I. ANTI-HIV AGENTS

A. The rise of integrase inhibitors

Raltegravir (Isentress) was the first integrase inhibitor to be approved for the treatment of HIV infection. This drug helps to quickly suppress production of HIV and is generally well tolerated and has few significant interactions with other drugs. Raltegravir can be used by people who are new to anti-HIV therapy or by treatment-experienced people. One possible drawback of this drug is that it must be taken twice daily; a randomized clinical trial found that it was not as effective when taken once a day. An advantage of raltegravir is that it has been in use for several years and has a good track record of safety and efficacy.

Two integrase inhibitors under development for HIV treatment are as follows:

- dolutegravir (S/GSK 1349572)
- elvitegravir

Preliminary results suggest that both of these drugs are likely to be as powerful as raltegravir and, in general, also well tolerated. The newer integrase inhibitors may offer one advantage over raltegravir—they can be taken once daily.

Elvitegravir

In the case of elvitegravir, once-daily dosing is made possible with the use of another anti-HIV drug that raises and maintains the concentration of elvitegravir in the blood. Drugs that are used to raise the concentrations of another drug are called PK boosters (pharmacokinetic boosters). An example of a PK booster commonly used today is ritonavir (Norvir). A small dose of ritonavir is taken
to boost the concentration of commonly used HIV medicines such as these:

- atazanavir (Reyataz)
- darunavir (Prezista)
- lopinavir (in Kaletra)

Gilead Sciences, the developer of elvitegravir, is also testing a novel PK booster for use with elvitegravir called cobicistat (GS-9350). This will allow Gilead to put several more of its drugs into one pill, for example:

- elvitegravir + cobicistat + tenofovir + FTC

This particular combination has been nicknamed the quad by researchers.

**Dolutegravir**

Dolutegravir is being developed by ViiV Health Care together with GlaxoSmithKline. It is therefore likely to be co-formulated with other drugs made by these companies, such as Kivexa, a fixed-dose combination of the anti-HIV drugs 3TC + abacavir.

All drugs have side effects and as both dolutegravir and elvitegravir get tested in larger numbers of people, doctors will have a better idea of their safety and effectiveness.

In this issue of *Treatment Update*, we feature some clinical trial results available for dolutegravir and elvitegravir as well as long-term data on raltegravir.

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**B. 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 (Intelence)

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

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%
- raltegravir – 2%

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 *TreatmentUpdate*, 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 at www.hivnet.ubc.ca/home/.

REFERENCES:

C. Interim results for dolutegravir
Dolutegravir (S/GSK 1349572) is an integrase inhibitor undergoing clinical trials. Previous clinical trials have revealed that a single 50 mg oral dose of dolutegravir results in a high concentration of this drug that remains elevated for about a day. This means that dolutegravir can be taken once daily and does not need a PK booster such as ritonavir (Norvir). In short-term clinical trials dolutegravir has potent anti-HIV activity.

A two-year study called Spring-1 is underway. In this study, researchers in Europe are comparing dolutegravir-based regimens to regimens based on efavirenz (Sustiva and in Atripla). Interim results from the first year of Spring-1 suggest that dolutegravir is well tolerated and that it has potent anti-HIV activity.

Study details
Spring-1 was designed to compare different doses of dolutegravir (10 mg, 25 mg or 50 mg) to efavirenz. Although all doses of dolutegravir had similar anti-HIV activity, the 50 mg dose has been selected for use in Phase III studies. We will therefore focus on the results from the 50 mg group. A total of 205 participants were randomly assigned to receive one of the dolutegravir regimens or efavirenz. Additionally, all participants received two nucleosides, namely one of the following combinations:

- Truvada (tenofovir + FTC)
- Kivexa (3TC + abacavir)

About 67% of participants received Truvada and 33% received Kivexa.

Those participants who were assigned to efavirenz received it as Atripla, a fixed-dose combination of efavirenz + tenofovir + FTC.

The average profile of participants who entered the study was as follows:

- 86% men, 14% women
- age – 37 years
- CD4+ count – 305 cells
- viral load – 32,000 copies/ml
- 21% of participants had a viral load greater than 100,000 copies/ml
- 9% of participants were co-infected with hepatitis C virus
Results
Among participants taking dolutegravir, viral load fell relatively quickly. By the 16th week of the study, most dolutegravir users had a viral load less than 50 copies/ml. This suppression of HIV generally continued throughout the first year of the study. Note that even before the 16th week of the study there were major changes in viral loads among dolutegravir users compared to efavirenz users, as follows:

Week 4
- dolutegravir – 66% of participants had a viral load less than 50 copies/ml
- efavirenz – 18% of participants had a viral load less than 50 copies/ml

Week 16
- dolutegravir – 90% of participants had a viral load less than 50 copies/ml
- efavirenz – 60% of participants had a viral load less than 50 copies/ml

Week 48
- dolutegravir – 90% of participants had a viral load less than 50 copies/ml
- efavirenz – 82% of participants had a viral load less than 50 copies/ml

Changes in CD4+ cell counts
On average, increases in CD4+ cell counts throughout the study were greater among dolutegravir users. By the 48th week of the study, the increases in CD4+ counts were distributed as follows:

- dolutegravir – 231 more cells
- efavirenz – 172 more cells

This difference was unexpected and needs to be confirmed in a larger study.

