Antiretroviral naive and treated patients: Discrepancies of B cell subsets during the natural course of human immunodeficiency virus type 1 infection

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To evaluate alterations of memory B cell subpopulations during a 48-wk period in human immunodeficiency virus type 1 (HIV-1) patients.

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Forty-one antiretroviral naïve and 41 treated HIV-1 patients matched for age and duration of HIV infection were recruited. All clinical, epidemiological and laboratory data were recorded or measured. The different B cell subsets were characterized according to their

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assess vaccine responses and tracing infections. Assessing these populations could potentially lead to improved understanding of vaccine responses and tracing infections. Assessing these populations could potentially lead to improved understanding of vaccine responses and tracing infections. Assessing these populations could potentially lead to improved understanding of vaccine responses and tracing infections.

**RESULTS**

Mean counts of BMCs were higher in treated patients. There was a marginal upward trend of IgM memory B cell proportions which differed significantly in the treated group (overall trend, \( P = 0.004 \)). ITS BMC increased over time significantly in all patients. Naive patients had of lower levels of EM B cells compared to treated, with a downward trend, irrespectively of highly active antiretroviral therapy (HAART) intake. Severe impairment of EM B cells was recorded to both treated (\( P = 0.024 \)) and naive (\( P = 0.023 \)) patients. Higher proportions of RM cells were noted in HAART group, which differed significantly on week 4 (\( P = 0.017 \)) and 48 (\( P = 0.03 \)). Higher levels of AM were preserved in HAART naive group during the whole study period (week 4: \( P = 0.018 \) and 48: \( P = 0.035 \)). HIV-RNA viremia strongly correlated with AM B cells (\( r = 0.54, P = 0.01 \)) and moderately with RM cells (\( r = -0.45, P = 0.026 \)) at baseline.

**CONCLUSION**

HIV disrupts memory B cell subpopulations leading to impaired immunologic memory over time. BMC, RM, EM and ITS BMC were higher in patients under HAART. Activated BMCs (AM) were higher in patients without HAART. Viremia correlated with AM and RM. Significant depletion was recorded in EM B cells irrespective of HAART intake. Perturbations in BMC-populations are not fully restored by antiretrovirals.

**Key words:** B cell subpopulations; Time-trend; Memory cells; Human immunodeficiency virus infection; Highly active antiretroviral therapy

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Core tip: During the progress of human immunodeficiency virus (HIV) infection and viral replication functional irritations of memory B-cell (BMC) compartment occur. Depletion of BMCs is one hallmark of deregulation in HIV-1 infection. Diminished levels of IgM+ BMCs are also noted. Additionally, resting BMCs are severely impaired and defective B-cell subsets, like exhausted and activated BMCs circulate in peripheral blood. Significant fluctuations of these B cells’ frequencies are recorded over time and antiretroviral therapy may play a role in this observation. Assessing these populations could potentially lead to improvement in assessing vaccine responses and tracing vulnerable patients to certain infections.
All quantitative data are presented as mean ± SD, median (IQR). HAART: Highly active antiretroviral therapy; VL: HIV RNA viral load; HIV: Human immunodeficiency virus; ART: Antiretroviral therapy; NA: Not applicable; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

**RESULTS**

The demographics, clinical and rest data of eighty two HIV individuals are illustrated in Table 1.

In order to confirm whether the percentages of B-cell subsets were altered among treated and antiretroviral naive HIV-1 individuals, the percentages of memory B, activated memory, resting memory, exhausted memory as well as isotype-switched and total B-cells were assessed. Significant differences were observed between the groups in relation to B cell subsets.

Mean counts of BMCs (CD19⁺CD27⁺) were higher in treated patients throughout the 48 wk (P = 0.987, NS), with a gradual declining trend by the end of the 48th week. Mean fraction of IgM memory B (CD19⁺CD27⁻IgM⁺) cell-population found higher in the treated group at baseline. There was a marginal upward trend of the proportions which differed significantly in the treated group (overall trend, P = 0.004) (Figure 1). Isotype-switched BMC (CD19⁺CD27⁺IgM⁺) were slightly elevated in patients without HAART compared to the other group. The time trend variation was equivalent in both groups, irrelevantly of HAART intake (P = 0.808). ITS B cell compartment raised significantly in all patients, concerning baseline levels (overall significance, P = 0.0005) (Figure 1).

