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:


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