TreatmentUpdate 244

Vol. 34, No. 1 · February 2022

Available online at
www.catie.ca/treatmentupdate

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I ANTI-HIV AGENTS

A. Long-acting HIV treatment – a major change begins

Until there is a safe, effective and simple-to-administer cure for HIV, treatment with a combination of anti-HIV drugs (ART) will remain vital. In the past 35 years, HIV treatments have become more effective and better tolerated. Furthermore, ART has become simpler—an entire regimen in one pill taken once daily for the average person initiating treatment. Now, a long-acting injectable regimen has become available. This treatment is called Cabenuva and consists of two drugs—cabotegravir and rilpivirine.

Why long-acting formulations?

People with chronic health conditions, including HIV, have to take pills every day. This means there is the possibility that people might inadvertently forget to take their pills. Some people with complex lives and competing issues may also find it difficult to engage in regular pill taking. Missing doses can result in less-than-ideal levels of HIV drugs in the body. If pill taking becomes intermittent, the concentration of medicine can fall to low levels repeatedly, which can give HIV the chance to adapt and overcome the effects of treatment.

Other issues

A survey of nearly 2,400 people with HIV enquired about issues related to daily dosing of medicines. People surveyed lived in North and South America, Europe, South Africa and East Asia. Researchers

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found that a significant proportion of people reported different issues, including the following:

- 31% had difficulty swallowing pills every day
- 33% felt stressed by the need to take HIV medicines every day
- 35% disclosed that the need to take HIV pills every day caused them to have a bad feeling about their medicines and recall bad memories from their past
- 38% worried that the need to take pills daily could inadvertently expose their HIV status to others

Some people said that having to take an HIV pill every day gave them control over the virus and their lives. However, not everyone surveyed felt this way.

Long-acting ART has the potential to address some of the psycho-social burdens of living with HIV. Another potential advantage is that Cabenuva consists of two drugs rather than the usual three drugs. As HIV treatment is lifelong, Cabenuva may offer the possibility of reduced long-term toxicity from taking medicine for decades.

Approval

In 2020 in Canada, then subsequently in the European Union and the U.S., a major change in HIV treatment began. Regulatory agencies approved the first long-acting injectable regimen for the treatment of HIV: Cabenuva, which contains cabotegravir and rilpivirine. Cabotegravir belongs to a class of drug called integrase inhibitors and rilpivirine belongs to a class called non-nukes (NNRTIs, non-nucleoside reverse transcriptase inhibitors).

Cabenuva is meant to be used as part of what is called a switch strategy. Prior to initiating Cabenuva, patients must already be on oral ART and virologically suppressed. If there are no potential barriers—such as the presence of HIV that is resistant to cabotegravir or rilpivirine, or if the person has a strain of HIV called A1 or A6 (which are less susceptible to cabotegravir and rilpivirine), or other issues—then an oral lead-in regimen can be initiated. That is, the person's existing regimen is switched to a combination of oral formulations of cabotegravir and rilpivirine. This combination is taken for four weeks to ensure that the drugs are tolerated and that there are no problems. At the end of this time, the patient changes from oral formulations to injectable formulations of cabotegravir and rilpivirine. The drugs are injected deep into the muscles of the buttocks, one injection of cabotegravir in one buttock and one injection of rilpivirine in the other buttock. Initially the injections are given once monthly, but after a couple of months of injections to raise levels of cabotegravir and rilpivirine in the blood, patients can change to a regimen of injections every two months.

Results from a recent clinical trial (detailed later in this issue of *TreatmentUpdate*) have found that in people on a dolutegravir pill-based regimen, it is possible to avoid the oral lead-in with pills of cabotegravir and rilpivirine and go directly to injecting these drugs. As a result, regulatory authorities in the European Union have made the oral lead-in optional. Regulatory agencies in Canada and the U.S. are reviewing the possibility of making the oral lead-in optional. We will have more information about research on direct-to-injection strategies later in this issue of *TreatmentUpdate*.

