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**Change in T lymphocytes count after HAART initiation in HIV-infected
patients with history of *Mycobacterium avium* complex infection**

Short title: Immune reconstitution & MAC infection

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Abstract

Objective: To compare changes in CD4+, CD8+ and total lymphocytes counts, after initiation of highly active antiretroviral therapy (HAART), between HIV-infected patients with and without a recent history of *Mycobacterium avium* complex (MAC) infection.

Method: Matched exposed-non exposed retrospective cohort study.

Results: 51 patients with a recent history of MAC infection (MAC+) started a combination of at least three antiretroviral drugs. They were individually matched to 145 patients without any history of MAC infection (MAC-) according to CD4+ count (± 30 cells/mm³), previous experience of antiretroviral treatment, AIDS clinical stage at the time of HAART initiation (baseline), age (± 10 years) and gender. MAC+ and MAC- patients presented comparable median levels of total lymphocytes (488 vs. 688/mm³, $p=0.09$), CD4+ (11 vs. 16/mm³, $p=0.15$), CD8+ count (359 vs. 386/mm³, $p=0.39$) and plasma HIV RNA (5.3 vs. 5.1 log₁₀ copies/mL, $p=0.22$) at baseline. After 6 months on HAART, the median increase of CD4+ count was 28 cells/mm³ (IQR 1; 63) in MAC+ and 72 cells/mm³ (IQR 34; 120) in MAC- patients ($p<0.0001$) while the percentage of CD4+ cells was not significantly different between the two groups ($p=0.13$). Comparable differences were observed for total lymphocytes and CD8+ cells ($p<0.001$). The six months decline of plasma HIV RNA was not significantly different according to MAC exposure (-1.6 in MAC+ vs. -1.8 log₁₀ copies/mL in MAC- patients, $p=0.65$). Results were confirmed after adjustment for other characteristics than the matching variables and after taking into account potential informative bias due to unbalanced number of deaths between the two groups.

Conclusion: MAC infection at the time of HAART initiation is an important deleterious factor for immune reconstitution. A better understanding of the underlying mechanism and an evaluation of additional treatment strategies are necessary to help immune restoration in such circumstances.

Keywords: HIV infection, Mycobacterium avium complex infection, Immune restoration, CD4 Lymphocyte Count, Highly Active Antiretroviral Therapy

Word count: abstract (295), text (2194), 41 references, 2 tables, 1 figure (7 panels)

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Introduction

Highly Active Antiretroviral Therapy (HAART) allows an immune reconstitution even in patients with advanced HIV disease [1]. Although the increase in CD4+ T-lymphocyte count does not represent the whole immune reconstitution [2], it is the main marker used in clinical practice and epidemiological studies to estimate immune reconstitution. The modifications of the CD4+ counts following HAART initiation are associated with T cell activation [3], plasma HIV RNA and proviral DNA [4] loads at the time of treatment initiation. A low nadir of CD4+ count or a sharp decline in CD4+ count before HAART initiation are important determinants of immune reconstitution [5, 6]. The other factors usually reported are an older age [7], AIDS staging [8], intravenous drug use [9], lack of adherence to HAART [10] and previous antiretroviral exposure [11].

Profound immune deficiency, in particular of the CD4+ T helper cell compartment, limits the control of specific diseases such as Cytomegalovirus infection (CMV) [12] or *Mycobacterium Avium* Complex (MAC) infection [13]. Conversely, restoration of immune function has led to the recommendation of discontinuation of opportunistic infections prophylaxis, including MAC infection [14, 15]. Although profound immune deficiency is an important detrimental factor for immune reconstitution with HAART, little is known on the role of specific opportunistic infections often present in this context [16]. For instance, the impact of HCV co-infection has been discussed [17-19]. A potential mechanism of the detrimental effect on immune restoration may be the activation of apoptosis through the infection of macrophage and expression of Fas-ligand [20, 21]. In the case of CMV infection, there is a known deficiency of hematopoiesis [22] due to (i) a direct cytotoxic effect of CMV which replicates inside hematopoietic progenitor cells and (ii) an inhibition of growth factors production [23]. The direct effect on CD4+ T cells regeneration may also be mediated through apoptosis [24]. Infection with MAC is also known to impair haematopoiesis [25]. However, to our knowledge, few information are available on the response to HAART of patients with history

of MAC infection [26, 27]. In the ACTG protocol 393 study evaluating whether antimycobacterial therapy for MAC could be withdrawn in subjects with history of MAC, the CD4+ count rose slowly (6 cells/mm³ every 2 months) [26]. We conducted a study within the ANRS Co3 Aquitaine Cohort of HIV-infected patients [28], to compare change in CD4+, CD8+ and total lymphocytes counts between HAART treated patients with and without a recent history of MAC infection.

