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Contents

I ANTI-HIV AGENTS

A. The evolution of integrase inhibitors

The first integrase inhibitor, raltegravir (Isentress), was licensed in Canada and other high-income countries a decade ago. In subsequent years, two other integrase inhibitors were approved:

- dolutegravir (Tivicay), and together with abacavir and 3TC in a pill called Triumeq
- elvitegravir in a pill called Stribild with cobicistat, tenofovir TF and FTC (emtricitabine)
- elvitegravir in a pill called Genvoya with cobicistat, TAF (tenofovir alafenamide) and FTC

In 2017 a new formulation of raltegravir, called Isentress HD, was approved in high-income countries. This formulation is available in Canada and is taken once daily.

Integrase inhibitors have earned a privileged place in many treatment guidelines because of their potency against HIV. When used as part of the initial therapy of HIV, integrase inhibitor regimens usually lower the amount of HIV in the blood (viral load) quickly compared to other regimens.

Regimens containing elvitegravir need a boosting agent called cobicistat. This latter drug raises and maintains the level of elvitegravir in the blood so that once-daily dosing is possible. However, a disadvantage of cobicistat is that it can interact with many other medicines, raising or lowering their levels in the blood, in a manner similar to an older boosting agent, ritonavir.

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Probably by mid-2018, a new integrase inhibitor called bictegravir will be approved in Canada. Bictegravir will be co-formulated (put into one pill) with two other anti-HIV drugs—TAF and FTC. This pill can be taken once daily. Unlike elvitegravir-containing regimens, bictegravir will not require boosting.

Later in this issue of *TreatmentUpdate* we will have reports from two pivotal clinical trials about the effectiveness and safety of bictegravir + TAF + FTC when compared to dolutegravir-containing regimens. In general, both regimens were effective and tolerated and had low rates of mental health and sleep issues. Such low rates are normal in randomized clinical trials of anti-HIV drugs. These trials enroll people who are relatively well. After licensure, it is important that large studies be conducted to monitor people in the community who use the approved medicines to assess if rates of side effects are different from those in randomized clinical trials. Real-world studies may also detect rare and, in some cases, long-term side effects that were not seen earlier.

A major drawback of the initial clinical trials for newer integrase inhibitors is that too few women were enrolled. As a result, pharmaceutical companies have been required to conduct studies with HIV-positive women. Such studies have been done with dolutegravir and are underway with bictegravir.

Back to bictegravir

A pill containing bictegravir + TAF + FTC will have the following advantages:

- Prior to initiating therapy, testing for possible hypersensitivity to abacavir will not be required (as it is with abacavir-containing regimens such as Triumeq, which also contains the integrase inhibitor dolutegravir).
- The combination of TAF + FTC will have potent activity against hepatitis B virus, which is useful for people co-infected with this virus.

Commenting on the pivotal bictegravir trials, doctors in London, England, and Johannesburg, South Africa, made the following points:

Rifampin (used in the treatment of tuberculosis)

> "Although dolutegravir can be co-administered with the strong [enzyme] inducer rifampin at a doubled dose of 50 mg twice daily, bictegravir dose adjustment data are unavailable and non-co-formulated bictegravir to promote such dose adjustments might not be available."

Pregnancy

> "Although there are accumulating data regarding safety in pregnancy for dolutegravir, both bictegravir and TAF need to show safety in pregnant women and their infants."

In treatment-experienced people

The first phase III clinical trials with bictegravir have focused on people new to treatment. However, clinical trials with treatment-experienced HIV-positive people are underway and results from this population will be released over the coming months.

REFERENCES:

1. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017; *in press*.

2. Margolis DA, Gonzales-Garcia J, Stellbrink H-J. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomized, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017 Sep 23;390(10101):1499-1510.

B. Bictegravir vs. dolutegravir

Bictegravir is an emerging integrase inhibitor that is co-formulated (put into one pill) with two other anti-HIV drugs—TAF (tenofovir alafenamide) and FTC.

