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Monocytes activation characterizes immune failure but not cognitive impairment on ART

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Background

Neurocognitive impairment (NCI) in HIV+ patients can occur despite effective ART and has been linked to increased CD16-bearing monocytes in circulation. We evaluated monocytes (M/M) phenotypes and activation markers in HIV+ patients under ART, aiming to define the role of innate immune activation on CD4+ T cell recovery and NCI.

Objective

- To evaluate the relationship between monocyte activation and CD4+ T cell count recovery in HIV positive patients undergoing ART.
- To assess the prevalence of NCI in patients with or without CD4+ T cell count reconstitution.
-To evaluate the relationship between monocyte activation and NCI in HIV positive patients undergoing ART.

Methods

Design: cross-sectional study.

Subjects: 84 HIV+ Italian patients with current CD4+ T cell count ≤ 350/µl (n=39, defined as Immune failure-IF) or ≥ 500/µl (n=45, defined as Immune Success-IS) after ≥ 18 months of ART and with HIV-RNA < 50 copies/ml for at least 12 months. The two groups were matched both by age and CD4+ T cell nadir.

Immune assays: peripheral M/M phenotypes (distinguished based on CD14 and CD16 surface expression on "classical" CD14++CD16-, "intermediate" CD14++CD16+ and "non classical" CD14+CD16++) as well as surface activation markers (CD163, CD11b, HLA-DR, CD38, CD69) were evaluated by flow cytometry.

Neuropsychological (NP) tests: all subjects underwent a NP battery including 11 tests exploring memory, attention, executive functions, psychomotor speed and language; scores were adjusted for age and years of education. Neurocognitive impairment (NCI) was defined as having Z score <-1SD on ≥2 tests.

Statistics: Wilcoxon test and Chi-square test.

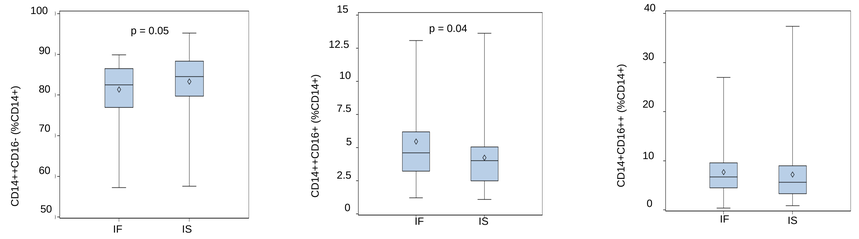
TABLE 1. Demographic, clinical and HIV-related characteristics of study population

*Chi-Square/Fisher Test: p<0.05	IF (n=39)	IS (n=45)
Age (years)	51 (46-54)	48 (45-52)
Sex (female)	15.4% (6)	15,6% (7)
History of IDU	20,5% (8)	11,1% (5)
Years from seroconversion	9 (4-20)	11 (6-21)
CD4+ T cell count Nadir (cell/µL)	49 (18-113)	87 (39-162)
Years of cART	6 (3-16)	9 (5-16)
HCV coinfection *	38.5% (15)	17.8% (8)
HBV coinfection	12.8% (5)	8.9% (4)
Diabetes	5.1% (2)	4.4% (2)
Current CD4+ T cell count (cell/µL)*	268 (218-314)	663 (555-850)
Current CD4+ T cell %*	17 (13-22)	29 (26-34)
Current CD8+ T cell count (cell/µL)*	696 (579-1017)	946 (699-1157)
Current CD8+ T cell %*	49 (42-55)	40 (35-45)
CD4+/CD8+ ratio*	0.36 (0.26-0.49)	0.76 (0.60-0.92)
Plasma HIV-RNA (1-40 cp/mL)	10.3% (4)	24.4% (11)

Data are represented as median and interquartile range or number and percentage, as appropriate.

