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## The re-emergence of dual therapy

In the past decade, attempts have been made in clinical trials to simplify combination HIV therapy (ART) from a standard mix of three active drugs to two or even one-drug maintenance therapy. The idea is that after using a standard number of drugs to initiate and suppress HIV levels to less than 50 copies/mL, therapy can be reduced to fewer drugs to maintain viral suppression. Most such simplification studies have had issues.

The pharmaceutical company Viiv Healthcare has been developing a simplified therapy with the following drugs taken orally:

- dolutegravir (Tivicay and in Triumeq)
- rilpivirine (Edurant and in Complera and Odefsey)

Dolutegravir is a potent integrase inhibitor and rilpivirine is a non-nuke. The combination of both drugs in one pill has been licensed in the U.S. and sold under the brand name Juluca. The U.S. Food and Drug Administration (FDA) has stated that dolutegravir-rilpivirine can replace a patient's current regimen as long as their viral load is undetectable (less than 50 copies/mL) and they have been "on a stable regimen for at least six months with no history of treatment failure and no known [mutations in their HIV] associated with resistance to [dolutegravir and rilpivirine]."

Dolutegravir-rilpivirine will likely be licensed in Canada and the European Union in the spring of 2018.

## Swords

The clinical trials that provided the data to support licensure of dolutegravir-rilpivirine are called Sword-1 and Sword-2. They showed that the combination of dolutegravir-rilpivirine is highly effective and generally safe. Furthermore, there was no increase in levels of inflammation in participants who switched from standard ART to dolutegravir-rilpivirine. This is important because HIV causes heightened inflammation that researchers suspect can accelerate injury to many organ-systems. This inflammation is partially reduced with standard ART and it is reassuring that it remains at reduced levels with dolutegravir-rilpivirine.

## Changes over time

The approval of dolutegravir-rilpivirine by the FDA represents a major change in what constitutes a regimen for maintaining the effects of HIV treatment. Prior to 1996, standard therapy consisted of one and then a combination of two drugs, usually nukes (nucleoside analogues). At best, these conferred temporary benefit, as nukes are relatively weak when taken on their own. Furthermore, the nukes in widespread use at that time were relatively toxic. However, in 1996 several pivotal trials showed that a combination of three drugs from two classes, usually a protease inhibitor and two nukes, generally resulted in dramatic and sustained improvements in health and survival. Subsequently, other classes of drugs—non-nukes and integrase inhibitors—became widely used but they too were combined with nukes. Combinations that include integrase inhibitors have been shown to be the most powerful against HIV. Integrase inhibitor-based combinations reduce viral loads quickly, tend to have the fewest interactions with other medicines and are usually well tolerated. Such combinations are recommended by leading treatment guidelines for the initial therapy of HIV.

## Why consider dual therapy?

Researchers estimate that about 50% of HIV-positive people in North America and Western Europe are at least 50 years old. As HIV-positive people age, they are likely to need multiple medicines to treat emerging health conditions, such as higher-than-normal blood pressure, abnormal lipid levels, pre-diabetes and diabetes, anxiety and depression, osteoporosis, and so on. Some researchers and doctors, particularly geriatric specialists, are concerned that the burden of so many medicines over time has the potential to adversely affect the body and a

person's health. They think there may be potential for reducing the total number of medicines a person takes, including, in some cases, HIV medicines. In particular, some doctors think that it is possible that some patients may benefit from reduced exposure to nukes.

## Overcoming a legacy of the past

Most clinical trials of simplified therapy have been imperfect. They have tended to be small, did not collect a wide range of data, had combinations that may not be as potent as those available today, or, if promising results were initially shown, they were not confirmed in another study. This has all changed with the development of a single pill containing dolutegravir-rilpivirine, which has been tested in two large randomized clinical trials. Both drugs complement each other and interfere with the production of copies of HIV by infected cells in different ways.

There are still other issues to consider about dolutegravir-rilpivirine, such as the following:

### Reservoir

What effect will this combination have on the pool (called the "reservoir" by researchers) of HIV-infected cells that is deep within parts of the body, such as the lymph nodes and lymphatic tissues, the brain, the bone marrow, the spleen? To be fair, under standard ART, this pool is maintained. However, studies are needed to compare the size of the reservoir in people taking dolutegravir-rilpivirine against people taking standard ART.

### Brain

What impact will there be on neurocognitive function? Both dolutegravir and rilpivirine can penetrate the cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, in quantities that can suppress HIV. So, it is very likely that relatively high concentrations of these drugs enter the brain. This is important because HIV-infected cells of the immune system can travel to and reside in the brain.

### Safety

In clinical trials, the combination was generally safe and well tolerated, though there was a small proportion of participants taking dolutegravir-rilpivirine who had neuropsychiatric problems—sleep difficulties, anxiety and depression. This has been seen in other clinical trials of dolutegravir. It is likely that, in the future, doctors who have patients with these pre-existing problems will steer them toward other combinations.

### More to come

The combination of oral dolutegravir-rilpivirine in one pill taken once daily with food represents the first of several powerful dual regimens that are being developed as simplified maintenance therapy. Clinical trials are underway with long-acting injectable formulations of the experimental integrase inhibitor cabotegravir and rilpivirine. Smaller studies have also occurred with another combination—dolutegravir + 3TC (lamivudine). In this issue of *TreatmentUpdate* we review clinical trials of dual therapy with dolutegravir and another drug, mostly as maintenance therapy but also as initial therapy.

—Sean R. Hosein

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