Methods

Design

The Aquitaine Cohort is a prospective hospital-based cohort of HIV1-infected patients, initiated in 1987 in the Bordeaux University Hospital and four other public hospitals in Aquitaine, South-western France [28]. Clinical, biological and therapeutical information are collected prospectively at each visit under routine clinical management proceeding.

In the present study, we constituted two groups of patients who started for the first time a combination including at least three antiretroviral drugs (defined as HAART). The exposed group (MAC+) included patients with a diagnosis of MAC infection between 12 months before and 6 months after HAART initiation. We hypothesized that diagnoses of MAC infection made in the first six months on HAART corresponded to infections that were already present at the time of treatment start but clinically silent. Robustness analyses excluding those patients gave similar results (data not shown). The unexposed group (MAC-) included patients of the Aquitaine cohort without any history of MAC or CMV infection during their entire follow-up, who were individually matched on CD4+ count (± 30 cells/mm³), previous experience of antiretroviral treatment (naïve or not), AIDS clinical stage at the time of HAART initiation, age (± 10 years) and gender. The matching ratio of exposed:unexposed was 1:3, with the exception of two exposed patient for whom this ratio was 1:2 and 1:1 for three exposed patients.

Diagnosis of MAC infection

Diagnosis of disseminated MAC infection was based on the isolation of MAC from cultures of blood, bone marrow, or other normally sterile tissue or body fluids. Diagnoses based only on compatible clinical signs and symptoms were not considered in the present study.

HIV RNA load and immunophenotyping

CD4+, CD8+ and total lymphocytes counts were performed by flow cytometry in a single laboratory. Plasma HIV RNA was quantified by different laboratory kits according to the period and the hospitals. The branched DNA assays (Chiron Quantiplex RNA HIV-1, Emeryville, CA) with lower limits of detection of $2.7 \log_{10}$ copies/mL (500 copies/mL) and $1.7 \log_{10}$ copies/mL (50 copies/mL) were most often used. The schedule of measurements was based on clinical practice, i.e. every 3 to 6 months.

Statistical methods

The primary analyses compared the different markers values at each time point by Wilcoxon test. Time points considered were baseline (date of HAART initiation), 6 months latter (M6), M12 and M24. For each time point and each patient, the measurement that was the closer to the time point in a 3 months window was analyzed. Also, we performed multiple linear regressions of CD4+ difference from baseline to six months follow up on treatment adjusted for all potential factors influencing markers levels at a given time point including the MAC exposure as the primary factor of interest. We observed an attrition of the number of patients followed due to early deaths and lost-to-follow-up. These monotone missing data may bias estimates because patients exposed to MAC infection were more likely to die. Therefore, we conducted robustness analyses by jointly modelling repeated measurements of CD4+ count and survival time. This type of model allows taking into account these biases due to informative dropout process [29]. Briefly, the longitudinal model was a piecewise linear model explaining change in squared root of CD4+ count by a slope before HAART initiation, a slope between HAART initiation and the first 6 months and a slope after 6 months. The survival model was a lognormal survival model for time from HAART initiation to death or 24 months visit. The link between the two models was defined by the random slopes.

Results

Study population

Among 356 HAART treated patients followed in the Aquitaine Cohort and who presented a MAC infection during their follow-up, 51 patients were included in the present study because they started a combination of at least three antiretroviral drugs and they presented a MAC infection between 12 months before HAART initiation and 6 months after. Among these 51 patients, 13 MAC infections were diagnosed between 12 months and 6 months before HAART initiation, 13 MAC infections within 6 months before HAART initiation, nine at the time of HAART initiation and 16 within 6 months after HAART initiation. These MAC patients were mostly treated by a triple antibiotic combination including clarithromycin, ethambutol and rifabutin (N=17) or azithromycin, ethambutol and rifabutin (N=15). The others were treated by dual antibiotic combinations (ethambutol and rifabutin in 6 cases) or single therapy (N=6). The HAART regimen was mainly based on the combination of two nucleoside reverse transcriptase inhibitors and one protease inhibitor (88%). The most commonly used nucleosides were zidovudine (N=98) and lamivudine (N=138) and the most common PI was indinavir (N=92). Zidovudine was associated with clarithromycin in 11 cases. Two MAC patients died in the first 6 months on treatment, 10 between 6 and 12 months and six between 12 and 24 months. The 51 MAC+ exposed patients were individually matched to 145 MAC- patients. These unexposed patients, who had very low CD4+ count at HAART initiation due to the matching, had history of Kaposi sarcoma (N=21), pulmonary pneumocystosis (N=27), candidiasis (but oral only) (N=22), toxoplasmosis (N=21), cryptococcosis (N=11), HIV encephalopathy (N=6), tuberculosis (N=11), lymphoma (N=5), cryptosporidiosis (N=3), recurrent bacterial pneumonia (N=1), progressive multifocal leucoencephalopathy (N=1) and salmonella septicaemia (N=1) but neither MAC nor CMV infection by design.