HIV prevention

In the U.S., the long-acting injectable formulation of cabotegravir has been approved for use to reduce the risk of getting HIV. Taking medicines to reduce the risk of getting HIV is called pre-exposure prophylaxis (PrEP). This formulation of cabotegravir is sold under the brand name Apretude. Regulatory authorities in the U.S. have advised that patients can initiate Apretude with or without a four-week oral lead-in with cabotegravir pills. An injection of the drug is given deep into muscles in the buttocks once a month for two consecutive months. After this, the drug can be injected every two months.

The manufacturer of cabotegravir, ViiV Healthcare, is planning to seek approval for Apretude in Canada and the European Union for HIV prevention.

In the current era

Although much anticipated by doctors and their patients, regulatory approval of long-acting HIV treatment has been met with a somewhat muted reception. The approvals occurred during the midst of a worldwide respiratory pandemic—COVID-19. Many people were concerned with maintaining their health and well-being because of this

pandemic. Initially, Cabenuva was only subsidized by private insurance. However, recently it has been listed on some public formularies in Canada (for information about formulary access consult your local pharmacist in your region).

A patient support program is available

In Canada, ViiV has facilitated a third-party support program that helps patients navigate public/private insurance and arrange injection appointments. Patients first discuss with their doctor if Cabenuva is right for them. Once the doctor and patient agree about using Cabenuva, they can discuss options for injecting. If they agree that injections should be administered away from the clinic, then the doctor can contact their ViiV representative about enrolling the patient in the support program. The program then contacts the patient, asks some questions and provides general information about Cabenuva. It also provides help in navigating private insurance or public reimbursement mechanisms in their province/territory. The program liaises with the patient's pharmacy and also helps the patient choose a location for the injection that is convenient (injections are not done at the patient's residence). The program also runs sites with dedicated nurses skilled at administering intramuscular injections.

Revolutionary but imperfect

Long-acting cabotegravir and rilpivirine have the potential to become widely used. The advent of these formulations is revolutionary because they ultimately only need to be taken every two months. In comparison, when potent combination HIV treatment was first introduced in 1996, and for years after, it was only available in pill form and had to be taken two or three times daily. Furthermore, some patients in that early treatment era had to take large quantities of pills daily.

In the future, it is likely that more people will choose to have injections every two months (vs. monthly). However, long-acting regimens, like all forms of ART, are imperfect and may not be for everyone.

Here are some issues that patients and doctors will likely need to consider when it comes to the use of long-acting regimens such as Cabenuva and other long-acting ART formulations in development:

Hepatitis B virus (HBV)

Some people with HIV are co-infected with HBV. Many oral regimens for HIV treatment contain a combination of antiviral drugs, which are effective not only against HIV but also, in some cases, against HBV. Cabenuva does not work against HBV. Therefore, people co-infected with HBV need to take daily oral treatment (a pill or pills) for this virus. Commonly used combinations that work against both HIV and HBV include the following:

- TDF (tenofovir disoproxil fumarate) + FTC
- TDF + 3TC (lamivudine)
- TAF (tenofovir alafenamide) + FTC

Pregnancy

Cabenuva has not been studied in large numbers of pregnant people. As a result, doctors are not sure about the potential effects of Cabenuva on the risk of miscarriage or birth defects. A clinical trial of Cabenuva is underway in pregnant people.

Persistence

Cabenuva is injected deep into muscle tissue in the buttocks, and from there it is slowly released into circulation. Although the levels of cabotegravir and rilpivirine decrease over time (hence the need for regular injections), the drugs can remain in the body for a long time even after a person stops taking them. For instance, in early studies of cabotegravir, levels of this drug remained at low but detectable levels for up to a year after the last injection. In the case of rilpivirine, levels of the drug remained at low but detectable levels more than a year after the last injection.

