Antiretroviral therapy: dolutegravir sets SAIL(ING)

Of all the antiretroviral therapy (ART) drugs in recent development, few have generated as much expectation as the HIV integrase strand transfer inhibitor dolutegravir. Raltegravir, the first in this class, has proved to be a very valuable drug, from treatment initiation to late salvage.1 However, in an era in which once daily therapy and single tablet regimens dominate the treatment initiation market, raltegravir has the relative disadvantage of twice daily dosing.

In 2012 the second-in-class integrase strand transfer inhibitor, elvitegravir, gained US Food and Drug Administration approval as a component of the new four-in-one single tablet regimen Stribild (Gilead Sciences Inc, Foster City, CA, USA). Elvitegravir requires pharmacological boosting because it does not support once daily dosing in its own right. Although this quadriple regimen has shown non-inferiority versus the first single tablet ART regimen of efavirenz, tenofovir, and emtricitabine (Atripla, Gilead Sciences Inc and Bristol-Myers Squibb Co, Princeton, NJ, USA)3 and ritonavir-boosted atazanavir, tenofovir, and emtricitabine,4 the need for boosting is a relative drawback with an increased potential for drug–drug interactions. Elvitegravir is not currently available as a single agent.

The third-in-class integrase strand transfer inhibitor likely to obtain approval, possibly within the next year, is dolutegravir. Dolutegravir’s half-life supports once daily dosing, and it is therefore the first stand-alone once daily drug in this class. Dolutegravir has shown non-inferiority in a double-blind comparison with raltegravir.5 Results presented at a recent conference were consistent with dolutegravir having superior efficacy in ART-naive participants when used as a component of a single tablet regimen (combined with abacavir and lamivudine) in a double-blind comparison with Atripla.6 In The Lancet, Pedro Cahn and colleagues7 publish the results of SAILING, a double-blind randomised controlled comparison of dolutegravir versus raltegravir with optimised background regimen, in 715 participants with HIV with previous failure of combination ART regimens and demonstrable resistance to drugs in at least two ART drug classes, but no history of previous exposure to an integrase strand transfer inhibitor. The investigators found that not only was dolutegravir non-inferior to raltegravir in the primary analysis of proportion of patients with plasma HIV-1 RNA of fewer than 50 copies per mL at 48 weeks, but that dolutegravir reached predefined criteria for superiority (251 [71%] vs 230 [64%] patients; adjusted difference 7·4%, 95% CI 0·7–14·2; p=0·03). Adverse event rates were similar between groups and led to discontinuation in nine (3%) participants on dolutegravir and 14 (4%) on raltegravir.

SAILING helps to broaden our understanding of dolutegravir through enrolment of a diverse cohort from countries in North and Latin America, Europe, Africa, and Asia. The study population was 32% female, nearly half had previously developed AIDS, and participants had a mix of HIV subtypes. The resistance results are provocative. Of those with virological failure and determinable genotypes or phenotypes, integrase-associated mutations were shown in four (25%) of 17 participants on dolutegravir and 16 (42%) of 38 on raltegravir. In those four participants on dolutegravir, none selected a treatment-emergent mutation conferring high-level resistance to dolutegravir or raltegravir, although two selected a unique integrase-mutation conferring minor loss of susceptibility to both drugs. For the 16 participants on raltegravir the treatment-emergent mutations were consistent with those described to date, conferring substantial resistance to raltegravir but limited cross-resistance to
dolutegravir. This finding is consistent with in-vitro data which showed that dolutegravir retains activity against HIV isolates with raltegravir-associated or elvitegravir-associated resistance mutations.8

This development within the integrase strand transfer inhibitor class is analogous to the evolution of drugs in the non-nucleoside reverse transcriptase inhibitor class of ART. Cross-resistance between efavirenz and nevirapine meant that the development of resistance to one drug inevitably conferred high-level cross-resistance to the other, rendering the class ineffective. The emergence of etravirine changed the paradigm and has proven a useful component of salvage ART in patients with limited resistance to non-nucleoside reverse transcriptase inhibitors.9 In much the same way we can envisage the sequential use of a second integrase strand transfer inhibitor being incorporated into regimens in which limited resistance has developed after initial exposure to a regimen containing a drug in this class. This possibility is supported by data from the VIKING-3 cohort study,10 in which dolutegravir retained antiretroviral activity in participants with previous exposure to an integrase strand transfer inhibitor. However, dolutegravir’s activity was blunted in patients with baseline integrase strand transfer inhibitor mutations and diminished further as the resistance patterns to these drugs evolved. A necessary condition to prevent the progressive evolution of integrase strand transfer inhibitor cross-resistance is the availability of frequent virological monitoring so that early virological failure can be detected. Notably, our current understanding of dolutegravir resistance in vivo is based on few data. Continued study of the patterns of resistance and their evolution is therefore important as more people become exposed to dolutegravir.

The results of SAILING and other phase 3 studies suggest that dolutegravir will be a valuable addition to HIV treatment options. In an era in which the ART drug development pipeline is relatively dry, the emergence of a new drug in an existing class that seems likely to extend the number of viable ART regimens is welcome. The appearance of dolutegravir should help reinvigorate research to help us to extract maximum value from the available drugs in support of long and healthy lives for people living with HIV.

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