Characteristics of included patients are depicted in table 1. At the time of HAART initiation, there were no differences between the two groups according to matching factors as well as other characteristics.

Markers evolution

At the time of treatment initiation, MAC+ and MAC- patients presented comparable median levels of total lymphocytes (488 vs. 688/mm³, p=0.09), CD4+ count (11 vs. 16/mm³, p=0.15) and CD8+ count (359 vs. 386/mm³, p=0.39) (Table 1). During follow-up, the two groups presented a significant increase in total lymphocytes, CD4+ and CD8+ counts. However, these increases were significantly more pronounced in MAC- than in MAC+ groups (Figure 1, panels a-c). After six months on HAART, the median increase of CD4+ count was +28 cells/mm³ (IQR +1; +63) in MAC+ and +72 cells/mm³ (IQR +34; +120) in MAC- groups (p<0.0001), while the percentage of CD4+ cells was not significantly different between the two groups (p=0.13) (Figure 1, panel d). Interestingly, plasma HIV RNA decreased significantly in the two groups and the decline was not significantly different according to MAC exposure (-1.6 in MAC+ group vs. -1.8 log₁₀ copies/mL in MAC- group at 6 months, p=0.65) (Figure 1, panel e). The proportions of patients reaching 500 copies/mL or less at 6 months were similar (48.8% and 49.5% in the MAC+ and MAC-, respectively, p=0.93). The effect of MAC exposure on the change of CD4+ count at 6 months was also confirmed after adjustment on other determinants (Table 2). Indeed, the factors significantly associated with a poorer CD4+ count increase were: MAC exposure, CD4 count nadir < 50 cells/mm³, higher baseline plasma HIV RNA and previous experience of antiretroviral treatment. Treatments including zidovudine and clarithromycin were associated with poorer CD4+ count increase at 6 months (p=0.03) but this effect did not remain after adjustment for other characteristics (p=0.51). The independent effect of MAC exposure was also confirmed at 12 and 24 months (data not shown). The effect of MAC exposure was also confirmed when modelling all repeated measures of CD4+ count taking into account potential informative drop-out due to death and adjusting for potential confounding factors. Thus, estimated CD4+ counts levels were significantly higher in the MAC- group compared to MAC+ patients at 6

months ($p < 0.0001$), 12 months ($p = 0.0002$) and 24 months ($p = 0.0047$) and not at M0 ($p = 0.17$). The estimated slopes within the first 6 months were $+19.4 \text{ cells/mm}^3/\text{month}$ ($[15.9; 22.8]$) in the MAC- group and $+9.5 \text{ cells/mm}^3/\text{month}$ ($[3.8 ; 15.1]$) in the MAC+ group ($p = 0.003$). After 6 months, the estimated slopes were $+2.9 \text{ cells/mm}^3/\text{month}$ ($[2.2; 3.5]$) and $+2.7 \text{ cells/mm}^3/\text{month}$ ($[1.5; 3.8]$), respectively ($p = 0.75$).

There was no significant effect of MAC exposure on haemoglobin and platelets levels during follow-up although haemoglobin levels tended to be lower in patients exposed to MAC infection (Figure 1, panels f-g).

Discussion

In this study, we showed that patients who experienced a MAC infection during their follow up and started a HAART regimen, presented a weaker increase in their total lymphocytes, CD4+ and CD8+ counts despite similar virological response. MAC infection is known to compromise hematopoiesis and in particular erythropoiesis and granulopoiesis. This mechanism is thought to be multi-factorial. First, during the course of MAC disease, infection massively widespread in bone marrow which must impair hematopoiesis [30]. Second, the presence of mycobacteria induces the production of immunosuppressive cytokines by the host adaptative immune response, the secretion of soluble factors that inhibit erythroblastic progenitors [31], the deleterious effect of TNF- α on haematopoiesis [32] and Fas Ligand expression [33] by infected macrophages known to induce the apoptosis of T lymphocytes. Apoptosis is also one of the mechanisms explaining the deficiency of haematopoiesis in the course of CMV [24] or HCV infections [20, 21] as well as it impaired immune restoration in HIV-infected patients [34]. Treatment of MAC infection such as clarithromycin might also contribute to these disorders. In fact, the association of clarithromycin and zidovudine in HIV-infected patients is known to suppress lymphopoiesis and hematopoiesis [35]. Nevertheless, the impact of MAC infection and its management was not observed on haemoglobinemia and platelets, favouring the hypothesis of a specific alteration of the lymphocyte lineage.

