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Paper Poster Session III

HIV/AIDS

Path analysis of the HIV tropism on predicting viral suppression under antiretroviral therapy

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Objectives: We evaluated the role of baseline co-receptor plasma tropism in achieving undetectable viremia within six months of antiretroviral therapy (ART) in naïve patients by path analysis, a form of structural equation modeling (SEM) analysis.

Methods: Either abacavir/lamivudine or tenofovir-emtricitabine were used as backbone, plus a third drug: a boostered PI (atazanavir or lopinavir), or an NNRTI (efavirenz or nevirapine). Baseline viral tropism (determined by sequencing and interpretation by genotopheno algorithm), CD4+ cell count, plasma HIV-RNA (log_{10} copies/ml), gender and age were included in the analysis.

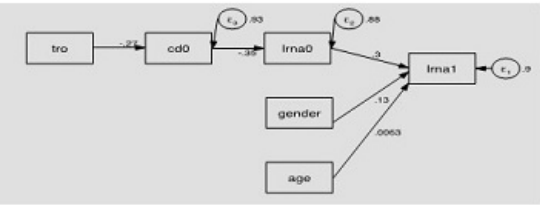
A preliminary approach consisted in a pairwise correlation. The pattern of correlations suggested a path analysis model for further evaluation. The scheme assigned the role of "mediator variables" to baseline CD4 ("cd0"), baseline plasma HIV-RNA ("lrna0") and plasma HIV-RNA after six months ("lrna1"). A path analysis model was set up, incorporating these variables, plus two demographic variables. The results were checked by splitting the data set into two parts, randomly, (training set and validation set) and applying the model to both, and by resampling the data (bootstrap, 100 replicates).

Results: A total of 244 patients were enrolled; median baseline CD4 count 220/ul (range 0-968), median baseline plasma HIV-RNA 5.2 log_{10}copies/ml (range 2.6-7). The coreceptor HIV tropism at baseline as X4 ("tro") correlated negatively to "cd0" ($P<0.05$), whereas "cd0" correlated negatively to "lrna0" ($P<0.05$). This in turn correlated positively to "lrna1" ($P<0.05$). Gender correlated positively to the final outcome, "lrna1", implying a lower plasma HIV-RNA reduction in the female patients ($P<0.05$). No other significant correlations were found. However, after bootstrapping, the variable "gender" lost its significance, whereas the other predictor maintained it.

A significant positive indirect effect of "tro" on "lrna1" was detected, however approximately ten times lower than the direct effect on "cd0". Moreover, a significant positive indirect effect of "tro" on "lrna0", and a significant negative indirect effect of "cd0" on "lrna1", were apparent.

The model is depicted in the figure 1.

Figure 1. Path analysis model explaining direct and mediated effects of "tro", "gender", "age", "cd0" and "lrna0" on the final outcome ("lrna1"), where "tro", "gender", and "age" are exogenous, cd0 and lrna0 are endogenous (mediators). Numbers on the arrows indicate direct effects. Circles indicate residuals related to endogenous/dependent variables; numbers near to circles are the corresponding variances



Conclusion: Path analysis showed the relevance of baseline tropism on the outcome of plasma viremia in naïve patients after 6 months of therapy. This approach overcame the limitations implicit in common multiple regression analysis. The role of mediator variables and indirect effects, suggested by the pairwise correlation, became clearer. Namely, besides a direct effect exerted by baseline plasma HIV-RNA level, a significant indirect effect on the end outcome was shown for HIV coreceptor tropism and for CD4 count.

The model is compatible with accepted biomedical causal links among the included variables. The structural equation analysis would appear helpful in the evaluation of the effects of ART agents in a clinical context where the randomization of the drug assignation is difficult to obtain, as phase IV trials.