Updates on the Resistance Profile of Integrase Inhibitors and Their Clinical Application in Treatment Failure and Treatment-Naïve Patients

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Integrase strand-transfer inhibitors (INSTI) were initially evaluated in patients with multidrug resistance and clearly demonstrated an ability to rescue those with few treatment options. Given their efficacy and tolerability profiles they have been subsequently evaluated in ARV naïve subjects and in switch/simplification. No drugs have demonstrated superiority against INSTI in clinical trials. Three agents are currently available: raltegravir, elvitegravir/cobicistat, and dolutegravir. Despite its high efficacy, both raltegravir and elvitegravir/cobicistat have a low barrier to resistance development, being N155H, Q148X, Y143X and E92Q the main pathways. Dolutegravir displays a remarkably different resistance profile. Its robust pharmacokinetic/pharmacodynamic properties - long plasma $t_{1/2}$, high plasma inhibition quotient, and slow dissociation rate from the integrase complex – suggest it should pose a high barrier to resistance development. This has been confirmed in pivotal phase III studies of initial therapy, with none out of 1,118 treated individuals selecting resistance-associated mutations at the integrase or reverse transcriptase. In integrase-naïve subjects with virological failure, a rescue intervention with dolutegravir has shown significantly higher rates of virological suppression than raltegravir, as well as significantly lower rates of selection of resistance both at the integrase and against the optimized background. Unanticipatedly, a mutation rarely selected in this scenario (R263K) induces a fitness cost that prevents HIV-1 from evading drug pressure, and accumulation of further secondary mutations does not occur and has not been able to compensate the replication capacity deficit in the aftermath of the appearance of a single drug resistance mutation. Therefore, both *in vitro* and *in vivo* it leads the virus to a previously unnoticed evolutionary pathway with low chances to develop resistance to both dolutegravir and other families of antiretrovirals present in the background. This high genetic barrier to resistance development in early stages of antiretroviral treatment can help preserving future treatment options in patients who fail antiretroviral therapy.