This co-formulated drug is undergoing clinical trials in people with HIV. The first phase III trials are reported in this issue of *TreatmentUpdate*. In this report we will focus on one of those trials that compared the following regimens:

- bictegravir + TAF + FTC + placebo
- dolutegravir + TAF + FTC + placebo

In this clinical trial, both regimens were highly effective and tolerated over the course of one year. Side effects were less common among bictegravir users (18%) compared to dolutegravir users (26%).

Study details

Researchers in the following countries enrolled more than 600 HIV-positive people for this study:

- Canada
- Australia
- Belgium
- Dominican Republic
- France
- Germany
- Italy
- Spain
- UK
- United States

Researchers analysed data collected from 320 people who received the bictegravir regimen and 325 people who received the dolutegravir regimen.

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

- 88% men, 12% women
- 60% of participants were in the U.S.
- nearly 90% of participants had no symptoms of HIV infection
- viral load – 28,000 copies/mL
- 15% of participants had a viral load greater than 100,000 copies/mL
- CD4+ count – 440 cells/mm^3
- hepatitis B virus co-infection – 3%
- hepatitis C virus co-infection – 2%

Results

After one year the results suggested that, overall, both study regimens had similar effects. Here are the proportions of participants on each regimen with a viral load less than 50 copies/mL after one year:

- bictegravir regimen – 89%
- dolutegravir regimen – 93%

This difference was not statistically significant.

When researchers tested blood samples with a viral load assay that had a lower limit of 20 copies/mL, here is the distribution of the proportions of participants with a suppressed viral load:

- bictegravir regimen – 82%
- dolutegravir regimen – 87%

This difference was not statistically significant.

The lower overall levels of virological suppression seen with bictegravir occurred because more participants (a total of 11) who took this drug left the study prematurely for a variety of reasons (such as losing touch with the clinic, moving, withdrawing consent for unspecified reasons, and so on). Among people who were taking the dolutegravir regimen, three people left prematurely for similar reasons. (The virological data from such people are not used in the final analysis of any drug's efficacy.)

The following factors did not affect a person's response to the study regimens:

- age
- race/ethnicity
- viral load
- CD4+ count
- region/country

The fourth week

When used as part of combination therapy (ART), integrase inhibitors can quickly lower viral load in the blood. At the fourth week of the study the proportions of participants with a viral load less than 50 copies/mL were as follows:

- bictegravir regimen – 75%
- dolutegravir regimen – 80%

This difference was not statistically significant.

Changes in CD4+ cell counts

After one year, CD4+ cell counts increased by the following average amounts in participants:

- bictegravir regimen – 180 cells/mm^3
- dolutegravir regimen – 201 cells/mm^3

This difference was not statistically significant.

Adverse events

The term *adverse events* is used to describe a range of unfortunate events that can occur to participants during a clinical trial. Such events may be driven by the underlying disease process, the study drugs or circumstances that have nothing to do with the study (such as accidents).

Adverse events that were bothersome or serious enough to cause people to prematurely leave the study were distributed as follows:

- bictegravir regimen – five people left prematurely
- dolutegravir regimen – one person left prematurely

People who were taking bictegravir prematurely left the study for the following reasons:

- heart stopped beating (cardiac arrest) – one person
- paranoia – one person
- chest pain – one person
- enlarged abdomen – one person
- a combination of sleeping problems, headache, depression and gastrointestinal problems – one person

An investigation concluded that all of these adverse events, except for cardiac arrest and paranoia, were related to the study drugs.

The person who was taking dolutegravir and who left the study prematurely did so because of red, itchy skin. This was not considered related to exposure to the study drugs.

