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Mutations in the protease gene associated with virological failure to lopinavir-containing regimens in clinical samples

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Purpose of the study

Lopinavir/ritonavir (LPV/r) is increasingly being introduced in resource-limited settings as second-line therapy. Data on selection of resistance mutations (RAMs) in treatment-experienced populations failing LPV/r could provide insight into future ramifications of this strategy. We investigated the RAMs in patients with prior or current LPV/r failure.

Methods

We identified 195 samples from multi-treated patients submitted for routine resistance testing. Seventy-one (36%) never received LPV/r, 75 (38.5%) had previously failed LPV/r, and 49 (25%) were currently on LPV/r. Medians, interquartile ranges or percentages, Kruskal-Wallis, $\chi 2$ or Fisher test were used whenever appropriate.

Summary of results

Median CD4 282 cells/μl (IQR:252), HIV-1 VL 4.17 log10 (IQR 1.35), and duration of HIV infection 13 years. Number of NRTI, NNRTI and PI RAMs: 5 (IQR:4), 1 (IQR:1), and 6 (IQR:4), respectively. Patients exposed to LPV/r had received more HAART regimens ($p < 0.001$), PIs ($p < 0.001$), and NRTIs ($p < 0.001$). RAMs significantly associated with prior or current LPV/r exposure were: L10I/F ($p = 0.02$, $p = 0.001$), K20R ($p = 0.023$), L24I ($p = 0.01$), L33F ($p < 0.001$), M36I ($p = 0.029$), M46I/L ($p = 0.023$, $p = 0.003$), I47V ($p = 0.022$), G48V ($p = 0.08$), F53L ($p = 0.017$), I54V ($p < 0.001$), A71V ($p < 0.001$), G73S ($p = 0.008$), V82A ($p < 0.001$), I84V ($p < 0.001$), and L90M ($p = 0.037$). Two NRTI mutations were also associated with LPV/r failure: E44D ($p = 0.002$) and V118I ($p = 0.048$). L76V was found in only one sample. RAMs associated only with current (and not previous) LPV/r failure were: L33F, M36I, M46I, I47V, G48V, A71V, G73S, I84V, L90M. These RAMs are all included in the IAS-USA LPV/r list, except M36I and G48V, found to be associated with prior saquinavir use ($p = 0.02$ and $p < 0.001$, respectively). Mutations included in the IAS-USA list for LPV but not found to be associated with LPV/r previous or current failure: L10R/V, K20M, V32I, I47A, I50V, I54L/A/M/T/S, L63P, A71T, I76V, and V82F/T/S.

Conclusion

In multi-treated patients, L33F, M36I, M46I, I47V, G48V, A71V, G73S, I84V, L90M, but not L10R/V, K20M, V32I, I47A, I50V, I54L/A/M/T/S, L63P, A71T, I76V, and V82F/T/S may be over-represented in LPV/r failure. Enrichment of these mutations should be expected in populations receiving widespread salvage with LPV/r. This may assist in considering future options, together with previous use of other PI and subtype prevalence.