Complications and side effects
According to the study team, “most participants experienced at least one adverse event over the 48 weeks of the study.” Most side effects reported by dolutegravir users were “of mild (48%) or moderate (34%) intensity,” the researchers stated.

One participant who was receiving dolutegravir 50 mg/day left the study because of the development of lymphoma. Investigators judged that this was not related to exposure to dolutegravir. No participant left the study because of side effects due to dolutegravir. However, four people stopped taking efavirenz because of side effects, which were described by the study team as follows:

- drug intolerance
- drug hypersensitivity
- abnormal dreams
- attempted suicide

Investigators judged that the attempted case of suicide was related to the use of efavirenz.

Mild and temporary headache was more common among dolutegravir users than efavirenz users.

Lab tests
Serious cases of abnormal lab test results occurred among 12% of dolutegravir users and 14% of people who received efavirenz. Side effects with dolutegravir did not increase or intensify at the 50 mg or 25 mg dose compared to the 10 mg dose.

Focus on creatinine
Increased levels of creatinine in the blood can occur with heightened muscle breakdown, something that happens temporarily after exercise. However, elevated creatinine in the blood can occur when kidney dysfunction is present. This happens because the kidneys have become less efficient at removing waste products (such as creatinine) from the blood. This makes creatinine useful when performing assessments of kidney health.

During the first 16 weeks of the study, small increases in the concentration of creatinine in the blood occurred among dolutegravir users but not among participants who received efavirenz. This difference in creatinine concentrations between drugs was statistically significant.

The increase in creatinine concentration among dolutegravir users occurred regardless of exposure to tenofovir (which can sometimes cause kidney dysfunction). These increases were generally mild, except for one case where it was moderate in severity. Creatinine concentrations returned to their pre-study values over the first year of the study. This suggests that the problem is reversible despite continued exposure to dolutegravir.

Beyond creatinine
As mentioned earlier, elevated creatinine suggests kidney dysfunction. If kidney dysfunction becomes serious, the body can begin to lose protein and other nutrients in urine. So technicians tested participants’ urine samples for protein. Overall, about 14% of dolutegravir users and 2% of efavirenz
users had detectable protein in their urine. In most cases, this level of protein was minimal.

There were four dolutegravir users who had moderate or serious elevations in protein in their urine. However, it is not clear what caused this because they also had health conditions that could have played a role in either inciting or making this problem worse, as follows:

- chronic hepatitis C virus infection
- higher-than-normal blood pressure
- diabetes

None of the participants who received dolutegravir left the study because of kidney dysfunction.

In both Spring-1 and the larger Phase III trials planned for this drug, more sophisticated assessments of kidney dysfunction will be done. A previous short-term placebo-controlled study of dolutegravir in HIV-negative people did not reveal any kidney dysfunction.

**Bear in mind**

Dolutegravir is generally well tolerated and common side effects—nausea and headache—were mostly of mild intensity. The unexpected and apparent kidney dysfunction associated with dolutegravir seems to resolve without any changes to treatment. The drug can be taken with or without food. Dolutegravir’s potency and once-daily dosing suggest that it will likely be roughly equivalent to efavirenz-based regimens. This possibility is being explored in Phase III studies. The developer of dolutegravir, ViiV Health Care, is also testing a fixed-dose formulation of the following three drugs in one pill:

- dolutegravir + abacavir + 3TC

This co-formulation can be taken once daily.

Data from other studies suggest that dolutegravir does not have clinically significant interactions with atazanavir-ritonavir.

**Role in therapy**

The role of dolutegravir in the treatment of HIV-positive people is not clear because clinical trials have not been completed. However, it is likely that if everything goes as expected, dolutegravir will be useful for HIV-positive people starting their first regimen. In lab experiments with cells as well as a small exploratory study, dolutegravir has some activity against strains of HIV that are resistant to raltegravir. However, precisely which treatment-experienced patients will benefit from dolutegravir needs to be understood by conducting a well-designed clinical trial. Moreover, because of complex regimens taken by treatment-experienced people, many potential drug interactions need to be studied.

