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## I ANTI-HIV AGENTS

### A. The debut of the quad pill

Pharmaceutical companies are increasingly putting two or more drugs into one pill; these are called fixed-dose co-formulations. One company that makes several co-formulations is Gilead Sciences, which sells the following anti-HIV drugs:

- tenofovir (Viread)
- FTC (emtricitabine, Emtriva)
- Truvada (tenofovir + FTC)
- Atripla (efavirenz + tenofovir + FTC)

Gilead is currently developing another anti-HIV drug, called elvitegravir, which belongs to the class of drugs called integrase inhibitors. These drugs work by impairing the activity of an enzyme called integrase, which is needed by HIV-infected cells to make new copies of HIV.

Elvitegravir needs to be taken with a booster—another drug that helps to raise and maintain levels of elvitegravir in the blood for a prolonged period. The impact of boosting results in a once-daily dosing requirement of elvitegravir. The booster that Gilead Sciences has been developing is called GS-9350 or cobicistat; there is currently no publicly available brand name for this compound.

Gilead has combined the following four drugs into one pill called a “quad”:

- elvitegravir
- cobicistat
- tenofovir
- FTC

At a dose of 150 mg per day, cobicistat can boost not only elvitegravir but also another anti-HIV drug called atazanavir (Reyataz). Atazanavir is

produced by



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sometimes taken with another booster called ritonavir (Norvir).

Gilead has conducted two short-term placebo-controlled Phase II studies to compare the preliminary safety and efficacy of the following combinations of drugs:

- quad vs. Atripla
- atazanavir + Truvada + cobicistat vs. atazanavir + Truvada + ritonavir

The quad pill shows excellent anti-HIV activity and appears to be well tolerated. However, larger and longer comparative studies called Phase III clinical trials are needed to assess the effects of the quad and other combinations that use cobicistat.

### Study details

Researchers assigned HIV-positive volunteers to the following combinations:

- quad – 48 people
- Atripla – 23 people
- atazanavir + Truvada + cobicistat – 50 people
- atazanavir + Truvada + ritonavir – 29 people

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

- 10% females, 90% males
- age – 36 years
- CD4+ count – 350 cells
- viral load – 40,000 copies/ml
- about 25% of participants had a viral load greater than 100,000 copies/ml

### Results

After 24 weeks the proportion of participants with a viral load in their blood less than 50 copies/ml in each group was as follows:

- quad – 90%
- Atripla – 83%
- atazanavir + Truvada + cobicistat – 84%
- atazanavir + Truvada + ritonavir – 86%

As previously mentioned, the quad pill contains the integrase inhibitor elvitegravir; in the present study viral loads fell rapidly in participants who received elvitegravir. In previous studies with the first approved integrase inhibitor, raltegravir (Isentress), viral loads also fell rapidly.

Bear in mind that the number of study volunteers was modest and firm conclusions about the long-term effectiveness of the quad pill or the safety of

cobicistat cannot yet be drawn. Nevertheless, the quad pill will likely be at least roughly equivalent in effectiveness to Atripla. Phase III trials comparing the quad to Atripla are expected to begin later in 2010.

### Safety

As new drugs get tested, it is important to assess their potential for side effects. Here are the overall proportions of participants who experienced side effects of any intensity:

- quad – 35%
- Atripla – 57%
- atazanavir + Truvada + cobicistat – 20%
- atazanavir + Truvada + ritonavir – 24%

Here is the distribution of some of the selected side effects:

Abnormal dreams, nightmares

- quad – 10%
- Atripla – 35%
- atazanavir + Truvada + cobicistat – 0%
- atazanavir + Truvada + ritonavir – 0%

Fatigue

- quad – 8%
- Atripla – 13%
- atazanavir + Truvada + cobicistat – 2%
- atazanavir + Truvada + ritonavir – 7%

Nausea

- quad – 4%
- Atripla – 4%
- atazanavir + Truvada + cobicistat – 10%
- atazanavir + Truvada + ritonavir – 3%

Diarrhea

- quad – 8%
- Atripla – 4%
- atazanavir + Truvada + cobicistat – 6%
- atazanavir + Truvada + ritonavir – 10%

Here is the proportion of participants who had moderate-to-severe elevations in the amount of total cholesterol in their blood:

- quad – 9%
- Atripla – 10%
- atazanavir + Truvada + cobicistat – 6%
- atazanavir + Truvada + ritonavir – 0%

Similar changes were seen for good (HDL) and bad (LDL) cholesterol as well as triglycerides.

