Analysis of intracellular human immunodeficiency virus (HIV)-1 drug resistance mutations in pluri-experienced HIV-1-infected patients treated with a salvage regimen: 4-years follow-up

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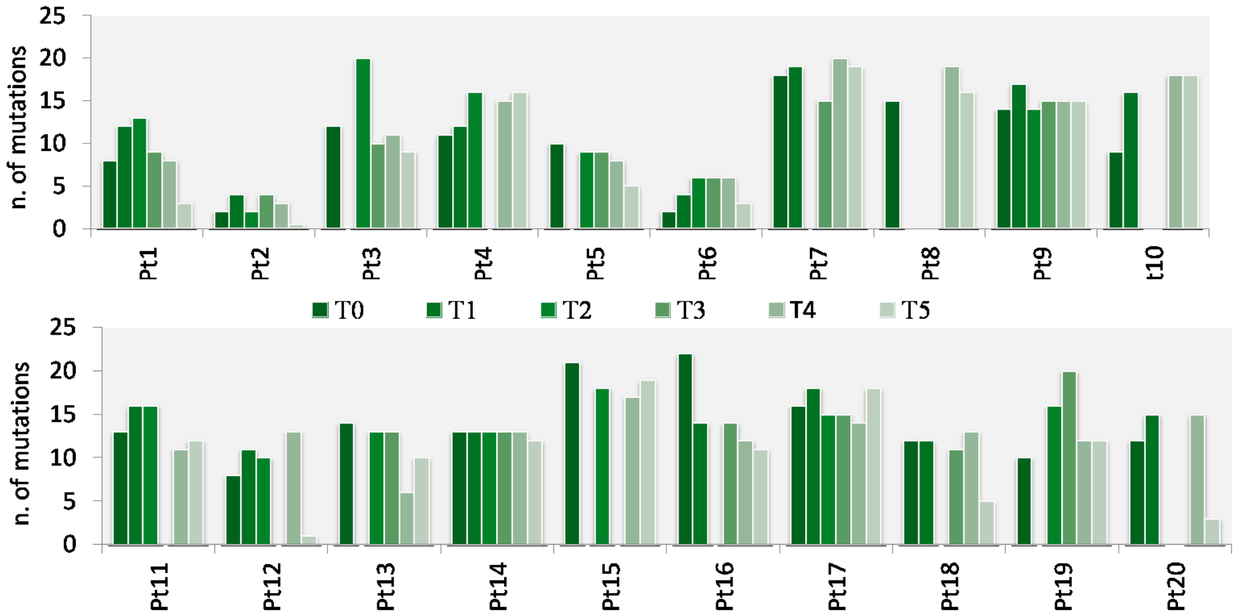
Objective. The role and the stability of mutational archive during HIV-1 infection have not been fully addressed and discordant data are available from literature. Deep investigations to explore the significance of the archived drug resistance mutations during suppressive antiretroviral therapy (ART) are necessary for a comprehension of their effects during long-term ART. The aim of this study was to examine the changes in intracellular drug resistance mutation (DRM) patterns and to assess the ability of archived viral variants to re-emerge in 20 multidrug-experienced HIV-1+ patients during 4 years follow-up of darunavir/ritonavir(DRV/r)-based salvage therapy.

Methods. All individuals were multidrug-experienced, with a mean treatment time of 17.6 years, and had failed several therapeutic regimens. Plasma HIV-RNA levels were monitored by Versant kPCR (Siemens Healthcare Diagnostics) and intracellular DRMs were examined in peripheral blood mononuclear cells (PBMCs) at T0 and after 18, 36, 54, 72, 176 and 192 weeks, using the TruGene HIV-1 Genotyping kit (Siemens Healthcare Diagnostics). Phylogenetic analysis was performed to investigate the evolution of archived variants during suppressive ART; phylogenetic trees were generated with the general-time reversible model (GTR+I+G) of nucleotide substitution.

