Dolutegravir vs. darunavir for the initial treatment of HIV

Darunavir (sold as Prezista) belongs to the class of HIV drugs called protease inhibitors. Darunavir is taken with a small dose of another protease inhibitor, ritonavir (Norvir), as ritonavir boosts darunavir levels in the blood so that once-daily dosing is possible. Taken this way, darunavir is a potent anti-HIV drug and an important part of treatment regimens for many HIV-positive people.

Researchers in the U.S and Europe conducted a study called Flamingo to assess the impact of dolutegravir-based combination therapy in the initial treatment of HIV infection. The comparison treatment in Flamingo was darunavir + ritonavir + two nukes (nucleoside analogues).

Results after one year suggest that both dolutegravir- and darunavir-based regimens are effective and generally safe. Dolutegravir-based regimens were found to be statistically superior to darunavir-based regimens. The implications of this and other findings are discussed later in this report.

Study details

Researchers analysed health-related data collected from HIV-positive participants who had never previously been treated and randomly assigned them to receive one of the following regimens once daily:

- dolutegravir 50 mg + two nukes
- darunavir + ritonavir + two nukes

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

- gender – 85% men, 15% women
- age – 34 years
- CD4+ count – 400 cells
- HIV viral load – overall: 31,000 copies/ml; but 25% of participants had a viral load greater than 100,000 copies/ml
- hepatitis B virus co-infection – 3%
- hepatitis C virus co-infection – 7%

Distribution of nukes used:

- Truvada – a fixed-dose combination of tenofovir + FTC – 67%
- Kivexa – a fixed-dose combination of abacavir + 3TC – 33%

Flamingo is expected to continue for several years. We now report results from the first 48 weeks of the study.

Results

At week 48, the proportions of participants with a viral load less than 50 copies/ml were as follows:

- dolutegravir-based regimens – 90%
- darunavir-based regimens – 83%

As a greater proportion of dolutegravir users had a low viral load at week 48, researchers judged dolutegravir to be “statistically” superior to darunavir.

We will explore the implications of this finding of statistical superiority as well as side effects later in this report.
Results by initial viral load

Researchers analysed the data by the initial (baseline) viral load that participants had when they entered the study.

Among participants whose baseline viral load was high (more than 100,000 copies/ml), here are the proportions that had a viral load less than 50 copies/ml at week 48:

- dolutegravir-based regimens – 93% had a viral load less than 50 copies/ml
- darunavir-based regimens – 70% had a viral load less than 50 copies/ml

Among participants whose baseline viral load was less than 100,000 copies/ml, here are the proportions with less than 50 copies/ml at week 48:

- dolutegravir-containing regimens – 88%
- darunavir-containing regimens – 87%

Another way to examine the results is to look at the nukes used, as follows:

Kivexa

- Kivexa + dolutegravir – 90% of participants achieved a viral load less than 50 copies/ml
- Kivexa + darunavir – 85% of participants achieved a viral load less than 50 copies/ml

Truvada

- Truvada + dolutegravir – 90% of participants achieved a viral load less than 50 copies/ml
- Truvada + darunavir – 81% of participants achieved a viral load less than 50 copies/ml

Changes in CD4+ cell counts

Increases in CD4+ counts were similar between dolutegravir and darunavir users. On average, participants’ counts increased by 200 more cells at week 48.

Resistance and virological failure

Two participants in each treatment group initially suppressed their viral load below the 50 copy/ml mark, but then their viral load became greater than 200 copies/ml after week 24 of the study.

Side effects and complications

Here are some common side effects and their distribution:

Diarrhea

- dolutegravir-based regimens – 17%
- darunavir-based regimens – 29%

Nausea

- dolutegravir-based regimens – 16%
- darunavir-based regimens – 18%

Headache

- dolutegravir-based regimens – 15%
- darunavir-based regimens – 10%

The presence of any side effect of moderate-to-severe intensity was distributed as follows:

- dolutegravir-based regimens – 10%
- darunavir-based regimens – 12%
Here is the distribution of severely abnormal lab tests:

**Cholesterol**
- dolutegravir-based regimens – 0%
- darunavir-based regimens – 1%

**LDL-C (so-called bad cholesterol)**
- dolutegravir-based regimens – less than 1%
- darunavir-based regimens – 2%

**ALT (alkaline aminotransferase; a liver enzyme)**
- dolutegravir-based regimens – 1%
- darunavir-based regimens – 2%

**Creatine kinase (an enzyme, elevated levels of which may be suggestive of muscle breakdown)**
- dolutegravir-based regimens – 7%
- darunavir-based regimens – 4%

No deaths occurred because of the study drugs.

**Why did statistical superiority occur?**

Dolutegravir has powerful anti-HIV activity but so does darunavir when boosted with a small dose (100 mg) of ritonavir. Furthermore, the proportion of participants who did not respond virologically to therapy was similar and was distributed as follows:

- dolutegravir-based regimens – 6% did not achieve a viral load less than 50 copies/ml
- darunavir-based regimens – 7% did not achieve a viral load less than 50 copies/ml

In part, what appeared to drive the differing overall virological outcomes between the two regimens at week 48 was the number of participants who left the study prematurely. These participants were distributed as follows:

- dolutegravir-based regimens – 4% left the study prematurely
- darunavir-based regimens – 10% left the study prematurely

In clinical trials, participants leave a study prematurely for reasons such as adverse reactions (side effects, complications), death, because they moved and so on. Since the study drugs were not lethal and few patients changed residence, researchers were able to focus on adverse reactions as a reason for premature withdrawal from the study, distributed as follows:

- dolutegravir-based regimens – 1% left because of adverse reactions
- darunavir-based regimens – 4% left because of adverse reactions

These findings suggest that dolutegravir-based regimens were likely easier to tolerate.

One question that does not have a clear answer is this:

Does statistical superiority mean that dolutegravir is clinically superior to darunavir?

Boosted darunavir remains an important treatment option and may be a more forgiving regimen (requiring the development of multiple resistance mutations before treatment failure occurs), as is generally the case with other boosted protease inhibitor regimens. Yet, dolutegravir’s potency and relative simplicity (the lack of boosting) may make it an attractive option for some doctors and their patients.

**In the future**

A once-daily pill containing the following three medicines is under development: dolutegravir + abacavir + 3TC.
REFERENCE:

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