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Here is the proportion of participants who had elevated levels of protein in their urine, suggestive of kidney damage:

- quad – 2%
- Atripla – 10%
- atazanavir + Truvada + cobicistat – 4%
- atazanavir + Truvada + ritonavir – 0%

Here is the proportion of participants who had mild decreases in levels of creatinine in their blood, also suggestive of kidney damage:

- quad – 2%
- Atripla – 0%
- atazanavir + Truvada + cobicistat – 12%
- atazanavir + Truvada + ritonavir – 0%

Here is the proportion of participants who had less-than-normal levels of phosphorus in the blood, also suggestive of kidney damage:

- quad – 0%
- Atripla – 0%
- atazanavir + Truvada + cobicistat – 2%
- atazanavir + Truvada + ritonavir – 3%

Here is the proportion of participants who had moderate-to-severe elevations in the levels of the liver enzyme **ALT** in their blood, suggestive of liver damage:

- quad – 0%
- Atripla – 0%
- atazanavir + Truvada + cobicistat – 2%
- atazanavir + Truvada + ritonavir – 3%

Here is the proportion of participants who had moderate-to-severe elevations in the levels of the liver enzyme **AST** in their blood, suggestive of liver damage:

- quad – 0%
- Atripla – 0%
- atazanavir + Truvada + cobicistat – 0%
- atazanavir + Truvada + ritonavir – 3%

Here is the proportion of participants who had moderate-to-severe elevations in the level of the waste product bilirubin in their blood:

- quad – 0%
- Atripla – 0%
- atazanavir + Truvada + cobicistat – 82%
- atazanavir + Truvada + ritonavir – 86%

Overall, the results from these Phase II trials suggest that combinations that use cobicistat have potent anti-HIV activity. However, larger and longer comparative trials—Phase III studies—are needed to determine the effectiveness of these new combinations over the long-term.

Although there were a modest number of volunteers in the studies, cobicistat appears to increase lipid levels to a similar degree as efavirenz (Sustiva and in Atripla) or ritonavir. This finding needs to be explored in larger Phase III studies. Similarly, cobicistat's impact on kidney health and a possible interaction between atazanavir and tenofovir and their impact on kidney health need to be further assessed. The potential for cobicistat to interact with other medications commonly used by HIV-positive people is also something that requires further study.

REFERENCE:

Cohen C, Shamblaw D, Ruane P, et al. Single-tablet, fixed-dose regimen of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 achieves a high rate of virologic suppression and GS-9350 is an effective booster. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 58 LB.

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## B. 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.

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### 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 in section C.

### 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.

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## 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:

Darr E, Tierney C, Fischl M, et al. ACTG 5202: Final results of abacavir/3TC or tenofovir/FTC with either efavirenz or atazanavir/ritonavir in treatment-naïve HIV-infected patients. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 59 LB.

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## C. ACTG 5224 — changes in bones and fat

Most large clinical trials have found that after starting highly active antiretroviral therapy (HAART) bone density decreases and then stabilizes. Researchers conducted a sub-study of the larger ACTG trial 5202 that focused on changes after two years in bones and limb fat when comparing different regimens. This sub-study was called ACTG 5224. For background information on ACTG 5202, please see the previous story in section B.

