

From *TreatmentUpdate* 222

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/mm³
- 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.

—Sean R. Hosein

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.

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