 3,290 participants were in the unblinded phase of the study. During this phase, researchers found that the use of LA cab continued to provide a lower risk of HIV infection compared to daily oral TDF + FTC. Specifically, participants who received LA cab had about a twofold lower risk of getting HIV.

However, researchers unexpectedly found that some participants were less adherent to the study interventions in the unblinded phase of the study. In the case of LA cab (which is injected by a healthcare provider deep into the muscles of the buttocks), there were delays in some participants visiting study clinics for their injections, which are ultimately given every two months.

About the LA cab study – unblinded phase

In the present study, cabotegravir was initially given at a dose of one pill (containing 30 mg) taken orally for five consecutive weeks. If participants tolerated this and took the pills as directed, they could then switch to injectable LA cab (600 mg in 3 mL of liquid). Initially, LA cab was given as a single injection every four weeks for two consecutive months, and then every eight weeks thereafter.

Participants who were supposed to get injections every eight weeks but missed clinic visits (that is, they did not go to the clinic every eight weeks as scheduled) were temporarily switched to receive injections every four weeks for two consecutive months, after which time they could resume clinic visits for their injections every eight weeks. The reason for this schedule of injections is that levels of cabotegravir in the blood need to be relatively high and then maintained to suppress HIV should participants be exposed to the virus. Late appointments for injections result in less-than-desirable cabotegravir levels, so more frequent injections (every four weeks) were temporarily needed.

At those clinic visits, participants gave blood samples, some of which underwent HIV testing and other assessments. Other blood samples were stored for later testing and analysis (for example, measuring levels of cabotegravir).

If a test result was positive for HIV at the clinic, the blood sample was sent to a central laboratory for further analysis and measurement of cabotegravir levels (or, if they were on TDF + FTC, for TDF levels).

In the unblinded phase of the study, data from 1,663 people taking LA cab and 1,627 taking TDF + FTC were analysed. Participants were in the unblinded phase for almost one year.

A total of 87% of participants identified as gay, bisexual or other men who have sex with men (gbMSM). Most of the remaining people identified as transgender women who had sex with men. Four people did not disclose their sexual identity. The average age of participants was 26 years old.

Trial HPTN 083 took place in the following countries:

- Argentina
- Brazil
- Peru
- South Africa
- Thailand
- U.S.
- Vietnam

Results – HIV infections

During the unblinded phase of the study, HIV infections were distributed as follows:

- LA cab – 12 new infections
- TDF + FTC – 32 new infections

When researchers combined data from both the blinded and unblinded phases, the distribution of infections was as follows:

- LA cab – 25 new infections
- TDF + FTC – 73 new infections

During the unblinded phase, some infections occurred under the following circumstances in people taking LA cab:

- one person received their injections on time and had expected levels of cabotegravir in their blood for most periods
- one person received their injections on time but their levels of cabotegravir unexpectedly fell rapidly between injections; researchers did not find any drug interactions or problems with injections and were puzzled by their findings
- three people had at least one delay of more than 10 weeks between injections
- other HIV infections occurred in people more than six months after the last LA cab injection

As a result of infections occurring during the study, some participants developed HIV with a degree of resistance to integrase inhibitors—the class of drugs to which cabotegravir belongs.

As mentioned above, in the unblinded phase of the study, two people developed HIV infection despite getting injections of LA cab on time. In the blinded phase of the study, four other people developed HIV infection despite getting injections on time. Researchers noted that this occurred in six out of 2,282 people who were taking LA cab in the blinded and unblinded phases of the study, which represents 0.26% of participants. These six people were subsequently treated with a combination of drugs, including NNRTIs (non-nucleoside reverse transcriptase inhibitors) or protease inhibitors and nucleoside analogues. They were all able to achieve undetectable viral load levels.

These six people developed HIV that was at least somewhat resistant to integrase inhibitors because of exposure to cabotegravir. Researchers do not know if these people would have been able to suppress HIV if their treatment included the leading integrase inhibitors bictegravir (in Biktarvy) or dolutegravir (in Dovato, Juluca and Triumeq).