These findings about drug levels have implications for potential treatment interruptions; in general, unsupervised treatment interruptions are not a good idea. Furthermore, in people who are using Cabenuva, such interruptions are fraught with the risk that HIV could develop resistance not only to cabotegravir and rilpivirine but to other related drugs as well. This could greatly reduce future treatment options.

Potential drug interactions

The prescribing information for Cabenuva lists a relatively small number of clinically significant drug interactions compared to older HIV drugs. However, as Cabenuva becomes more widely used, it is possible that some unexpected drug interactions may occur. These may be difficult to manage because it is virtually impossible to

quickly remove cabotegravir and rilpivirine from the body once they have been injected deep into muscle. Therefore, consultation with a pharmacist is important both before initiating treatment with Cabenuva, and, if currently taking Cabenuva, before taking other prescription medicines, over-the-counter medicines and supplements.

Is one dose right for everyone?
As people age, their organs become less efficient at breaking down medicines. Research needs to be done with older people with HIV and Cabenuva to find out if different doses are needed. The doses of cabotegravir and rilpivirine are the same regardless of a person's weight or body mass index (BMI). Research also needs to be done to better understand if people with a high BMI require a larger dose of long-acting cabotegravir or rilpivirine. Doctors in Switzerland plan to assess blood samples from a diverse range of people who are taking Cabenuva to try to find answers to some of these questions.

Other populations
Long-acting formulations of cabotegravir and rilpivirine have largely been tested in highly motivated adults who did not have competing issues and health conditions in their lives. These people were virologically suppressed prior to initiating Cabenuva and had a history of good adherence. However, Cabenuva's long intervals between dosing may make it attractive for people who have complex lives and for whom adherence to daily pill taking has been difficult. The U.S. National Institute of Allergy and Infectious Diseases is sponsoring a clinical trial called Latitude. Potential participants will have a history of difficulty with adherence to oral ART.

Other injection sites
Currently Cabenuva is approved for injection deep into the buttocks. However, such injections are only possible with the help of healthcare personnel. Studies need to be done to explore other parts of the body, such as the thighs, that could be potential injection sites. It is possible that if the thigh muscle could be shown to be a depot for injectable treatment, then people who want the option of being able to self-inject Cabenuva could do so. This would add convenience and remove the need for visits to a healthcare provider just to get the drug injected.

About injecting

In multiple clinical trials, Cabenuva has been found to be generally safe and effective. The most common side effect involved reactions at the injection site. Data from clinical trials suggest that injection site reactions included redness, swelling and/or pain. In general, these side effects were mostly mild and resolved within a few days without intervention. Over time, injection site reactions became less common and less bothersome for many people.

The participants who were drawn to clinical trials of Cabenuva would have likely wanted long-acting treatment and were largely willing to tolerate discomfort and any pain that they would have experienced. Outside of clinical trials, it is likely that people who are interested in Cabenuva would also be willing to undergo regular intramuscular injections every month or two.

For the future

Cabenuva is the first long-acting regimen for HIV; several more will likely be developed in the years ahead. Doctors, patients, scientists and health policy people will be closely watching the deployment of Cabenuva. This scrutiny will help inform ways of improving access to Cabenuva and future formulations of long-acting HIV treatment.

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B. Five-year safety of Cabenuva

Most clinical trials of long-acting formulations of cabotegravir + rilpivirine (the combination is called Cabenuva) have lasted one to two years. However, data collected from 274 participants who were taking Cabenuva every four or eight weeks for up to five years is now available. This data showed that between 74% and 94% of participants maintained an undetectable viral load. Although injection site reactions were common, only 2% of participants stopped using Cabenuva because of them. Three people experienced serious adverse reactions and three people died (their deaths were not likely due to Cabenuva). In general, long-term use of Cabenuva was well tolerated and effective.

Study details

A clinical trial called Latte-2 began in 2014 and recruited participants from the following countries:

- Canada
- France
- Germany
- Spain
- U.S.

Latte-2 was a randomized clinical trial with a complex design.

