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I ANTI-HIV AGENTS

A. 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

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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:

1. Gotuzzo E, Nguyen B-Y, Markowitz M, et al. Sustained antiretroviral efficacy of raltegravir after 192 weeks of combination ART in treatment-naïve HIV-1-infected patients. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 514.

B. Raltegravir vs. efavirenz – focus on lipodystrophy, lipids and other changes

Abnormal levels of lipids—cholesterol and triglycerides—and blood sugar as well as unwelcome changes to body shape have occurred in some clinical trials, particularly trials of older anti-HIV drugs. To find out if raltegravir (Isentress) is associated with similar problems, researchers conducted a metabolic study comparing raltegravir-based regimens to ones based on efavirenz (Sustiva and in Atripla). After two years, they found that raltegravir was associated with minimal changes in levels of fats and sugar in the blood. Furthermore, no changes in body shape were detected with either study regimen.

Study details

A large randomized, placebo-controlled trial called Startmrk enrolled nearly 600 participants and randomly assigned them to receive regimens based on either raltegravir or efavirenz. All participants in this study 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.

Researchers conducted a metabolic sub-study of Startmrk with participants who received low-dose X-ray scans called DEXA. These are useful when objectively trying to assess changes in the body's composition of bone, muscle, fat and so on. Particular attention was paid to lipid levels in the blood of participants. In the metabolic sub-study,

55 people received raltegravir and 57 received efavirenz. All participants were from North America.

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

- 20% females, 80% males
- age – 40 years
- CD4+ count – 152 cells
- viral load – 100,000 copies
- 16% had a history of AIDS

Results

After two years, on average there were relatively small increases in lipid levels in the blood of raltegravir users. Triglyceride levels even fell during the study.

In contrast, lipid levels rose to a larger degree among efavirenz users. Indeed, the difference in lipid levels between raltegravir and efavirenz users after two years was statistically significant for the following lipids:

- total cholesterol
- good cholesterol (HDL-C)
- bad cholesterol (LDL-C)
- triglycerides

Blood sugar levels rose slightly among raltegravir users but increased blood sugar levels were more common among efavirenz users. This difference was also statistically significant.

For the most part, increased lipid levels exceeded critical threshold levels only in the cases of LDL-C and triglycerides among some efavirenz users.

Changes in body fat were small and not significantly different between the two treatments.

Overall, the results from this metabolic sub-study suggest that after two years of treatment, raltegravir, when used with Truvada, had a minimal impact on lipid and sugar levels in the blood as well as on body shape.

REFERENCE:

1. DeJesus E, Cohen C, Lennox J, et al. Metabolic profiles and body composition changes in treatment-naïve HIV-infected patients treated with raltegravir 400 mg twice-daily vs. efavirenz 600 mg each bedtime combination therapy: 96-week follow-up. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 720.

C. Raltegravir in hepatitis co-infection

Due to shared routes of infection—including re-use of equipment for substance use and tattooing, as well as unprotected sex—co-infection with hepatitis B virus and hepatitis C virus is relatively common among some HIV-positive people. Hepatitis-causing viruses infect and damage the liver and increase the risk of liver cancer in the medium- and long-term.

The liver plays a vital role for the body, filtering and metabolizing foreign substances. Many drugs are broken down by the liver, and when this organ is damaged by hepatitis-causing viruses, its ability to break down drugs is weakened. This leads to the buildup of drugs in the blood, which can lead to side effects. In some cases of co-infection, depending on the health of the liver, reduced doses of anti-HIV and other drugs may become necessary.

Researchers at the University of Bonn, Germany, have been analyzing data from three clinical trials in which raltegravir was tested in a relatively small proportion of co-infected people. They found that higher-than-normal levels of liver enzymes in the blood were more common in co-infected people than in people with HIV infection alone. Raltegravir was effective and “well tolerated” by most people, according to the research team.

Study details

This German analysis reviewed data from the following trials:

- Startmrk
- Benchmrk-1
- Benchmrk-2

The average profile of participants at the time they entered **Startmrk** was as follows:

- 20% females, 80% males
- age – 37 years
- CD4+ count – 210 cells
- viral load – 100,000 copies

The average profile of participants at the time they entered the **Benchmrk** trials was as follows:

- 12% females, 88% males
- age – 45 years
- CD4+ count – 120 cells
- viral load – 60,000 copies

In the **Benchmrk** trials, participants had never previously used anti-HIV drugs and they were

randomly assigned to receive one of the following regimens:

- raltegravir + optimized background therapy
- placebo + optimized background therapy

In **Startmrk**, participants were treatment experienced and randomly assigned to receive one of the following regimens:

- raltegravir + Truvada
- efavirenz + Truvada

Results—Two years later

Co-infected people achieved a rate of virologic success similar to that seen in people infected with HIV only. Increases in CD4+ cell counts were also similar whether or not people were co-infected.