Common side effects

Most side effects reported were generally of mild-to-moderate intensity. Below is the distribution of common side effects:

Headache
- bictegravir regimen – 13%
- dolutegravir regimen – 12%

Diarrhea
- bictegravir regimen – 12%
- dolutegravir regimen – 12%

Nausea
- bictegravir regimen – 8%
- dolutegravir regimen – 9%

Lack of energy
- bictegravir regimen – 6%
- dolutegravir regimen – 8%

Difficulty falling asleep and/or staying asleep
- bictegravir regimen – 5%
- dolutegravir regimen – 4%

Serious symptoms of side effects were rare, occurring in less than 2% of participants on either regimen.

Deaths

Three people died while in the study, distributed as follows:

- bictegravir regimen – one person developed an infected and inflamed appendix and subsequently the infection became overwhelming and his heart stopped beating
- dolutegravir regimen – one death was from an unknown cause and the other from a suspected blood clot in the lung

It seems unlikely that the study medicines caused these deaths.

Pregnancy

Three women on each study regimen became pregnant during the study. In all cases the women's doctors changed their regimens to other combinations. In four cases the women decided to carry the fetus to term and no deformities were found in the infants.

Note that due to the small proportion of women present in this study no firm conclusions about the safety of bictegravir can be drawn (a clinical trial of dolutegravir regimens in women has already been conducted). A clinical trial of a bictegravir regimen is underway among HIV-positive women.

Lab test results

Several abnormal laboratory test results occurred in the following proportions of participants on each regimen:

- bictegravir regimen – 17%
- dolutegravir regimen – 13%

No trend with these abnormal results was seen in participants. However, researchers noted that participants who took bictegravir and who had higher-than-normal levels of liver enzymes (AST,

ALT) generally had a number of health issues that affected the liver when they entered the study:

- elevated levels of AST and ALT
- infection with hepatitis A virus
- excessive drinking of alcohol

People who take bictegravir or dolutegravir tend to develop a small but elevated level of the waste product creatinine in their blood. This also occurs if people, regardless of their HIV infection status, take the anti-ulcer medicine cimetidine (Tagamet). The modest elevation of creatinine that occurs during the use of bictegravir or dolutegravir is not considered harmful by researchers and normalizes when these drugs are discontinued.

There were no cases of kidney injury during the study.

No significant changes in levels of cholesterol and triglycerides in the blood were detected.

Bear in mind

1. Regimens that contained bictegravir or dolutegravir were generally well tolerated and symptoms of serious side effects were rare, occurring in less than 2% of participants.
2. Both bictegravir and dolutegravir have powerful anti-HIV activity.
3. The study team stated that a regimen of bictegravir + TAF + FTC in a single pill "could be a simple, effective and well-tolerated initial treatment for HIV."
4. A relatively small proportion of participants had severely weakened immune systems (12%) and/or high viral loads (19%) prior to entering the study. Ten years ago, these proportions probably would have been greater. What changed during the intervening decade is that data increasingly suggested that starting ART earlier in the course of HIV disease results in better health. Also during that period, treatments became easier to tolerate. So the small proportion of people with severely weakened immune systems and/or high viral loads seen in the present study is likely to be reflected in many clinics in high-income countries.

Availability

A single pill containing bictegravir + TAF + FTC will likely first be approved in the U.S. later in 2017 and then by mid-2018 in the European Union and Canada. The manufacturer of these drugs, Gilead Sciences, seems unlikely to make a pill containing bictegravir alone.

REFERENCE:

Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017; *in press*.

C. Bictegravir + TAF + FTC vs. Triumeq

Triumeq is a complete HIV treatment in one pill, which contains the following medicines:

- dolutegravir (Tivicay) + abacavir + 3TC

Bictegravir is an emerging integrase inhibitor that will likely be licensed in Canada by mid-2018.

In a randomized, placebo-controlled clinical trial with about 600 HIV-positive people who had not previously taken HIV treatment, researchers randomly assigned participants to receive one of the following regimens:

- bictegravir + TAF (tenofovir alafenamide) + FTC
- Triumeq

After one year, researchers found that both regimens were highly effective at suppressing HIV and helping to raise CD4+ cell counts. The proportions of participants who experienced side effects were similar with both regimens. However, nausea was more common among participants who took Triumeq (17%) compared to participants who took the bictegravir regimen (5%). The researchers say that this difference was probably due to the presence of abacavir in Triumeq.