All participants were not taking HIV treatment (ART) before they began taking the study medicines in Latte-2. Participants were given once-daily oral formulations of HIV treatment for a total of 20 weeks—a combination of pills containing cabotegravir, abacavir and 3TC. For the final four weeks, the drug rilpivirine was added. This oral lead-in period was meant for patients to achieve an undetectable viral load and to assess their tolerance for the medications. When Latte-2 started in 2014, not much was known about the safety and tolerability of cabotegravir in combination with rilpivirine.

Today, people initiating Cabenuva have a much shorter oral lead-in—usually four weeks. Furthermore, other clinical trials have found that an oral lead-in may become optional in the future, as cabotegravir is very well tolerated. Rilpivirine is an older medication, and so doctors are familiar with its safety.

Participants in Latte-2 who completed the first 20 weeks of oral therapy were randomly assigned to one of the following groups:

- long-acting formulations of injectable cabotegravir + rilpivirine given every four weeks – 115 people
- long-acting formulations of injectable cabotegravir + rilpivirine given every eight weeks – 115 people
- continued oral cabotegravir + abacavir + 3TC for 96 weeks, followed by a switch to injectable therapy – 56 people

Note that doses and volumes of injectable medicines given every eight weeks are greater than those given every four weeks.

After 96 weeks, participants who were on oral ART were offered the opportunity to switch to long-acting formulations of injectable cabotegravir + rilpivirine, given every four or eight weeks. This study design ensured that all participants had the chance to receive long-acting therapy—a factor that likely motivated enrollment.

The first two groups—long-acting cabotegravir and rilpivirine given every four and eight weeks—were called the randomized groups by the researchers. The third group—prolonged use of oral meds—was called the extension group by the researchers.

About injectable cabotegravir and rilpivirine

Once the injection phase of a particular group commenced, nurses injected participants in one buttock with long-acting cabotegravir and the other buttock with long-acting rilpivirine—for a total of two injections. People who received long-acting drugs every eight weeks received a greater dose and volume of these drugs than people who were injected every four weeks.

About the participants

Upon entry to the study, participants, on average, were in their 30s, more than 90% were men, and they were mostly White (80%) or Black (10%). CD4+ cell counts were between 450 and 500 cells/mm^3 and viral load was 30,000 copies/mL.

Results

After five years, the proportions of participants with a suppressed viral load were as follows:

- long-acting formulations of injectable cabotegravir + rilpivirine given every four weeks – 74%
- long-acting formulations of injectable cabotegravir + rilpivirine given every eight weeks – 88%
- extension group – 90% among those getting injections every four weeks; 94% among those getting injections every eight weeks

Note that the third group in this study consisted of people who were on oral ART for 96 weeks and then switched to injectable therapy and remained on injectable therapy for more than three years (though they were in the trial for a total of five years).

By the fifth year of the study, different proportions of people on each regimen left the study prematurely because of adverse events (these are explained later in this report). As a result, there was no information about these people's viral loads by the fifth year of the study. To minimize statistical bias when interpreting the virological results at year five, the people who dropped out are considered to have a detectable viral load and still counted as being in the trial for the overall results. Cases of confirmed virological failure among people who remained in the study appear below.

Confirmed virological failure

Participants were considered to have virological failure with two successive viral load test results of 200 copies/mL or greater. Using this metric, virological failures were distributed as follows:

- randomized to injections every four weeks – 3% had virological failure
- randomized to injections every eight weeks – 0% had virological failure
- extension group – 3% had virological failure; all were getting injections every eight weeks

Adverse events

The term *adverse events* in clinical trials describes any unfortunate events that occur. These may be caused by drug side effects, the underlying disease process or activities outside of the trial (such as accidents).

