Virological response to modern first-line antiretroviral regimens in HIV-infected patients enrolled in a large cohort according to their pre-therapy viral load and type of regimen started

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Abstract:
Background: Whether failure of modern first-line combination antiretroviral treatment (cART) in people with high viral load (VL) is due to imperfect adherence or insufficient potency of 3-drug based therapy is still debated.

Objectives: To test whether the level of VL pre-cART influences the time to viral response to first cART and whether the effect is consistent across type of regimens started.

Methods: HIV-infected individuals in the Icona Foundation Study who started cART (exactly 3 drugs with currently used PI/r or EFV and regimens with >3 drugs) from ART-naïve after the year 2000 were grouped according to pre-cART VL levels (501-100k, 100k-300k, 300k-500k and >500k copies/mL). Survival analysis was used to evaluate the time to virological success (VS) ≤200 copies/mL and to viral failure (VF) >200 copies/mL (defined at the time of the first of 2 consecutive values after ≥6 months of cART) and VL groups were compared. The percentage of patients with a VL≤200 copies/mL was also calculated in an on-treatment (OT) analysis censoring at time of discontinuation of ≥1 drug in the original regimen. For the OT analysis, multivariable logistic regression with interaction terms was used to test whether this percentage varied by type of regimen started and level of initial VL.

Results: 3,973 individuals were included: 57% with VL of 501-100k copies/mL, 23% with VL 100k-300k, 7% with VL 300k-500k and 12% with VL >500k. Median age was 40 years (IQR:34-48), 24% females, 36% MSM, 17% HCV co-infected. Drug regimens started were as follows: 19% LPV/r, 20% ATZ/r, 18% DRV/r, 40% EFV, 4% with >3 drugs (51% of these, n=80, were on RAL). 67% started TDF+FTC, 14% ZDV+3TC, 9% ABC+3TC and 4% TDF+3TC. Of 113 patients with a genotypic test performed while VL was decreasing, 9% had ≥1 IAS-defined NRTI mutation (DRM), 16% ≥1 NNRTI DRM and 7% ≥1 major PI DRM. From the adjusted Cox regression analysis, people with a VL of 501-100k and of 100k-300k were, respectively, 63% and 22% more likely to achieve a VL≤200 copies/mL than those with a VL>500k (p=0.001). Similarly, a VL of 100k-300k was associated with a 50% reduction in risk of VF compared to the >500k group (p=0.001). The table shows the percentages with VS according to the regimen started and level of initial VL in the subset of 2,020 (OT analysis). The difference by regimens tended to vary by viral load with the >3 drugs regimens appearing to perform better than other regimens at very high viral loads (interaction p=0.001).

Conclusions: Even at VL levels >100k copies/mL there seems to be a trend for a reduced chance of viral response with higher VL levels. Detection of drug resistance on the pathway to VL suppression implies that low viral potency might have been one of the determinants of lack of VS. New regimens including >3 drugs, with or without RAL, seemed to have greater potency than that of 3-drug based regimens at viral loads >500k copies/mL. This question should be addressed in a randomized study.