Results—Side effects

Drug-related side effects occurred in similar proportions of people regardless of co-infection. However, serious drug-related side effects occurred more frequently in co-infected people (5.2%) than in mono-infected people (2.3%).

Results—Liver enzymes

A large proportion (around 6%) of co-infected people taking raltegravir developed severely elevated levels of liver enzymes in their blood—more than 10 times the upper limit of normal. This problem occurred in less than 1% of mono-infected people.

However, it is noteworthy that such high elevations of liver enzymes also occurred in co-infected people who received efavirenz or placebo.

Focus on the liver

In **Startmrk**, none of the co-infected people developed any of the following complications:

- liver failure
- liver pain
- fatty liver
- jaundice
- swollen liver
- portal hypertension

However, one or more of these problems occurred in about 1% of people who took raltegravir or efavirenz and who were **not** co-infected. A similar trend was seen in the **Benchmrk** trials when comparing raltegravir and placebo.

Bear in mind that the proportion of co-infected people in this study was relatively small. Co-infected people who have moderate-to-severe degrees of liver damage may need careful laboratory and clinical monitoring while being treated for HIV infection. Such people are not typical of the population initially recruited into HIV clinical trials.

REFERENCE:

1. Rockstroh J, Teppner H, Zhao J, et al. Hepatic safety and efficacy of raltegravir in patients co-infected with HIV and HBV or HCV. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 662.

II COMPLICATIONS AND SIDE EFFECTS

A. EuroSIDA study finds a signal of kidney toxicity with tenofovir or atazanavir

The kidneys are a target of HIV infection. Long-term infection causes inflammation, which slowly degrades these organs.

The EuroSIDA dataset contains health-related information on almost 17,000 HIV-positive people from 35 countries. EuroSIDA can provide a powerful tool to analyse health-related trends in HIV-positive people.

Tenofovir and the kidneys

The anti-HIV drug tenofovir (Viread, and in Atripla and Truvada) is an effective part of combination therapy for HIV.

The kidneys process tenofovir and there have been rare cases of tenofovir users developing serious kidney dysfunction. To investigate the issue of chronic kidney disease, researchers from EuroSIDA reviewed their large database of information on HIV-positive people who initiated anti-HIV therapy with or without tenofovir. They found that some tenofovir users had a detectable and significant decline in kidney health.

Study details

Researchers reviewed data collected from 2004. They checked eGFR (estimated glomerular filtration rate) to get an idea of how the kidneys were working. Chronic kidney disease was defined in the following way:

- having an eGFR of 60 or less if they entered the study with an eGFR greater than 60
- a 25% decrease in eGFR if at the start of the study their eGFR was less than 60

Researchers assessed the use of anti-HIV therapy over time to find out if there was any relationship between kidney damage and specific therapies.

In reviewing their dataset, researchers focused on data from 6,843 people who had used tenofovir and for whom multiple eGFR assessments were available.

At the start of the study, the profile of these people was as follows:

- 25% females, 75% males
- 86% were white
- 43% were gay or bisexual
- 31% previously had AIDS
- 90% used anti-HIV therapy
- CD4+ count – 450 cells
- 22% had high blood pressure (a risk factor for kidney damage)
- 5% had diabetes (another risk factor for kidney damage)

Participants were monitored for an average of four years.

Understanding risk

Before discussing the latest analysis from the EuroSIDA study, it might be helpful to review how researchers talk about risk.

Normally, when we speak about risk, we mean overall (or absolute) risk, which tells us the probability that a certain event (such as developing chronic kidney disease) will happen over a given period of time. Generally speaking, the overall risk of chronic kidney disease in HIV-positive people who are taking tenofovir is low.

Overall, about 3% of nearly 7,000 people in the EuroSIDA study developed chronic kidney disease, so in the EuroSIDA study, chronic kidney disease is generally uncommon. However, everyone's overall risk for chronic kidney disease is different, so some people living with HIV may have a much higher overall risk depending on risk factors such as whether or not they have high blood pressure, diabetes or a family history of poor kidney health.

When researchers want to study the risk of chronic kidney disease associated with taking a particular drug, they try to measure the percentage change

in the overall risk that results from taking that drug. This is called the relative risk. The relative risk provides information about how much more (or less) likely chronic kidney disease will be if the person is taking the particular drug studied compared to if they are not taking the drug. For example, a study may find a 70% increase in the relative risk of chronic kidney disease. This means that the risk of developing chronic kidney disease is 70% higher among people taking the drug than among people who are not taking the drug. The relative risk measures a change in risk, it does not measure the overall risk.