More people in the group randomized to receive injections every four weeks left the study prematurely for the following reasons:

- acute kidney injury
- attempted suicide
- coronary artery disease
- persistent fatigue
- complications of addiction
- muscle weakness
- persistently swollen lymph nodes
- hepatitis C virus infection
- excessive blot clot formation

For the most part, it is very unlikely that these were related to the study medicines. Indeed, few adverse events related to treatment were sufficiently bothersome that participants left the study. Two of those adverse events are as follows:

- injection site pain – two people receiving injections every eight weeks and one every four weeks
- injection site nodule

Common side effects while receiving injectable formulations were mainly injection site reactions—swelling, redness, discomfort and pain. These side effects were generally mild or moderate and resolved without treatment after a few days. Over the course of the study, injection site reactions became less common.

Other side effects after injection included the following:

- fever
- back pain
- fatigue

These were usually temporary.

Three people who were receiving injections every four weeks died during the study for the following reasons:

- seizures – this was unrelated to the study medicines; death occurred at week 30
- coronary artery disease – possibly caused by use of cocaine; death occurred at week 223

- heart attack – potentially related to the study medicines but ViiV and Janssen (the study sponsors) dispute this; death occurred at week 139

Lab tests

Severely abnormal lab test results occurred with 13% of participants who received long-acting therapy having elevated levels of the enzyme creatine kinase in their blood samples. There are several subtypes of creatine kinase, and the subtypes in these cases was not revealed. However, elevated creatine kinase can occur with inflammation and injury of skeletal muscles, the heart or brain. This adverse effect was temporary.

Another severely abnormal laboratory test result—elevated levels of the enzyme lipase— occurred with 8% of participants who received injectable therapy. Lipase is an enzyme produced by the pancreas gland. Excessive levels of lipase in the blood may suggest inflammation of the pancreas gland. However, there were no accounts of abdominal pain associated with elevated lipase in the report on Latte-2 released by ViiV. This adverse event was temporary.

Less than 1% of participants had elevations in total cholesterol and LDL-cholesterol (so-called "bad" cholesterol).

Cardiograms done at the start and end of the study did not find any abnormalities.

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C. Predictors of virological failure with Cabenuva

Clinical trials have found that the use of Cabenuva is generally safe and effective in people with HIV. A very small proportion of people—less than 2%—have developed confirmed virological failure during these trials.

A team of researchers reviewed information collected from three pivotal trials of Cabenuva to better understand factors at the start of the study that could be used to explain why some people experienced virological failure. This information would also be useful for doctors who screen patients for possible use of Cabenuva.

The review encompassed data from more than 1,000 people who had never used Cabenuva prior to entering the trials.

In these three pivotal phase III studies (code-named Atlas, Atlas-2M and Flair), researchers found that the presence of at least two of the following factors at the start of the studies was associated with an increased risk of virological failure:

- two mutations in HIV's genetic material that are associated with resistance to rilpivirine
- subtypes of HIV labelled A1 or A6
- having a body mass index (BMI) of at least 30 kg/m^2

Study details

Researchers pooled data from the three clinical trials for their analysis. No patient profile was provided.

Results

There were 13 people (1.3%) who had confirmed virological failure—defined as two consecutive viral load measures of 200 copies/mL or greater.

After performing extensive statistical and other analyses, researchers found the following possible factors (which were present when some participants entered the study) associated with an increased risk of virological failure:

- two mutations in HIV's genetic material that are associated with resistance to rilpivirine
- subtypes of HIV labelled A1 or A6
- having a body mass index (BMI) of at least 30 kg/m^2

Most participants in the pooled analysis from the three trials had either none of these risk factors (71% or 732 people) or just one of them (26% or 272 people). In the entire study, only a relatively

small proportion of people had two of these risk factors (3.4% or 35 people).

However, among people with confirmed virological failure, having two risk factors was relatively common. This was found in 9 out of 13 people (nearly 70%). Only one participant had all three risk factors at the start of the study.

Most people who developed virological failure had concentrations of cabotegravir and rilpivirine in their blood that were less than ideal at the eighth week of the study (9 of 13 participants). This happened whether or not participants were being injected every four or eight weeks. People with a high BMI (30 or greater) tended to have less-than-ideal levels of study drugs at week eight.

