Elvitegravir in treatment-experienced people

Elvitegravir is an emerging integrase inhibitor. When elvitegravir is taken with a low dose of the drug ritonavir (Norvir), the concentration of elvitegravir in the blood rises and remains elevated for about a day. The manufacturer of elvitegravir, Gilead Sciences, is also developing another pharmacokinetic (PK) booster called cobicistat, which will be co-formulated with elvitegravir in the future.

Presently, raltegravir (Isentress) is the only integrase inhibitor approved by regulatory authorities. Raltegravir is active against strains of HIV that are resistant to several classes of anti-HIV drugs, such as:

- nukes (nucleoside analogues)
- non-nukes (NNRTIs)
- protease inhibitors

Elvitegravir is also effective against such drug-resistant strains of HIV. In a Phase II study that ran for 48 weeks, elvitegravir when taken as part of combination therapy was effective in significantly reducing viral load in treatment-experienced patients.

Researchers have also conducted a randomized placebo-controlled study comparing elvitegravir to raltegravir in treatment-experienced people. After one year, elvitegravir was found to be roughly equivalent to raltegravir in its effectiveness.

Study details

Clinics in Canada, Australia and the U.S. screened 1,335 HIV-positive volunteers to find potential participants for this clinical trial. Eligible volunteers were randomly assigned to one of the following study groups:

- elvitegravir 150 mg and ritonavir 100 mg, both drugs once daily + background regimen
- raltegravir 400 mg twice daily + background regimen

All participants had blood samples drawn so that their virus’ resistance to therapy could be analysed. Based on this testing, doctors selected a protease inhibitor that was “fully active” against their HIV. A third anti-HIV drug was also included. This third drug, which may or may not have had anti-HIV activity (depending on the person’s resistance profile), was one of the following:

- a nuke
- maraviroc (Celsentri)
- etravirine (Intelenec)

Overall, 351 volunteers were assigned to receive elvitegravir and 351 others to receive raltegravir.

All participants received placebos to help disguise who received which integrase inhibitor. Some placebos had to be taken twice daily.

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

- 82% men, 18% women
- age – 45 years
- hepatitis B virus co-infection – 4%
- hepatitis C virus (HCV) co-infection – 15%
- viral load – 24,000 copies/ml
26% of participants had a viral load greater than 100,000 copies/ml
36% of participants had been diagnosed with AIDS

Commonly used protease inhibitors were darunavir (Prezista), followed by lopinavir-ritonavir (Kaletra) and atazanavir (Reyataz). Less-commonly used protease inhibitors were fosamprenavir (Telzir) and tipranavir (Aptivus).

The study is scheduled to last for two years and results from the first year have been made available.

**Results—effectiveness**

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

- elvitegravir – 59%
- raltegravir – 58%

Changes in CD4+ cell counts after one year were as follows:

- elvitegravir – 119 more CD4+ cells
- raltegravir – 127 more CD4+ cells

As the differences in viral load and CD4+ count between regimens were minor, elvitegravir can be considered to be no worse than raltegravir (the statistical term for this is “non-inferior”).

Similar proportions of participants in each group were able to quickly suppress HIV. This effect is unique to integrase inhibitors.

**Effectiveness within sub-groups of people**

The data were also analysed according to the composition of different groups of participants. For instance, in some previous studies of other drugs, participants with high viral loads (more than 100,000 copies/ml) did not always respond as quickly and as well to therapy as people with lower viral loads.

Rates of virologic failure among people with high viral loads in this study were not significantly different between the study groups:

- elvitegravir – 27 of 90 participants
- raltegravir – 28 of 90 participants

The pattern of resistance mutations that developed among participants in this study suggests that, in general, HIV that is resistant to elvitegravir will likely also be resistant to raltegravir and vice versa.

Both integrase inhibitors worked well with the protease inhibitors used in this study.

**Complications and side effects**

Here are potential side effects that occurred that were at least moderate in intensity:

**Diarrhea**

- elvitegravir – 12%
- raltegravir – 7%

**Depression**

- elvitegravir – 5%
- raltegravir – 4%

**Bone and/or joint pain**

- elvitegravir – 4%
Although elvitegravir users experienced more diarrhea than raltegravir users, this decreased somewhat after the first month of use. No one left the study because of diarrhea.

Overall, 23% of participants taking elvitegravir and 20% taking raltegravir reported side effects. Serious side effects occurred in 1% of elvitegravir users and 2% of raltegravir users.

Two participants taking elvitegravir and eight taking raltegravir died during the study. However, given the causes of their death—complications of HCV co-infection, sudden heart failure, heroin overdose, car accidents and so on—it seems unlikely that either elvitegravir or raltegravir was the cause of their deaths.

Lab tests

In general, participants had similar changes in the level of lipids in blood tests. More participants taking raltegravir (5%) had elevated levels of liver enzymes (AST, ALT) in their blood than people who took elvitegravir (2%).

Adherence

Taking medicines every day, sometimes several times a day, is not normal human behaviour. Therefore, it should not be surprising that in many health conditions (type 2 diabetes, heart disease, higher-than-normal blood pressure, chronic bacterial infections), adherence—the ability of the affected person to take their medicines every day, exactly as prescribed by their doctors—is not always ideal. Among people with HIV, adherence is an issue because at the individual level poor adherence can affect a person’s health, increase the chances of HIV developing resistance to drugs and thereby reduce future treatment options. When problems occur with adherence among many people, such as those in a clinical trial, it could affect the results of the trial.

