Dolutegravir – results from the Single study after one year

Dolutegravir is an experimental drug undergoing clinical trials in HIV-positive people. This drug works by weakening the activity of a key enzyme called integrase, which is needed by HIV-infected cells to make more copies of HIV. Dolutegravir is therefore classed as an integrase inhibitor. This drug is taken once daily as part of potent combination therapy for HIV (commonly called ART or HAART). Dolutegravir has activity against some strains of HIV that are resistant to other integrase inhibitors such as raltegravir (Isentress) and elvitegravir (in Stribild).

Raltegravir is the first integrase inhibitor licensed for the treatment of HIV-positive people. This drug is well tolerated and is taken twice daily as part of ART.

Another integrase inhibitor, soon to be approved in Canada, is elvitegravir. Elvitegravir will become available in a fixed-dose combination called Stribild together with the following drugs:

- tenofovir and FTC (these have activity against HIV and hepatitis B virus)
- cobicistat – this drug is a booster (a pharmacokinetic enhancer). Its purpose is to raise and maintain levels of elvitegravir in the blood so that once-daily dosing of Stribild is possible. Without cobicistat, elvitegravir would need to be taken twice daily.

Back to dolutegravir

Dolutegravir is being tested in several ongoing clinical trials, one of which is called Single. In this study, researchers are comparing the effects of two regimens as follows:

- dolutegravir + Kivexa (a fixed-dose combination of abacavir + 3TC) + placebo
- Atripla – a fixed-dose combination of efavirenz (Sustiva) + tenofovir + 3TC + placebo

Participants enrolled in Single have not previously been exposed to ART. Results after one year with almost 700 participants have found that, overall, 81% of Atripla users and 88% of dolutegravir users achieved a low viral load in the blood (less than 50 copies/ml). According to the design of the study, this finding suggests that dolutegravir was statistically superior to Atripla. The importance of this finding is discussed later in our report.

Study details

Researchers in Canada, Australia, the European Union and the U.S. screened nearly 1,100 HIV-positive volunteers for Single. After making decisions about recruitment, they randomized the following numbers of participants to one of two groups:

- 422 participants – dolutegravir 50 mg + Kivexa + placebo
- 422 participants – Atripla + placebo

The average profile of participants upon entering the study (baseline) was as follows:

- 84% men, 16% women
- age – 35 years
- viral load – 48,000 copies/ml
- 32% had a viral load greater than 100,000 copies/ml
- CD4+ count – 338 cells
- 53% had a CD4+ count of less than 350 cells

Results
Single is an ongoing study. Here are the main results after 48 weeks. The following percentage of participants achieved a viral load of less than 50 copies/ml after 48 weeks:

- dolutegravir + Kivexa – 88%
- Atripla – 81%

This difference between the two groups was statistically significant. The result favoured dolutegravir; this means that dolutegravir + Kivexa was statistically superior to Atripla. The importance of this will be discussed later in this report.

Participants who received dolutegravir achieved a viral load less than 50 copies/ml faster than those on Atripla, as shown below:

- 50% of participants taking dolutegravir achieved a viral load less than 50 copies/ml just four weeks after initiating therapy
- 50% of participants taking Atripla took 12 weeks before they were able to achieve a viral load less than 50 copies/ml

This difference was statistically significant.

**Results—Impact of pre-study viral load**

Among participants whose viral load at the start of the study was more than 100,000 copies/ml, here are the results at week 48:

- proportion of dolutegravir + Kivexa users whose viral load was less than 50 copies/ml – 83%
- proportion of Atripla users whose viral load was less than 50 copies/ml – 76%

Among participants whose viral load at the start of the study was 100,000 copies/ml or less, here are the results at week 48:

- proportion of dolutegravir + Kivexa users whose viral load was less than 50 copies/ml – 90%
- proportion of Atripla users whose viral load was less than 50 copies/ml – 83%

**Results—Impact of pre-study CD4+ cell counts**

Among participants whose CD4+ cell counts were 200 cells or less at the start of the study, here is the virologic response at week 48:

- proportion of dolutegravir + Kivexa users whose viral load was less than 50 copies/ml – 79%
- proportion of Atripla users whose viral load was less than 50 copies/ml – 77%

Among participants whose CD4+ cell counts at the start of the study were greater than 200 cells, here is the virologic response at week 48:

- proportion of dolutegravir + Kivexa users whose viral load was less than 50 copies/ml – 89%
- proportion of Atripla users whose viral load was less than 50 copies/ml – 81%

**Results—Changes in CD4+ counts after one year**

At week 48, CD4+ counts increased by the following amounts in each regimen:

- dolutegravir + Kivexa – 267 more cells
- Atripla – 208 more cells

This difference of almost 60 cells was statistically significant.