In trial 5224, researchers analysed data collected from 269 participants whose average profile at the start of the study was as follows:

- 15% females, 85% males
- age – 38 years
- CD4+ count – 233 cells
- viral load – 42,000 copies/ml

### Results—changes in the spine and hips

For the first six months of the study, the spines of participants became thinner. After this time they started to increase in density. The increase was greatest among users of Kivexa compared to Truvada, and this difference in improved bone density was statistically significant; that is, not likely due to chance alone. The hipbones of Truvada users became thinner.

Similarly, after the first six months, efavirenz users had increased bone density in their spine compared to atazanavir-ritonavir users. This difference was statistically significant. Neither efavirenz nor atazanavir-ritonavir had a significant effect on bone density in the hip.

Overall, about 4% of participants had a fracture. However, fracture rates were not different among the different study regimens.

### Results—limb fat

Some medicines used for the treatment of HIV infection can cause the fatty layer just under the skin (subcutaneous fat) to disappear. This can affect the appearance of the face and limbs. To assess changes in subcutaneous fat, studies use low-dose X-ray scans, called DEXA, of the limbs. Combinations that contained either Kivexa or Truvada had increased limb and trunk fat. Use of atazanavir-ritonavir resulted in a greater increase in limb fat than efavirenz

On average, about 16% of participants on each of the four study regimens lost at least 10% of subcutaneous fat in their limbs. Using this metric—a 10% or greater loss of limb fat—there were no statistically significant differences among study regimens.

### Summary

- All regimens seemed to have been associated with accelerated bone loss at the onset, but bone density became stable after the first year.
- Truvada was linked to greater loss of bone density in the hip and spine than Kivexa. Use of atazanavir-ritonavir was linked to greater loss of bone density in the spine compared to efavirenz.
- Regimens containing either Kivexa or Truvada had increased limb and trunk fat.
- Use of atazanavir-ritonavir resulted in a greater increase in limb fat than efavirenz.
- Fat wasting occurred in about 16% of participants and did not differ by study regimen.

### REFERENCE:

McComsey G, Kitch D, Darr E, et al. Bone and limb fat outcomes of ACTG 5224s, a substudy of ACTG A5202: a prospective, randomized, partially blinded phase III trial of abacavir/3TC or tenofovir/FTC with efavirenz or atazanavir/ritonavir for initial treatment of HIV-1 infection. In: Program and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections, 16–19 February 2010, San Francisco, U.S. Abstract 106 LB.

## D. Odin — darunavir-ritonavir once or twice daily

Darunavir (Prezista) is a protease inhibitor that is an effective part of HAART when prescribed at a dose of 600 mg, taken with 100 mg of ritonavir (Norvir), both drugs taken *twice* daily. The presence of ritonavir raises and prolongs the levels of darunavir in the blood, allowing for *once* daily dosing of darunavir when used at a dose of 800 mg together with 100 mg of ritonavir.

In the clinical trial Odin (TMC 144-229), researchers compared the effects of once-daily vs. twice-daily darunavir-ritonavir, both regimens taken with two nukes in moderately treatment-experienced participants. Importantly, all participants had HIV that was sensitive to darunavir and none had previously used drugs such as T-20 (enfuvirtide, Fuzeon), tipranavir (Aptivus) or darunavir.

Results after 48 weeks showed that once-daily darunavir-ritonavir was similarly effective to twice-daily darunavir-ritonavir.

### Study details

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

- 36% females, 64% males
- age – 40 years
- CD4+ count – 225 cells
- viral load – 16,000 copies

### Treatment history

About 45% of participants had never previously used a protease inhibitor. Indeed, most participants (85%) had HIV that was sensitive to the antiviral activity of approved protease inhibitors.

Based on treatment history and HIV resistance testing, most participants (75%) received two nukes in addition to darunavir-ritonavir.

Researchers randomly assigned participants to receive one of the following regimens:

- darunavir 800 mg together with 100 mg ritonavir, both taken once daily
- darunavir 600 mg together with 100 mg ritonavir, both taken twice daily

### Results

After 48 weeks, the proportion of participants whose viral load was less than 50 copies/ml was as follows:

- once-daily darunavir-ritonavir – 72%
- twice-daily darunavir-ritonavir – 71%

Another way to assess the effectiveness of study medications is to examine the proportion of people whose viral loads at the start of the study were more or less than 50,000 copies/ml and how treatment affected the proportion whose viral loads later fell below 50 copies/ml.