In order to know what the relative risk, reported by researchers, means for you, you need to also consider your overall risk for chronic kidney disease. Your doctor can help you determine your overall risk. If your overall risk of chronic kidney disease is low prior to starting the drug, a 70% increased relative risk might not be significant compared to someone else whose initial overall risk for chronic kidney disease is very high. And bear in mind that a 70% increase in relative risk does NOT mean that there is a 70% chance you will get chronic kidney disease.

Now, onto the EuroSIDA study.

Results

Researchers found that 3% of people (225 people) developed chronic kidney disease over an average of four years. The vast majority of these 225 people entered the study with an eGFR greater than 60.

The researchers took into account many factors that have the potential to play a role in affecting the results, including these:

- age
- CD4+ count
- viral load
- hepatitis C virus co-infection
- gender
- heart attack
- stroke
- use of drugs with the potential to harm the kidney

Taking all of these (and likely other) factors into account, the EuroSIDA analysis found that the following drugs were associated with an increased relative risk for developing chronic kidney disease as follows:

- tenofovir – a 16% increased relative risk for every year this drug was used

- indinavir (Crixivan) – a 12% increased relative risk for every year this drug was used (this effect was independent of tenofovir use)
- atazanavir (Reyataz) – a 21% increased relative risk for every year this drug was used (this effect was independent of tenofovir use)

The EuroSIDA team performed several different analyses and each confirmed their results.

Effect of stopping specific anti-HIV therapy

Compared to people who never used tenofovir, among participants who stopped taking tenofovir, the risk of developing chronic kidney disease when they stopped using tenofovir was as follows:

- within the first 12 months of stopping therapy – a 400% increased relative risk for developing chronic kidney disease
- *after* 12 months of stopping tenofovir therapy – a 12% increased relative risk for developing chronic kidney disease.

The high rate of relative risk after stopping tenofovir therapy probably arose because their doctors thought that these patients were at high risk of kidney damage and wanted them to stop using tenofovir, noted EuroSIDA researcher Dr. Ole Kirk.

In contrast to the findings from tenofovir users, when participants stopped taking atazanavir or Kaletra, their risk of developing chronic kidney disease was low and similar to that seen in people who were not using these drugs.

Caution needed

The EuroSIDA study design is that of a cohort study. Such studies are very good at finding associations—in this case, between the use of certain drugs and an increased relative risk of kidney damage. However, observational studies by their nature can only find associations; they cannot prove cause and effect. That is, they cannot prove that taking a particular medicine(s) will indeed cause a particular effect (serious kidney damage).

Furthermore, confounding or channeling bias is a problem that bedevils observational studies and makes drawing firm conclusions difficult when interpreting the data. Observational studies are useful for finding associations that can later be explored in studies of a more robust design.

Despite these caveats the EuroSIDA analysis is important and raises a red flag: It is possible that

a number of anti-HIV drugs, particularly tenofovir, may have a negative impact on the kidneys over the long-term, even for a year after people stop taking this drug. EuroSIDA also raises concern about the safety of atazanavir for the kidneys.

It is likely that these problems were not seen in the initial clinical trials of these two drugs because they enrolled relatively healthy people (as do most trials testing new compounds). The patients in the EuroSIDA cohort are reflective of the reality of living with HIV for many years and the burden of having multiple health conditions.

At present, EuroSIDA does not have sufficient information to assess the impact of the following drugs on chronic kidney disease:

- darunavir (Prezista)
- etravirine (Intelence)
- maraviroc (Celsentri)
- raltegravir (Isentress)
- tipranvir (Aptivus)

Long-term studies are needed to continue to provide information about the effect of these and other medicines. Other important datasets, such as the following, need to conduct their own analyses to confirm, extend or refute EuroSIDA's initial findings:

- ART-CC
- CANOC
- DAD
- French Hospital Database
- ICONA
- NA-ACCORD

In the years ahead these analyses will be eagerly awaited and much debated and discussed among doctors and statisticians.

REFERENCE:

1. Kirk O, Mocroft A, Reiss P, et al. Chronic kidney disease and exposure to ART in a large cohort with long-term follow-up: the EuroSIDA study. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 107LB.

Disclaimer

Decisions about particular medical treatments should *always* be made in consultation with a qualified medical practitioner knowledgeable about HIV-related illness and the treatments in question.

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