News on Approved Antiretrovirals

Truvada and Epzicom are similar at suppressing HIV

Data from the Australian STEAL study show Truvada (tenofovir + emtricitabine) is equal to Epzicom (abacavir + lamivudine) in their abilities to suppress viral loads. Each of the combination pills had unique side effects, which likely mark the major difference when deciding which therapy to choose.

STEAL enrolled 360 people on stable HIV regimens with 2 NRTIs plus either a NNRTI or protease inhibitor (PI). All had undetectable viral loads for at least 12 weeks at study entry. None were on unboosted Reyataz, had prior hypersensitivity to other HIV drugs, or were positive on an HLA-5701 test, which determines whether abacavir is likely to cause a severe allergic reaction.

Average age of the volunteers was 45 and the study included predominantly white (86%) men (97%). About 17% had been diagnosed with AIDS, length of time living with HIV averaged 10 years, and average CD4 count was around 620.

All continued either their NNRTI or PI, with half randomly assigned to take Truvada and the other half Epzicom. The primary objective of the study was to look at failure to maintain an undetectable viral load. Researchers also gathered information on serious non-AIDS events, bone density levels (BMD), lipid levels and death.

Both Truvada and Epivir were about equal at suppressing HIV levels. Epzicom was associated with more side effects in general than Truvada. Epzicom showed a higher risk of heart disease and more than double the risk for changes in lipid levels. However, Truvada showed a higher risk for changes in BMD with lower density scores found in the hip and spine. Though there were some cases of kidney and liver disease and diabetes in both groups, there were no significant differences between the two combination pills and their risks on these conditions.

Truvada and Epzicom suppress HIV levels and maintain CD4 counts at about the same rate. The decision to choose one over the other would likely come down to possible issues of side effects. Loss of BMD is a concern for many with HIV, so choosing Truvada may put a person more at risk for it. Truvada’s side effects in general seem more tolerable than Epzicom’s. On the other hand, Epzi-
Com appears to cause more changes in blood fats and more heart disease, perhaps from the abacavir in it. Although abacavir has been implicated as a risk factor for heart disease, it’s still unclear whether that’s the case. Several studies presented at CROI 2009 show a connection though a few others do not.

**News on Approved Antiretrovirals**

**Two studies show Kaletra and Isentress similarly suppress HIV, yet have different side effects**

Results from two studies show that switching from a stable and effective Kaletra (lopinavir/ritonavir) regimen to one with the new integrase inhibitor Isentress (raltegravir) results in similar (though slightly less robust) levels of HIV suppression, yet improved the levels of blood fats (lipids). The percent of people maintaining optimal viral suppression was slightly higher among those on Kaletra in both studies. Side effects were similar between groups, though Isentress did not cause the abnormal lipid levels seen with Kaletra.

The two identical studies (called SWITCHMRK 1 and 2) enrolled 702 people who were on stable regimens with Kaletra. Average CD4 counts were above 400, average age was about 42, and 80% were men. Some volunteers showed resistance mutations for NRTIs, NNRTIs and PIs, and many had extensive therapy experience and had regimens fail one or more times. All were off lipid-lowering drugs for at least 12 weeks before study start.

In both, volunteers took at least 2 NRTIs and either stayed on Kaletra or switched to Isentress. After 24 weeks in SWITCHMRK 1, 81% of those on Isentress and 87% on Kaletra reached undetectable viral loads. In SWITCHMRK 2, 88% of those on Isentress and 94% on Kaletra achieved undetectable viral suppression. At week 12, Isentress showed better results for changes in total cholesterol and triglycerides. As for suppressing HIV levels at week 24, 88% of those on Isentress had reached undetectable viral loads while 94% of those on Kaletra were undetectable. The rate of side effects were similar between the two drugs (Isentress 13% and Kaletra 20%).

For those who switched to Isentress, the drug was well tolerated with somewhat milder side effects and improved lipid levels compared to Kaletra. Isentress didn’t suppress HIV quite as well as Kaletra, though its suppression was similar.

**Isentress equal to Sustiva in first line therapy**

Results from the STARTMRK study results show that the first-in-class integrase inhibitor Isentress (raltegravir) works at least as well as Sustiva (efavirenz) at suppressing HIV levels. It also showed that using Isentress resulted in higher CD4 counts.

STARTMRK included 563 people who had never been on HIV therapy. Half received Isentress (400mg, 2x a day) or Sustiva (600m, 1x a day) with Truvada (tenofovir/Viread + emtricitabine/Emtriva). At study entry, none showed resistance to Sustiva or Truvada, all had viral loads above 5,000 with more than half above 100,000, and nearly half had CD4 counts below 200.
The study included 19% women and 58% people of color, while the average age was 37 years. Nearly 1 in 5 had a type of HIV different from subtype B, a common type found in the US. The study assessed the number of people who had undetectable HIV and the rate of change in CD4s. Side effects were also studied, including effects on the central nervous system (CNS) and changes in fats/cholesterol levels (called lipid levels).