Adverse events

The term *adverse events* is used in clinical trials to describe all unfortunate events that occur. Some of these events are caused by the study intervention (in this case drugs). Others can be caused by an underlying illness or infection. Some adverse events may be caused by other issues unrelated to the study drug. Below are some selected adverse events experienced by participants in the present study and their distribution:

Increased blood pressure
- LA cab – 19 people
- TDF + FTC – two people

Increased cholesterol levels
- LA cab – 33 people
- TDF + FTC – 14 people

Increased levels of so-called bad cholesterol (LDL-C)
- LA cab – 41 people
- TDF + FTC – 23 people

Weight gain
- LA cab – 0.84 kg per year
- TDF + FTC – 0.80 kg per year

The above differences in weight gain between people taking different drugs were minor and not statistically significant.

Among people taking LA cab, 23% had injection site reactions (these tend to become less common over time). None of the people with such reactions quit the study.

Bear in mind

The increased cases of high blood pressure among LA cab users were unexpected and require further study. It is possible that such an increase occurred because cabotegravir belongs to a class of drugs called integrase inhibitors. In some people taking these drugs, there have been reports of an increased risk for high blood pressure, abnormal blood sugar levels and increased cardiovascular disease risk. However, bear in mind that only 19 of the 1,627 people who took LA cab in the unblinded phase developed high blood pressure; this represents about 2% of participants on the drug, which is low. This finding is encouraging. However, as LA cab gets used by more people in the future, some of whom may be older and may have pre-existing cardiovascular disease, doctors and nurses will need to monitor participants for this and other related issues.

Infections among daily oral PrEP users

According to the researchers, when adherence to daily TDF + FTC is high, new cases of HIV infections are rare. In the present study, the researchers stated that "almost all of the infections observed in the daily oral PrEP group…occurred in participants with poor adherence or no evidence of drug dosing [based on analysis of their blood samples]." These participants were subsequently offered treatment and were able to suppress HIV.

REFERENCES:

Landovitz RJ, Hanscom BS, Clement ME, et al. Efficacy and safety of long-acting cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV infection in cisgender men and transgender women who have sex with men 1 year after study unblinding: a secondary analysis of the phase 2b and 3 HPTN 083 randomised controlled trial. *Lancet HIV*. 2023 Dec;10(12):e767-e778.

Landovitz RJ, Donnell D, Clement ME, et al Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. *New England Journal of Medicine*. 2021 Aug 12;385(7):595-608.

C. Safety and effectiveness of long-acting cabotegravir for prevention in cisgender women

A clinical trial called HPTN 084 took place with cisgender women at high risk of HIV. These women were recruited from countries in Sub-Saharan Africa. This study had a similar design to the trial in men and transgender women (HPTN 083) discussed in the previous article.

In HPTN 084, participants were adults who were assigned female at birth (cisgender women). Participants were randomly assigned to receive either oral cabotegravir or oral tenofovir DF + FTC (sold as Truvada and available in generic forms; hereafter abbreviated to TDF + FTC). All pills were taken daily.

Cabotegravir was initially dispensed one pill (30 mg) taken daily for five consecutive weeks. After this time, participants were switched to the liquid long-acting formulation of cabotegravir (LA cab). This formulation was injected by healthcare personnel deep into the buttocks once monthly for two consecutive months (to raise and maintain high levels of cabotegravir in the blood). After this period, injections occurred every two months.

To add to the complexity of the study, participants did not know if they received cabotegravir or TDF + FTC, as participants who received cabotegravir injections were given fake TDF + FTC pills and participants who received TDF + FTC were given injections of fake LA cab.

Researchers enrolled 3,224 women—1,614 were assigned to receive cabotegravir and 1,610 were assigned to receive TDF + FTC.

Participants were an average of 25 years old when they enrolled in the study and were in the following seven countries:

- Botswana
- Eswatini
- Kenya
- Malawi
- South Africa
- Uganda
- Zimbabwe

Results

A total of 40 new cases of HIV infection were detected during the study and distributed as follows:

- cabotegravir – four women
- TDF + FTC – 36 women

According to the study researchers, their findings showed that "although both [interventions] for HIV prevention were generally safe, well-tolerated, and effective, cabotegravir was superior to TDF+FTC in preventing HIV infection in women.

Focus on infections – cabotegravir

According to the researchers, two of the four women in the cabotegravir group who developed HIV infection "did not receive any cabotegravir injections." What's more, when researchers analysed blood samples from these participants, they did not have any detectable cabotegravir at the time their HIV was first detected.

In the third woman, HIV infection was first detected when she began cabotegravir injections. However, HIV was subsequently found in her blood samples that were taken around the time she enrolled in the study. It is possible that she had been infected a few days before enrolling in the study. In such cases, HIV testing at that time would not have detected the infection.