HAART patients preserved higher proportions of EM B cells (CD19⁺CD21⁺CD27⁻) compared those without treatment, with a downward trend along with the progression of the disease, irrespectively of HAART intake. These changes were not significant among groups (overall significance, P = 0.876). Significant depletion of EM B cells was recorded to both ART-naive (P = 0.023) and rest individuals (P = 0.024) (Figure 1). The fraction of RM cells (CD19⁺CD21⁻CD27⁺) in patients under HAART were higher and significantly different on week 48 (P = 0.017) and 48th (P = 0.03). The fluctuation over time of RM was nearly the same though, in both groups (P = 0.201) with treated patients having a significant overall increase (P = 0.003). Patients HAART-naive maintained higher levels of AM (CD19⁺CD21⁻CD27⁺) during the whole study period, with the downward trend being significant in the treated group (P = 0.004) (Figure 1).

HIV-RNA viremia strongly correlated with AM B cells (r = 0.54, P = 0.01) and moderately with RM B cells (r = -0.45, P = 0.026) at baseline, supporting the impact of viral replication on these subsets (data not shown).

**DISCUSSION**

HIV infection impels to a broad amplitude of B cell defects, like cell switching, depleted numbers of B cells, production of uncommon B cell populations and dysfunctional immune responses even in patients under HAART. Furthermore, it is generally accepted to augments the risk of several infections. Very scarce and
conflicting data are currently available illustrating the significance of B cell subsets that mediate satisfactory and protective immune responses\textsuperscript{[6,7]}. Our study promotes the scouting and assessment of specific BMC subpopulations interfered in humoral responses, confirming few other authors claiming that, not solely ITS and IgM BMC, but also AM and RM\textsubscript{e} might contribute to impaired protection against certain bacteria\textsuperscript{[7-12,14]}. Recent studies focus on B cell memory and immunological response post immunizations, though most constitute solely cross-sectional studies\textsuperscript{[6-12,14]}. BMCs were increased in patients on HAART compared to naive on an annual basis, as confirmed in other studies as well\textsuperscript{[2,15]}. We showed rise of BMCs in both groups, which depleted throughout time in a similar pattern, that is in line with previous studies\textsuperscript{[27]}. Interestingly, slight rise in IgM BMC was confirmed in all patients. Patients on treatment preserved high frequencies of them, confirming authors suggesting that HAART preserves the levels of this specific subset\textsuperscript{[15]}. Both treated and naive patients maintained their IgM BMC over time, which is controversial in literature\textsuperscript{[15]}. EM B cells are believed to be increased in naive patients\textsuperscript{[2,6]}. Although in our study we did not confirmed the former observation, gradual decrease has been recorded irrespectively of HAART. Patients under HAART had decreased AM cells compared to those without treatment, explaining the effect of HAART which restricts their expansion during the progress of HIV infection\textsuperscript{[2]}. We additionally confirmed that AM B cells are preserved in continuous viral replication\textsuperscript{[13]}. Even though effective HAART is regarded to have no impact on RM, in our study maintenance of high levels especially in the treated group, implies that some restoration may be feasible upon HAART initiation, regardless being not during primary infection\textsuperscript{[5,14]}. Studies have shown that isotype switched B cells are not affected in healthy individuals\textsuperscript{[7]}, but these are dramatically impaired in HIV infection irrespectively of HAART\textsuperscript{[15]}. Despite few studies that confirmed high frequencies of ITS B cells in patients under HAART\textsuperscript{[2,15]}, our study confirmed more recent authors\textsuperscript{[15]} showing no effect of HAART, which underlies the need for further investigation on this specific memory subset. HAART introduction lead to further investigation on these populations, concluding that most divergences are reversible, implying that viremia has a causal relationship. Viremia has been associated with the
elevated frequency of AM cells\textsuperscript{14}. However, the impact of HIV viremia has not been fully explained, apart from in limited studies\textsuperscript{14}. Our study in line with other authors has shown that viremia was linked to certain B cell populations\textsuperscript{14}.

In conclusion, the data of our study points out that significant divergences occur in specific BMC populations in HIV patients. Natural course of HIV infection has an immunological impact on distinct B cells, sparking modifications on their absolute numbers and functions in the peripheral blood of HIV adults. Furthermore, HAART administration affects subsets like RM and AM which are significant in secondary immune responses, while has controversial implication in other BMC compartments. We propose that evaluation of BMC might implicate in immunization and have clinical utility in forecasting all susceptible HIV adults to bacterial and other viral infections.

The significance of the paper lies to the fact that HAART prompt initiation may alter few of the disturbances that HIV infection itself promotes. Similar findings for the significance of immediate initiation of antivirals have been published recently, which insist that HAART is necessary to be started once the diagnosis of HIV infections has been confirmed\textsuperscript{17}.

Additionally, concerning the HIV vaccine development design, new scientific trends lean towards the role of B cells in HIV pathogenesis and their possible use to design and develop a proper vaccine for preventing HIV infections. Multiple studies try to assess and isolate the responsible B cell subsets that interfere to the pathogenesis of HIV infection and will lead to the vaccine development\textsuperscript{18,19}.

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