After 48 weeks on therapy, Isentress suppressed HIV as well as Sustiva. Isentress increased CD4 counts higher than Sustiva, but it’s not clear if this increase was statistically meaningful. Isentress was, in general, better tolerated. Fewer overall side effects occurred with Isentress than Sustiva and notably there were fewer CNS affects with Isentress. As for effects on the liver in those with or without hepatitis B or C, both drugs performed similarly.

Isentress was developed and approved for use in treatment experienced individuals. However, this study is one of many that are looking at its effectiveness when used in first line therapy. Here, compared against the most widely used NNRTI, Isentress seems to be an equal choice for people starting therapy for the first time.

The decision to choose one strategy over the other would likely come down to concerns about side effects. From this and other studies, Isentress seems well tolerated, but since it’s a very new drug we don’t know its possible side effects over the long-term. On the other hand, Sustiva has been well studied and its effects on the CNS are well documented and have long been a concern for many. These include sleep disturbances, unusual dreams and trouble concentrating as well as rash, dizziness and diarrhea. Some people tolerate Sustiva very well; many others experience at least some degree of side effects which may affect their adherence. At this point, it may just come down to which drug is better tolerated by a given individual and what side effects a person is willing to live with.

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**NEWS ON APPROVED ANTIRETROVIRALS**

**Prezista fares better than Kaletra in first line therapy**

Two year (96-week) results from the ARTEMIS study show Prezista (darunavir + ritonavir) superior to Kaletra (lopinavir/ritonavir) at suppressing HIV levels in people taking therapy for the first time. Both drugs are potent protease inhibitors, but these results continue to show Prezista’s excellent ability at suppressing HIV over time.

ARTEMIS studied people who had never taken therapy and randomly assigned them to take either once-daily Prezista or once-daily Kaletra along with Truvada (tenofovir + emtricitabine). A self-rated M-MASRI questionnaire was given to the volunteers to rate their level of adherence to their regimens. A person’s ability to maintain adherence impacted results on suppressing HIV levels.

A total of 689 people with viral loads above 5,000 enrolled. The study included 70% men, 58% people of color and the average age was 35. At study start, volunteers, on average, had been HIV-positive for about two years, had CD4 counts about 220, and viral levels were 4.86 logs. Treatment failure was defined as:

- stopping therapy for any reason,
- not achieving undetectable viral loads on at least two consecutive visits, or
- showing detectable viral levels on two consecutive visits.
Results at 96 weeks show that 79% of those taking Prezista achieved undetectable viral loads compared to 71% of those on Kaletra. Of those taking Prezista, 82% who were optimally adherent (took their meds as prescribed more than 95% of the time) had undetectable viral loads compared to 78% of those on Kaletra. As for those who were not optimally adherent (below 95% of the time), 76% of those on Prezista were undetectable while only 53% of those on Kaletra were. People on Prezista had more pronounced HIV suppression even when they were less adherent to their regimens.

Diarrhea was the most common side effect, occurring in 4% of those on Prezista and 11% on Kaletra. As for changes in levels of blood fats (lipid levels), Prezista also performed better than Kaletra on triglyceride (18% vs 28%) and cholesterol (4% vs 13%) levels.

Factors that affected a better response to therapy included lower viral levels at study entry, older age, race and level of adherence to the regimens. Those who were more adherent to their regimens, who started the study at lower baseline viral loads, and who were not black had better suppression of their HIV. CD4 count at study entry did not significantly affect anti-HIV response rates.

Prezista is the latest protease inhibitor approved by the FDA. Its development focused on overcoming the resistance found in other protease inhibitors in efforts to give treatment experienced individuals a potent option should they need to find a new regimen. Given these encouraging results, it appears that Prezista is also becoming a potent option for those starting on their first HIV regimens.

**NEWS ON EXPERIMENTAL ANTIRETROVIRALS**

**Acyclovir: the next new HIV drug?**

Acyclovir, a drug used to treat herpes, shows that it also inhibits HIV during the reverse transcription (RT) step in the virus’s life cycle. Two studies looked at how acyclovir affected the RT enzyme, which may pave the way to using the drug to treat HIV infection either on its own or together with herpes therapy.

In the first study, in an attempt to find compounds with novel anti-HIV activity, a team from John Hopkins School of Medicine and Howard Hughes Medical Institute searched through nearly 3000 FDA-approved drugs or other drugs in phase II studies. Twenty were found to have moderate activity against HIV and 18 were selected for this study.

