Exploring possible treatment options after virological failure with raltegravir

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There are several classes of anti-HIV drugs, the newest of which is integrase inhibitors.

The first licensed integrase inhibitor was raltegravir (Isentress) and the second was elvitegravir (in Stribild). These two drugs represent the first generation of integrase inhibitors. HIV that is resistant to raltegravir can often also be resistant to elvitegravir and vice versa. When HIV is resistant to more than one drug in a class, this type of resistance is called cross-resistance.

The next integrase inhibitor that was licensed was dolutegravir (Tivicay and in Triumeq). This drug belongs to the second generation of integrase inhibitors.

In general, integrase inhibitors are well tolerated, have potent anti-HIV activity and, in the case of raltegravir and dolutegravir, have relatively few interactions with other drugs.

Results from some trials

In clinical trials with heavily treatment-experienced people who received raltegravir, strains of HIV that can resist raltegravir (and in some cases also elvitegravir) have emerged in up to 60% of participants. In contrast, in clinical trials of raltegravir with participants who had never previously been exposed to anti-HIV therapy, up to 8% of participants have developed strains of HIV that are resistant to this drug.

In the clinic

The world of clinical trials is akin to a carefully controlled environment, with only highly selected participants who do not usually represent the full range of people seen at hospitals and clinics. It is therefore important that observational studies are conducted with clinic populations after a drug is licensed.

In France

Physician-researchers at leading infectious disease clinics in France have conducted an observational study of their patients whose regimens were based on raltegravir (that is, raltegravir was likely the most potent drug in their combinations). The doctors were particularly interested in how HIV might have changed or mutated to resist the effect of raltegravir and perhaps other integrase inhibitors and what this might mean for future therapeutic options. All participants were experiencing virological failure, defined by researchers as the results of two consecutive viral load test results that were greater than 50 copies/ml.

In an analysis of blood samples from just over 500 participants, technicians found that 61% had HIV that was still susceptible to all integrase inhibitors. In cases where HIV was resistant to raltegravir, 14% were also resistant to dolutegravir. Other findings appear later in this CATIE News bulletin.

Study details

Researchers recruited 502 participants from 17 clinics across France. All participants were using raltegravir-based regimens that were failing. Their average profile was as follows:
• age - 48 years
• gender - 74% men, 26% women
• viral load – between 200 and 6,310 copies/ml
• CD4+ count – 218 cells/mm³
• average number of previously used anti-HIV drugs – 8
• most common strain (or subtype) of HIV – subtype B (the most common strain in North America, Western Europe and Australia)

Researchers defined virological failure as two consecutive viral load test results that were greater than 50 copies/ml. Virological failure occurred on average 11 months after raltegravir-based regimens were initiated.

Commonly used drug combinations at the time of virological failure were as follows:

• raltegravir + two nucleoside analogues (also called “nukes”)
• raltegravir + nukes + protease inhibitors
• raltegravir + protease inhibitors

Results

The good news is that technicians found that in 61% (306) of participants HIV was susceptible to all integrase inhibitors, including raltegravir.

Cross-resistance associated with raltegravir resistance

The researchers presented data on 194 participants who had HIV that was resistant to raltegravir. Among these 194 people, there was only a small proportion—11% (21 of 194 participants)—in whom elvitegravir could be used because of lack of cross-resistance. In contrast, among those with HIV that was resistant to raltegravir, 64% (124 of 194 participants) had HIV that was susceptible to dolutegravir.

Linked to resistance

The development of HIV that was resistant to raltegravir was associated with the following:

• having a viral load greater than 1,000 copies/ml
• having HIV that was only modestly susceptible to the non-raltegravir component in regimens

The researchers said that doctors treating raltegravir-using patients should take this information into account. They also stated that minimizing the time patients spend on a failing regimen containing raltegravir or elvitegravir is very important. The longer HIV is exposed to a failing regimen of either of those integrase inhibitors, the more likely it is to develop and accumulate mutations that can help it to also resist dolutegravir.

—Sean R. Hosein

REFERENCES:


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