Discordant reconstitution of HIV-1- and CMV-specific responses in cART-treated HIV-1+ patients – what can we learn from co-infection?

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Introduction

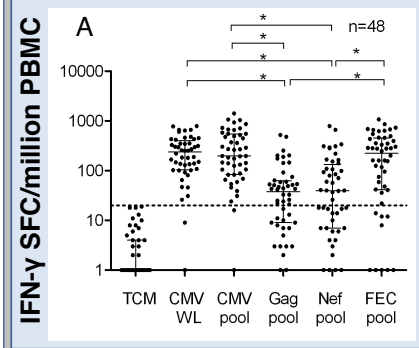
Combination (c)ART reduces HIV-1 RNA load and results in CD4 T-cell count recovery in the majority of HIV-1+ individuals (1, 2). Despite this, both CD4 and CD8 T-cell responses to HIV-1 remain deficient, exhibiting low proliferative capacity and cytolytic function (3). In contrast, cART has been shown to restore functional responses to recall antigens such as Epstein-Barr Virus (EBV) and human Cytomegalovirus (CMV) (4). In HIV-1+ patients co-infected with CMV, initiation of cART reduces the incidence of CMV end-organ disease, however CMV viraemia is still associated with faster HIV-1+ disease progression (5). CMV induces strong T-cell responses (~10% of CD4+ and CD8+ T cells have been shown to be CMV-specific) (6). This may indirectly or directly affect T-cell immune responses to other pathogens such as HIV-1, warranting further study. This study aims to evaluate the effect of cART on HIV-1- and CMV-specific functional responses (IFN- γ, IL-2 and IL-10), in order to elucidate the mechanisms behind the discordant restoration of HIV-1- and CMV-specific responses.

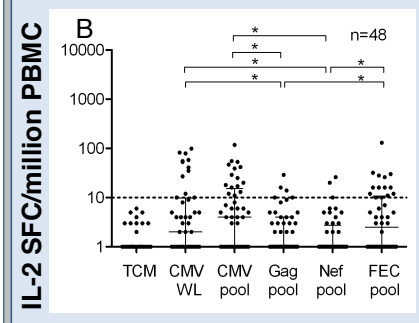
Methods

PBMC of 57 HIV-1+ individuals were stimulated with CMV whole lysate (WL), CMV pp65 peptide pool, HIV-1 Gag and Nef peptide pools and FEC peptide pools and were assessed for IFN-γ, IL-2 and IL-10 production using the ELISpot assay. 48 patients produced IFN-γ in response to either CMV WL or CMV pool and were classified as CMV responders (Figure 1 A, B and C).

HIV-1+ patients were further classified as aviraemic (<50 HIV-1 RNA copies/ml plasma; n=31) and viraemic (≥10000 HIV-1 RNA copies/ml plasma; n=10; Figure 2 A, B and C), for an inter-group analysis.

Significantly higher CMV-specific responses compared with HIV-1 Gag and Nef.





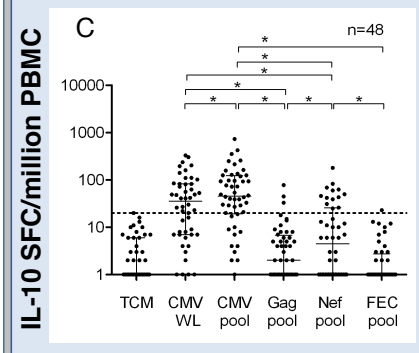
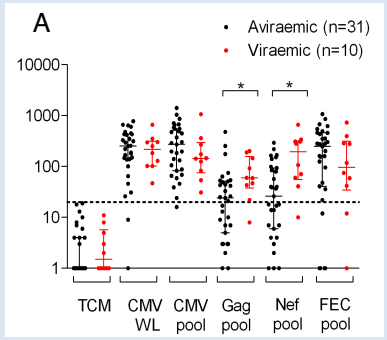
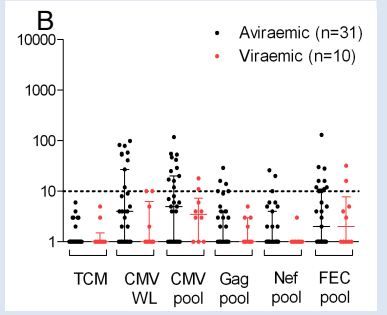


Figure 1. IFN-γ (A), IL-2 (B) and IL-10 (C) release (spot forming cells per million PBMC), in response to various antigen and peptide pools. We observed significantly higher CMV-specific responses compared to HIV-1 Gag p24 and Nef peptide pools.

Viraemic HIV-1+ patients produce significantly higher IFN-γ in response to Gag and Nef peptide pool





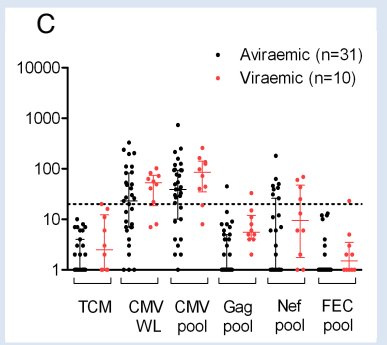


Figure 2. Comparison of IFN-γ (A), IL-2 (B), and IL-10 (C), responses to various antigen and peptide pools in aviraemic and viraemic patients. Significantly higher IFN-γ responses to HIV-1 Gag and Nef peptide pools were observed. No difference between CMV-specific responses.

Results

Significantly higher IFN-γ, IL-2 and IL-10 responses were observed in response to CMV WL and CMV pp65 peptide pool compared to Gag p24 ($p<0.003$) and Nef ($p<0.001$) peptide pools (Figure 1 A, B and C). Viraemic CMV responders exhibited significantly higher IFN-γ responses to Gag p24 ($p=0.018$) and Nef ($p=0.004$) pools compared to aviraemic CMV responders (Figure 2 A). However, no significant difference was observed for IL-2 or IL-10 production between the two groups (Figure 2 B and C).

Conclusions

- Polyfunctional (both IFN-γ and IL-2 production) responses to CMV are restored in HIV-1+ individuals receiving suppressive cART, whilst CD8+ and CD4+ T cells specific to HIV-1 remain dysfunctional, the majority only producing IFN-γ (Figure 1 A and B).
- High levels of IL-10 production (an anti-inflammatory cytokine known to inhibit Th1 responses) (7), in response to CMV stimuli may suppress immune responses such as those to HIV-1 (Figure 1 C).
- The lower IFN-γ response observed in aviraemic patients to HIV-1 Gag p24 and Nef peptide pools may be due to cART-mediated reduction of antigenic stimulation (Figure 2 A).

Clinical implications

cART-mediated restoration of CMV-specific responses should be considered in the context of persistent CMV replication and resulting immunosuppression. This highlights the need for further studies into the effect of CMV-specific therapy on both anti-CMV and anti-HIV-1 T-cell responses.

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