Why these risk factors at baseline?

The analysis of more than 1,000 participants was not pre-planned but was done after the study was completed to try to explain something that happened. Such analyses, which are called "post-hoc" analyses by researchers, are not ideal. However, nothing can be done about this because the problem of virological failure apparently was not anticipated and pooling data from several studies was the only way to get enough virological failures to be useful in a statistical analysis.

Mutations associated with resistance to rilpivirine

Rilpivirine belongs to a group of drugs commonly called "non-nukes" (NNRTIs, non-nucleoside reverse transcriptase inhibitors). Some people who developed virological failure in the three pivotal studies had HIV that was at least partially resistant to rilpivirine (and possibly other non-nukes). This problem may have arisen because they had used non-nukes in the past and developed partial resistance to this class of drug or because they were infected with a strain of HIV that had acquired at least partial resistance to non-nukes. This underscores the importance of obtaining an HIV resistance testing to assess the possibility of resistance prior to initiating treatment with Cabenuva.

HIV subtypes A1 and A6

There are two main types of HIV: HIV-1 and HIV-2. HIV-1 is the virus found in most of the world; it is the most common form of the virus. HIV-2 is most commonly found in parts of West Africa. HIV-1 can be divided into subtypes (A, B, C and so on) based on its genetic information. Subtypes can sometimes be further subdivided, such as A1, A6 and so on. Note that although some subtypes are relatively common in some regions, these can spread due to migration and tourism.

Subtype A appeared to have originated in Central Africa and subsequently spread to other parts of that continent. Later it spread to Eastern Europe, the former Soviet Union and adjoining countries. Subtype A6 appears to have arisen from subtype A1 (itself an offshoot of subtype A). Some scientists think that subtype A6 originated in the former Soviet Union and adjoining countries. Indeed, all but one of the participants with virological failure who had subtype A1 or A6 were from Russia. However, one of the people with these subtypes who developed virological failure was from Canada.

It is plausible that subtypes A1 and A6 somehow have reduced susceptibility to cabotegravir and/or rilpivirine.

Body mass index

People who were obese or very obese had an increased risk for virological failure. Previous research showed that after intramuscular injection in the buttocks, cabotegravir is initially released more slowly into the blood of people whose BMI is 30 or greater than in people whose BMI is less than 30 kg/m^2. The same research found that 20 to 24 weeks after initiating cabotegravir injections and continuing to inject the drug at regular intervals, concentrations of cabotegravir in the blood are similar in people with or without obesity. BMI does not appear to have an impact on rilpivirine concentrations.

In the three pivotal studies that were analyzed for virological failure, participants with a BMI of 30 kg/m^2 or greater who experienced virological failure had received intramuscular injections of Cabenuva with standard-length needles. At the time of Cabenuva's approval by regulatory authorities, ViiV encouraged healthcare providers to use needles at least two inches long when administering Cabenuva in people with obesity to ensure that Cabenuva gets injected into muscle rather than fat.

Bear in mind

This analysis of data from people who developed virological failure found that at least two of the above risk factors are needed for failure to likely

occur. All of these risk factors can be assessed prior to initiating Cabenuva and can help healthcare providers in their screening of patients for whom Cabenuva may be beneficial.

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D. Bypassing the oral lead-in period for Cabenuva in a clinical trial

When clinical trials of long-acting formulations of cabotegravir and rilpivirine began in 2014, researchers first gave participants oral formulations of these drugs for at least 20 weeks. The reason for this relatively long oral lead-in was so that researchers could find out more about the tolerability of oral cabotegravir in particular. At that time, cabotegravir was a new drug; rilpivirine had been in use for eight years so much was already known about it. Since that trial in 2014, oral and long-acting formulations of cabotegravir have been tested in combination with rilpivirine in at least 1,500 people with HIV. These drugs have been found to be generally safe and effective. The combination of the long-acting formulations of these two drugs is called Cabenuva and it is approved in Canada and other high-income countries.

