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HIV Subtype D Is Associated with Rapid CD4 Decline in ART-naive Ugandan Children

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Background: HIV subtype D is associated with rapid CD4 loss compared to A in adults, but there have been no prospective data from children who have distinct and developing immune systems.

Methods: HIV^+ children not meeting age-specific criteria for ART initiation and having at least 3 CD4 counts participating in an observational cohort in Kampala, Uganda were studied. HIV subtype was determined with a real time PCR-based assay that utilizes subtype-specific probes in 5 different genome regions (env, gag, pol, vpu, gp-41) on banked plasma specimens. Patients received all care in the study clinic; CD4 count and plasma HIV-RNA were obtained every 12 weeks. ART was initiated per Ugandan/WHO guidelines. CD4 and CD8 activation were defined by % HLA-DR and CD38 co-expression on peripheral blood mononuclear cells from within 180 days of enrollment. Predictors of the slope of CD4 decline were examined using Kruskal Wallis and simple linear regression analyses.

Results: In this study, 168 children had a median age of 6.4 years (IQR 5.0 to 8.0), CD4 count of 802 cells/μL (IQR 596 to 1116), plasma HIV RNA of 4.9 (log10 copies/mL, IQR 4.5 to 5.3) and WHO stage distribution (I:68, II:72, III:28). Subtype was determined in at least one region for 140 (83%) children, 50 D-containing (D-Con, includes recombinant strains), 85 pure A (single or multiple regions), or 5 other (C or CA recombinant). In univariate analysis, D-con strains were associated with a mean CD4 decline of 172 vs 72 cells/year for non-D-containing strains (P =0.019). Age less than 5 (P =0.012), low baseline CD4 (P <0.001) and advanced WHO stage (P =0.013) were associated with CD4 decline, while baseline CD4% (P =0.132), plasma HIV RNA (P =0.725), CD4 (P =0.604) and CD8 activation (P =0.792) were not. In multivariate linear regression (coefficient, 95% confidence interval), D-con subtype (-76, -137 to -14), higher baseline CD4 count (-0.19, -0.26 to -0.13), and advanced WHO Stage (48, 6.7 to 89) remained predictive of CD4 decline.

Conclusions: In ART-naive Ugandan children >1 year of age, HIV subtype D was associated with more rapid CD4 decline compared to non-D strains that is not explained by differences in baseline CD4 count, CD4%, HIV RNA, CD4 or CD8 activation. Further study of recombinant strains and the association of subtype with CXCR4/CCR5 co-receptor tropism may yield insight into this subtype-specific increased pathogenicity.