# A Human Immunodeficiency Virus Controller With a Large Population of $CD4^+CD8^+$ Double-Positive T Cells

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**Human immunodeficiency virus (HIV) controllers are patients who control viral replication without antiretroviral therapy. We present the case of an HIV controller who had CD4 and CD8 coexpressed on 40% of his T cells. Although a recent study found that double-positive T cells had superior antiviral capacity in HIV-1 controllers, in this case, the $CD4^+CD8^+$ T cells did not have strong antiviral activity.**

***Keywords.*** AIDS; double-positive cells; elite controllers; HIV; HIV controllers; immune activation; long-term nonprogressors; viremic controllers.

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## CASE PRESENTATION

The patient is a 62-year-old African American male with human immunodeficiency virus (HIV) infection diagnosed 12 years ago. His CD4 count was 711 cells/μL, and his viral load was 141 copies/mL plasma without antiretroviral therapy (ART) at diagnosis. His viral load remained undetectable to low (<400 copies/mL), and although his absolute CD4 count was very high, his $CD4^+$ T cell percentage was low and his $CD8^+$ T cell percentage was elevated (Figure 1A). At year 3, it was noted that 26% of lymphocytes coexpressed CD4 and CD8 and the proportion eventually peaked at 40%. These cells were not reported before year 3, but the aggregate percentage of $CD4^+$ and $CD8^+$ T cells exceeded 100%, suggesting that $CD4^+CD8^+$ cells had always been present. A malignancy workup included a polymerase chain reaction (PCR) for clonal T cell rearrangement (negative), fluorescent in situ hybridization for B-cell chronic lymphocytic leukemia (negative), and cytogenetics (normal chromosomes). Human T-lymphotropic virus type-1 serology was negative.

Flow cytometry showed that the density of CD4 was lower on $CD4^+CD8^+$ T cells than on $CD4^+$ T cells (Figure 1B). Because HIV infection results in down-regulation of CD4, we measured the frequency of HIV infection with semiquantitative PCR. Infection was detected in 0.01% of $CD4^+$ T cells but <0.001% of $CD4^+CD8^+$ cells (Table 1); therefore, double-positive cells were not a major infection target. Consistent with this finding, expression of CCR5 and CXCR4 was lower in $CD4^+CD8^+$ T cells than in $CD4^+$ T cells, and there was less viral entry of $CD4^+CD8^+$ T cells than $CD4^+$ T cells after spinoculation with CCR5-tropic and CXCR4-tropic viruses (Table 1).

A much larger fraction of $CD8^+$ and $CD4^+CD8^+$ T cells was activated compared with $CD4^+$ T cells as measured by HLA-$DR/CD38^+$ expression (Table 1). The percentage of activated $CD8^+$ T cells was comparable to that seen in untreated individuals and higher than that in treated patients, HIV controllers, and uninfected individuals (Figure 1C).

$CD4^+CD8^+$ and $CD8^+$ T cell fractions contained high levels of effector memory cells (Table 1) that exceeded the percentage seen in healthy donor and HIV-infected subjects (Figure 1D). The $CD4^+CD8^+$ T cells, $CD4^+$ T cells and $CD8^+$ T cell produced comparable levels of cytokines in response to polyclonal stimulation (Table 1), but the pattern of the cytokine production in $CD4^+CD8^+$ T cells was more similar to $CD8^+$ T cells than $CD4^+$ T cells (Figure 1E). To determine whether the cells were HIV-1 specific, they were stimulated with HIV-1 antigens. A similar