Overall apparent good adherence

There is no perfect and cheap method of assessing adherence; each method has its own weakness. In the present study, nurses assessed adherence by pill counts—counting the number of pills remaining in each bottle when participants returned them to the clinic for a refill. According to this method, researchers estimated that participants took about 95% of their pills. However, as previously mentioned, all assessments of adherence have drawbacks and in this study there were significant problems with relying on pill counts.

Blood tests uncover bad adherence

Indeed, analysis of blood samples from participants whose regimens failed found a surprising finding: Rates of resistance to integrase inhibitors were relatively low—27% among elvitegravir users and 21% among raltegravir users. For HIV to develop resistance to a drug a person has to be taking that drug (at least some of the time), otherwise there is nothing for HIV to resist. In particular, resistance develops when the concentration of a drug in the blood is not sufficient to suppress HIV. This is why taking anti-HIV drugs at the same time each day on a regular basis is best for preventing the development of drug-resistant virus.

Moreover, integrase inhibitors, although very powerful, are relatively easy for HIV to overcome under the right circumstances (low concentrations in the blood). Therefore, if participants were taking their integrase inhibitors intermittently, rates of integrase resistance should have been much greater than detected in the present study. For instance, in a previous trial of raltegravir called Benchmrk, conducted several years ago in treatment-experienced participants, when raltegravir-based regimens failed, rates of integrase resistance were about 68%.

The finding of low rates of integrase resistance in the present study among people whose regimens failed suggests that they were not taking either elvitegravir or raltegravir.

Future studies need more robust measures of adherence, as relying on pill counts alone can lead to the wrong conclusions.

A many-sided puzzle

Here is an unexpected finding from the present study: Generally, the more active drugs in a participant’s regimen,
the more likely they were to voluntarily leave the study. Conversely, in the present study, the fewer active drugs in a participant's regimen, the more likely they were to stay enrolled in the study and be adherent.

The first trend was unexpected because it had not been previously seen in trials in this century of potent drugs such as etravirine, maraviroc or raltegravir when tested with treatment-experienced volunteers.

The following participants with one active background drug (in addition to the integrase inhibitor and protease inhibitor assigned) achieved a viral load less than 50 copies/ml at week 48:

- elvitegravir + one active background drug – 78% had less than 50 copies/ml
- raltegravir + one active background drug – 68% had less than 50 copies/ml

The following participants with two active background drugs achieved a viral load less than 50 copies/ml at week 48:

- elvitegravir + two active background drugs – 59% had less than 50 copies/ml
- raltegravir + two active background drugs – 55% had less than 50 copies/ml

One possible explanation for the behaviour of participants in the present study was that for those with significant treatment options, the burden of being in a clinical trial and taking many pills as scheduled was too much and so they quit the study.

**Positioning elvitegravir**

Elvitegravir is potent and likely will have a future role in the treatment of HIV infection. However, the ideal patient for whom elvitegravir should be prescribed (once it is approved) is not yet clear because clinical trials of this drug have not been completed.

As mentioned earlier in this issue of *Treatment Update*, a pill nicknamed the quad and containing the following four drugs is being tested:

- elvitegravir + cobicistat + tenofovir + FTC

This pill is expected to have similar efficacy to other regimens, such as:

- Atripla (efavirenz + tenofovir + FTC)
- raltegravir + tenofovir + FTC

An advantage of the quad will be the simplification of once-daily dosing. A possible disadvantage may be any potential side effects associated with exposure to either elvitegravir or cobicistat, or both drugs. Cobicistat works by interfering with the activity of enzymes in the intestine and liver. Ordinarily these enzymes would break down elvitegravir. However, cobicistat impairs the activity of these enzymes so that elvitegravir levels remain high for prolonged periods. No one knows the safety of having the activity of these enzymes impaired for many years with cobicistat. However, ritonavir (Norvir) is another drug used to inhibit enzymes and has been used in this way since the late 1990s. Ritonavir as an inhibitor of enzymes seems to be generally safe for most HIV-positive people, though care must always be taken to monitor for interactions with other drugs. The use of ritonavir is also associated with diarrhea.

**Future studies**

Several clinical trials of Gilead’s anti-HIV drugs against other anti-HIV drugs may occur in the future, including these:

- GS-7340 vs. tenofovir
- switching from a ritonavir-boosted protease inhibitor to the quad
- quad vs. Atripla

GS-7340 is converted into tenofovir once it is inside the body. Researchers refer to drugs that are converted into another drug inside the body as pro-drugs. Preliminary results suggest that taking GS-7340 results in somewhat less tenofovir in the blood than taking tenofovir directly. This may mean that GS-7340 causes less kidney dysfunction than tenofovir while still retaining its anti-HIV activity. However, clinical trials will be needed to assess this. Presumably if GS-7340 is roughly equivalent to tenofovir in anti-HIV activity, Gilead plans to replace tenofovir
with GS-7340.

For information about clinical trials in Canada, visit the [Canadian HIV Trials Network](#).

— Sean R. Hosein

**REFERENCES:**


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