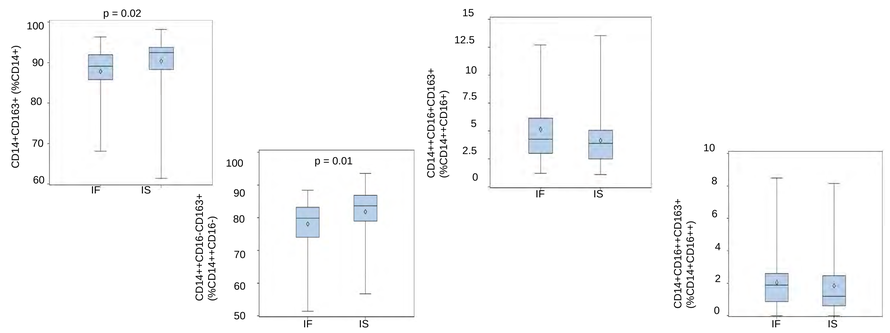
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FIGURE 1. Monocyte subsets in IF and IS



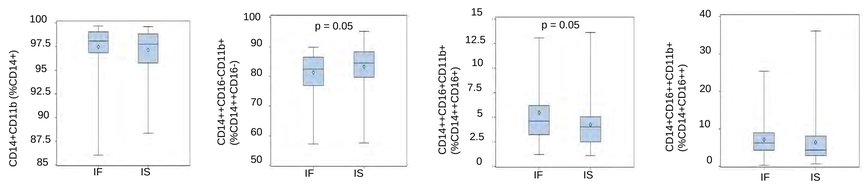
Compared to IS subjects, IF patients showed significantly lower levels of "classical" (p=0.05) and higher levels of "intermediate" monocytes (CD14++CD16- 82.5% of total CD14+ [IQR 77.0-86.5%] versus 84.5% [IQR 7.0-86.5%], p=0.05; CD14++CD16+ 4.6% of total CD14+ [IQR 3.2-6.2] versus 4.0% [IQR 3.2-6.2], p=0.04). "Non classical" monocytes were not significantly different between groups (CD14+CD16++ 6.7% of total CD14+ [IQR 4.5-9.6] versus 5.6% [IQR 3.3-9,0]) .

FIGURE 2. Evaluation of CD163 on monocyte subsets in IF versus IS



IF patients diplayed significantly lower expression of CD163 compared to IS patients, both on total and "classical" monocytes (CD14+CD163+ 89.1% of total CD14+ [IQR 85.8-91.9] versus 92.5% [IQR 88.3-93.8], p=0.01).2; CD14++CD16-CD163+ 79.9% of CD14++CD16- [IQR 74.0-83.2] versus 83.7% [IQR 78.9-86.9], p=0.01). Although higher in IF, we found no significant differences between the two groups in the proportion of CD14++CD16+CD163+ (4.3% of CD14++CD16+ [IQR 3.0-6.2] versus 3.9% [IQR 2.5-5.1], p=0.07) and CD14+CD16++CD163+ monocytes (1.9% of CD14+CD16++ [IQR 0.9-2.6] versus 1.2% [IQR0.6-2.5], p=0.35).

FIGURE 3. Evaluation of CD11B on monocytes subsets in IF versus IS



The frequency of CD14+CD11b+ did not differ substantially between the two groups (median IF 98.1% of total CD14+ [96.8-99.1] vs IS 97.8% [95.8-98.8], p 0.4). In contrast, IF patients showed significant lower proportion of CD14++CD16-CD11b+ (82.5% of CD14++CD16- [77.0-86.5] vs 84.5% [79.8-88.3], p <0.05) and higher proportion of CD14++CD16+CD11b+ monocytes (4.6% of CD14++CD16+ [3.2-6.2] vs 4.0% [2.5-5.1], p <0.05). Levels of nonclassical CD14+CD16++ monocytes expressing CD11b+, whilst higher in IF patients did not differ significantly between the two groups (IF 6.2% of CD14+CD16++ [4.3-8.9] vs IS 4.3% [2.9-8.1], p 0.08).

No differences in the expression of HLA-DR, CD38 and CD69 on M/M were found in the two groups.

