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A persistent and strong HIV-gag specific CD8+ T cell response during 22 years of post-treatment control

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Background

A minority of HIV-infected individuals is able to control viral replication after cessation of antiretroviral therapy, a phenomenon referred to as 'post-treatment control'. Comprehension of the underlying mechanism is pivotal for future cure strategies. Here, we present a case of an HIV-infected individual who has been able to control viral replication for over 22 years after temporary antiretroviral therapy.

Aim

We aim to investigate virological and immunological characteristics that are involved in post-treatment control in this patient.

Methods

Viral reservoir assessments were performed by HIV pol qPCR and the Intact Proviral DNA Assay. Virus isolation was performed using a quantitative viral outgrowth assay and viral replication kinetics was determined on donor peripheral blood mononuclear cells (PBMC). IgG levels directed against HIV envelope subdomains and broadly neutralizing antibody levels were determined. Immune phenotyping of PBMC and HIV-specific T cell responses (cytokine production and proliferation) upon peptide pool stimulation were performed by flowcytometry.

Results

Virus was readily detectable in peripheral blood using a quantitative *pol* PCR (1500 copies/10^6 cells) and IPDA (37 copies/10^6 cells). Replication-competent virus could be isolated from patient CD4 T cells within the first month after infection (48 IU/10^6 CD4 T cells) but viral outgrowth from later timepoints (>1 year after diagnosis) failed (<0,03 IU/10^6 CD4 T cells). PBMC obtained from the patient were susceptible to HIV infection and viral replication was not restricted. Moreover, the virus obtained from the patient was able to replicate efficiently (figure 1).

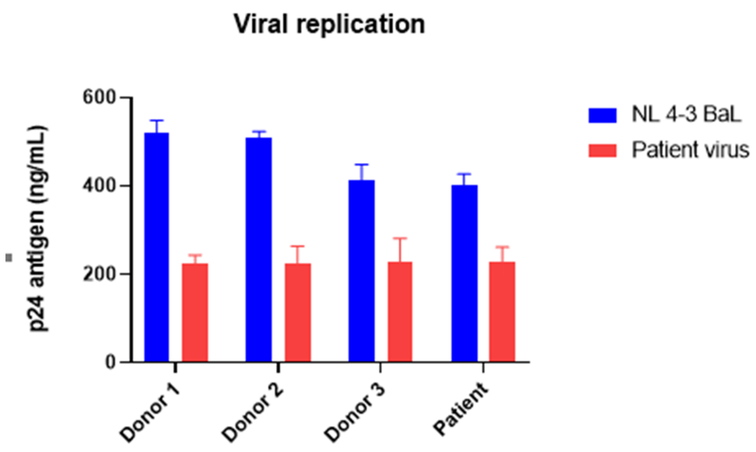

Figure 1: Viral replication rates in PBMC is determined by HIV p24 production in the culture medium. Replication of the lab strain NL 4-3 BaL (blue) and the patient viral variant(red) was determined in PBMC from blood bank donors and the patient.

Immune phenotyping showed low levels of T cell activation (CD38/HLA-DR), exhaustion (PD-1) and senescence (CD57 and loss of CD27/CD28) in CD4 and CD8 T cells from the patient 18 years post-treatment comparable to blood donors (figure 2).

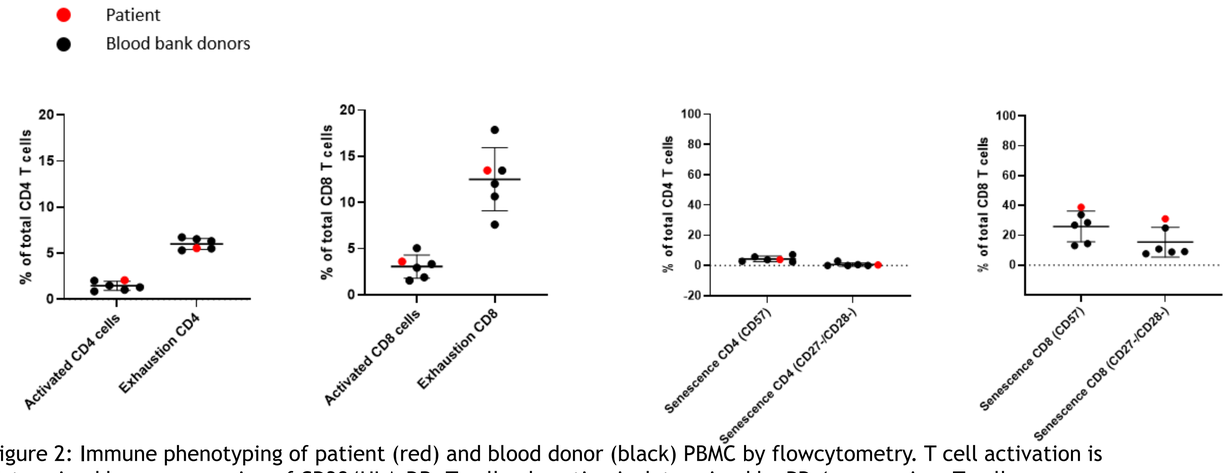

Figure 2: Immune phenotyping of patient (red) and blood donor (black) PBMC by flowcytometry. T cell activation is determined by co-expression of CD38/HLA-DR; T cell exhaustion is determined by PD-1 expression; T cell senescence is determined by CD57 expression or the loss of CD27/CD28.