Study details

Researchers enrolled participants from the following countries:

- Canada
- Dominican Republic
- France
- Germany
- Italy
- Spain
- UK
- United States

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

- age – 32 years
- 91% men, 9% women
- 91% had no symptoms of HIV infection
- HIV viral load – 30,000 copies/mL
- CD4+ count – 450 cells/mm^3
- estimated glomerular filtration rate (eGFR – an assessment of kidney health) – 125 mL/min

This study is expected to last for up to three years; here we present results from the first year on 314 participants on a bictegravir regimen and 315 on a dolutegravir regimen.

Results—Changes in viral load and CD4+ cell counts

After one year, the proportions of participants with a viral load less than 50 copies/mL were distributed as follows:

- bictegravir regimen – 92%
- dolutegravir regimen – 93%

This difference was not statistically significant and therefore the bictegravir regimen could be considered to be roughly equivalent, or non-inferior, to the dolutegravir regimen.

When researchers analysed blood samples with a more sensitive viral load assay with a lower limit of 20 copies/mL, the proportions of participants with a viral load less than 20 copies/mL were as follows:

- bictegravir regimen – 87.6%
- dolutegravir regimen – 86.3%

This difference between the two regimens was not statistically significant.

CD4+ cell counts increased by about 230 cells/mm^3 over the course of the study and were similar between the two regimens.

Adverse events

The term *adverse events* is used to describe a range of unfortunate events that can occur to participants during a clinical trial. Such events may be driven by the underlying disease process, the study drugs or circumstances that have nothing to do with the study (such as accidents).

In this study, researchers stated that, overall, "both [regimens] were well tolerated with most adverse events reported as mild or moderate in severity."

Adverse effects that were bothersome or serious enough to cause people to leave the study prematurely occurred in four people (1%), all of whom were taking the dolutegravir regimen. These side effects were distributed as follows:

- nausea and rash – one person
- less-than-normal levels of platelets in the blood – one person
- inflammation of the pancreas gland and excess fat in stools – one person
- depression – one person

According to the researchers, in general, "central nervous system and psychiatric adverse events were evenly distributed between [regimens]." This point is important because there have been reports from individual physicians and observational studies that suggest that dolutegravir may be associated with the following side effects in some people (usually between 2% and 6%):

- difficulty falling asleep and/or staying asleep
- poor concentration
- irritability
- anxiety
- depression

That the rates of such problems are similar between bictegravir and dolutegravir should not be surprising, as bictegravir is structurally similar to dolutegravir.

As mentioned earlier in this issue of *TreatmentUpdate*, phase III clinical trials tend to enroll people who are relatively well and who are likely to stay on the study medications. However, once a drug is approved and begins to be widely used in the community by patients who have health issues (in addition to HIV infection), more side effects may be reported. A future issue of *TreatmentUpdate* will explore reports of possible side effects, particularly mental health issues, associated with integrase inhibitors.

No one died during this study.

Rates of common side effects (graded as mild or moderate) were as follows:

Nausea
- bictegravir regimen – 10%
- dolutegravir regimen – 23%

Headache
- bictegravir regimen – 11%
- dolutegravir regimen – 24%

Diarrhea
- bictegravir regimen – 13%
- dolutegravir regimen – 13%

Difficulty falling asleep and/or staying asleep
- bictegravir regimen – 4%
- dolutegravir regimen – 6%

Unexpected tiredness
- bictegravir regimen – 6%
- dolutegravir regimen – 9%

Vomiting
- bictegravir regimen – 4%
- dolutegravir regimen – 5%

Bone mineral density (BMD)

People with HIV infection are at increased risk for thinner-than-normal bones (reduced BMD). Furthermore, upon initiation of combination therapy (ART), BMD tends to decrease by about 2% to 4% and then stabilize after a year or two. The reasons for this are not yet clear.

