THE SUBPHENOTYPES OF EARLY-TREATED CHILDREN LIVING WITH HIV-1

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BACKGROUND

Subphenotypes have been identified in several heterogeneous diseases. Having a specific subphenotype often has therapeutic implications or disease progression. In this study, we aimed to assess if children with HIV may show subphenotypes according to clinical, virological and immunological features.

METHODS

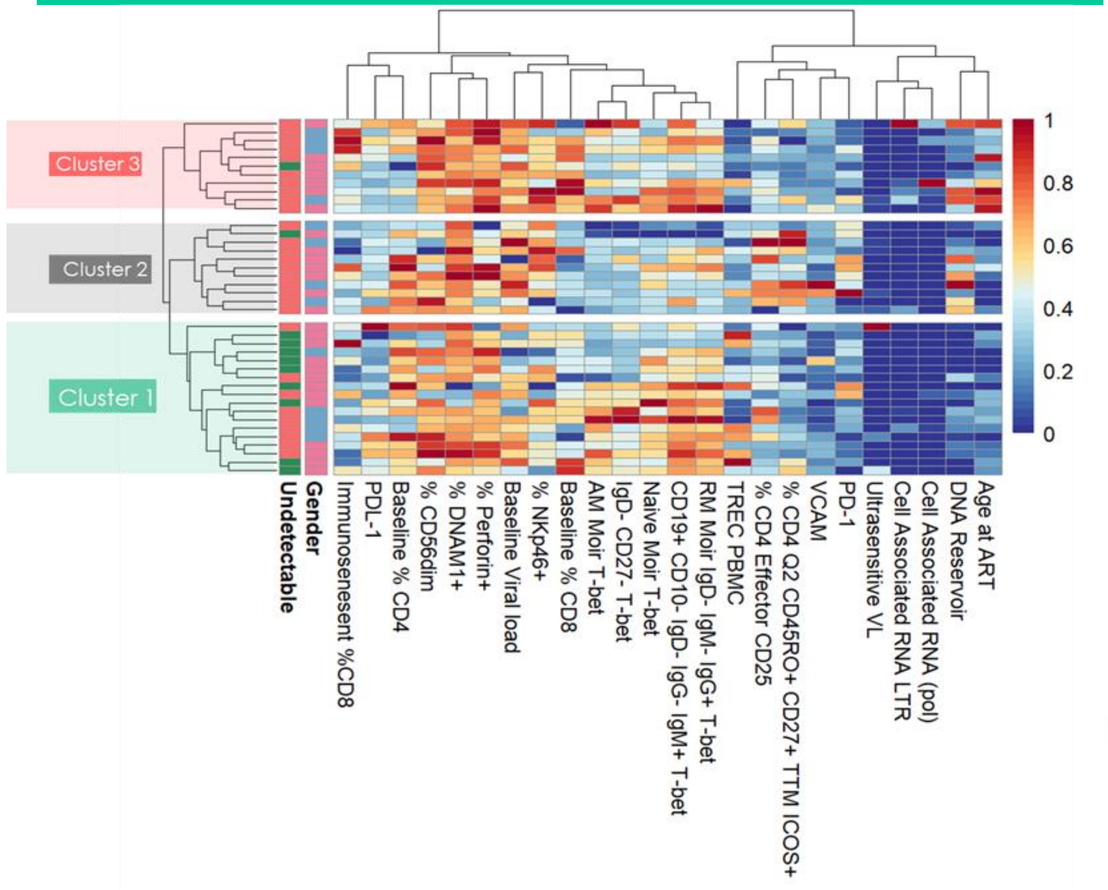
40 HIV+ CHILDREN included in a cross-sectional multicentric study cohort (CARMA Study, EPIICAL Consortium

All children commenced ART <2 years, suppressed (viral load, (VL) <50 copies/ml) within 12 months and remained suppressed for >5 years. Immunological and virological assays were performed at a median of 12 years after ART initiation.

- Clinical and sociodemographic features
- Baseline viral load, CD4 and CD8 data
- HIV-1 reservoir size, cell-associated RNA
- CD4 subsets (T effector CD25+, activated memory cells), humoral-specific HIV response (T-bet B cells)
- Innate response (CD56dim NK cells, NKp46+, perforin), exhaustion markers (PD-1, PD-L1, DNAM)
- CD8 immunosenesence, and biomarkers for naive T-lymphocyte reservoir (TREC)
- Endothelial activation (VCAM).

To build the subphenotypes, the most informative variables were selected using an unsupervised penalty selection. Hierarchical clustering was performed using Pearson correlation as distance metric and Ward.D2 as clustering method. Internal validation was applied to select the best number of clusters.

Three HIV pediatric subphenotypes were identified, one of which is categorized by a good clinical outcome, the other by a more severe cytotoxic response, and another with lower t-bet expression. Response to different therapies could be different across the different clusters.



RESULTS

Three subphenotypes were revealed (Cluster 1 n=18, 45%; Cluster 2 n=11, 27.5%; Cluster 3 n=11, 27.5%). Cluster 1 (best controllers) consisted of early ART-treated patients with high baseline %CD4, low HIV reservoir size, low WB score, high TREC values, and low VCAM values. In contrast, Cluster 3 (worse control) consisted of later ART-treated patients with low baseline %CD4, high reservoir size, low TREC values, high innate response and immunosenescence markers and high VCAM. Cluster 2 (low-level viremia, altered immune response) consisted of early-treated patients with low-level (10 to 50 c/mL) VL, high DNA reservoir size, but low CA-RNA, higher activated Treg CD4 than in the other clusters, low TREC, weak innate response and lower levels of T-bet expression.

CONCLUSIONS

Three subphenotypes with decreasing levels of viral control and increasing levels of immune well-being were discovered. Response to different therapies may be different across the different clusters.