DNA METHYLATION SIGNATURES ASSOCIATED WITH HIV SUPPRESSION AFTER TREATMENT IN INFANTS

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BACKGROUND

- Recent studies report differences in host DNA methylation (DNAm) profiles between individuals with and without HIV.
- We found distinct profiles within the blood DNA methylome in perinatally HIV-infected children at 4-9 years of age compared to similarly-aged HIV-uninfected children from the same community.
- No studies have examined epigenetic changes in the context of early antiretroviral therapy (ART) in infants with HIV.
- We tested if blood DNAm profiles pre- and post-ART are different between infants who do and do not achieve viral suppression by 1 year on ART.

METHODS

- We selected samples from 75 early-treated infants with HIV who initiated LPV/r-based ART <6 months of age as part of a clinical trial in Johannesburg, South Africa, including 48 who achieved viral suppression, defined as attaining plasma HIV-1 RNA <400 copies/ml for ≥3 months within the first 12 months on ART (suppressed), and 27 who did not (unsuppressed).
- Genomic DNA (50ng/μL) was isolated and quantified from peripheral blood mononuclear cells collected pre-ART and ~6 months post-ART with PicoGreen (Life Technologies, Carlsbad, CA).
- DNAm was assayed using the Infinium MethylationEPIC array (Illumina, San Diego, CA).
- Pre-processing was performed with the *ewastools* package in R.
- We tested for differentially methylated CpG sites (Bonferroni-corrected) between suppressed and unsuppressed groups pre- and post-ART using the limma package, adjusted for sex.
- We also tested for changes in methylation on CpG sites between the two timepoints, within group.

Early-treated infants who attained viral suppression within 12 months of initiating LPV/r-based ART had **distinct epigenetic signatures 6 months after ART initiation** compared to infants who were unsuppressed. Before ART initiation, few epigenetic differences were present between infants who went on to suppress or not.

RESULTS

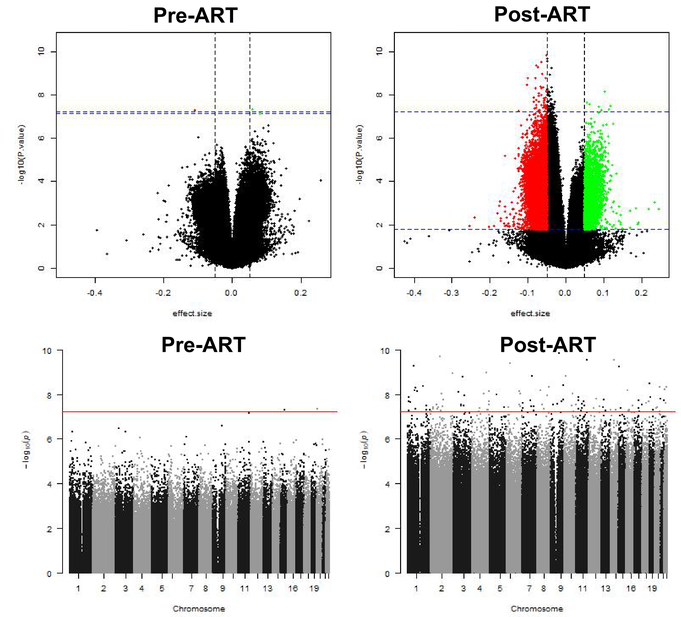
- As shown in the **Table**, mean ages pre-ART (4.4 vs. 4.6 months) and post-ART (10.5 vs. 9.3 months) were similar between groups, as was the proportion of females (54.2 vs. 44.4%).
- 75% had a pre-ART viral load >750,000 copies/ml and pre-ART CD4 % was higher in the suppressed vs. unsuppressed group (24.6 vs. 18.9%, p=0.016).

Table: Characteristics of 48 infants who achieved viral suppression (suppressed), and 27 who did not (unsuppressed)

Characteristic	Suppressed (N=48)	Unsuppressed (N=27)	p-value
Female, %	54.2%	44.4%	0.43
Age at ART initiation (months), Mean (SD)	4.5 (1.2)	4.7 (1.5)	0.59
Pre-ART CD4 Percentage, Mean (SD)	24.6 (8.2)	18.9 (10.0)	0.016
Pre-ART HIV-1 RNA ≥ 750000 (copies/ml), %	72.7%	88.9%	0.22
Weight-for-age Z-score, Mean (SD)	-2.1 (1.5)	-3.1 (2.0)	0.029
Height-for-age Z-score, Mean (SD)	-2.8 (1.6)	-4.0 (2.2)	0.013
Age at pre-ART sample (months), Mean (SD)	4.4 (1.3)	4.6 (1.4)	0.58
Age at post-ART sample (months), Mean (SD)	10.5 (2.5)	9.3 (3.4)	0.16

- Pre-ART, there were 3 differentially-methylated CpG sites between the two groups corresponding to 3 unique genes (SMAD6, FERMT1, SIK3) (**Figure**). SMAD6 is upregulated by interaction between HIV envelope protein gp120 and α4β7 interaction.
- Post-ART, there were 118 differentially-methylated CpG sites between groups corresponding to 66 genes, including SMAD6 and SIK3 (**Figure**).
- The suppressed group experienced a large number of changes in DNAm from pre- to post-ART (988 sites significantly different between timepoints). Changes from pre- to post-ART were not detected in the unsuppressed group (0 sites different).

Figure: Volcano plots and Manhattan plots of DNA methylation CpG sites associated with HIV suppression in early-treated infants at pre- and post- ART



CONCLUSIONS

- Epigenetic signatures by 6 months after initiating LPV/r-based ART distinguished early-treated infants who attained suppression from those who did not.
- Before ART initiation, few epigenetic differences were present between infants who went on to suppress or not.
- Further interrogation may provide insight into specific epigenetic signatures of ART regimens or viral control in early-treated infants.

ACKNOWLEDGEMENTS

The study was supported in part by grants HD061255, HD073977, and HD073952 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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