



Discordant responses during anti-retroviral therapy: role for immune activation and T cell redistribution

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Introduction

A proportion of HIV-1 infected individuals on highly active anti-retroviral therapy (HAART) experiences virus relapse after initial adequate control. A subset of these patients is able to maintain peripheral blood T cell numbers despite high levels of plasma HIV-1 RNA (discordant responders).

This has been attributed to protease inhibitors (PIs) that may enhance CD4⁺ T cell survival, or to PI or reverse transcriptase (RT) - resistant virus strains that may be less cytopathic to mature or immature (intrathymic) CD4⁺ T cells (Sloand ea, Blood 1999; Stoddart ea, Nat Med 2001).

HIV-1 infection is characterized by increased levels of immune activation. Associated upregulation of homing receptors and cytokine levels results in increased sequestration of T cells in lymphoid tissues. Effective HAART is associated with release of these T cells into the circulation (Pakker ea, Nat Med 1998).

Thus, fluctuations in plasma HIV-1 RNA levels such as during virologic failure could result in changes in peripheral blood T cell numbers due to migration of T cells.

Aim of the study

To study the effect of T cell activation on peripheral blood T cell numbers during virologic failure to HAART.

Approach

Patients

Participants of the Amsterdam Cohort Studies on HIV-1 Infection and AIDS of whom cryopreserved PBMC were available before and during HAART, who initially experienced sustained virus suppression (plasma HIV-1 RNA undetectable ≥ 6 months), but subsequently developed virologic failure (plasma HIV-1 RNA ≥ 1 log increase) for ≥ 6 months.

Individuals that complied with these very strict criteria (n=4) were male, seropositive when they entered the Cohort and median age was 31.5 years (range: 22.8 - 46 years). Follow-up was between 40 and 70 months.

T cell subsets and peripheral T cell division

FACScan analysis of naive (CD27⁺ CD45RO⁻), CD27⁺ memory (CD27⁺ CD45RO⁺), CD27⁻ memory (CD27⁻ CD45RO⁺) and effector (CD27⁻ CD45RO⁻) CD4⁺ and CD8⁺ T cell numbers and Ki67 expression by these subsets.

Tetramer staining

Patient 6181 was HLA-B8 positive; patient 3558 HLA-B8 and HLA-A2 positive. The other two patients did not have a HLA-type for which tetramers were available.

MHC class I tetramers: B8-restricted p24 Gag and Nef; A2-restricted p17 Gag (Kostense ea, Eur J Immunol 2001).

Plasma HIV-1 RNA

Roche Amplicor Monitor Standard Assay or Ultra Monitor Assay (Roche Diagnostics, Branchburg, NJ); NucliSens HIV-1 QT Assay and NASBA HIV-1 RNA QT (Organon Teknika, Boxtel, The Netherlands); Quantiplex HIV-1 RNA 3.0 bDNA Monitor Assay (Chiron Corp., Emeryville, CA).

