Resistance to integrase inhibitors

HIV has the ability to mutate (or change) and develop the capacity to resist the effects of treatment. The chance of such changes greatly increases when doses of treatment are missed or skipped.

Researchers in North Carolina have been studying HIV’s ability to resist treatment, particularly the class of medicines called integrase inhibitors. Members of this class are as follows:

- raltegravir
- elvitegravir
- dolutegravir

In this recent study, U.S. researchers analysed HIV in blood samples from 3,022 participants that had been collected to assess HIV’s ability to resist drugs. The type of resistance testing done was genotypic testing. This type of testing can identify known mutations in genes that allow HIV to resist the effect of therapy.

Researchers found that about 16% of participants had HIV with at least one major mutation in the integrase gene. Common mutations were as follows:

- N155H
- Q148H/K/R

These mutations were equally common.

Based upon these and other findings, the researchers predicted that high-level resistance (this would very likely lead to treatment failure) to the following drugs was present in the following proportion of participants in their study:

- raltegravir - 15% of participants had high-level resistance to this drug
- elvitegravir - 13% of participants had high-level resistance to this drug
- dolutegravir - 2% of participants had high-level resistance to this drug

The 2% figure above was derived from all 3,022 participants. However, among participants who had at least one major mutation to integrase inhibitors, 12% had high-level resistance to dolutegravir. In other words, it is very likely that dolutegravir would not have been an effective treatment option for these people because of the development of cross-resistance.

About cross-resistance

Bear in mind that exposure to a failing regimen containing an integrase inhibitor can, in some cases, lead to the development of mutations in HIV that can cause not only resistance to the integrase inhibitor being used but also cross-resistance to other integrase inhibitors that have not yet been used. In the present study, some people using raltegravir not only developed resistance to this drug but also cross-resistance to other integrase inhibitors—even though they had never used these other drugs (elvitegravir and, to a lesser extent, dolutegravir). Cross-resistance is also an issue with other classes of HIV drugs.

The study took place over four years between January 2009 and December 2012. During this time, raltegravir is likely the integrase inhibitor that patients would have used. Elvitegravir was only approved four months prior to the study, so it is unlikely that elvitegravir users would have been part of it. Also, because anyone who participated in a clinical trial of integrase inhibitors was excluded, it is extremely unlikely that anyone in the study was exposed to dolutegravir, which was only approved in the U.S. in August 2013.
Additional findings

Researchers found that there were 239 participants with a high degree of resistance to integrase inhibitors. These participants were very treatment experienced, and HIV resistance testing revealed that they appeared to have limited treatment options. Among these 239 participants, here are some additional results of resistance testing:

- nukes – 14% did not have a nuke that was fully active against HIV
- non-nukes – 27% did not have a non-nuke that was fully active against HIV
- protease inhibitors – 5% did not have a protease inhibitor that was fully active against HIV

Overall, the study’s findings underscore the need to screen patients for resistance testing, particularly those whose integrase-based regimens may be failing.

CATIE’s *Positive Side* magazine has a very useful resource to help people understand HIV and its ability to resist therapy.

REFERENCE:

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