The fourth woman's HIV infection occurred during the period when she had switched to cabotegravir injections. However, clinic records indicated that her injections were not given on time and that the amount of cabotegravir in her blood was below a protective level.

None of these four women had HIV that had significant resistance to integrase inhibitors, the class of drugs to which cabotegravir belongs. Other integrase inhibitors that are commonly used as part of HIV treatment include the following:

- bictegravir (in a pill called Biktarvy)
- dolutegravir (in a pill called Tivicay and co-formulated with other HIV drugs and sold under the brand names Dovato, Juluca and Triumeq)
- raltegravir

Focus on infections – TDF + FTC

All 36 infections in women assigned to receive TDF + FTC occurred after participants entered the study. According to researchers, "none of these cases had [levels of TDF] consistent with six to seven doses/per week." In other words, participants who developed HIV infection were not taking TDF + FTC as directed.

One participant who developed HIV infection had a history of poor adherence to TDF + FTC. She had HIV that was resistant to FTC and 3TC.

Adverse events

The term *adverse events* is used to describe unfortunate events that occur in clinical trials. Some of these events are caused by the study intervention (in this case drugs). Others can be caused by an underlying illness or infection. Some adverse events may be caused by other issues unrelated to the study drug.

In general, researchers found that the rate of moderate or more severe adverse events were similar whether participants received cabotegravir or TDF + FTC.

The researchers stated that "most" of the severe adverse events were due to temporarily abnormal lab test results and that these were "seldom clinically significant."

Adverse events led to a very small proportion of participants leaving the study prematurely:

- cabotegravir – 1.1%
- TDF + FTC – 1.4%

Selected adverse events that were graded at least of moderate intensity included the following:

Nausea and/or diarrhea
- cabotegravir – 21%
- TDF + FTC – 23%

Abnormal uterine bleeding
- cabotegravir – 19%
- TDF + FTC – 19%

Headache
- cabotegravir – 17%
- TDF + FTC – 17%

Focus on injection site reactions

Injection site reactions were more commonly reported in women who received LA cab (38%) than in women who received TDF + FTC (11%). Recall that participants who received TDF + FTC also received injections of fake (placebo) LA cab.

Injection site reactions that were moderate or of greater severity occurred in 13% of women who received LA cab and 2% of women who received TDF + FTC.

Pain was the most common injection site reaction.

According to researchers, "most injection site reactions were reported at the first injection and diminished over time." For instance, among women who received LA cab injections, 29% reported injection site reactions at their first injection. However, by the fourth injection, only 2% of participants reported such reactions. Other clinical trials have reported a decreased risk of injection site reactions with LA cab over time. None of the participants left the study because of injection site reactions.

Focus on pregnancy

At the start of the study, all participants were taking long-acting contraceptives. Despite this, there were 49 confirmed pregnancies during the study, distributed as follows:

- cabotegravir – 29 pregnancies
- TDF + FTC – 20 pregnancies

At the time the data were analysed, researchers had data on the results of 31 out of 49 pregnancies (the remaining women had not yet given birth). According to the researchers, "most pregnancies resulted in a live birth," distributed as follows:

- cabotegravir – 13 out of 18 pregnancies were live births
- TDF + FTC – 10 out of 13 pregnancies were live births

According to researchers, the remaining women on whom they had data experienced miscarriages or terminated their pregnancies.

None of the infants were born with birth defects.

Serious side effects and deaths

The vast majority of adverse events were not graded as serious. Indeed, researchers only considered six adverse events to be serious, as follows:

- cabotegravir – two women had serious adverse events; one was hospitalized for "fetal distress" and another for a "respiratory tract infection"
- TDF + FTC – four women had serious adverse events; one had liver toxicity, two had liver injury and one had a seizure

There was a total of three deaths; all occurred in women assigned to receive cabotegravir. However, researchers judged that none of these deaths were caused by use of cabotegravir. Rather, according to the researchers, the deaths were due to high blood pressure and heart disease (one woman), a stroke (one woman), and "an unexplained headache that could not be further investigated."

Focus on weight gain

On average, studies report that adults in the general public are gaining weight over time. Studies in people with HIV who are taking treatment indicate that some participants gain weight.

In the present study, researchers found that participants initially gained a small amount of weight (less than half a kilogram) but subsequently gained about 2 kg per year—2.4 kg in people who took cabotegravir and 2.1 kg in people who took TDF + FTC.