In the lab, CD4 cells were infected with HIV and then exposed to 10 uM of acyclovir. Cultures were also individually exposed to the other 17 compounds. Viral load tests were done to assess the reduction of HIV levels. Other tests were used to confirm whether the RT enzyme was the drug’s target. Herpes infection and activity were also examined. Acyclovir, along with the other compounds, was shown to suppress HIV replication.

The second study looked at the activity of acyclovir on HIV in various tissues from the tonsils, lymph nodes, rectum and genital tract, all co-infected with various human herpes viruses. After treating HIV-infected cells with acyclovir, viral loads and RT activity were assessed.

If the cells had both HIV and herpes viruses in them, then acyclovir suppressed HIV reproduction in those cells. Conversely, if the cells didn’t have herpes virus in them, then acyclovir didn’t suppress HIV. However, when cells infected with herpes virus only were added to treated co-infected cell cultures, then acyclovir suppressed HIV again. This suppression of HIV appears to affect HIV that uses both R5 and X4 co-receptors.
More study is needed to discover how acyclovir interacts with HIV, both with and without the presence of a herpes infection. One main concern here is how acyclovir may affect HIV mutations. For example, when people with HIV are simply treating their herpes and not their HIV, they may actually be on “HIV monotherapy” which may then lead to poorer HIV therapy outcomes. This data comes in light of studies from CROI 2008 (www.projectinform.org/news/08_croi/020608a.shtml) that showed using acyclovir in herpes-infected individuals increased the risk of HIV infection.

**news on experimental antiretrovirals**

**Thin pipeline reveals three possible HIV drugs**

Three possible new compounds with anti-HIV activity were highlighted at CROI 2009. The three compounds, from a very thin pipeline of possible new HIV drugs, are all in early safety study. Should any of these show effectiveness at suppressing HIV, it will still be a couple of years before they would find their way to market.

**MPC-9055**

A maturation inhibitor called MPC-9055 entered study for its safety and tolerability at various doses in healthy HIV-negative volunteers. Maturation inhibitors work at the last stages in the life cycle of HIV, as newly formed HIV exit immune cells. These drugs prevent the creation of HIV’s core called the capsid, which protects its genes. This, in turn, leads to the production of non-infectious HIV that could not infect other cells and theoretically not damage the immune system.

A single-dose of MPC-9055 at 1, 2, 4, 8, 16, 32, and 48 mg/kg were given to 55 non-smokers on a fasting schedule and placebo was given to 20 people. The 8mg and 16mg doses were also evaluated to see how high- or low-fat food impacted the doses. Results showed that no serious adverse events or lab trends were found. However, one-third of those on MPC-9055 did experience at least one side effect. These were generally mild and included headache, nausea, diarrhea and stomach pain. Food increased blood-levels of the drug two-fold. A multiple dose-finding study is being planned for HIV-positive volunteers.

**RDEA427**

Safety information from both animal and human study were made available for a new NNRTI called RDEA427. The drugs in the NNRTI class (see Drug ID chart on page 5) are highly cross-resistant to one another, and like the latest addition to this class, Intelence (etravirine), a new NNRTI will have to overcome these resistance issues.

This study examined the reaction of both wild type and NNRTI-resistant viruses when exposed to the compound. Injections of RDEA427 were given to several types of animals and to 4 humans to check on its safety and activity.

The results showed that RDEA427 has sustained activity against many of the most common viruses resistant to NNRTIs, including the most commonly transmitted mutation to treatment-naïve individuals, K103M. Against K103M, the compound exhibited anti-HIV affect for more than 100 days, and also showed longer suppression of K103M virus than Intelence and the experimental NNRTI called rilpivirine (TMC278). It appears that RDEA427 has equal activity against both wild type
and NNRTI-resistant viruses. However, another virus with a common NNRTI-resistant mutation, Y181C, was not controlled by the new drug, a drawback of Intenence and rilpivirine as well.

No adverse events or significant lab abnormalities were seen in the study. However, a possible drawback to using this compound will likely be due to it requiring an injection for dosing. Though it may only be dosed once a day, a daily injection may still be too much for many to even consider.

**OBP-601**

Another safety study reported data on an NRTI called OBP-601 a derivative of the FDA-approved NRTI, Zerit (stavudine). A single dose of the drug, called festinavir, was examined for safety and tolerability. Lab results, vital signs and safety were assessed at regular intervals. The study followed 64 HIV-negative men in a placebo-controlled single dose escalation study.

There were no serious adverse events and the drug was well tolerated, although mild symptoms such as fatigue, diarrhea and vomiting did occur among a few people. No abnormal lab results were also seen, and food did not have an effect on the drug’s absorption in the body.