In the present study BMD decreased by an average of 1% in participants after one year. There were no significant differences in the change in BMD between the two regimens.

Kidneys

No participants developed serious kidney injury. Complex assessments of kidney health did not detect any subtle kidney injury, attesting to the safety of the study regimens.

Lipids—Cholesterol and triglycerides

There did not appear to be any clinically significant differences in lipid levels between the two regimens.

Bear in mind

According to the researchers, regimens based on bictegravir or dolutegravir have several advantages, including the following:

- When used with two nucleoside analogues they are generally effective at lowering viral load.
- They do not need a boosting agent such as cobicistat (found in Genvoya and Stribild) or ritonavir.
- They are available as a complete treatment in one pill.

As mentioned elsewhere in this issue of *TreatmentUpdate*, some researchers have noted that the combination of bictegravir + TAF + FTC offers the following advantages:

- It contains two anti-hepatitis B drugs (TAF and FTC) in one pill, which should be useful for people co-infected with HIV and hepatitis B virus.
- There is no need for pre-treatment testing for hypersensitivity (in the case of regimens containing abacavir, such as Triumeq, testing for hypersensitivity to abacavir must first be performed to assess the risk of this problem occurring).

For the future

- A single pill containing bictegravir + TAF + FTC should be approved in Canada in the summer of 2018.
- A clinical trial of bictegravir + TAF + FTC is underway in HIV-positive women.
- Results of bictegravir in treatment-experienced people should become available in the months ahead.

REFERENCE:

Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017; *in press*.

D. Long-acting drugs for HIV

Long-acting formulations of two anti-HIV drugs are being tested in clinical trials:

- cabotegravir – an experimental integrase inhibitor made available in oral and injectable formulations
- rilpivirine – the oral formulation of this non-nuke (NNRTI) has been approved for HIV treatment for many years but the long-acting formulation is experimental

In clinical trials these drugs have been given via intramuscular injection deep into the buttocks every four to eight weeks.

In a study called Latte-2, researchers tested long-acting (LA) regimens of cabotegravir and rilpivirine in participants who had not previously used HIV treatment. Participants were first given oral formulations of treatment for five months, and after this time, once their viral loads had become suppressed, they were randomly assigned to continue oral formulations or switch to one of two LA regimens. Researchers found that LA drugs were generally effective at continuing to keep HIV in the blood suppressed. Side effects of LA drugs—usually caused by swelling and discomfort at the injection site—were mostly mild and temporary. Severe side effects with LA formulations were not common.

Phase III clinical trials, the final stage of drug development before licensure, are underway with LA formulations of cabotegravir and rilpivirine. One trial called Flair has been used to initiate ART in people and the other trial called Atlas is for treatment-experienced people.

Study details

The design of Latte-2 involved participants initiating ART with the following medicines taken orally once daily:

- cabotegravir – 30 mg
- abacavir – 600 mg
- 3TC – 300 mg

After 20 consecutive weeks of this combination, participants who had a viral load less than 50 copies/mL were randomly assigned to one of the following regimens:

- continued oral formulation
- LA cabotegravir 400 mg + LA rilpivirine 600 mg via two intramuscular injections every four weeks (the four-week regimen)
- LA cabotegravir 600 mg + LA rilpivirine 900 mg via two intramuscular injections every eight weeks (the eight-week regimen)

In the four-week regimen, two injections containing 2 mL of fluid each were injected. In the eight-week regimen, two injections containing 3 mL of fluid each were injected.

Participants were recruited from the following countries:

- Canada
- France
- Germany
- Spain
- United States

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

- age – mid-30s
- 92% men, 8% women
- viral load – 25,000 copies/mL
- 18% of participants had a viral load greater than 100,000 copies/mL
- CD4+ count – 490 cells/mm^3
- 3% of participants were co-infected with hepatitis C virus

A total of 309 participants entered the study; 286 participants had a suppressed viral load at week 20.