Virologic success when baseline viral loads were more than 50,000 copies:

- once-daily darunavir-ritonavir – 53%
- twice-daily darunavir-ritonavir – 53%

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Changes in CD4+ cell counts were as follows:

- once-daily darunavir-ritonavir – 100 more CD4+ cells
- twice-daily darunavir-ritonavir – 94 more CD4+ cells

### What about drug levels?

Although darunavir levels in the blood of participants taking the once-daily regimen were less (1,896 ng/ml) than detected in participants who took this drug twice daily (3,197 ng/ml), it was still many times greater than needed to suppress HIV.

### Resistance

The proportion of participants with virologic failure in both groups was as follows:

- once-daily dose – 22%
- twice-daily dose – 18%

This difference was not statistically significant. In most cases of virologic failure, participants' regimens were never able to suppress their viral loads below the 50-copy/ml mark. A detailed analysis of why this happened has not yet been publicly released. Preliminary findings suggest that only one case of resistance to darunavir developed in people with virologic failure.

### Side effects

Historically, protease-inhibitor-based regimens have been difficult to tolerate. However, newer regimens based on lopinavir (in Kaletra), atazanavir (Reyataz) or darunavir are generally better tolerated. Regarding some specific side effects, here is the proportion of participants who experienced mild-to-moderate symptoms that researchers stated were “at least possibly related to darunavir”:

#### Nausea

- once-daily darunavir – 4%
- twice-daily darunavir – 4%

#### Vomiting

- once-daily darunavir – 2%
- twice-daily darunavir – 3%

#### Diarrhea

- once-daily darunavir – 4%
- twice-daily darunavir – 4%

The proportion of participants who had severe-to-life-threatening adverse events were as follows:

- once-daily darunavir – 8%
- twice-daily darunavir – 15%

Unfortunately, no details are yet publicly available about these adverse events.

Two people died in the once-daily group and six in the twice-daily group, but investigators did not consider these deaths to be related to exposure to darunavir.

### Lab tests

In general, levels of lipids—triglycerides, total cholesterol and bad (LDL) cholesterol—in the blood were greater among people taking the twice-daily rather than the once-daily regimen; these differences were statistically significant.

The proportion of people with elevated liver enzymes (ALT and AST) ranged between 2% in the once-daily group and 4% in the twice-daily group, but these differences were not statistically significant.

### Summary

In moderately treatment-experienced participants, half of whom had never used a protease inhibitor before, a regimen that included once-daily darunavir-ritonavir 800-100 mg was similarly effective to a twice-daily regimen of darunavir-ritonavir 600-100 mg.

Rates of virologic failure were low and in only one case did resistance to darunavir develop.

The once-daily regimen was well tolerated with low rates of diarrhea and few dropouts due to side effects.

Results from Odin suggest that once-daily darunavir-ritonavir 800-100 mg could be considered for people whose previous regimens have failed and who have no mutations in their HIV that enable it to resist the effect of darunavir.

### REFERENCE:

Cahn P, Fourie J, Grinsztejn B, et al. Efficacy and safety at 48 weeks of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1 patients with no darunavir resistance-associated mutations: the Odin trial. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 57.