As a result of the experience gained with Cabenuva in recent clinical trials, the oral lead-in was shortened to just four weeks once the drug was approved.

Since Cabenuva is well tolerated and has not been associated with dangerous side effects, some scientists have questioned the need for the oral lead-in period. The manufacturer of Cabenuva, ViiV Healthcare, has embarked on clinical trials to explore the impact of bypassing the oral lead-in period entirely.

In an ongoing clinical trial called Flair, researchers sought adult volunteers who had never previously used HIV treatment (ART). They were given oral formulations of the combination of dolutegravir + abacavir + 3TC for 20 consecutive weeks. Participants who achieved a suppressed viral load (less than 50 copies/mL) were then randomly assigned to do one of the following:

- receive intramuscular injections of cabotegravir + rilpivirine once every four weeks
- continue to take the oral regimen

After 96 weeks, participants who were on oral therapy could either switch to injectable treatment or withdraw from the study.

People who chose to receive injectable therapy could then choose to do one of the following:

- have an oral lead-in with cabotegravir and rilpivirine pills (taken for four weeks)
- after discussion and agreement with a study physician, skip the oral lead-in and go directly to injection of intramuscular formulations of cabotegravir + rilpivirine every four weeks (researchers called this choice "direct-to-injection")

The vast majority of participants (92%; 232 out of 253 people) who had been taking oral ART for at least 96 weeks chose to subsequently initiate injectable therapy; the remainder left the study.

Among these people who chose injectable therapy, their distribution was as follows:

- 52% (121 people) chose a four-week oral lead-in
- 48% (111 people) decided to initiate direct-to-injection long-acting formulations

Researchers found that Cabenuva was safe whether or not an oral lead-in was used.

Assessment of blood samples of people who were using injectable treatment found that levels of cabotegravir and rilpivirine were similar whether or not participants had previously used an oral lead-in.

These favourable results have encouraged regulatory authorities in the European Union to make the oral lead-in (with pills of cabotegravir + rilpivirine) optional. What that means is that initiating injectable therapy is still restricted to people who have first suppressed HIV on an oral regimen. However, in the EU, the transition from a regimen of pills containing cabotegravir and rilpivirine before starting injectable therapy with long-acting formulations of these drugs is now optional.

Important to note

It is important for readers to note that people in Flair were all initially on a regimen of pills containing the drug dolutegravir (in combination with other oral drugs). Dolutegravir is similar in shape (or structure) to cabotegravir, so it is not surprising that cabotegravir was well tolerated. It is not clear if the results from Flair would be similar if people on different oral regimens subsequently initiated direct-to-injection with long-acting formulations of cabotegravir and rilpivirine. That is, would people on these other oral regimens also have minimal side effects? Clinical trials are planned or underway to explore this issue and confirm the safety of skipping the oral lead-in with more participants.

Study details

Flair took place in the following countries:

- Canada
- France
- Germany
- Italy
- Japan
- The Netherlands
- Russia
- South Africa
- Spain
- U.K.
- U.S.

The average profile of participants in Flair was as follows:

- age – 37 years; 14% were 50 and older
- 82% men, 12% women
- major ethno-racial groups: White – 74%; Black – 19%
- CD4+ count – 735 cells/mm^3

Results

As mentioned earlier, people who took oral treatment for at least 96 weeks subsequently chose one of the following courses of action:

- 52% (121 people) chose a four-week oral lead-in followed by injections of long-acting formulations
- 48% (111 people) decided to initiate direct-to-injection long-acting formulations

The proportions of participants with an undetectable viral load 24 weeks after entering one of the above dose regimens was as follows:

- oral lead-in followed by injectable therapy – 93%
- direct-to-injection – 99%

The reason that the proportion of people with viral suppression was lower in the above group with the oral lead-in was that more people left that group (and the study), so there were fewer people with data. The reasons that they left were as follows:

