

Reverse transcription and integration

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Primary resistance against dolutegravir decreases HIV integration

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Background: Dolutegravir is an integrase inhibitor that has shown a high genetic barrier against the emergence of resistant strains. No resistance substitution has been observed in treatment-naïve individuals treated with this drug. In tissue culture experiments, we have identified the R263K resistance substitution as a signature substitution for HIV resistance against dolutegravir, an observation that was later confirmed in highly treatment-experienced individuals. Given the importance of DNA integration in the establishment of HIV persistence, we tested the ability of dolutegravir-resistant HIV strains to integrate within human DNA.

Methods: We used an Alu-mediated quantitative PCR to measure levels of integration of dolutegravir-resistant variants in primary human PBMCs. Levels of integration were normalized using the b-actin gene. These experiments were performed using subtype B and C viruses.

Results: Our results show that dolutegravir-resistant variants are impaired in their ability to integrate within human DNA. The integration levels of subtype B and C R263K variants were decreased by 30% and 40% compared to WT viruses, respectively. More important, the addition of several secondary substitutions failed to restore integration to a level comparable to WT and, in some cases, further lowered integration to only 20% of WT.

Conclusions: The relative inability of dolutegravir-resistant variants to integrate within human DNA may contribute to a progressive decrease in the viral reservoir of individuals who develop these substitutions.

Under embargo until 11.00 on 21 July 2015