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## E. Monotherapy with darunavir-ritonavir—the Monet study

In December 2009, the U.S. Department of Health and Human Services (DHHS) updated its guidelines for the treatment of HIV-positive people. These guidelines recommend specific regimens (which the DHHS calls “preferred” regimens) for doctors and their patients to consider, including these:

- efavirenz (Sustiva) + tenofovir (Viread) + FTC
- atazanavir (Reyataz) + low-dose ritonavir (Norvir) + Truvada (tenofovir + FTC)
- darunavir (Prezista) + low-dose ritonavir + Truvada
- raltegravir (Isentress) + Truvada

For pregnant women, the guidelines prefer that the following combination be used:

- lopinavir-ritonavir (Kaletra) + AZT (zidovudine, Retrovir) + 3TC (lamivudine); the latter two drugs are co-formulated into one pill and sold as Combivir

Each of the DHHS preferred combinations contains three or more drugs. All combinations have been proven effective at reducing the production of HIV in the blood and raising CD4+ cell counts, leading to a return to health. Because HAART does not cure HIV infection, this therapy has to be taken for life. Yet some of these combinations are relatively new in the history of HIV treatment and no one knows what their long-term side effects might be. This lack of long-term data puts HIV-positive people and their doctors in a difficult position when it comes to weighing the risks and benefits of each combination, knowing that lives can be saved but that problems might appear in the future.

One possible way to make a regimen more tolerable, easier to adhere to and perhaps safer may be, in some cases, to drastically reduce the number of drugs to just one powerful anti-HIV drug. Some researchers are exploring this experimental concept in clinical trials. In the past several years, studies that have investigated this idea have used highly adherent volunteers whose viral load had been suppressed for many months and who had their therapy simplified to a boosted protease inhibitor, usually lopinavir-ritonavir. The latest drug to undergo testing as monotherapy is darunavir-ritonavir. In this case, the sole purpose of low-dose ritonavir is to boost and maintain levels

of darunavir in the body. This type of therapy is essentially monotherapy.

### Painting with a different brush

The manufacturer of darunavir, Tibotec, is conducting a study called Monet which is expected to last for up to three years. Volunteers for Monet had been taking HAART for at least six months prior to entering the study and for that time had a viral load less than 50 copies/ml. In total, 256 people were randomly assigned to one of the following regimens:

- darunavir-ritonavir 800-100 mg once daily (monotherapy group)
- darunavir-ritonavir 800-100 mg once daily + two nukes (triple-therapy group)

A virological comparison of the two regimens after 48 weeks suggests that both regimens have similar effectiveness.

### Study details

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

- 19% females, 81% males
- age – 44 years
- CD4+ cell count – 574 cells
- length of time previously on HAART – 7 years
- 25% had never used protease inhibitors before
- 13% were co-infected with hepatitis C virus

### Results

After 48 weeks, the proportion of participants whose viral loads were less than 50 copies were as follows:

- monotherapy – 86%
- triple therapy – 88%

By the statistical rules underpinning Monet, these results show that switching to darunavir-ritonavir from darunavir-ritonavir-based HAART is roughly equivalent, at least for 48 weeks.

CD4+ cell counts remained stable in each study group throughout the trial.

### Focus on failure

In this study, treatment failure was defined very strictly—any participant who had two consecutive viral load assessments that were greater than 50 copies/ml by week 48 or who had otherwise quit the study. Using this strict definition, a total

of 20 participants who received darunavir monotherapy had treatment failure. But 18 of these (90%) had a viral load below the 50-copy/ml mark at week 48. According to the study researchers, most of the repeated elevations in viral load were in the range of 50 to 200 copies/ml and occurred at times of poor adherence or co-infections.

In the triple-therapy arm there were 19 cases of treatment failure; 17 of these (89%) had a viral load below the 50-copy/ml mark either at week 48 or at their last test.

Upon investigating cases of elevated viral load in both groups, researchers found that hepatitis C co-infection was somehow linked to an increased risk for elevated HIV viral load. However, no details were released to explain this finding.

Researchers were able to analyse blood samples to check for HIV that was resistant to therapy in only 57% of cases (35 of 61) where viral load was greater than 50 copies. In 33 out of 35 cases, HIV was sensitive to the effects of all ritonavir-boosted protease inhibitors and to non-nukes.

### Complications and side effects

Serious adverse events were seen in 18 participants, nine in each arm of the study. Side effects that were graded by investigators as moderate-to-life-threatening in intensity were mostly nausea, vomiting or diarrhea.

