Mortality linked to higher inflammation in kids with perinatal HIV

806

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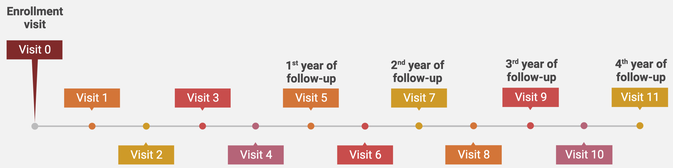
BACKGROUND

Mechanisms underlying mortality in some early ART-treated children with perinatal HIV infection remain unclear. The prospective EARTH study (Early Anti-Retroviral treatment in HIV- infected children), enrolled in 6 African centers, 220 perinatally HIV-infected children collecting clinical data and peripheral blood (< 2weeks of age). Trying to identify biomarkers predictive of mortality risk at enrollment visit, we assessed the differential plasma concentration of pro-inflammatory molecules in 3 different groups: deceased (dead-HIV+), non-deceased HIV+ children (HIV+) and healthy control (HC) study participants.



METHODS

Selection of patients was done using Nearest Neighbor matching 1:2. A propensity score distance was used to select 40 individuals (HIV+), within the EARTH cohort, with similar characteristics at entry (see figure 1) to 20 deceased children. Plasma samples were analyzed using an Inflammation panel proximity extension assay (Olink platform; T96) and benchmarked to 13 HC HIV unexposed controls.

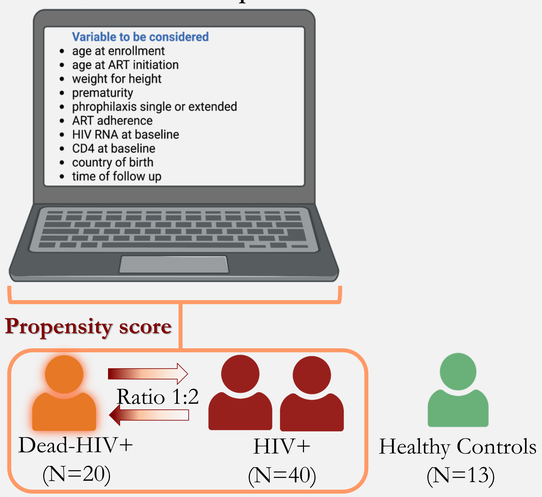


Figure 1

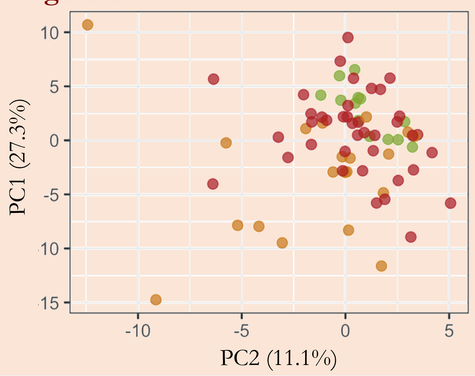
1 µl of plasma to identify, at early time points, protein signatures of death in children with HIV



RESULTS

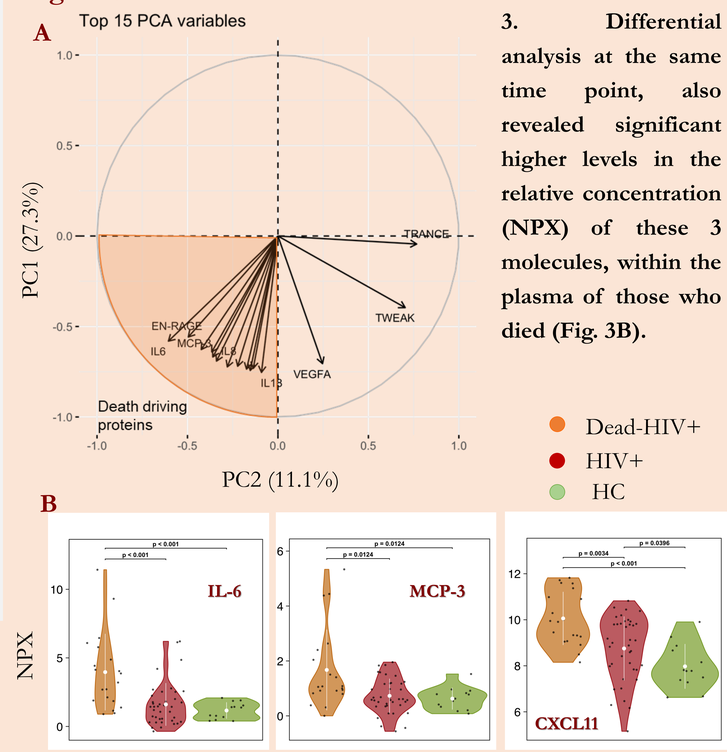
1. PCA analysis on proteomic data revealed a gradient in the distribution of samples with dead-HIV+ clustering separately from HC and matched HIV+ participants (Figure 2).

Figure 2



2. Top 15 loading proteins highlighted molecules as pro-inflammatory IL-6, CXCL11 (potent agonist of CXCR3, involved in activated T cells chemotaxis) and CCL7 (also known as MCP-3, important for the activation and chemoattraction of macrophages) as death driving proteins (Fig.3A).

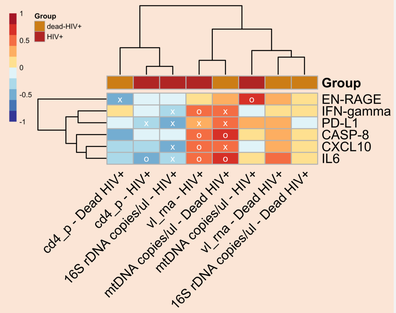
Figure 3



3. Differential analysis at the same time point, also revealed significant higher levels in the relative concentration (NPX) of these 3 molecules, within the plasma of those who died (Fig. 3B).

4. Plasma samples of kids with HIV+ were investigated for Damage Associated Molecular Patterns (DAMPS) levels, expressed as mtDNA. Pro-inflammatory molecules (e.g. IL6, IFN-g) were found to positively correlate with DAMPs only in Dead-HIV+ group, while negatively correlating with CD4+ levels in HIV+ group.

Figure 4



CONCLUSIONS

HIV+ children who prematurely died demonstrated higher concentrations of inflammatory molecules at enrollment, suggesting a possible role of inflammation in driving eventual mortality. Larger studies are needed to confirm early molecular correlates of mortality in HIV+ children which may identify actionable biomarkers and inform trials of novel immunomodulatory drugs to reduce mortality.

FUNDINGS

This work was supported by the EPIICAL project, a scientifically independent grant funded by ViiV Healthcare.

ACKNOWLEDGEMENTS

We acknowledge all the collaborators that contributed to this work and the all patients and guardiands that agreed to participate to the EARTH (Early Anti-Retroviral treatment in HIV- infected children) study.

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