Dolutegravir in treatment-experienced people who have not previously used an integrase inhibitor

Researchers in Australia, Latin America, North America, Europe, South Africa and Taiwan recruited 715 HIV-positive people for a double-blind, placebo-controlled study comparing regimens containing dolutegravir to regimens containing raltegravir. All participants had previously used anti-HIV therapy (commonly called ART or HAART) and nearly half of participants had a history of AIDS. Moreover, according to researchers, nearly half of participants had HIV that was resistant to “at least one drug in each of three or more [classes of drugs].”

After one year, researchers found that, in general, a dolutegravir-containing regimen was statistically superior to a raltegravir-containing regimen. This finding was driven by virologic results with fewer dolutegravir users developing treatment failure.

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

- gender – 32% women, 68% men
- age – 43 years
- 70% of participants had a viral load of 50,000 copies or less
- CD4+ count – 200 cells
- history of AIDS – 46%
- 79% had HIV that was significantly resistant to protease inhibitors or did not use the powerful protease inhibitor darunavir (Prezista)
- HIV resistant to three or more classes of drugs – nearly 50%
- duration of previous HIV therapy – 6 years
- co-infection with hepatitis B virus (HBV) – 5%
- co-infection with hepatitis C virus (HCV) – 11%
- co-infection with both HBV and HCV – 1%

Researchers referred to the drugs used in addition to dolutegravir or raltegravir as the “background” regimens. Drugs commonly used as background regimens in this study were as follows:

- darunavir (Prezista) + ritonavir (Norvir) + tenofovir (Viread)
- lopinavir-ritonavir (Kaletra) + tenofovir
- darunavir + ritonavir + etravirine (Intence)
- lopinavir-ritonavir
- atazanavir (Reyataz) + ritonavir + tenofovir
- darunavir + ritonavir + maraviroc (Celsentri)

Participants were randomly assigned to receive dolutegravir or raltegravir, so that their regimens were as follows:

- dolutegravir + background regimen + placebo
- raltegravir + background regimen + placebo

The double-blind, placebo-controlled part of the study lasted for 48 weeks. After this, participants who received dolutegravir and who completed the first 48 weeks of the study were told which drug they received. They were also offered continued treatment with dolutegravir and will be monitored every 12 weeks.

Results—Changes in viral load

In both study groups the proportion of participants with a viral load less than 50 copies/ml rose sharply during the
first four weeks, then less so over the subsequent four weeks. After the eighth week of the study, the proportion of participants with a low viral load (less than 50 copies/ml) remained relatively stable. The swiftness of the initial decline in viral load is something that is associated with integrase inhibitors.

The proportion of participants with a viral load less than 50 copies/ml at the 48th week of the study was distributed as follows:

- dolutegravir-based regimens – 71%
- raltegravir-based regimens – 64%

Researchers performed calculations and concluded that dolutegravir’s anti-HIV effect was “statistically superior” to that of raltegravir.

Why the difference?

Both dolutegravir and raltegravir are good drugs when used as part of combination therapy. However, the finding of statistical superiority favouring dolutegravir arose according to the researchers because virologic failure “occurred earlier and more frequently in [participants who took raltegravir (12%) compared to participants who took dolutegravir (6%)].”

Furthermore, 42% of 45 participants who took raltegravir and who developed virologic failure were termed “non-responders” by researchers. Essentially, non-responders did not have a major decrease in viral load and were not able to have their viral load fall below the 400-copies/ml mark. This contrasts with only 10% of 21 participants who took dolutegravir and who developed virologic failure and who were also virologic non-responders.

Darunavir plays a role

Darunavir is a powerful protease inhibitor. When taken with a small dose of ritonavir, darunavir can be taken once daily. When researchers analysed the data from Sailing among participants who took darunavir-ritonavir with dolutegravir or raltegravir, dolutegravir’s anti-HIV effect was found to be roughly equivalent in potency to raltegravir. However, bear in mind that the majority of participants did not use darunavir.