- injection site pain – one person
- excessive weight gain (8 kg) – one person

These reasons were related to the study medicine. However, five other people from the oral lead-in group also left the group and study due to other reasons, including:

- finding travel to the study clinic burdensome
- having to take a medicine that was not allowed in the study
- moving residence
- finding the study procedures difficult
- pregnancy

Among people who began long-acting treatment earlier in the course of the study, 80% had an undetectable viral load after 126 weeks of Cabenuva. Four people out of 283 (2%) eventually

had virological failure, all before week 48 of injectable treatment. Eight other people left the study because of "lack of efficacy," but this was not further explained and is considered different from virological failure.

The reason that other people in this group did not have a detectable viral load (or any blood samples for analysis at the end of the study) was that there was no data. The reasons for the lack of data were related to premature departure from the study, mostly due to adverse events (some of which are explained later in this report) and some for reasons that were not specified and were listed as "other reasons."

One person developed virological failure after week 48. He had HIV that was classified as subtype A6. This subtype is relatively common in countries of the former Soviet Union. As explained earlier in this issue of *TreatmentUpdate*, subtype A6 is associated with an increased risk of virological failure in people on Cabenuva. This person did not have resistance to cabotegravir or rilpivirine at the start of the study. At the time Cabenuva began to fail, his viral load was 887 copies/mL, and a subsequent blood test shortly after found that it went up to 1,112 copies/mL. Analysis of his blood samples when his viral load was detectable found that his HIV had acquired a very high level of resistance to cabotegravir and rilpivirine. This resistance occurred despite the man having relatively high concentrations of both drugs in his blood.

People who developed resistance to treatment while in the study were successfully transitioned to other (oral) regimens and subsequently were able to resuppress HIV.

Adverse events

Common adverse events while on injectable therapy included the following:

- injection site pain – as in previous studies of Cabenuva, this pain was temporary, generally mild to moderate and resolved in the vast majority of people within a few days

Injection site reactions were more common among people who engaged in direct-to-injection. For instance, after the first injection, rates of injection site reactions were distributed as follows:

- direct-to-injection – 71%
- oral lead in – 56%

The discomfort/pain/swelling associated with injection site reactions were similar whether or not people had an oral lead-in.

Over the course of the study, participants reported reduced intensity of injection site reactions (mostly reduced pain) regardless of whether or not they had an oral lead-in.

Other adverse events

Over the course of the study, four people had elevated liver enzyme levels, three of which resolved without intervention. In the fourth person, study researchers decided to temporarily stop administering Cabenuva while his condition was investigated. Subsequently he was diagnosed with liver inflammation caused by syphilis. Treatment with penicillin resulted in his liver enzyme levels returning to normal and he then restarted Cabenuva.

Among the direct-to-injection group, only one of the participants prematurely left the study because of a serious adverse event. He developed a case of Hodgkin lymphoma. The study physician could not rule out that Cabenuva might have been related to this. The study sponsors—the pharmaceutical companies ViiV Healthcare and Janssen—dispute this. Readers should note that since 1996 when potent combination HIV treatment became available, there has never been any evidence that ART somehow causes cancer. Previous research has linked HIV itself (along with the herpes virus Epstein-Barr virus) to an increased risk for lymphomas.

No one developed a hypersensitivity reaction to the study medicines.

For the future

Some patients and their doctors may find that skipping the oral lead-in period is convenient. Other patients and their doctors may find a four-

week oral lead-in to be a reassuring step prior to initiating injectable treatment.

In the European Union, the oral lead-in is optional. Regulatory agencies in North America are reviewing data from Flair about the adverse events that occur with and without an oral lead-in and it is possible that they too will make the oral lead-in optional for some patients.

Other clinical trials assessing the impact of skipping the oral lead-in for Cabenuva are underway. Hopefully, future trials will have participants that are more diverse.

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ISSN 1181-7186 (print)
ISSN 1927-8918 (online)

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

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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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