Drug Resistance Mutations in HIV-Infected Patients in the Spanish Drug Resistance Database Failing Tipranavir and Darunavir Therapy

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The presence of resistance mutations in patients failing tipranavir or darunavir was examined at the national drug resistance database of the Spanish AIDS Research Network. Although mutations emerging during tipranavir and darunavir failures differed considerably, cross-resistance was found in up to half of the patients tested. Interestingly, mutation 54L, which is associated with tipranavir hypersusceptibility, was selected in half of the darunavir failures. Thus, resistance testing seems mandatory to ensure the benefit of the sequential use of these drugs.

The protease inhibitors (PI) tipranavir (TPV) and darunavir (DRV) have shown potent antiviral activity against most PI-resistant viruses, reflecting the fact that they display the greatest genetic barrier to resistance within the PI class. The effectiveness of these drugs seems to depend largely on either a unique binding affinity (DRV) or an exclusive nonpeptidomimetic structure (TPV) (5, 9). The RESIST and POWER trials were the first to demonstrate significantly greater reductions in plasma HIV RNA and increases in CD4 counts using TPV and DRV, respectively, over controls using other ritonavir-boosted PIs in HIV-infected patients with extensive PI resistance (3, 7).

Early information on TPV resistance derived from the RESIST trials identified 21 mutations located at 16 protease positions associated with a reduced virological response to TPV (2). The presence of more than eight of these changes was associated with a loss of optimal response to TPV. Phenotypic data permitted the splitting out of changes with the most (I47V, I54A, V82T) and least (I13V, K20R, M36I, M46L) impact on TPV susceptibility (10). Subsequently, a TPV weighted score was developed by using the data from the RESIST trials. The mutations I47V, I54A/M/V, Q58E, T74P, V82LT, and N83D had the greatest weights, while the others were considered less important. Interestingly, the mutations L24I, I50L/V, I54L, and L76V were associated with increased TPV susceptibility (hypersusceptibility) and accordingly had negative scores (12). More recently, a new TPV weighted score using additional data from an Italian cohort has been proposed (13).

Eleven mutations have been specifically associated with DRV resistance (9). The presence of three or more of these changes was associated with impaired DRV activity in the POWER trials. Although a DRV weighted score is not currently in use, specific changes are known to display the greatest impact (e.g., I50V, I54L, L76V, and I84V), while others show a lesser effect on DRV susceptibility (e.g., V32I, L33F, I47V, V11L, I54M, T74P, and I89V) (6).

Information about the selection of drug resistance mutations in patients failing TPV and DRV outside clinical trials is still scarce. Herein, we report results obtained by examining the protease gene in a relatively large group of antiretroviral-experienced HIV-1-infected individuals failing TPV and DRV for whom information was available at the national drug resistance database of the Spanish AIDS Research Network. This is a large clinical database in which viral genotypes derived from more than 3,500 HIV-1-infected patients with a history of prior antiretroviral drug failure outside clinical trials at 12 Spanish clinics have been recorded from 1999 until now (1).

TPV resistance-associated mutations (RAMs) were interpreted using the latest TPV weighted score (version 2.1) (14), and DRV RAMs were interpreted using the latest International AIDS Society—USA panel list (December 2009) (8). From a total of 4,813 genotypes derived from 3,299 different HIV-1-infected patients, 105 genotypes belonged to subjects failing TPV (n = 81) or DRV (n = 24).

Most of the genotypes examined belonged to highly antiretroviral-experienced patients. Overall, 97.1% had received other PIs. A total of 66.4% had been exposed to three or more PIs before beginning a TPV- or DRV-based regimen, with lopinavir, atazanavir, and fosamprenavir being the most widely used.

In TPV failures, the prevalence of TPV RAMs was as follows: L10V, 35.4%; L33F, 60.4%; M36I, 64.6%; K43T, 43.8%; M46L, 29.2%; I47V, 18.8%; I54A, 20.8%; Q58E, 22.9%; V82L, 29.2%; V82T, 45.8%; V84V, 50% (Fig. 1). The changes T74P and N83D were not found. The median number of TPV RAMs was 4 (interquartile range, 2 to 6). The most frequent patterns were 33F plus 36I (37.5%), 36I plus 43T (35.4%), 82T plus 36I (29.2%), 82T plus 43T (20.8%), and 82T plus 84V (20.8%).
In DRV failures, the prevalence of DRV RAMs was as follows: V11I, 25%; V321, 58.3%; L33F, 83.3%; I47V, 33.3%; I54L, 50%; I54M, 16.7%; I84V, 33.3%; L89V, 8.3% (Fig. 1). The changes I50V, T74P, and L76V were not found. The median number of DRV RAMs was 3 (interquartile range, 1 to 4). The most frequent resistance pattern was 32I plus 33F (58.3%), 32I plus 54L (50%), 33F plus 46I (50%), and 32I plus 33F plus 43T (50%). Half of the genotypes from DRV failures belonged to patients who had previously failed to fosamprenavir/ritonavir, although I50V was not present in any of them.

In agreement with prior observations by others (4, 11, 15), the overlap between protease RAMs in patients failing either TPV or DRV in our study was limited. In fact, only the mutations 33F, 47V, 54M, 74P, and 84V were seen in both groups of patients, with L33F being the most common shared change. It should be noted that this mutation has only minimal impact on TPV or DRV susceptibility. Of the changes considered to produce TPV hypersusceptibility (L24I, I50L, I50V, I54L, and L76V), three (50V, 54L, and 76V) lead to the greatest impairment of DRV susceptibility. Interestingly, only I54L was recognized in patients failing DRV in our study. Overall, cross-resistance between TPV and DRV failures that could preclude their sequential use was recognized in 50% of our patients.

The rate of response to DRV as part of salvage therapy in patients who have failed other PIs is relatively high (3, 9), which is in agreement with the robust resistance profile of DRV (9, 15). Our study suggests that in case of DRV failure, TPV-based rescue interventions may be a good option for highly antiretroviral-experienced patients with limited therapeutic options. In fact, only TPV of all of the other PIs might be active in this setting.

In summary, although distinct PI resistance-associated mutations emerge in antiretroviral-experienced HIV-1-infected patients failing TPV and DRV, half of these individuals may display cross-resistance. Thus, resistance testing seems warranted to ensure the maximal benefit of the sequential use of these drugs. The frequent selection of the mutation I54L in DRV failures must be highlighted since this change results in TPV hypersusceptibility.

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REFERENCES

FIG. 1. Prevalence of TPV and DRV resistance-associated mutations in 105 HIV-1-infected patients failing antiretroviral therapy with either TPV or DRV in our study was limited. In fact, only the mutations 33F, 47V, 54M, 74P, and 84V were seen in both groups of patients, with L33F being the most common shared change. It should be noted that this mutation has only minimal impact on TPV or DRV susceptibility. Of the changes considered to produce TPV hypersusceptibility (L24I, I50L, I50V, I54L, and L76V), three (50V, 54L, and 76V) lead to the greatest impairment of DRV susceptibility. Interestingly, only I54L was recognized in patients failing DRV in our study. Overall, cross-resistance between TPV and DRV failures that could preclude their sequential use was recognized in 50% of our patients.

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