Common abnormalities in blood tests results were elevated lipids and liver enzymes. The number of participants with severe elevations in liver enzymes (AST and/or ALT) was as follows:

- monotherapy – six people
- triple therapy – two people

According to investigators, most of these people had recent infections with various hepatitis-causing viruses, which likely accounted for the elevated liver enzyme levels.

Sustained increases in total cholesterol levels graded as severe were distributed as follows:

- monotherapy – five people
- triple therapy – two people

### Putting it in perspective

The overall results from Monet are an exciting development. They suggest that in some highly adherent people whose viral loads are suppressed

with HAART, simplification to once-daily monotherapy with boosted darunavir is usually able to continue providing virologic and immunologic benefit, at least for 48 weeks. The Monet data cannot be extended to assume that initiating therapy with boosted darunavir (or any other protease inhibitor) alone instead of HAART would be adequate.

In general, protease inhibitors do not penetrate the brain and spinal cord—the central nervous system (CNS)—well. However, in the Monet trial, neuropsychiatric events occurred at a similar rate in both study arms, suggesting that there was no increased risk of these problems in the monotherapy arm. There was no sub-analysis using functional MRI or other state-of-the-art imaging techniques of the CNS. Nor was there extensive neuropsychological testing of the kind that is used in studies of neuro-cognitive function and HIV infection by neurologists. Therefore, subtle changes to parts of the brain that deal with higher intellectual functions, memory and thinking may not have been detected by the Monet researchers.

The research team stated that its results suggest that “a switch to darunavir monotherapy can be considered in treatment-experienced patients who have a history of [viral load] below 50 copies/ml on other treatments but who are wishing to avoid toxicities related to nucleoside analogues, non-nucleosides or other antiretrovirals.”

Since HIV-positive people will likely be taking therapy for life, longer studies are needed to assess the effects of darunavir monotherapy. If further studies confirm its potential benefits and treatment guidelines endorse the use of darunavir (or other protease-inhibitor-based) monotherapy, this approach would not be for every HIV-positive person. Doctors will need to check their patients’ medical history, assess the presence of co-infections (particularly hepatitis B virus) and carefully screen potential monotherapy users for factors that can affect adherence, including anxiety, depression and substance use.

For now, the DHHS considers monotherapy in HIV infection to be experimental. But as long-term data on the effectiveness of monotherapy accumulate, the position of this approach to therapy may be reconsidered by treatment guidelines.

### REFERENCES:

1. Arribas JR, Horban A, Gerstoft J, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for

patients with HIV RNA below 50 copies/ml. *AIDS*. 2010 Jan 16;24(2):223-30.

2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. [Accessed March 30, 2010]

## F. Surprising changes in body fat with darunavir monotherapy

Exposure to the nukes d4T (stavudine, Zerit) and, to a lesser extent, AZT (zidovudine, Retrovir) can cause the loss of subcutaneous fat (the fatty layer just under the skin). The wasting away of this fatty layer is called lipoatrophy. This wasting of subcutaneous fat can alter a person's appearance, causing the veins in the arms and legs to appear as if they are bulging and causing parts of the face, particularly the cheeks and temples, to sink.

In high-income countries, safer nukes such as these are commonly used:

- tenofovir + FTC co-formulated into one pill called Truvada
- abacavir + 3TC co-formulated into one pill called Kivexa

Researchers at several hospital clinics in France are conducting a study called Monoï (ANRS 136). In this study, the effects of monotherapy with darunavir-ritonavir are compared to HAART regimens darunavir-ritonavir. Preliminary results from Monoï suggest that participants who received darunavir monotherapy had a statistically increase in the fat content of their limbs. This intriguing finding is discussed later in our report.

