Early ART in primary HIV infection may also preserve lymphopoiesis capability in circulating haematopoietic progenitor cells: a case report

Veronica Bordoni1*, Rita Casetti1, Domenico Viola1, Isabella Abbate2, Gabriella Rozera2, Alessandra Sacchi3, Eleonora Cimini3, Nicola Tumino3, Chiara Agrati3,

Nicoletta Orchi2, Carmela Pinnetti3, Adriana Ammassari3 and Federico Martini1

1Cellular Immunology Laboratory, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’ IRCCS, Rome, Italy; 2Virology Laboratory, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’ IRCCS, Rome, Italy; 3Clinical Department, National Institute for Infectious Diseases ‘Lazzaro Spallanzani’ IRCCS, Rome, Italy

*Corresponding author. Tel: +39-06-55170935; Fax: +39-06-55170962; E-mail: veronica.bordoni@inmi.it

Keywords: antiretroviral treatment, HPCs, T cells

Sir,

ART effectively suppresses viral replication and controls infection for an undefined period of time; however, viral eradication is not achievable because of long-lived cellular HIV reservoirs.1,2 We previously showed that, in chronically infected subjects with undetectable plasma HIV-RNA, bone marrow CD34+ haematopoietic progenitor cells (HPCs) are apparently free of HIV replication, but are blunted in differentiation capability,3 and may harbour HIV-DNA even after a long period on successful ART.4 Moreover, in patients treated with successful ART for a very long time, a persistent impairment in the lymphopoietic capability of circulating CD34+ HPCs was found, and lymphopoiesis exhaustion resulted correlated to systemic immune activation, only partially reversed by prolonged ART.5 To date, the mechanisms of HIV-related lymphopoiesis dysfunction remain largely unexplained, and in particular, little information is available on the possibility of limiting the occurrence of irreversible damage by early ART introduction.

We herein describe immune activation levels, T cell profile/response and circulating HPC kinetics in a patient with primary HIV infection receiving early treatment with ART. The patient was further followed for 12 months, and blood samples were analysed before (baseline) and after 2, 24 and 48 weeks of ART.

A young adult male was recently diagnosed with HIV acute infection (Fiebig IV stage according to Fiebig et al.). Baseline plasma HIV-1 RNA was 1868262 copies/mL, and CD4+ T lymphocyte count was 389 cells/mm³. Ritonavir-boosted darunavir, tenofovir+emtricitabine and raltegravir were started on day 3 after diagnosis. After 12 weeks of ART, viral load dropped <40 copies/mL and ART was simplified to rilpivirine+emtricitabine+tenofovir. Plasma HIV-RNA remained undetectable at all timepoints thereafter.

The viro-immunological parameters are shown in Figure 1(a). CD4+ cell count steadily increased over time: 534, 1218 and 1072 cells/μL at weeks 2, 24 and 48, respectively. Proviral HIV-DNA, determined as described in Rozera et al., was 82 479 copies/10⁶ PBMC at baseline and 21534, 1752 and 6809 copies/10⁶ PBMC at weeks 2, 24 and 48, respectively.

CD8+ T cell activation, measured as CD38 expression by flow cytometry, paralleled plasma HIV-RNA viral load, reaching at week 24 the level found in healthy donors. On the other hand, the level of early CD8+ T cells, evaluated by CD127 expression, steadily increased from baseline to week 48 (Figure 1b).

Peripheral blood CD4+ and CD8+ T cell differentiation was evaluated by CD45RA and CCR7 expression.8 As shown in Figure 1(c), the variation in CD4+ subsets included a decrease in effector memory (EM; CD45RA+/CCR7−) and an increase in...
Figure 1. Clinical case of early ART in primary HIV infection followed for 48 weeks and analysed at the times indicated for: (a) evolution of HIV-RNA, HIV-DNA and CD4+ count; (b) expression of activation markers CD38 and CD127 on CD8+ T cells; (c) and (d) differentiation profiles of CD4+ and CD8+ T cells; (e) polyfunctional HIV-specific CD8+ T cell response; and (f) HPC frequency and L-HPC frequency. As a comparison, the expression levels of CD38 and CD127, the percentages of CD4+ and CD8+ T cell subsets and the percentages of HPCs (CD34+Lin−) and L-HPCs for healthy donors (HDs) are indicated as median values. w2, week 2; w24, week 24; w48, week 48; CM, central memory.
naive (CD45RA+/CCR7+) cells at week 2. Levels remained stable and similar to healthy donors. CD8+ T cells at week 2, when compared with baseline, showed an increase in naive cells, and stable levels afterwards. In parallel, a decrease in the CD8+ T EM subset and an increase in terminal effector memory (TEMRA CD45RA+/CCR7−) were observed (Figure 1d).

Polyfunctional CD8+ T cell response to HIV antigens was performed at baseline and at week 48 by evaluating CD107a, IFNγ, IL-2, MIP1β and TNFα expression (Figure 1e). The predominant CD8+ T cell subset response performing five functions at baseline changed over time to tri-, bi- and mono-functional CD8+ T cell subsets. Interestingly, a shift towards subsets expressing CD107a was observed, suggesting a principally cytotoxic CD8+ response capability at week 48, paralleling and confirming CD8+ T cell phenotype results.

Circulating HPCs (defined as CD34+Lin−) and, among these, the lymphoid CD10+ CD45RA+ CD117− subset (L-HPCs) were analysed at baseline and over time (Figure 1f). In respect to baseline, a steady repopulation of HPCs was found, suggesting an early consumption linked to high HIV-RNA levels, and a rapid increase after viral load control. Interestingly, L-HPC levels transiently dropped between weeks 2 and 24, returning to baseline levels at week 48, suggesting possible consumption due to a shift from L-HPC to naive T cells.

In conclusion, albeit limited to a single clinical case, this report adds a further point to the literature underlying the pivotal importance of the earliest possible introduction of ART in HIV-infected individuals, in order to avoid irreversible systemic immune activation.

Funding
This work was supported by the Italian Ministry of Health (Ricerca Corrente).

Transparency of declarations
None to declare.

References