Raltegravir vs. efavirenz – four years later

Raltegravir, sold as Isentress, is the first of a new class of drugs called integrase inhibitors and is used as part of combination therapy against HIV infection.

Although already approved in high-income countries and regions, clinical trials with raltegravir continue to explore its effects.

In Study 004, researchers in Australia, North and South America and Thailand conducted a randomized, double-blind, placebo-controlled clinical trial comparing a regimen based on raltegravir to one based on efavirenz (Sustiva and in Atripla). All 198 participants received a combination of two other anti-HIV drugs as follows:

- tenofovir (Viread)
- FTC (emtricitabine, Emtriva)

A fixed-dose combination of these two drugs is sold as Truvada.

Overall, both raltegravir-based and efavirenz-based regimens were similarly effective after four years. Side effects were less common in people who received raltegravir.

**Study details**

Researchers recruited participants who had not previously used anti-HIV drugs and who had HIV that was susceptible to the medications used in the study.

In Study 004, raltegravir was initially given at different doses (100, 200, 400 or 600 mg twice daily). However, after the first year of the study the dose of raltegravir was fixed at 400 mg twice daily.

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

- 20% females, 80% males
- age – 36 years
- CD4+ count – 300 cells
- viral load – 60,000

Participants were randomized in a 4 to 1 ratio to receive the two study regimens, resulting in the following distribution:

- raltegravir – 160 people
- efavirenz – 38 people

**Results—Effectiveness**

The proportion of participants with a viral load less than 50 copies by the fourth year of the study was as follows:

- raltegravir – 74%
- efavirenz – 74%

The following proportion of participants had their viral load rise and remain elevated (virologic failure) during the study:

- raltegravir – 3%
- efavirenz – 5%
Results—Safety

Overall, reported side effects were similar in most participants, regardless of which regimen they were on. However, neuropsychiatric symptoms were more common among efavirenz users (63%) than raltegravir users (38%). Most of these problems occurred within the first year of the study.

Examples of neuropsychiatric symptoms given by the researchers included:

- nightmares
- psychosis
- hallucinations
- depression
- difficulty falling asleep
- feeling drowsy during the daytime
- thoughts about suicide

Common side effects occurred as follows:

**Diarrhea**
- raltegravir – 7%
- efavirenz – 11%

**Nausea**
- raltegravir – 13%
- efavirenz – 11%

**Dizziness**
- raltegravir – 9%
- efavirenz – 26%

**Headache**
- raltegravir – 9%
- efavirenz – 24%

**Abnormal dreams**
- raltegravir – 6%
- efavirenz – 18%

**Nightmares**
- raltegravir – 0%
- efavirenz – 11%

**Difficulty falling asleep**
- raltegravir – 8%
- efavirenz – 13%

**Cancer**

As with all new drugs used in people with weakened immunity, there is a concern that there may be an increased risk for cancer. The following proportion of participants developed tumours during the study:
- raltegravir – 3%
- efavirenz – 3%

Types of cancers detected included:

- B-cell lymphoma – 1 person
- Kaposi’s sarcoma (KS) – 2 people
- both basal cell carcinoma and squamous cell cancer – 1 person
- both squamous cell cancer and gastrointestinal cancer – 1 person

**Lab tests**

Efavirenz users were more likely to develop severely abnormal levels of fatty substances—cholesterol and triglycerides—in their blood. This issue will be detailed in another report in this issue of *TreatmentUpdate*.

More efavirenz users had abnormally high levels of liver enzymes in their blood—AST and ALT—but these results were based on a small proportion of people. Further information on the safety of raltegravir in people co-infected with hepatitis-causing viruses appears later.

In summary, regimens based on either raltegravir or efavirenz were similarly effective; 74% of participants had their viral load fall below the 50-copy mark and remain there for four years. CD4+ cell counts increased in all participants, regardless of regimen. Efavirenz seemed to cause severely elevated levels of bad cholesterol and triglycerides compared to raltegravir.

**REFERENCE:**

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