### Study details

Monoï is an ongoing study that enrolled HAART users whose viral load had been less than 50 copies/ml and randomly assigned them to one of the following regimens:

- darunavir-ritonavir 600-100 mg twice daily (monotherapy)
- darunavir-ritonavir 600-100 mg twice daily and two nukes (HAART)

A sub-study of Monoï (144 out of 225 participants) included DEXA scans of the limbs and other parts of the body. Assessments of limb fat are used in some HIV clinical trials to help researchers determine whether subcutaneous fat

(the fatty layer just under the skin) is increasing or decreasing. The participants who had DEXA scans were distributed as follows:

- monotherapy – 67 people
- HAART – 74 people

The average profile of participants who received DEXA scans was as follows:

- 22% females, 78% males
- age – 45 years
- length of time HIV positive – 12 years
- weight – 70 kg (154 lbs)
- body mass index (BMI) – 24
- total limb fat – 5 kg

### Results—changes in limb fat

Over the course of the study, limb fat changed in each regimen group as follows:

- monotherapy – an increase of 340 g
- HAART – a decrease of 20 g

This difference was statistically significant.

Over the course of the study, changes in fat in the trunk of the body were as follows:

- monotherapy – an increase of 730 g
- HAART – an increase of 600 g

This difference was not statistically significant.

The proportion of participants who lost at least 20% of the fat in their limbs during the study was as follows:

- monotherapy – 2% (1 out of 67 people)
- HAART – 11% (8 out of 74 people)

This difference was also not statistically significant.

### Results—fat and sugar

Differences in triglycerides and cholesterol levels in the blood between the two study regimens were not statistically significant.

Blood sugar levels fell in the HAART group and rose modestly in the monotherapy group. This difference was statistically significant.

### Further analyses

Taking into account many factors, researchers found that people who lost their subcutaneous fat in this study tended to be younger (averaging 39 years) compared to people who did not lose this fatty layer (averaging 46 years). Because of the

relatively small number of people with fat wasting, it is not clear if this finding is clinically meaningful or an accidental discovery.

The study team also found that participants who gained fat deep within their bellies were more likely to have a high level of belly fat at the start of the study compared to people who tended to not gain belly fat.

The regimens that volunteers took prior to joining Monoi did not apparently have any impact on subsequent changes in body composition during the study.

### **Putting it in perspective**

Monoi is ongoing and an analysis of its data is needed after the two-year mark to find out if the changes noted during the first year are sustained.

While an average increase in limb fat of about 340 grams (less than one pound) with DEXA scans in people taking monotherapy is intriguing, it is not clear if this increase will be noticed by people taking these medicines, at least over the first year of therapy. The finding that there was an increase in limb fat in people **not** taking nukes is unusual and, if sustained, may require confirmation in another, larger, study. The number of people affected by fat loss in Monoi is relatively small and while eight cases occurred in the group taking HAART, one case did occur in a person taking darunavir-ritonavir monotherapy. Altogether, the interim results from Monoi are provocative and interesting and may stimulate debate among researchers. The two-year results are eagerly awaited.

### **REFERENCES:**

1. Valantin M-A, Flandre P, Kolta S, et al. Fat tissue distribution changes in HIV-infected patients with viral suppression treated with darunavir/ritonavir monotherapy versus 2 NRTI + darunavir/r in the Monoi-ANRS 136 randomized trial: results at 48 weeks. In: Program and abstracts of the *17th Conference on Retroviruses and Opportunistic Infections*, 16–19 February 2010, San Francisco, U.S. Abstract 721.
  2. Degris E, Delpierre C, Sommet A, et al. Longitudinal study of body composition of 101 men with lipodystrophy: DXA criteria for lipodystrophy evolution. *Journal of Clinical Densitometry*. 2010; *in press*.
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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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CATIE (the Canadian AIDS Treatment Information Exchange) is committed to improving the health and quality of life of all people living with HIV/AIDS in Canada. CATIE serves people living with HIV/AIDS, and the people and organizations that support them, by providing accessible, accurate, unbiased and timely treatment information. CATIE provides such information through a comprehensive Web site, a bilingual toll-free phone service, electronic and print publications, a national reference library and workshops and exhibits at conferences across Canada.

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