Note that a proportion of participants experienced what the researchers called "abnormal weight loss," distributed as follows:

- cabotegravir – 5%
- TDF + FTC – 7%

For most participants experiencing this issue, the weight loss was of moderate intensity. However, a small proportion of women experienced more intense weight loss, distributed as follows:

- cabotegravir – 1%
- TDF + FTC – 2%

Bear in mind

Overall, the researchers found that LA cab provided "an adherence advantage over daily oral pill-taking. An injection every eight weeks is convenient and discreet, and might overcome the difficulties with pill-swallowing, HIV stigma, intimate partner violence, and discrimination."

REFERENCE:

Delany-Moretlwe S, Hughes JP, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *Lancet.* 2022 May 7; *399*(10337):1779-1789.

D. Long-acting cabotegravir - focus on transgender women

The overall results from trial HPTN 083 were previously reported in this issue of *TreatmentUpdate*. In this trial, researchers compared the protective effects of daily oral tenofovir DF + FTC (sold as Truvada and available in generic formulations; hereafter abbreviated to TDF + FTC) vs. long-acting injectable cabotegravir (LA cab). Analysis found that LA cab was safe and highly effective in reducing the risk of HIV infection.

The trial enrolled 570 transgender women—304 were assigned to received TDF + FTC and 266 were assigned to receive injectable cabotegravir.

At the time they entered the study, participants were on average around 23 years old. Almost half of the participants reported emotional intimate partner violence, while almost one-third reported physical intimate partner violence. Nearly 30% of all transgender women reported that they were not at risk for HIV infection. Nearly 25% of transgender participants reported what researchers termed "clinically significant" symptoms of depression.

Results

There was a total of nine newly diagnosed HIV infections during the study, distributed as follows:

- TDF + FTC – seven infections
- LA cab – two infections

Researchers found that participants assigned to take TDF + FTC who developed HIV had no or very low blood levels of TDF. In other words, they did not take sufficient medication. Indeed, in five of the seven participants who tested positive for HIV, no concentration of TDF could be detected in their blood samples.

One participant had HIV infection detected at the fourth week of the study, while they were supposed to be taking the oral formulation of cabotegravir prior to switching to the injectable formulation. Adherence was not directly observed, so researchers are not certain if the participant used oral cabotegravir consistently. Researchers stated that "it is possible that the participant acquired HIV shortly after enrollment and that this was not detected until the week four visit [to the study clinic]."

The other participants acquired HIV several years after their last injection of cabotegravir. Analysis of their blood samples around the time of infection did not detect any cabotegravir.

Hormones

Upon study entry, 44% of transgender women reported that they were using gender-affirming hormones. Subsequently, a further 14% of participants reported use of these hormones.

Commonly used hormones for gender affirmation by participants in this study included the following:

- estradiol valerate
- spironolactone
- estradiol
- cyproterone acetate

There were no differences in types of gender-affirming hormones used among participants who received TDF + FTC and those who received LA cab.

Use of gender-affirming hormones did not result in significant increased weight in transgender participants during the study.

Based on data from a sub-study of 53 transgender women, use of gender-affirming hormones did not affect cabotegravir levels in the blood.

Adverse events

Adverse events is the term used to describe unfortunate events that occur in a clinical trial. Adverse events can be caused by the study drug(s), an underlying illness or infection, or other issues unrelated to the study.

Adverse events were similar in participants regardless of whether they received TDF + FTC or LA cab. They were also similar in transgender women and cisgender men (data on these men came from the overall study analysis previously reported).

Two transgender people died during the study; their deaths were not related to the study medicines. Details were not released by the research team.

For the future

Based on the analysis of data from transgender women, the researchers stated that "an injection [of long-acting cabotegravir] every 2 months is convenient and discreet and might address the barriers to daily oral pill-taking, such as competing life priorities, HIV stigma, discrimination and violence" faced by transgender women.

The researchers used a relatively small number of transgender women to collect data about the potential for gender-affirming hormones to interact with cabotegravir (and vice versa). They called for additional studies to better understand this issue.

REFERENCE:

Marzinke MA, Hanscom B, Wang Z, et al. Efficacy, safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir for HIV pre-exposure prophylaxis in transgender women: a secondary analysis of the HPTN 083 trial. *Lancet HIV*. 2023 Nov;10(11):e703-e712.