FIGURE 4. Neuropsychological evaluation in IF and IS

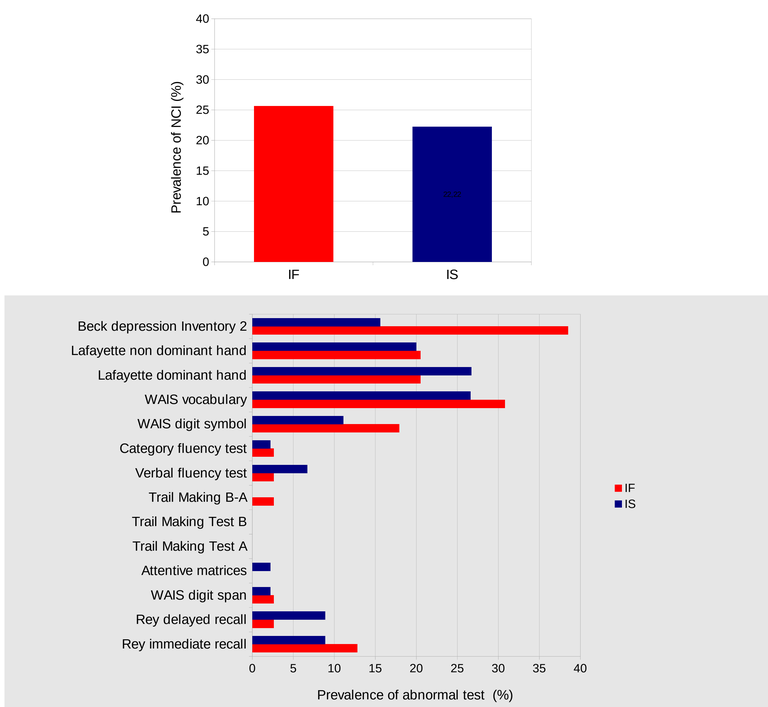


TABLE 2. Monocyte phenotypes in NCI versus controls

* Test-t /Wilcoxon test: p<0.05	NCI (n=20)	Controls (n=64)
CD14+(%)	6.1 (4.3-7.4)	6.2 (4.7-7.3)
CD14++CD16- (%CD14+)	83.4 (75.3-85.7)	83.7 (79.6-87.8)
CD14++CD16+ (%CD14+)	3.8 (2.9-6.3)	4.3 (2.8-5.7)
CD14+CD16++ (%CD14+)	7.5 (4.5-8.4)	6.4 (3.3-9.6)
CD14+CD163+ (%CD14+)	90.1 (85.9-92.6)	90.9 (86.9-93.7)
CD14++CD16-CD163+ (%CD14++CD16-)	80.3 (72.6-84.1)	81.8 (77.8-86.4)
CD14++CD16+CD163+ (%CD14++CD16+)	3.8 (2.9-6.2)	4.0 (2.7-5.3)
CD14+CD16++CD163+ (%CD14+CD16++)	1.5 (0.7-2.2)	1.6 (0.7-2.7)
CD14+CD11b+ (%CD14+)	83.4 (75.3-85.7)	83.7 (79.6-87.8)
CD14++CD16-CD11b+ (%CD14++CD16-)	3.8 (2.9-6.3)	4.4 (2.8-5.7)
CD14++CD16+CD11b+ (%CD14++CD16+)	5.1 (3.3-7.5)	5.7 (3.0-8.9)
CD14+CD16++CD11b+ (%CD14+CD16++)	97.8 (96.1-98.8)	97.9 (96.5-99.0)
CD14+HLA-DR+(%CD14+)	92.6 (90.3-94.1)	94.1 (90.1-96.5)
CD14+CD38+(%CD14+)*	97.5 (95.4-98.7)	98.5 (97.3-99.2)
CD14+CD69+(%CD14+)	34.6 (21.2-58.1)	33.3 (22.2-55.0)

Conclusions

A shift on M/M phenotype from the "classical" towards "intermediate" and altered expression of monocyte activation markers, CD163 and CD11b, correlate with immune failure on ART. HIV-infected subjects with NCI on ART do not have a distinct monocyte phenotype using the variables we studied.