**REFERENCES:**


**D. Raltegravir—long-term results**

Knowledge about the long-term safety and effectiveness of potent combination HIV therapy (commonly called ART or HAART) is essential particularly if HIV-positive people are expected to take these medicines for the rest of their life. As mentioned earlier, raltegravir is the first integrase inhibitor approved for use by HIV-positive people. Long-term clinical trials with this drug continue. In one trial, researchers are comparing regimens based on raltegravir to those based on efavirenz (Sustiva and in Atripla). After four years of study, both combinations demonstrated good overall anti-HIV activity, although results appear to be better with raltegravir.
Study details
Researchers randomly assigned 281 HIV-positive volunteers to receive raltegravir and 281 others to receive efavirenz. No participant had previously taken anti-HIV drugs. All participants also received tenofovir + FTC (Truvada).

The average profile of participants when they enrolled in the study was as follows:
- 81% men, 19% women
- age – 37 years
- CD4+ cell count – 200 cells
- viral load – 100,000 copies/ml
- 6% were co-infected with hepatitis C virus (HCV)

Results—effectiveness
Here are the proportions of participants who had a viral load less than 50 copies/ml at different points in time:

Year 1
- raltegravir – 86%
- efavirenz – 82%

Year 2
- raltegravir – 81%
- efavirenz – 79%

Year 3
- raltegravir – 78%
- efavirenz – 70%

Year 4
- raltegravir – 76%
- efavirenz – 67%

These results suggest that raltegravir is no worse than efavirenz (the technical term for this is “non-inferior”) over the short term. Moreover, over the long term there is the possibility that raltegravir may be superior to efavirenz.

Among participants whose viral load at the start of the study was more than 100,000 copies/ml, here are the proportions who had a suppressed viral load four years later:
- raltegravir – 89%
- efavirenz – 89%

Changes in CD4+ cell counts
In general, raltegravir users had slightly greater CD4+ cell counts throughout the study. By the fourth year of the study, changes in CD4+ counts (compared to their values at the start of the study) were as follows:
- raltegravir – 361 more CD4+ cells
- efavirenz – 301 more CD4+ cells

Dropouts
Participants left the clinical trial for several reasons, distributed as follows:

Raltegravir
Overall, 20% of participants prematurely left the study.
- 5 people left because their regimen failed
- nurses could no longer contact 8 people
- 13 people left because of adverse events
- 32 people left for a variety of other reasons

Efavirenz
Overall, 30% of participants prematurely left the study.
- 8 people left because their regimen failed
- nurses could no longer contact 17 people
- 26 people left because of adverse events
- 34 people left for a variety of other reasons

Factors such as gender and race did not affect the results of the study.

Changes in lipids and blood sugar
In general, efavirenz users had statistically significant increases in the following assessments of lipids and glucose in the blood:
- total cholesterol
- good cholesterol (HDL-C)
- bad cholesterol (LDL-C)
- triglycerides
- glucose

However, a change in the ratio of total cholesterol to HDL-C among efavirenz users was not statistically significant. This ratio is useful in predicting the risk for cardiovascular disease.

Side effects and complications
The proportion of participants in each group who had side effects to the study drugs was as follows:
- raltegravir – 50%
- efavirenz – 80%

However, for most participants such side effects were not serious and could be tolerated.
The proportion of participants who left the study because of the intensity of side effects was not significantly different between study regimens. Here is the distribution of several side effects:

**Diarrhea**
- raltegravir – 5%
- efavirenz – 10%

**Nausea**
- raltegravir – 9%
- efavirenz – 10%

**Fatigue**
- raltegravir – 4%
- efavirenz – 9%

**Dizziness**
- raltegravir – 6%
- efavirenz – 35%

**Headache**
- raltegravir – 9%
- efavirenz – 14%

**Abnormal dreams**
- raltegravir – 7%
- efavirenz – 13%

**Nightmares**
- raltegravir – 3%
- efavirenz – 5%

**Difficulty falling asleep**
- raltegravir – 7%
- efavirenz – 8%

**Rash**
- raltegravir – 1%
- efavirenz – 8%

Over the course of the study, 10 participants died, distributed as follows:

- raltegravir – six deaths
- efavirenz – four deaths

The causes of death were as follows:

- cancer – lung cancer, Kaposi’s sarcoma (KS)
- drug overdose
- blood poisoning due to overwhelming bacterial infections
- bleeding in the brain

None of these deaths were caused by the study medication.

**REFERENCE:**
Disclaimer
Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.
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© CATIE, Vol. 24, No. 1
February 2012

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