Clinical trials and antiretroviral therapy in children and adolescents

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Low but Detectable IFN-γ Responses against Clade-Matched HIV-1 Peptides in Early-Treated Vertically-Infected Children with Long-Term Sustained Viral Suppression

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Background: Absence of detectable cell-mediated immune responses to HIV-1 is a recurring finding in early-treated HIV-1 vertically-infected children in whom sustained viral suppression is achieved and maintained for an extended period. It has been assumed that levels of viral antigens were too low to trigger or maintain HIV-1-specific immune responses. However, re-emergence of these responses following viral rebound is well documented. Here, IFN-γ responses were measured in peripheral blood mononuclear cells (PBMC) from 4 early-treated vertically-infected children with long-term sustained viral suppression (Bitnun et al., Clin Infect Dis 59: 1012-1019, 2014).

Methods: PBMC were obtained from 4 children who were initiated on combination antiretroviral therapy (cART) within 72 hours of birth and achieved sustained virologic suppression (HIV-1 viral load < 50 copies/mL). At the time of blood sampling, virologic suppression had been maintained for 3.9 to 8.1 years. IFN-γ production in response to HIV-1 clade-matched peptide pools (clade A [23 pools; 122 peptides] and clade C [22 pools; 121 peptides] consensus peptides) were measured using ELISpot. PBMC from HIV-uninfected subjects and a 29 year old HIV clade C-infected adult without sustained viral suppression (140,573 copies/mL) were used as controls. ELISpot positivity was defined according to standard criteria (>50 spot-forming units [SFU] per 106 cells and >2 SD over negative controls).

Results: Low-level HIV-specific IFN-γ responses were detected in all 4 children but not in HIV-uninfected controls. Responses ranged from 0 SFU to 121 SFU/106 PBMC in Case 1, 0 to 98 SFU/106 PBMC in Case 2, 0 to 165 SFU/106 PBMC in Case 3, and 0 to 98 SFU/106 PBMC in Case 4. These responses were substantially lower than clade-matched IFN-γ responses measured in the control subject without long-term viral suppression (0-1858 SFU/106 PBMC) and significantly lower than anti-CD3, CMV-specific and VZV-specific responses.

Conclusions: Low but significant frequencies of cells producing IFN-γ in response to stimulation with HIV-1 clade-matched peptides were detected in early cART-treated children with sustained viral suppression under cART thereafter. These responses may be contributing to long-term control of HIV replication in vertically-infected children, and these dynamics of host-pathogen interaction may qualitatively or quantitatively differ from those observed in HIV-infected adults.