E. In context – long-acting cabotegravir for HIV prevention

Australian researchers reviewed data from the unblinded phase of trial HPTN 083 and noted that infections were distributed as follows:

- long-acting cabotegravir (LA cab) – 12 new HIV infections
- TDF + FTC – 32 new HIV infections

Adherence

According to the Australian researchers, "the majority of new HIV infections in both the long-acting and oral daily PrEP groups occurred in the context of [drug] interruptions or challenges with adherence. This highlights the importance of adherence to PrEP, which notably decreased in both groups during the unblinded phase."

LA cab is a new technology for HIV prevention. Clinics will need to determine which patients will benefit most from this way of preventing HIV. They will need to find ways to ensure that patients return to clinics for regular injections and screening for HIV and other sexually transmitted infections (STIs).

LA cab—the first long-acting formulation of PrEP—will likely be in demand because of its infrequent dosing schedule, but not everyone who initiates it may be able to stay on it. Also, some people may not want to initiate it because they dislike injections. Therefore, studies will need to be done to find out why some people stop taking long-acting forms of PrEP and whether other forms of HIV prevention can meet their needs.

HIV screening

Regular screening for STIs (including HIV) is a routine part of care for people who take PrEP. The Australian researchers noted that HIV drugs used for PrEP can sometimes result in a delayed diagnosis of HIV in the very rare cases when infections occur. This delay can happen because of the anti-HIV effects of PrEP – these effects initially keep HIV levels low until the virus can develop the ability to overcome PrEP. The researchers underscored that a combination of HIV screening assays, including antibody tests and viral load assays (which seek the genetic material of HIV), should be used in people who are taking long-acting PrEP.

Risk factors

In the HPTN 083 trial, more people taking LA cab experienced a higher rate of issues associated with cardiovascular disease (compared to those taking TDF + FTC). These issues included high blood pressure, abnormal lipid levels (cholesterol) in their blood and "a trend towards increased blood glucose levels." Although the proportion of such cases was very small, the researchers called for longer-term monitoring in people who take LA cab to better understand which people develop these issues. Also, researchers stated that healthcare providers need to "consider existing comorbidities" when selecting PrEP, particularly for older people.

People use PrEP during seasons of risk and are unlikely to use long-acting or other forms of PrEP permanently. The adverse effects seen in a small proportion of people who used LA cab will likely resolve upon cessation of this drug.

The number of infants born to people who took cabotegravir while pregnant is low in published studies. Further study of cabotegravir during pregnancy is needed.

In clinics

In the everyday world of clinics that prescribe PrEP, studies will need to be done to assess how they are able to deliver LA cab (if they encounter any barriers and how they are overcome) and the proportion of eligible patients who accept and continue to use it over time.

In Canada

Long-acting cabotegravir for HIV prevention has been approved in the U.S., European Union and other regions, where it is sold under the brand name Apretude.

LA cab for prevention will hopefully be approved in Canada by late Spring 2024. Note that after approval by Health Canada, it may take up to three months before private insurance companies agree to place it on their lists of subsidized medicines. The manufacturer of cabotegravir, ViiV Healthcare, will engage in negotiations with provincial and territorial ministries of health over the cost of the drug. If both the company and ministries of health can agree on a price, then LA cab will be subsidized. Typically, such negotiations can take a year, sometimes even longer.

REFERENCE:

Griffin DW, Hoy JF, McMahon JH. Long-acting cabotegravir PrEP: a time for cautious optimism. *Lancet HIV*. 2023 Dec; 10(12):e756-e757

F. Learning from a case of breakthrough infection with long-acting cabotegravir for prevention

Long-acting cabotegravir (LA cab, sold as Apretude) has been approved in the U.S. and European Union. LA cab is used as pre-exposure prophylaxis (PrEP) to reduce the risk of HIV infection.

In large clinical trials, HIV infections were relatively rare among people who used LA cab, who received injections on schedule and whose levels of cabotegravir in blood samples were in the expected range. In these trials, about 0.3% of these people became infected. The reason(s) that they became infected is not clear.

Diagnosing HIV

Researchers found that levels of HIV were initially very low in people who used LA cab and became infected. As a result, production of HIV antibodies by the immune system was greatly delayed—by several months after infection had occurred. These effects of a delayed antibody response to HIV infection can lead to a delayed diagnosis of HIV when using routine screening tests that rely

on antibodies or HIV proteins. Prolonged and undetected HIV infection in people on LA cab could allow HIV to develop the ability to resist cabotegravir and other drugs that have a similar structure to it. These drugs are called integrase inhibitors.