Results

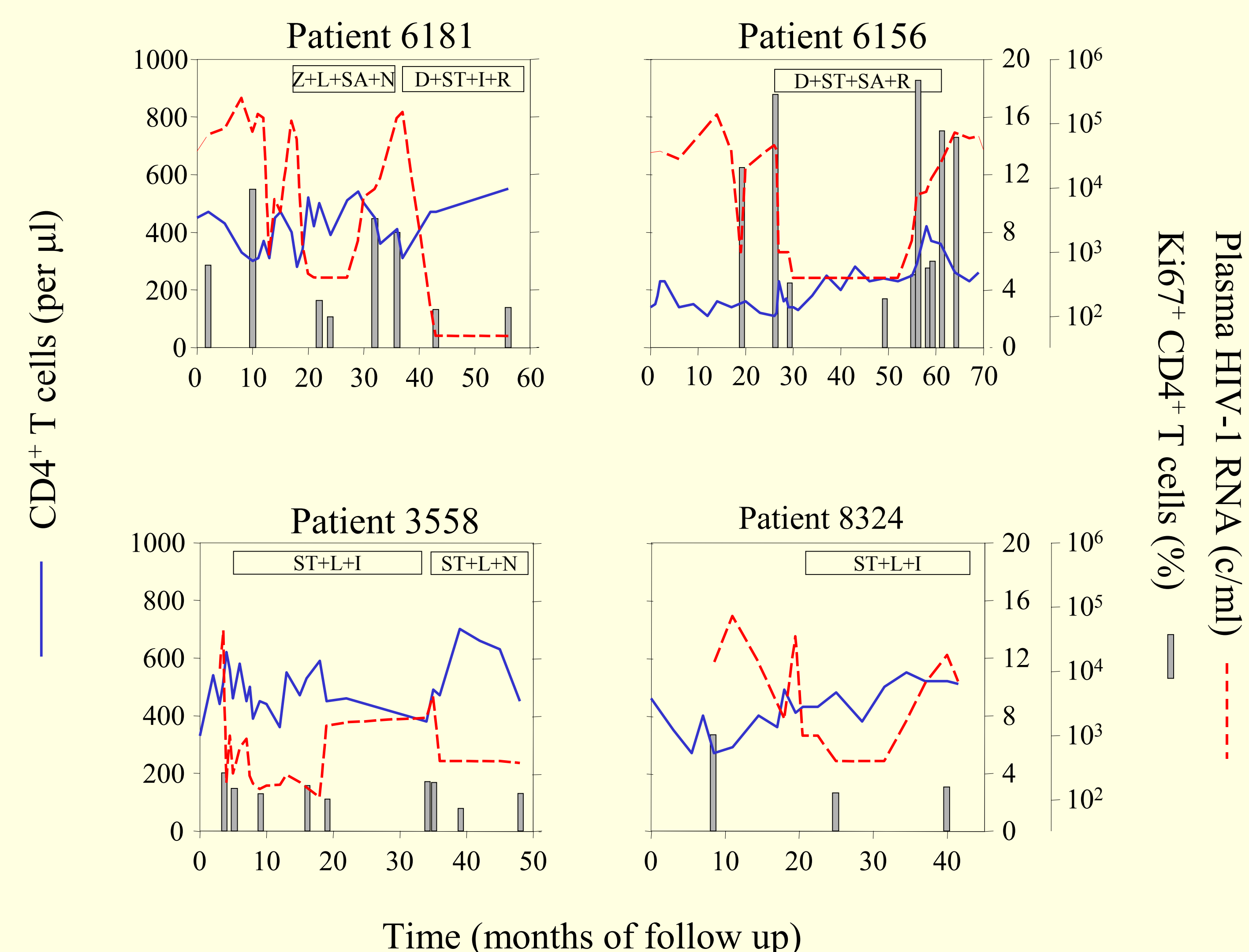


Figure 1 Individual data of the four selected patients.

Peripheral blood CD4⁺ T cell numbers increased and plasma HIV-1 RNA and Ki67 expression rapidly declined with successful HAART. During subsequent virologic failure, 2 patterns could be distinguished:

Patients 6181 and 6156:

High plasma HIV-1 RNA levels were associated with increased proportions of Ki67⁺ T cells and a decline in CD4⁺ T cell numbers.

Patients 3558 and 8324:

Virus rebound was associated with relatively low proportions of Ki67⁺ T cells and stable CD4⁺ T cell numbers.

Horizontal bars: period during which each patient was treated with HAART. Characters represent drugs: Z zidovudine, L lamivudine, SA saquinavir, N nelfinavir, D didanosine, ST stavudine, I indinavir, R ritonavir.

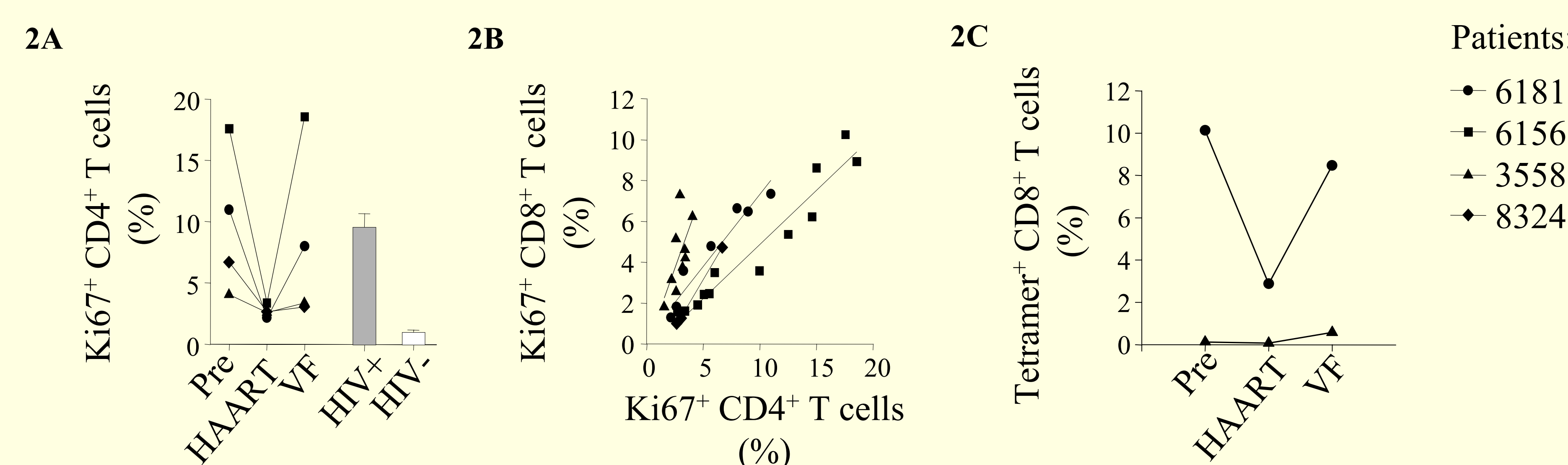


Figure 2

(a) Immune activation (Ki67 expression) rebounded to pre-treatment levels during virologic failure. Pre: pre-HAART; HAART: successful virus suppression; VF: virologic failure; HIV⁺: control group of untreated HIV⁺ individuals (n=16); HIV⁻: healthy controls (n=5). (b) The proportion of Ki67⁺ CD4⁺ T cells correlated with the proportion of Ki67⁺ CD8⁺ T cells at all timepoints, and so did the proportions of Ki67⁺ naive, memory and effector CD4⁺ and CD8⁺ T cells (not shown). (c) Patient 6181 who had relatively high proportions of Ki67⁺ CD4⁺ T cells during virus rebound had elevated levels of Gag- and Nef-specific tetramer⁺ CD8⁺ T cells at the same timepoint, whereas immune reactivity measured as the proportion of tetramer⁺ CD8⁺ T cells in patient 3558 remained low, similar to his low Ki67⁺ CD4⁺ T cell values.

Conclusion

Changes in peripheral blood CD4⁺ T cell numbers during virologic failure may depend on the level of immune activation that is elicited: low reactivity to rebounding virus may preserve normal T lymphocyte distribution over blood and tissues and thereby stable peripheral blood T cell numbers.

This suggests that transient reductions in peripheral blood CD4⁺ T cell numbers during virologic failure but also during for example structured treatment interruptions (STI) in chronically HIV-1 infected patients may be related to immune activation and tissue sequestration of T cells, rather than to actual physical loss.