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Resistance following failure of injectable cabotegravir/rilpivirine may limit future treatment options

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Although virological failure of injectable cabotegravir/rilpivirine is rare, viral rebound can lead to resistance mutations that may exclude future treatment with widely used antiretrovirals, studies presented last week at the 20th European AIDS Conference (EACS 2025) in Paris show.

While the integrase inhibitor cabotegravir has a high barrier to the development of resistance mutations, resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine can emerge quickly after viral rebound. This is especially true if the virus already carries naturally occurring mutations that increase susceptibility to rilpivirine resistance.

Long-acting injectable treatment can overcome the adherence difficulties that often lead to treatment failure, but injectable cabotegravir/rilpivirine (CAB/RPV) treatment may fail due to other factors such as low drug concentrations. If treatment fails, the resistance profile is uncertain.

In the first study, Dr Maria Mazzitelli of Rome Catholic University and colleagues in the Netherlands carried out a review of all published cases of virologic failure of CAB/RPV that included resistance data. They assessed the reported resistance mutations against data on the sensitivity of viruses with the reported mutations to doravirine and etravirine (both NNRTIs) as well as to dolutegravir and bictegravir (both integrase inhibitors).

They identified 94 cases of virologic failure (representing 1.3% of those who initiated CAB/RPV in the reported populations). Data on NNRTI resistance and integrase inhibitor resistance at the time of virologic failure were available in 78 and 79 cases, respectively. Pre-switch data were reported in 75 and 65 cases, respectively.

Those experiencing virologic failure had been taking antiretroviral treatment for a median of nine years and had a median CD4 count of 618 at the time of virologic failure. Information on delayed dosing was available for 71 people; it was reported in three cases.

Full information on other known risk factors for virologic failure of injectable CAB/RPV (BMI> 30, baseline rilpivirine resistance mutations or HIV subtype A1/A6 virus) were reported in 45 cases; 57% had no risk factors for virologic failure and 37% had one risk factor. Two cases reported two risk factors.

Drug concentration data were available for 45 people with full or unknown drug susceptibility; 29% had low concentrations of either drug, but this did not differ from the control population of people who remained virally suppressed on CAB/RPV, so the investigators concluded that drug concentrations alone were insufficient to explain virologic failure.

Resistance testing after virologic failure showed that 56% of those tested had resistance to both rilpivirine and cabotegravir, 27% had reduced susceptibility to rilpivirine alone and 5% had reduced susceptibility to cabotegravir alone.

Extrapolating from the resistance mutations detected after virologic failure by using the Stanford resistance database, the investigators concluded that 44% of those who experienced virologic failure would have reduced susceptibility to dolutegravir and bictegravir, while 39% would show reduced susceptibility to etravirine and 35% to doravirine. However, high-level resistance was less common, offering the prospect that in the majority of cases, second-generation integrase inhibitors could be used in combination with other fully active agents.

A second study examined real-world data from the French Dat'AIDS cohort, which follows around 65,000 people with HIV. Of the 2196 people who had started CAB/RPV by the end of 2023, 42 (1.3%) experienced virologic failure. Resistance test results were available for 26 people, and new resistance mutations were detected in 13. Among those with new mutations, nine developed NNRTI resistance; two had no remaining NNRTI options but the others remained sensitive to doravirine. Integrase inhibitor resistance was detected in 12 people, three of whom had no remaining integrase inhibitor options. The other nine would require twice-daily dolutegravir to achieve sufficiently high concentrations.

Finally, a systematic review and meta-analysis of seven clinical trials in which CAB/RPV was compared to a three-drug oral regimen containing dolutegravir showed a five times higher risk of developing integrase inhibitor resistance after virologic failure in people taking CAB/RPV. Although the risk of virologic failure was similar in people taking CAB/RPV or a three-drug regimen, 67% of people who experienced virologic failure on CAB/RPV developed integrase inhibitor resistance mutations compared to none of those taking a three-drug oral regimen containing dolutegravir (risk ratio, 5.5, 95% CI 1.43-21.18). However, of the 16 people who developed integrase inhibitor resistance in the clinical trials, only three developed confirmed high-level resistance and three developed intermediate-level resistance. The remaining 10 cases showed only low-level resistance.

References

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