Commonly used integrase inhibitors for the treatment of people with HIV include the following:

- bictegravir (in Biktarvy)
- dolutegravir (in Dovato, Juluca, Tivicay and Triumeq)
- raltegravir

Both bictegravir- and dolutegravir-containing regimens are highly effective, generally well tolerated and have relatively few interactions with other medicines. So, the development of HIV that is resistant to these drugs has consequences. Such resistance not only reduces future treatment options but may cause future combinations of treatment to be complex.

A team of researchers in the U.S. has noted that rare breakthrough infections that occur in people who use oral PrEP (tenofovir + FTC) can also result in delayed production of antibodies. However, such delays happen less often than they do with LA cab. The researchers noted that "the overwhelming majority of [tenofovir + FTC] breakthrough infections are a consequence of non- or poor adherence." As a result of having low or no tenofovir + FTC in their blood, the chance of HIV developing resistance to these drugs is very small.

In 2021, the U.S. Centers for Disease Control and Prevention (CDC) recommended a combination of antibody and antigen testing and, in some circumstances, the addition of a viral load test to help clinicians uncover recent HIV infection in PrEP users. The CDC's guidance is available here:

HIV Guidelines - Preventing New HIV Infections

Case details

A team of U.S. researchers recently published a report of the first documented case of HIV infection in a person who was taking LA cab outside of a clinical trial.

The patient was a young adult described by the researchers as a "sex diverse" person assigned male at birth. They had been taking tenofovir alafenamide (TAF) + FTC for PrEP once daily. The combination of TAF + FTC is sold as Descovy. The patient disclosed to their healthcare provider that they missed a dose of PrEP once a week. Therefore, they were interested in LA cab, as it could make adherence easier.

The researchers noted that the patient had hypothyroidism (low levels of thyroid hormone) that was poorly controlled with prescribed therapy. The patient also engaged in what the researchers described as "unsupervised" injections of testosterone. These injections, the researchers stated, led to "frequent injection site [bacterial infections of skin and soft issue]."

The person had oral and condomless anal sex with between 20 and 30 cisgender male partners a month. They had also begun to engage in receptive anal fisting. In the past six months they had been diagnosed with syphilis and anogenital mpox infection (formerly called monkeypox).

The person's primary partner had HIV that was kept suppressed for the past two years on a combination of darunavir, cobicistat and dolutegravir.

The patient's doctors stopped prescribing TAF + FTC and switched them directly to LA cab 600 mg injected into their left buttock on day zero and again 27 days later. At those times, HIV testing for antibodies and antigens was negative. HIV viral load testing (with a lower limit of 20 copies/mL) was also negative.

On day 76, the patient reported a flu-like illness. They tested positive for SARS-CoV-2 (the cause of COVID-19) and were prescribed a five-day course of Paxlovid (nirmatrelvir + ritonavir). This helped to clear their symptoms quickly.

On day 91, the patient received their third injection of LA cab. At this time, antibody and antigen tests for HIV were negative. However, a viral load test revealed that the person was likely infected with HIV, as their viral load was 30 copies/mL.

On day 100, the patient returned for repeat testing and the antibody and antigen tests were positive. Viral load was then 20 copies/mL. Subsequently that day, doctors prescribed TAF + FTC (Descovy)

in addition to the LA cab that they were already taking.

On day 112, further blood tests revealed that the person's antibody and antigen tests were negative and viral load was not detected. However, this does not mean that they were cured of HIV. Rather, their infection was caught relatively early, and their regimen was keeping the virus suppressed. As their viral load was too low to analyse for HIV that could be resistant to different drugs, and in order to ensure that the patient's viral load stayed suppressed, doctors changed the regimen to darunavir, cobicistat and dolutegravir. This was the same combination that the patient's partner was taking.

On day 128, the level of cabotegravir in the person's blood was still relatively high.

On day 191, the person's blood samples continued to test negative for HIV antibodies and antigens and their viral load was undetectable.

Long-acting early viral inhibition syndrome (LEVI)

According to the researchers, this person's lab tests, minimal symptoms of early HIV infection, and delayed or "flickering" HIV antibody/antigen reactivity were consistent with long-acting early viral inhibition syndrome (LEVI). This has been recently described in people in clinical trials of LA cab who became infected with HIV. In contrast, in people who are not on long-acting PrEP, recent HIV infection is associated with a flu-like syndrome of varying severity and people test positive for HIV much sooner.