Results

After 20 consecutive weeks of oral formulations, 286 participants had a viral load less than 50 copies/mL and were randomly assigned to continue oral or LA regimens in a 1:2:2 ratio, as follows:

- continued oral formulations – 56 people
- injections of LA formulations every four weeks – 115 people
- injections of LA formulations every eight weeks – 115 people

Results—Week 32
At the 32nd week of the study, the proportions of participants whose viral loads were less than 50 copies/mL were as follows:

- continued oral formulations – 91%
- injections of LA formulations every four weeks – 94%
- injections of LA formulations every eight weeks – 95%

These results suggest that both of the LA regimens have similar effectiveness to the oral regimen.

Results—Week 48
Almost a year after the start of the study, the following proportions of participants had a viral load less than 50 copies/mL:

- continued oral formulations – 89%
- injections of LA formulations every four weeks – 91%
- injections of LA formulations every eight weeks – 92%

Results—Week 96
Almost two years after entering the study, the proportions of participants with a viral load less than 50 copies/mL were as follows:

- continued oral formulations – 84%
- injections of LA formulations every four weeks – 87%
- injections of LA formulations every eight weeks – 94%

Focus on virology

At week 48 there were a total of 10 participants who did not have a suppressed viral load, distributed as follows:

- continued oral formulations – one person
- injections of LA formulations every four weeks – one person
- injections of LA formulations every eight weeks – eight people

Five of the eight people taking LA formulations had a detectable viral load—between 50 and 200 copies/mL. Four of these five continued in the study and eventually achieved a viral load less than 50 copies/mL.

Researchers in Australia who were unaffiliated with the study suggested that in some cases of initially unsuppressed viral loads in people on the eight-week regimen, perhaps temporary co-infections (colds, the flu and so on) could have caused their immune systems to become temporarily activated. This would have caused their viral loads to rise above the 50-copy mark. Once these infections had resolved, the viral loads would have then fallen back below the 50-copy mark.

As none of the participants in the four-week regimen had any virological failure or persistently detectable low viral loads, the developer of the LA formulations, Viiv Healthcare, has selected a dosing regimen that is injected every four weeks for phase III clinical trials.

Adverse events

The term *adverse events* is used to describe a range of unfortunate events that can occur to participants during a clinical trial. Such events may be driven by the underlying disease process, the study drugs or circumstances that have nothing to do with the study (such as accidents).

Receiving deep intramuscular injections with 2 or 3 mL of fluid is at best discomforting and likely painful. It is therefore not surprising that in Latte-2 the most commonly reported side effect in

participants who received intramuscular injections was pain at the injection site:

- injections of LA formulations every four weeks – 97% reported pain
- injections of LA formulations every eight weeks – 96% reported pain

According to researchers, most (84%) participants who reported pain at the injection site described it as mild, while the remaining 16% described it as moderate. Pain at the injection site tended to fade within three days after injection.

Only two participants quit the study prematurely because of reactions at the injection site.

Other side effects were distributed as follows:

Diarrhea
- oral formulation – 20%
- injections of LA formulations every four weeks – 28%
- injections of LA formulations every eight weeks – 23%

Headache
- oral formulation – 20%
- injections of LA formulations every four weeks – 23%
- injections of LA formulations every eight weeks – 25%

Only one serious adverse event was linked to exposure to the study drugs: migraine during the initial oral phase of the study.

Deaths

Two people died in the study.

The first death occurred during the initial part of the study when all participants received oral formulations of medicines. This participant died in a vehicle accident. There was no evidence that the study drug played a role in the accident.

The second death occurred in a participant who was using the LA regimen injected every four weeks. He had been in the study for one year and developed a seizure. Researchers stated that this was likely linked to "evidence of recreational drug use."