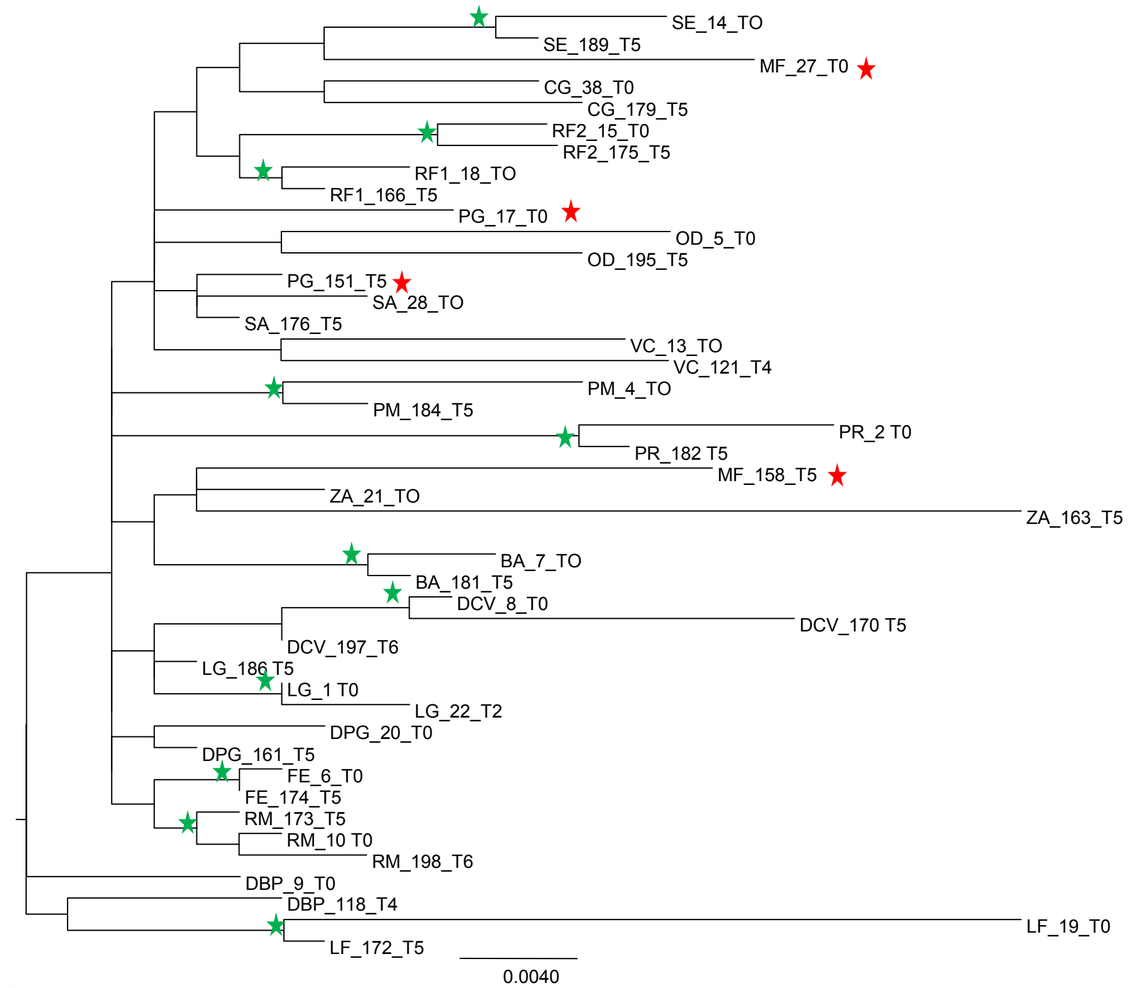
Results. During 192 weeks of follow-up, all patients maintained undetectable viral loads (<37 copies/mL) with two patients experiencing an isolated blip of viremia (<200 copies/mL). As expected, at T0 all patients showed a high number of intracellular DRMs, the mean being 12(±5.2). All mutations were related to therapeutic regimens previously received, but in the majority of patients a fluctuation in the number of mutations was detected during the follow-up, independently of residual viremia (Fig. 1).

Figure 1. Number of mutations detected during follow-up in each patient



Moreover, the analysis of DRV/r RMs revealed that 18 patients had intracellular mutations associated with resistance at T0, six of them with score >3.5; after 192 weeks, in four patients the score changed, owing to loss and/or acquisition of some DRV/r RMs. Phylogenetic analysis revealed that most of viral variants displayed polymorphisms in *pol* region, but no evolutionary divergence was observed. Moreover, the analysis of APOBEC-induced hypermutations, performed by Hypermut 2.0 (www.hiv.lanl.gov), showed that archived viruses were potentially able to replicate.

Figure 2: Phylogenetic tree of HIV-1 *pol* region sequence at T0 and T5. Green stars indicate the clusters of HIV-1 statistically significant; red stars indicate the absence of the clusters.



Conclusions The results of this study suggest that, in multidrug-resistant patients treated with salvage therapy, the archived drug-resistant viral variants may change during suppressive ART but this does not affect virological success. These data question the benefit of proviral genotypic resistance tests to assess the risk of virological failure

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