The U.S. researchers stated that their findings "underscore the significance of screening patients on long-acting PrEP agents with HIV-1 RNA assays rather than standard fourth generation antigen/antibody tests alone." They added: "Had the standard HIV screening algorithm been utilized, this case would have gone undiagnosed potentially for several more weeks, increasing their risk of [resistance to integrase inhibitors]. Clinical trial data suggest that when fully suppressive ART [antiretroviral therapy] is initiated early after LEVI detection, [resistance to integrase inhibitors] may be avoided."

Why did HIV infection occur?

The researchers are not sure why HIV infection occurred in this case. One possibility is a drug interaction—perhaps the use of Paxlovid reduced cabotegravir levels in the blood. However, this has not been previously reported and there is no background data to support it.

The researchers advanced the idea that perhaps the patient was exposed to a very high viral load that could have overwhelmed the protective effect of cabotegravir. Given the patient's sexual history, the researchers suggested that injury to the anal mucosa could have occurred via fisting or from sexually transmitted infections. Syphilis and mpox can cause ulcers on the delicate anal mucosa, augmenting the amount of HIV that could get into the body.

The researchers noted the "transition from TAF + FTC to long-acting cabotegravir without overlap may represent a period of vulnerability [to HIV]." Infection during the period between the first and second injections of LA cab could also have occurred. The researchers underscore that some people can have low levels of cabotegravir in their blood after their first injection.

The researchers stated that an overlap of one month between tenofovir + FTC and the first injection of LA cab "may warrant further discussion."

Note that in clinical trials that have enrolled thousands of people, participants first take oral cabotegravir (30 mg) in one pill per day for several weeks to raise and maintain the concentration of cabotegravir in the blood. After this, they then begin injections of LA cab. In the case of the person reported here, there was no initial phase of taking oral cabotegravir.

Cabotegravir concentrations

Research by scientists outside of this case report suggests that blood levels of cabotegravir when there is no oral lead in period (no pills are used and the patient goes directly to injection of LA cab) reach high protective levels in 90% of patients about three days after the first injection. A week after the first injection 95% of patients have high protective levels of cabotegravir in their blood.

The amount of cabotegravir in the blood that is considered protective is based on experiments with monkeys exposed to high concentrations of SHIV (simian human immunodeficiency virus). This virus is used in experiments with monkeys as it is infectious and can cause disease relatively quickly.

The dose of LA cab used in studies with people was chosen based on the data from monkeys so that maximal protection from HIV would occur in people. This is why researchers stated that rates of infection were "rare" among people who received injections on time in such trials. To put such infections in context, the researchers stated that in clinical trials, "we have now identified six cabotegravir infections to date that occurred despite on-time injections." Furthermore, the researchers stated that these six cases occurred "among 2,282 participants assigned to long-acting PrEP (LA cab)." Note that six out of 2,282 is 0.26%.

The present case report likely represents a very rare event. Note that very rare cases of breakthrough infection have also occurred in people who used tenofovir DF + FTC as PrEP. However, the data to date suggest that when used as directed for PrEP, either LA cab or tenofovir + FTC reduces the risk of HIV infection by more than 99%.

For the future

The researchers noted that the present case "highlights the diagnostic and management challenges that may occur with such PrEP failures. Prescribers of long-acting PrEP agents need to be able to identify LEVI syndrome and act urgently to prevent possible [resistance to integrase inhibitors]." Furthermore, they added that "this potential benefit of including HIV-1 RNA testing in diagnostic algorithms must be carefully balanced against the possibility of false positive results that can lead to delays in PrEP administration and significant emotional distress for the patient and confusion/frustration for the medical team."

The researchers call for "robust" partnerships between academic medical centres and healthcare providers working in the community "to ensure access to provider education and resources."

As mentioned earlier, the patient's intermittent positive HIV antibody/antigen tests and very low viral load in the context of long-acting PrEP use, combined with early detection of HIV, may have implications for cure research. For instance, it is possible that the pool of infected cells in their body is relatively low compared to what would typically be found in a person not taking PrEP who became infected. If this is the case, then the researchers suggest that perhaps attempts at effecting a cure for HIV may have a greater chance of success in someone who was on LA cab and whose infection was caught early than in someone not on LA cab. This idea needs to be tested in clinical trials.

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