Complications and side effects

Rates of side effects were similar whether participants were taking dolutegravir or raltegravir. There are at least two possible reasons for this. First, as a class, integrase inhibitors are generally well tolerated. Secondly, the background regimens for nearly all participants were combinations of protease inhibitors. These drugs can cause a range of side effects, mostly affecting the gastrointestinal tract (nausea, vomiting, diarrhea). Such side effects may have dwarfed any, more minor side effects that may have occurred with exposure to integrase inhibitors. Researchers noted that, in general, side effects were mostly of mild-to-moderate intensity.

No deaths occurred among participants who received dolutegravir. Although there were three deaths among raltegravir users, investigators found that none were caused by raltegravir (two cases of unrelated cancer and one case of multi-organ failure).

Some commonly reported side effects appear below. Bear in mind that many participants were taking complex regimens, so it is difficult to connect exposure to the study drugs with specific side effects.

Diarrhea

- dolutegravir – 20%
- raltegravir – 18%

Lung/throat infections

- dolutegravir – 11%
- raltegravir – 8%

Headache
- dolutegravir – 9%
- raltegravir – 9%

Vomiting
- dolutegravir – 6%
- raltegravir – 6%

Fatigue
- dolutegravir – 4%
- raltegravir – 7%

Rash
- dolutegravir – 5%
- raltegravir – 5%

Joint pain
- dolutegravir – 3%
- raltegravir – 5%

**Severely abnormal lab test results**

**ALT (alanine aminotransferase – a liver enzyme)**
- Elevated levels of liver enzymes in the blood are suggestive of inflammation and injury to the liver. A similar proportion of participants receiving dolutegravir (3%) and raltegravir (2%) developed markedly increased levels of ALT (at least five times the upper limit of normal). These cases were reviewed by an independent panel of doctors and they judged the severe increases in liver enzymes to be related to HBV or HCV co-infection. Specifically, these rises in ALT levels likely occurred because upon entering the Sailing study and receiving a potent drug (integrase inhibitor), the immune systems of participants subsequently partially recovered. As a result, their immune systems were able to sense and attack liver cells infected with HBV or HCV. The ensuing attack by the immune system was responsible for the rise in liver enzyme levels. Another reason for elevated liver enzymes was the inadvertent removal of participants’ anti-HBV therapy just prior to entering the study, as physicians focused on optimizing their anti-HIV regimens.

**Cholesterol**
- dolutegravir – 2%
- raltegravir – 4%

**Creatinine**
- Measuring levels of the waste product creatinine in the blood is one way to assess general kidney health. Higher-than-normal levels of creatinine are suggestive of kidney injury. In the present study, severe or serious elevations of creatinine in the blood were rare—occurring in less than 1% of participants who received dolutegravir or raltegravir. Upon investigation, most of these cases were related to pre-existing conditions that can affect kidney health, such as higher-than-normal blood pressure, diabetes or infections (other than HIV).
- However, as a group, dolutegravir users had slightly elevated levels of creatinine in the blood that persisted throughout the study. This effect was apparently not harmful and has also been seen in clinical trials where participants received the drug cobicistat, one of the drugs found in the pill called Stribild. In the case of Stribild users, the elevation in creatinine levels is also apparently not harmful.

**Higher-than-normal blood sugar**
- dolutegravir – 1%
- raltegravir – 2%

**Elevated levels of creatine phosphokinase (CPK)**
- CPK is one of several enzymes (specifically called CPK-3) whose levels in the blood increase in cases of muscle
inflammation and injury. In rare cases, muscle inflammation can occur with raltegravir and likely other integrase inhibitors. In the present study, elevated levels of CPK were distributed as follows:

- dolutegravir – 2%
- raltegravir – 1%

For the future

Dolutegravir is expected to be approved as part of combination therapy for HIV-positive people in the U.S. by September and in Canada later this year.

A future issue of *TreatmentUpdate* will explore the issue of kidney health and dolutegravir.

—Sean R. Hosein

REFERENCE:

Disclaimer

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