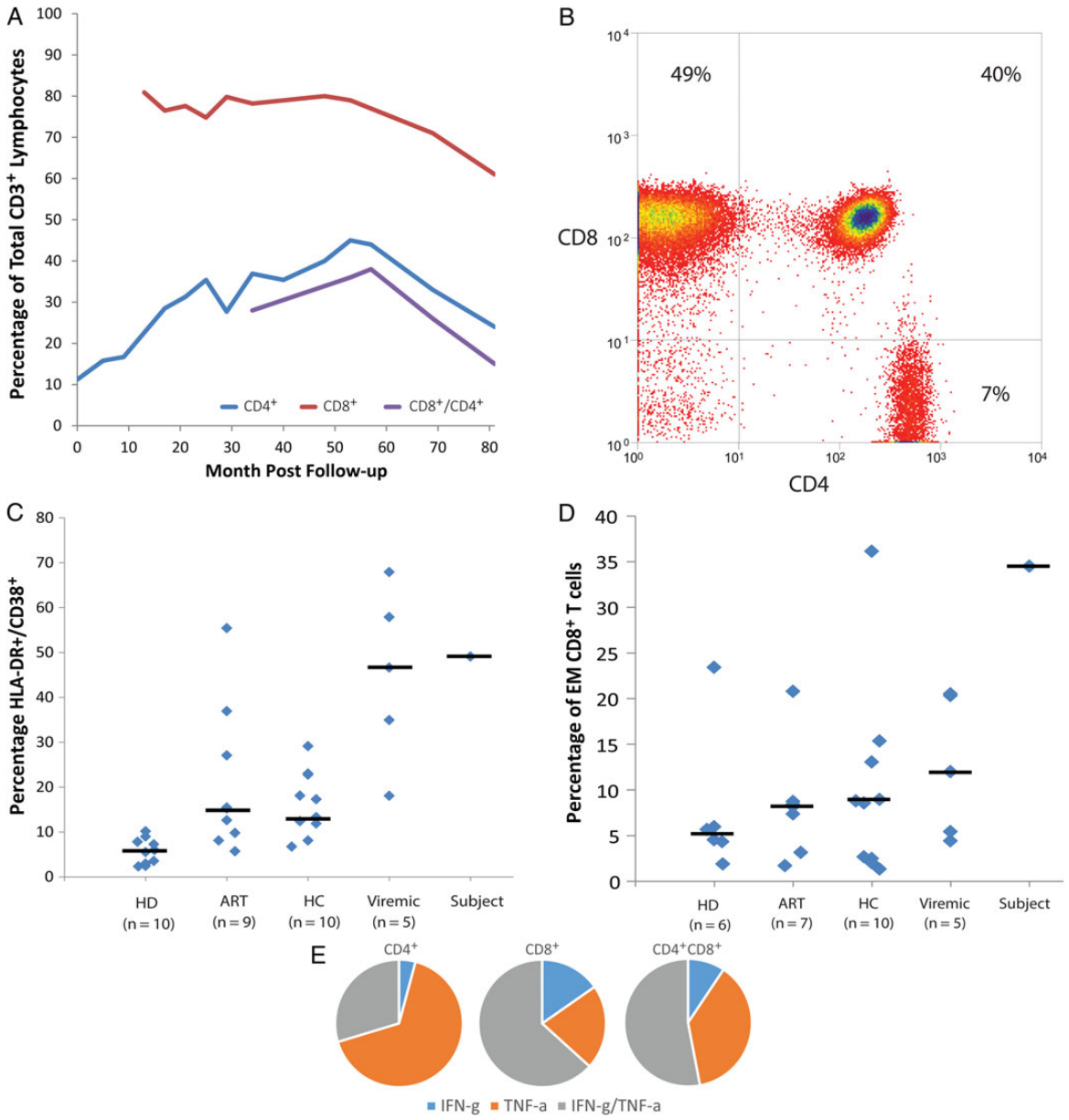


**Figure 1.** Percentage of different T cell populations over time in the subject (A). Flow cytometry showing the large population of $CD4^+CD8^+$ T cells (B). Comparison of activated (C) and effector memory (EM; D) $CD8^+$ T cells in the subject compared with healthy donors (HD), untreated viremic patients, patients on antiretroviral therapy (ART), and human immunodeficiency virus controllers (HC). The percentage of $CD4^+CD8^+$ T cells was too low in the other patients for a meaningful comparison to be performed. Percentage of cells that expressed interferon-γ or tumor necrosis factor-α alone or in combination after stimulation with anti-CD3 and anti-CD28 monoclonal antibodies.

proportion of all 3 cell populations expressed TNF-α in response to stimulation with Gag peptides (Table 1). In contrast to a prior study in which $CD4^+CD8^+$ T cells were often multifunctional [2], <0.1% of $CD4^+$, $CD8^+$, and $CD4^+CD8^+$ simultaneously expressed TNF-α, IFN-γ, and IL-2 (Table 1). Furthermore, although $CD8^+$ T cells had a modest inhibitory effect on viral replication, $CD4^+CD8^+$ T had no detectable effect (Table 1).

## CONCLUSIONS

We present the case of an HIV controller with a very large, persistent population of $CD4^+CD8^+$ T cells (15%–40%). There is a prior report of an HIV-infected individual with progressive disease who had elevated $CD4^+CD8^+$ T cells (approximately 7.5%) over 8 years [3]. In that case, $CD4^+CD8^+$ T cells had a low CD8 density and were phenotypically similar to $CD4^+$ cells, whereas in