Abnormal laboratory test results

Severe or more seriously abnormal lab test results occurred in 32 participants, distributed as follows:

- oral formulation – 21%
- injections of LA formulations every four weeks – 28%
- injections of LA formulations every eight weeks – 18%

Severe or more serious elevations in blood levels of the liver enzyme ALT were distributed as follows:

- oral formulation – three people
- injections of LA formulations every four weeks – four people
- injections of LA formulations every eight weeks – four people

According to the researchers, this problem was "largely attributable" to recent infection with hepatitis C virus (which infects the liver and causes inflammation in this organ).

Liver injury occurred in two participants who were both taking oral cabotegravir (with abacavir and 3TC). One case occurred during the first 20 weeks of the study and another later on. Both participants were symptom-free and this problem was only detected via lab testing of blood samples. Once these participants stopped taking the study medicines, their liver enzyme levels returned to normal.

Satisfaction

Surveys revealed that 97% of participants expressed high levels of satisfaction with their regimens, whether they were oral or injectable. Furthermore, more than 99% of participants taking the injectable regimens stated that they would like the opportunity to continue to do so if offered. Among participants taking the oral regimen, 78% said that they would opt to continue to take oral formulations of medicines if offered the choice.

The extremely high issue of satisfaction with injectable formulations likely arises because of what other researchers call "selection bias." That is, the study recruited people who hoped to receive injections of LA formulations. Such people, for the most part, would want to continue to receive injections of LA formulations and would

not mind being injected or the temporary pain and discomfort that accompany intramuscular injections. In the everyday world of an HIV clinic outside of a clinical trial, it is not yet clear what proportion of people would be willing to accept an offer of LA therapy (should it be approved).

Bear in mind

Latte-2 is the first study to analyse the long-term safety and effectiveness of two LA regimens in HIV-positive people.

Both LA regimens were able to maintain a suppressed viral load in a similar proportion of participants as the oral regimen.

There were only two cases of virological failure (viral loads that were persistently greater than 200 copies/mL) among the 230 participants who received LA regimens.

Injection site reactions (pain) were common, but these were usually mild to moderate and generally faded after a few days.

REFERENCE:

Margolis DA, Gonzales-Garcia J, Stellbrink H-J. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomized, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017 Sep 23; 390(10101):1499-1510.

E. What's next for long-acting HIV drugs?

Two phase III trials are underway with long-acting (LA) formulations of HIV drugs. These trials will explore the safety and effectiveness of LA formulations in people new to HIV treatment (Flair) and in people who are treatment experienced (Atlas). The interim results from these two pivotal studies should be available in the latter half of 2018.

If the results from Flair and Atlas are favourable, the manufacturer of the LA drugs, Viiv Healthcare, will submit a dossier of the data to regulatory authorities. Approval should occur a year later, perhaps in the fall of 2019.

The studies we have reported on have tested LA formulations of HIV drugs as treatment. There are other studies underway in which LA cabotegravir is being tested as a form of HIV prevention. Drugs used for this purpose are called pre-exposure prophylaxis (PrEP). Results from these studies should become available in 2019.

Unresolved issues

Commenting on Latte-2, Australian researchers have said that injectable ART "might be attractive for some or many people living with HIV." However, they also underscore that "there will inevitably be a trade-off between the convenience of not having to adhere to oral therapy and the inconvenience and discomfort associated with injectable LA ART."

There are other issues associated with LA therapies that will affect the deployment of these medicines. For instance, the Australian researchers noted that "healthcare systems are generally not configured to facilitate regular, recurrent injections in a timely way to people who are well. Changing this will take innovation, political will and time."

Other pharmaceutical companies are closely watching Viiv's foray into LA formulations. If Viiv's efforts are financially successful, then it is possible that one or more companies may enter the field of LA therapy for HIV.

Resource

Long-acting therapies—safety and other issues to consider – *TreatmentUpdate* 214

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Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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

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What CATIE Does

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

For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

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

CATIE Publications

TreatmentUpdate
CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to *TreatmentUpdate* and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

CATIE News
CATIE's bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

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

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

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

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