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Uncoupled cellular and plasma markers of monocyte activation in early HIV infection

Montse Jiménez[1*], Lucia Pastor[1,2,3*], Victor Urrea[1], Nuria Izquierdo-Useros[1], Javier Martinez-Picado[1,4,5], Chenjerai Jairoce[3], Inacio Mandomando[3], Bonaventura Clotet[1,5], Jorge Carrillo[1], Denise Naniche[2,3], Julià Blanco[1,5]

[1]AIDS Research Institute-IrsiCaixa, Institut Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain. [2]ISGlobal, Barcelona Institute for Global Health, Hospital Clínic–Universitat de Barcelona, Barcelona, Spain. [3]Centro de Investigação em Saúde da Manhiça (CISM), Maputo, Mozambique. [4]Institució Catalana de Recerca I Estudis Avançats (ICREA), Barcelona, Spain. [5]Universitat de Vic - Universitat Central de Catalunya, Vic, Barcelona, Spain

Background and Objective

Monocytes are chronically activated in HIV infection, showing increased expression of CD16 and downregulation of CD14. This observation is concomitant to increased plasma levels of sCD14 and sCD163, which are usually considered surrogate markers of monocyte activation. Nevertheless, phenotypic abnormalities of monocytes during primary HIV infection (PHI) are not fully characterized.

The **objective** of this study is the characterization of the monocyte compartment dynamics in a cohort of acute HIV infected patients recruited at Manhiça District in Mozambique.

Methods

We longitudinally studied monocytes in individuals at PHI (n=40) followed for 1 year. HIV-uninfected individuals (n=58) and treated or untreated chronic HIV infected individuals (CHI; n=56) were also cross-sectionally analyzed. Participants were recruited at the Manhiça District Hospital in Mozambique.

Monocyte activation was assessed by multicolor flow-cytometry, while plasma levels of sCD14, sCD163 and IFN-a were assessed by ELISA or Luminex.

STUDY POPULATION

The study population was enrolled between 2013 and 2014 and all participants were recruited at the **Manhiça District Hospital** in Southern Mozambique [Figure 1]. The present analysis is a sub-study of a prospective cohort of primary HIV-infected adults enrolled and followed up for 12 months in the gastrointestinal biomarkers in acute-HIV infected Mozambican adults study (GAMA)[1].

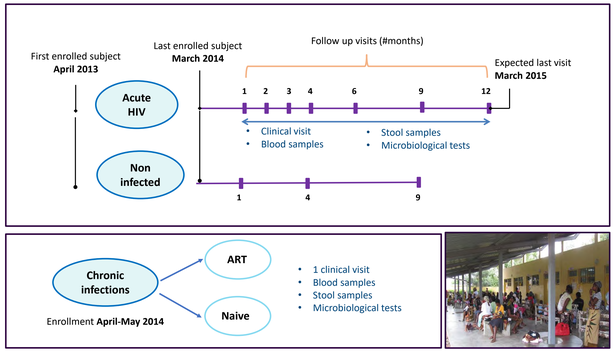


Figure 1. Schematic representation of patient recruitment and follow-up. Enrollment of acute HIV and non infected patients started at April (2013) and the last enrolled subject was at March (2014). Acute patients had a follow up visits at month 1, 2, 3, 4, 6, 9 and 12 ending at march 2015. The visits included blood and stool samples recollection and microbiological tests. Non infected individuals were visited at month 1, 4 and 9. Chronic infected patients were enrolled between April and May (2014) and were separated in ART and naïve groups.

