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Both a Protective and a Deleterious Role for the L76V Mutation

The L76V mutation, unknown in clinical isolates before 2001, has been described as associated with lopinavir resistance (LPV/r) (2, 6, 7), appearing to confer high levels of resistance to LPV and amprenavir; subsequently, it has also been included among darunavir resistance (DRV/r)-associated mutations (3).

Lambert-Niclot et al. (5) suggested that the virological failure of a DRV/r-based regimen was due to the selection of mutations which, although increasing the level of DRV/r, did not affect tipranavir (TPV) susceptibility; moreover, L76V was found to be protective for the development of additional DRV-associated mutations. L76V has also been reported to increase TPV susceptibility (8, 9); nevertheless, the real clinical implication of this mutation in response to TPV-containing regimens is still unknown.

We studied 176 human immunodeficiency virus type 1 (HIV-1)-infected multiexperienced patients previously exposed to a median of four protease inhibitors, who were administered a TPV resistance-based regimen. The impact on the TPV virological responses of both mutations included in the TPV mutation score (1, 4) and other protease mutations detected in >10% of the study population was evaluated. Virological success was defined as achieving a plasma viral load (pVL) of <50 cp/ml and a pVL decrease of >1 log after 12 and 24 weeks of a TPV-based regimen. While no association between L76V and the virological outcome was observed using the pVL level of <50 cp/ml as the primary end point (unpublished data), when considering a pVL decrease of at least 1 log cp/ml, L76V correlated with virological response at week 12 (0.19 odds ratio [OR]; 0.04 to 0.86 95% confidence interval [CI]; $P = 0.031$) with univariate analysis. In the multivariate analysis, in which a stepwise estimation model with a backward procedure was used to select the set of mutations most strongly associated with virological response, three mutations (E34Q, I72VTL, and Q92K) were correlated with treatment failure, while L76V was still associated with virological success (0.04 OR, 0.01 to 0.31 95% CI, and P of 0.002 at week 12 and 0.18 OR, 0.036 to 0.088 95% CI, and P of 0.034 at week 24). Mutation I50LV, also associated with TPV hypersusceptibility, was detected in 7% of the patients and therefore was not included in the analysis. Furthermore, the CD4 nadir, the number of previous protease inhibitors, and CDC stage C classification were also significantly ($P < 0.05$) associated with virological failure.

Therefore, the L76V mutation seemed to have a beneficial impact on virological response to TPV in our population with both analyses, thus extending the results of previous studies supporting the ability of L76V to resensitize HIV isolates to atazanavir and saquinavir (6).

The molecular basis for this ambivalent behavior (which renders L76V either deleterious or protective) might depend on the particular location of residue 76 within the HIV protease. Because of its position in a secondary protein shell, residue 76 is directly in contact with the residues of the S2 pocket; while LPV, DRV, amprenavir, and indinavir develop a strong and penetrating hydrophobic binding within this pocket, atazanavir, saquinavir, and TPV do not deeply penetrate the shell, leading to no change or increased susceptibility (7).

Our data strengthen the observations of Lambert-Niclot et al. (5), suggesting the noninvalidation of TPV susceptibility by DRV-associated mutations; in our experience, virological response to TPV benefited from the presence of L76V. In this respect, we agree with Lambert-Niclot et al., who stated that TPV may remain active after DRV use and that its presence could be useful to construct an optimal salvage regimen in multiexperienced patients.

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