From TreatmentUpdate 178

ACTG 5202 — effectiveness of different treatments

There are several potential choices when it comes to the initial treatment of HIV infection. In the American trial ACTG 5202, researchers explored the following questions:

- Is a fixed-dose combination of the nukes abacavir + 3TC (Kivexa) equivalent to the fixed-dose combination of the nukes tenofovir + FTC (Truvada) when combined with either efavirenz (Sustiva) or atazanavir-ritonavir (Reyataz-Norvir)?
- Is atazanavir-ritonavir equivalent to efavirenz when used in combination with either Kivexa or Truvada?

ACTG 5202 enrolled 1,857 HIV-positive volunteers and randomly assigned them to one of the following four groups:

- efavirenz + Truvada and placebo
- efavirenz + Kivexa and placebo
- atazanavir-ritonavir + Truvada + Kivexa placebo
- atazanavir-ritonavir + Kivexa + Truvada placebo

Participants were enrolled between 2005 and 2007.

In January 2008, an interim analysis found that participants who entered ACTG 5202 with a high viral load (more than 100,000 copies) and who also received Kivexa were at increased risk for treatment failure. The Data Safety Monitoring Board (DSMB) overseeing the study recommended that the nuke portions of the study be unblinded and participants then had the option of continuing to take their assigned nukes or changing them. After this change the trial continued, assessing the impact of the various study medications among people with viral loads less than 100,000 copies/ml. As a result of this finding, treatment guidelines in the U.S. and E.U. now recommend that Kivexa be used with caution in people with high viral loads.

Study details

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

- 16% females, 82% males
- age – 38 years
- CD4+ count – 230 cells
- viral load – 51,000 copies/ml
- 17% had a history of AIDS
- 7% had hepatitis C virus co-infection

Results—effectiveness

In reviewing data from participants who entered the study with a viral load less than 100,000 copies/ml, here is the proportion of participants who subsequently had their viral loads fall below the 50-copy/ml mark after two years:

- efavirenz + Truvada – 89%
- efavirenz + Kivexa – 87%
- atazanavir-ritonavir + Truvada – 90%
- atazanavir-ritonavir + Kivexa – 88%

None of these differences among any of the above combinations were statistically significant.

When participants’ regimens failed, people taking efavirenz-based regimens were likely to develop HIV that could
resist the effect of efavirenz or nukes, compared to atazanavir-based regimens. This difference was statistically significant.

**Results—specific adverse events**

**Heart attacks**

- efavirenz + Truvada – 8%
- efavirenz + Kivexa – 6%
- atazanavir-ritonavir + Truvada – 4%
- atazanavir-ritonavir + Kivexa – 6%

About 1% or fewer participants in each group developed any other cardiovascular complications such as the following:

- coronary artery disease
- peripheral vascular disease
- heart pain
- stroke

**Cancers unrelated to AIDS occurred as follows:**

- efavirenz + Kivexa – 4%
- efavirenz + Truvada – 4%
- atazanavir-ritonavir + Truvada – 4%
- atazanavir-ritonavir + Kivexa – 4%

**Kidney toxicity occurred as follows:**

- efavirenz + Kivexa – 3%
- efavirenz + Truvada – 1%
- atazanavir-ritonavir + Truvada – 3%
- atazanavir-ritonavir + Kivexa – 3%

**Bone fractures occurred as follows:**

- efavirenz + Kivexa – 5%
- efavirenz + Truvada – 5%
- atazanavir-ritonavir + Truvada – 5%
- atazanavir-ritonavir + Kivexa – 3%

Details on changes in bone density and fractures appear in the following report.

**Results—lipids and kidneys**

In general, lipid levels rose to their highest levels in people who used efavirenz + Kivexa. The exception to this was seen in users of atazanavir-ritonavir + Kivexa, where there was an increase in triglyceride levels in the blood.

During the study, kidney health generally improved regardless of the regimen used. However, people using atazanavir-ritonavir + Truvada showed a modest decline in kidney health compared to people using atazanavir-ritonavir + Kivexa. This difference was statistically significant. This finding about atazanavir-ritonavir + Truvada was unexpected and requires further study to understand why it occurred.

**Conclusions—comparing nukes**

Here are some of the conclusions that the ACTG team arrived at when comparing Kivexa to Truvada:

- Both combinations have similar anti-HIV activity when used with efavirenz or atazanavir-ritonavir in people with viral loads less than 100,000 copies/ml.
• There is a relatively greater increase in CD4+ cell counts when efavirenz rather than atazanavir-ritonavir is used with either nuke combination.
• Abacavir (in Kivexa) was associated with an increased risk of elevated lipids in the blood whether efavirenz or atazanavir-ritonavir was used.

Historically, about 8% of abacavir users were at risk for developing a hypersensitivity reaction to this drug. However, hypersensitivity testing via a simple blood test is increasingly done by doctors before abacavir is prescribed, so the risk of this reaction is now very, very low in most high-income countries. In ACTG 5202, hypersensitivity testing was not part of the protocol and so there was an increased risk of suspected hypersensitivity reactions among people assigned to receive Kivexa, which contains abacavir.

Conclusions—comparing atazanavir and efavirenz

Here are some of the conclusions that the ACTG team arrived at when comparing atazanavir-ritonavir to efavirenz:

• Both regimens seemed equally effective. However, when a regimen failed, users of atazanavir-ritonavir were less likely than efavirenz users to develop resistance to nukes.
• There was a greater increase in CD4+ cells when atazanavir-ritonavir was used with Truvada compared to efavirenz and Truvada.
• Atazanavir-ritonavir was generally associated with smaller increases in lipid levels with any nuke compared to efavirenz.
• When used with Truvada, atazanavir-ritonavir may modestly affect kidney health.

REFERENCE:

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