American study finds efavirenz linked to fat wasting

Since many potential therapies for HIV infection are available in high-income countries, it is important that different combinations get tested so that doctors and their patients can know more about their effectiveness, side effects and potential drug interactions. Having this knowledge should help simplify decision-making when choosing a treatment regimen.

Researchers with the American government-funded AIDS Clinical Trials Group (ACTG) conducted a study (ACTG 5142) using three different combinations of anti-HIV agents to try to better assess their effectiveness and safety. The most commonly used medications for HIV infection fall into three groups—nukes, non-nukes and protease inhibitors. Each of the three regimens that the researchers tested excluded drugs from one of these categories. The reason for doing so was to help make it easier to find out which group of drugs caused particular side effects. Here are the three combinations tested:

- a nuke-free regimen: lopinavir/r (Kaletra) + efavirenz
- a non-nuke-free regimen: lopinavir/r + 2 nukes
- a protease-inhibitor-free regimen: efavirenz + 2 nukes

The nukes used were as follows:

- AZT + 3TC
- d4T + 3TC
- tenofovir + 3TC

In this study, researchers used a conservative definition of lipodystrophy: Participants would be diagnosed with this syndrome if they lost at least 20% of the fat in their limbs. Assessments of body fat were done with the use of low-dose X-rays called DEXA scans. These were performed before, during and after the study—up to two years after participants had entered this clinical trial. A total of 753 HIV positive people who had never previously used anti-HIV medications were enrolled and their average profile at the start of the study was as follows:

- 20% female, 80% male
- age – 38 years
- CD4+ cell count – 191 cells
- viral load – 100,000 copies
- 13% had hepatitis C virus co-infection

Note that the following proportions of participants received the following drugs:

- AZT – 42%
- d4T – 24%
- tenofovir – 34%

**Results—Changes in body shape**

The ACTG team performed a detailed analysis of its results. No matter which way the combinations were assessed, it was clear that efavirenz was always associated with a greater degree of fat loss than lopinavir/r.

Lipoatrophy was defined by the study researchers as fat loss in the arms and legs of at least 20% compared to pre-study levels. The proportion of participants in each group who experienced lipoatrophy after two years was as follows:
lopinavir/r + efavirenz – 9%
lopinavir/r + 2 nukes – 17%
efavirenz + 2 nukes – 32%

These differences between lopinavir/r and efavirenz were statistically significant.

**Lipoatrophy and nukes**
Because exposure to nukes is also associated with lipoatrophy, the study team assessed fat loss by use of each nuke. They found that d4T was associated with the most lipoatrophy, followed by the other drugs. The proportion of participants who used each nuke or nucleotide analogue and who experienced lipoatrophy was as follows:

- d4T – 42%
- AZT – 27%
- tenofovir – 9%

Then the ACTG team analysed lipoatrophy by assessing exposure to efavirenz or lopinavir/r and nukes. Again, use of efavirenz was always associated with a greater degree of lipoatrophy than use of lopinavir/r. Here is the proportion of participants who experienced lipoatrophy with each pairing of lopinavir/r and efavirenz:

- efavirenz + d4T: 51%
- lopinavir/r + d4T: 33%
- efavirenz + AZT: 40%
- lopinavir/r + AZT: 16%
- lopinavir/r + tenofovir: 6%
- efavirenz + tenofovir: 12%

Taking many factors into account, the risk of developing fat wasting in this study after two years with efavirenz was three times greater than with lopinavir/r.

In general, fat in the chest and belly increased between 12% and 16% over the course of this two-year study among all participants.

**Results—Changes in lipids**
All participants had increased cholesterol levels, which were greatest among those who received the combination of lopinavir/r + efavirenz. Increases in cholesterol were similar among participants who received efavirenz + 2 nukes or lopinavir/r + 2 nukes.

Another fatty substance, triglycerides, rose in all participants, reaching its highest level among those who used the combination of lopinavir/r + efavirenz. Increases in so-called “good” cholesterol (HDL-c) were greatest in the group that received the combination of lopinavir/r + efavirenz.

The findings from this study are unique to the drugs tested, and presenter Dr. Richard Haubrich cautioned that we should not draw conclusions about other protease inhibitors and non-nukes based on the results of this study.

Further information on efavirenz and lipoatrophy appears next.

**REFERENCE:**
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