The anti-HIV activity of the compound persists longer than other NRTIs in test tube study, including against the common NRTI-resistance mutation, M184V. OBP-601 seems to effectively suppress HIV in both wild type and multidrug resistant forms of the virus. The 100mg dose given once a day provided good suppression of virus for 24 hours and is currently under study to further assess its safety and effectiveness in HIV-positive people.

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**News on Experimental Pharmaceutical Enhancers**

**Two newcomers may challenge ritonavir’s position as the only booster for HIV therapy**

Two companies announced development of boosters, or pharmaceutical enhancers, that could replace ritonavir’s sole position in that role. These enhancers, when used to treat HIV disease, increase the level of other HIV drugs in the blood, thereby bolstering their potency by increasing the length of time those drugs remain active and at optimal levels to fight HIV.

Currently, ritonavir is co-formulated as a booster with lopinavir and sold as Kaletra, but it’s also recommended as a booster for other protease inhibitors to augment their anti-HIV activity. However, ritonavir has a rather long list of troublesome side effects and drug interactions. The prospect of having other boosting compounds to choose from without these confounding side effects from ritonavir would be welcomed by many.

Both companies report that their compounds are not active against HIV, as is ritonavir. Also, while both compounds seem to inhibit the same liver enzyme (P450 [CYP3A]) as ritonavir, their sponsors claim they do this in a more specific way, which they contend will be beneficial at the end of the day. Moreover, it’s asserted that these compounds will not affect lipid or glucose levels, which hopefully will result in fewer metabolic changes and fewer cases of elevated blood fats or insulin resistance. Only further study will whether either of these claims is true.

**Gilead’s GS-9350**

Gilead Sciences reported results from two phase I proof-of-concept studies of GS-9350 and theorized on its possible co-formulation with their experimental integrase inhibitor, elvitegravir. Gilead
is positioning GS-9350 to be co-formulated with elvitegravir and their combination pill Truvada (tenofovir + emtricitabine) as a single pill competitor to Atripla. Atripla is currently the only one-pill, once-a-day regimen. Atripla contains 2 NRTIs and 1 NNRTI while Gilead’s proposed combination is an integrase inhibitor combined with 2 NRTIs plus the booster.

A single and 14-day multiple dose escalating study compared 18 people taking 50, 100 or 200mg of GS-9305 once a day to 18 people on 100mg ritonavir on the ability of the drug to block P450. The two higher doses performed at equal levels to ritonavir. No one experienced grade 4 adverse events or grade 3 or 4 lab abnormalities. The GS-9305 did not appear to impact fats (lipids) or sugar (glucose).

In the partially randomized study (GS-236-0101), GS 9350 was given together with elvitegravir and Truvada in 44 volunteers. The regimen was compared to ritonavir + elvitegravir + Truvada at 100 and 150mg doses of GS 9350. The 150mg dose was comparable in effect as ritonavir. The only grade 3 or 4 adverse event occurred in one volunteer.

Gilead is planning to start this year a phase II study of this one-pill, once daily regimen in people going on first line therapy. The company is also planning to study GS-9350 as a booster for several protease inhibitors such as Prezista (darunavir) and has already started lab study of the booster with Reyataz (atazanavir).

**Sequoia’s SPI-452**

In laboratory studies, SPI-452 by Sequoia Pharmaceuticals shows no added HIV activity and comparable activity to ritonavir when combined with 8 protease inhibitors in addition to an HCV drug. Like Gilead’s compound, SPI-452 showed strong inhibition of the P450 enzyme.

Phase I of the first proof-of-concept study (0452-001) followed 47 people divided into 6 groups, with each group getting doses ranging from 25–600mg. Phase II included 10 volunteers in each of two arms comparing three different once-a-day regimens: SPI-452 + saquinavir, saquinavir + placebo, or placebo + placebo.

From these two phases of the first study, the compound was considered generally safe though 19 people experienced 1 or more adverse events such as headache, which were usually mild. Based on the results, the 25, 50 and 200mg doses were moved forward into a second proof of concept study in regimens with darunavir and atazanavir. In the second study, 45 experienced 1 or more adverse events such as headache, nausea or diarrhea.

Combining the data from both studies, the company reported that the compound appears to boost the activity of the protease inhibitors Prezista and Reyataz comparable to ritonavir while also being a potent inhibitor of P450. And, like Gilead’s compound, SPI-452 seems to have a tolerable side effects profile and does not significantly alter lipid levels.

The results show promise for long overdue competitors to ritonavir. Though these proof-of-concept studies may not result in an actual booster for another year or two, they nevertheless represent a positive step in improving the safety and efficacy of HIV drugs taken today.