Results

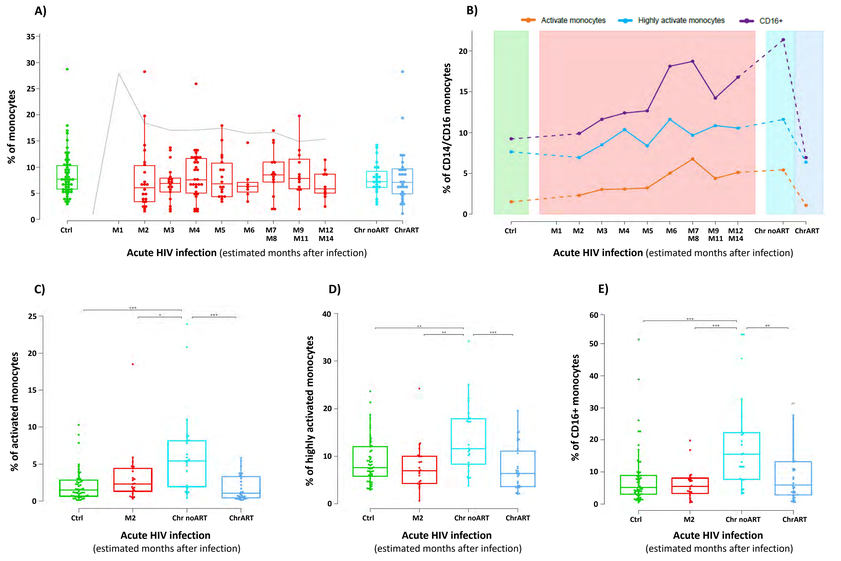


Figure 2. Dynamics of monocyte frequency and activation during Acute HIV infection. (A) Plasma HIV viremia peaked at one month after infection and virological (VL) plateau was reached after four months of infection (grey line). The percentage of circulating monocytes was stable during PHI. M, months after infection. Box as IQR, middle line as median, whiskers as maximum and minimum, and dots as individual observations. Groups: Control (green); acute HIV patients (red); chronic HIV patients without or with ART (light blue and dark blue, respectively). **(B)** Dynamics of **activated** (CD14+CD16+; orange line), **highly activated** (CD14–CD16+; blue line) and **total CD16+** (purple line) monocytes, during PHI. Activated **(C)** and highly activated **(D)** monocytes were unaltered in PHI and significantly increased in untreated CHI patients compared to HIV-uninfected individuals ($p<0.005$). This trend is similar for **total CD16+** monocytes. **(E)**. Graphic description and color code as described in figure 2A.

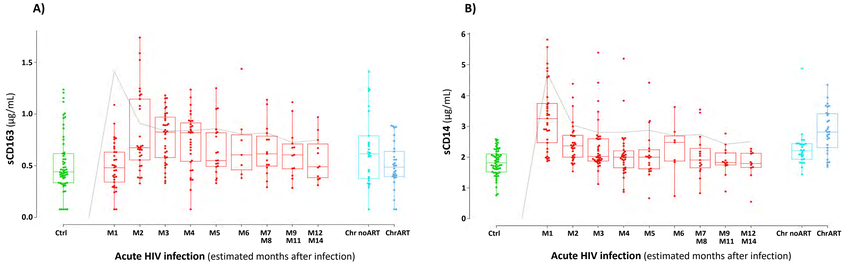


Figure 3. Plasma levels of sCD163 and sCD14 during Acute HIV infection. In contrast to monocyte activation, plasma **sCD163 (A) and sCD14 (B)** levels peaked at month 2-3 and 1 after infection, respectively. Graphic description as in figure 2A.

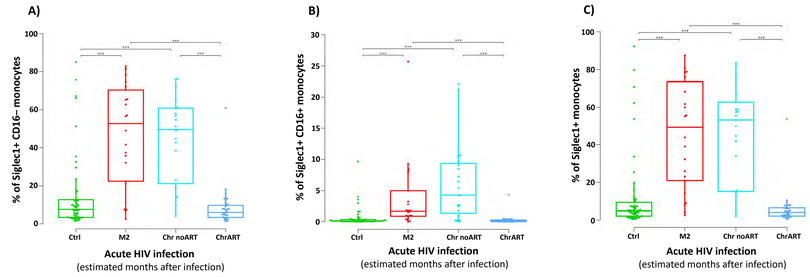


Figure 4. Siglec-1 expression in monocytes during Acute HIV infection. The expression of the Type-I IFN regulated protein **Siglec-1**[2] on monocytes was increased early after infection in **CD16–** monocytes **(A)** in **CD16+** monocytes **(B)** and total monocytes **(C)** and remined high in chronic patients without ART (noART), recovering the levels showed in control group once ART is initiated. Graphic description and color code as described in figure 2A.

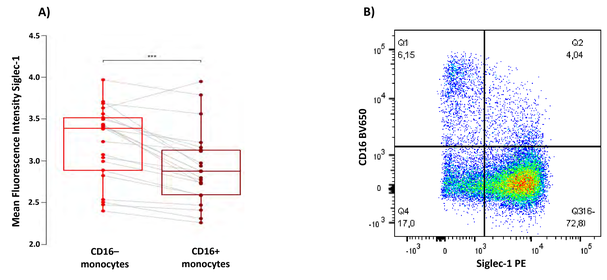


Figure 5. CD16 and Siglec-1 identify different monocyte subsets in PHI (M2). Siglec-1 expression levels (MFI, Y axis) in CD16– (light red) and CD16+ (dark red) monocytes. Wilcoxon signed rank test pval = 0.00026 **(A)**. Dot-plot showing the mutually exclusive trend in the expression of CD16 (Y axis) and Siglec-1 (X axis) **(B)**.

Conclusions

- These data suggest that CD16+ and Siglec-1+ monocytes were activated by different pathways.
- **Early monocyte activation** is associated with type-I IFN response, which triggers **Siglec-1 expression**.
- In contrast, **CD16 expression** significantly increased after 6 months of infection and was uncoupled from plasma sCD14 and sCD163 levels.
- Considering the role of activated monocytes in cardiovascular disorders and aging of the innate immune system, an **early treatment may potentially reduce monocyte activation, resulting in long-term clinical benefit.**

References

[1] Pastor, L. *et al.* A cytokine pattern that differentiates pre- from post-seroconversion phases of primary HIV infection. *J Acquir Immune Defic Syndr.* **74**:459–66 (2017).
[2] Perez-Zsolt, D. *et al.* When Dendritic Cells Go Viral: The Role of Siglec-1 in Host Defense and Dissemination of Enveloped Viruses. *Viruses.* **12, 8** (2020).