**Results—Virologic failure**

Most virologic failures that occurred and that could be confirmed happened between 50 and 400 copies/ml.

**Results—Adverse effects**
Common adverse effects were distributed as follows:

Abnormal dreams
- dolutegravir + Kivexa – 7%
- Atripla – 17%

Dizziness
- dolutegravir + Kivexa – 9%
- Atripla – 35%

Difficulty falling asleep
- dolutegravir + Kivexa – 15%
- Atripla – 10%

Nightmares
- dolutegravir + Kivexa – 4%
- Atripla – 2%

Rash
- dolutegravir + Kivexa – 3%
- Atripla – 14%

Headache
- dolutegravir + Kivexa – 13%
- Atripla – 13%

Fatigue
- dolutegravir + Kivexa – 13%
- Atripla – 12%

Diarrhea
- dolutegravir + Kivexa – 17%
- Atripla – 18%

Nausea
- dolutegravir + Kivexa – 14%
- Atripla – 14%

Anxiety
- dolutegravir + Kivexa – 3%
- Atripla – 6%

Depression or depressed mood
- dolutegravir + Kivexa – 6%
- Atripla – 8%

Withdrawals, serious adverse events and deaths

In clinical trials, adverse events sometimes occur that cause people to prematurely leave the study. These were distributed as follows:
- dolutegravir + Kivexa – 2% of participants
- Atripla – 10% of participants

Serious side effects were distributed as follows:

- dolutegravir + Kivexa – 1 person developed a hypersensitivity reaction
- Atripla – 8 people developed problems as follows: 4 cases of psychiatric problems, 2 cases of drug hypersensitivity, 1 stroke and 1 case of kidney failure

Deaths were distributed as follows:

- dolutegravir + Kivexa – no deaths
- Atripla – two deaths occurred (one due to overwhelming blood poisoning and another from pneumonia); none were judged to be caused by Atripla

**Kidney safety**

No signals of kidney damage were detected during the study.

**Liver safety**

Elevated levels of liver enzymes in the blood, suggestive of liver injury, were distributed as follows:

- dolutegravir + Kivexa – 2%
- Atripla – 9%

**Statistical vs. clinical meaning**

Overall in this study, a regimen based on dolutegravir + Kivexa was found to be statistically superior to Atripla at one year due to the following reason:

More participants taking dolutegravir + Kivexa (88%) achieved a viral load less than 50 copies/ml compared to those who took Atripla (81%).

There is no doubt that dolutegravir is a very effective and generally safe drug after one year of use, as shown in the present study. Nor is there any doubt that a combination of dolutegravir + Kivexa is statistically superior to Atripla.

It is noteworthy that far more people on Atripla prematurely left the study (for various reasons) than did those who dolutegravir + Kivexa, as follows:

- dolutegravir + Kivexa – 12%
- Atripla – 20%

It is possible that a greater rate of premature withdrawal among Atripla users (in some cases due to side effects) could have affected the study’s results. With fewer people remaining in the Atripla group, there would be fewer people to assess at the 48-week mark. This also suggests that a regimen of dolutegravir + Kivexa is better tolerated.

There was a difference of 60 CD4+ cells favouring participants who received dolutegravir + Kivexa. Is this difference clinically meaningful? It is not yet clear.

**In the future**

Hopefully, all will go well in Single and other studies and dolutegravir will ultimately be licensed by regulatory authorities. When that happens, dolutegravir’s impressive and rapid antiviral activity, good tolerability and favourable impact on CD4+ cells may make it especially useful for initiating therapy in people with low CD4+ counts, pregnant women and as post-exposure prophylaxis in people who have been exposed to HIV.

—Sean R. Hosein

REFERENCES:


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