Results

During follow-up, stable plasma IgG levels against HIV gp120, gp41 and V3 subdomains, but no neutralizing antibodies were observed (figure 3).

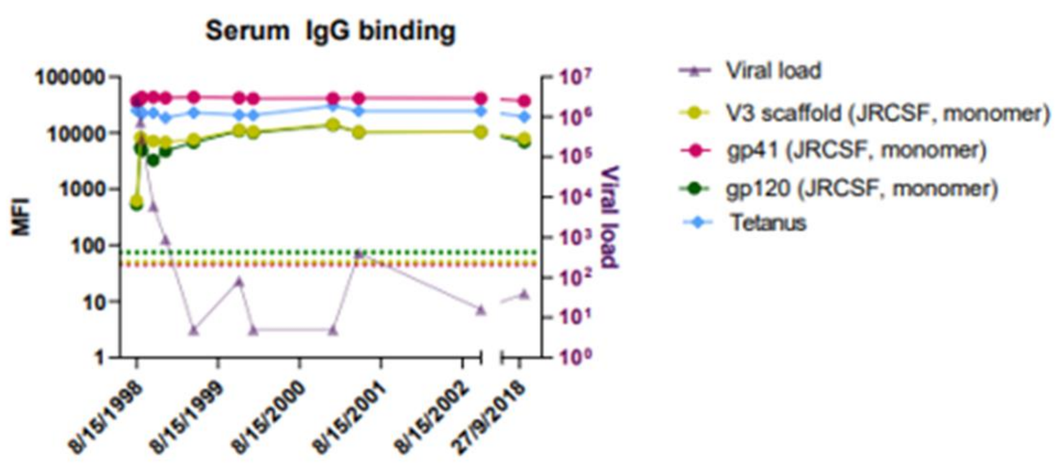

Figure 3. Longitudinal serum IgG binding to several Env proteins combined with viral load (copies/mL) measurements.

Analysis of the functionality of the HIV-1 specific T cell response at 18 years post-treatment demonstrated that cytokine production upon gag peptide stimulation in CD4 and CD8 T cells was comparable to those observed in untreated, chronically infected individuals. However, a strong proliferative response of $CD8^+$ T cells targeting the gag protein was observed (figure 4). Longitudinal analysis demonstrated that a strong gag specific CD8 T cell response, but not nef, pol or env, with a high precursor frequency was present during 22 years of follow-up (figure 5).

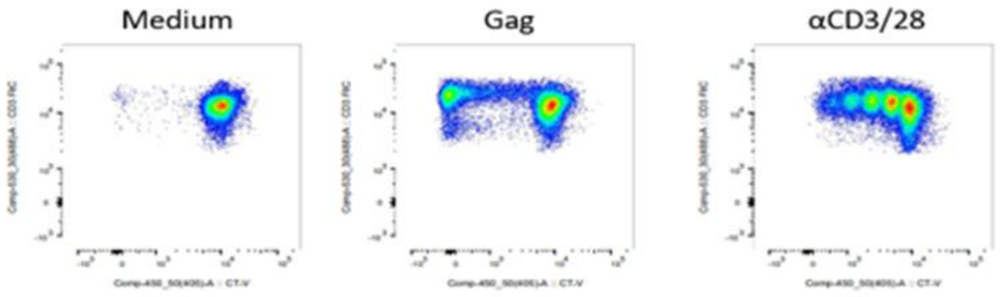

Figure 4: Proliferation of HIV specific CD8 T cells. Gag-peptide stimulation gives a high proliferation of CD8 T cells compared to medium (negative control). The anti-CD3/CD28 stimulation was included as well as a positive control. Cells are stained with CellTrace Violet (x-axis).

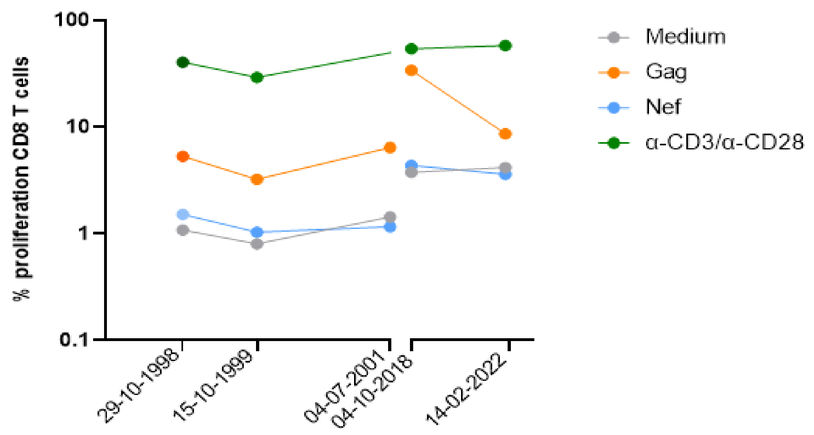

Figure 5: Longitudinal analysis of the fraction CD8 T cells that is able to respond to HIV peptide pools (Gag, Nef). Medium and anti-CD3/CD28 stimulation was included as negative and positive control respectively.

Conclusions

The data provide evidence that this patient was infected with a replication-competent virus, and developed a highly potent HIV-gag specific $CD8^+$ T-cell response within the first months after infection. Upon treatment interruption, this gag-specific response remained present and was likely able to maintain long-term control of HIV. Understanding the mechanism behind the initiation and preservation of a potent T-cell response could give direction to optimizing HIV vaccination, possibly in combination with broadly neutralizing antibodies.

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