This study presents three main limitations. First, we were not able to compare the effect of different opportunistic infections at the time of treatment initiation on the entire Aquitaine cohort because of the limited number of individual opportunistic infections in about 3000 HAART-treated patients. This calls for the need of analyses of this kind in multi-cohort collaborations [36]. Second, we do not considered the possible effects of adherence, ethnicity or social class which may vary in the two groups because it was not recorded in our database.

Third, it would be useful to perform more specific measurements (apoptosis, naive and memory cells, activation...) to better characterize the mechanisms in this context [2].

With respect to clinical care, hematotoxic drugs should be avoided in patients presenting MAC infection. Furthermore, immunotherapy may be indicated in such a context. The G-CSF and GM-CSF factors activate destruction of intracellular bacteria and stimulate the granulocyte colony. These factors have been successfully proposed to treat patients with MAC infection [37]. Moreover, such treatment might help in immune restoration [38]. Il-2 may also be a good candidate because of its stimulating effect on CD4+ proliferation [39] and its inhibitory effect on cell apoptosis [40], thus increasing the survival of CD4+ T lymphocytes [41].

In conclusion, MAC infection at the time of HAART initiation seems to be an important deleterious factor for immune reconstitution. A better understanding of the underlying mechanism and an evaluation of additional treatment strategies are necessary to help immune restoration in such circumstances.

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Appendix: Composition of the GECSA

Scientific committee: Prs J. Beylot, M. Dupon, M. Longy-Boursier, JL. Pellegrin, JM. Ragnaud and R. Salamon (Chair)

Scientific coordination: Prs G. Chêne and F. Dabis (Coordinator), Dr S. Lawson-Ayayi, C. Lewden, R. Thiébaud

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Participating Hospital Departments (participating physicians):

Bordeaux University Hospital: Pr J. Beylot (Pr P. Morlat, Drs N. Bernard, M. Bonarek, F. Bonnet, D. Lacoste and R. Vatan), Pr P. Couzigou, Pr H. Fleury (Pr ME. Lafon, Drs B. Masquelier and I. Pellegrin), Pr M. Dupon (Dr H. Dutronc, F. Bocquentin and S. Lafarie), Pr JL. Pellegrin (Pr JF. Viillard, Drs O. Caubet, E. Lazaro and C. Nouts), Pr M. Longy-Boursier (Pr P. Mercié, Dr D. Malvy, T. Pistonne and C. Receveur), Pr JF. Moreau (Dr P. Blanco), Pr JM. Ragnaud (Pr D. Neau, Drs C. Cazorla, D. Chambon, C. De La Taille, and A. Ochoa); Dax Hospital: Dr P. Loste (Dr L. Caunègre); Bayonne Hospital: Dr F. Bonnal (Drs S. Farbos and MC. Gemain); Libourne Hospital: Dr J. Ceccaldi (Dr S. Tchamgoué); Mont-de-Marsan Hospital: Dr S. de Witte

Table 1. Baseline demographic and clinical characteristics at the time of initiation of HAART of patients exposed to Mycobacterium avium complex infection (MAC+) and matched patients unexposed to MAC infection (MAC-). ANRS Co3 Aquitaine Cohort.

	MAC+ (N=51)		MAC- (N=145)		p value
	N or median	% or IQR	N or median	% or IQR	
Age (years)	37	32 ; 49	37	33 ; 43	0.74
Male gender	39	76.5	115	79.3	0.67
HIV transmission group					
Intravenous Drug Users	14	27.4	43	29.7	0.91
Men who have sex with men	21	41.2	47	32.4	
Heterosexuals	11	21.6	39	26.9	
Others	5	9.8	16	11.0	
Baseline calendar period					
[06/03/1995 - 31/12/1999]	42	82.4	118	81.4	0.88
[01/01/2000 - 13/05/2003]	9	17.6	27	18.6	
Clinical stage					
A	2	3.9	4	2.7	0.88
B	7	13.7	20	13.8	
C	42	82.4	121	83.4	
Treatments					
Number of treatment regimens before HAART initiation*					
None (naïve patients)	17	33.3	46	31.7	0.98
Between 1 and 4 regimens	19	37.3	57	39.3	
More than 4 regimens	15	29.4	42	29.0	
Treatment regimen at HAART initiation					
2 NRTIs and 1 PI	45	88.2	134	91.8	0.13
2 NRTIs and 1 NNRTI	2	3.9	8	6.2	
3 NRTIs	4	7.9	2	1.3	
2 NRTIs and 1 PI and 1 NNRTI	0	0.0	1	0.7	
MAC prophylaxis					
Clarithromycin	0	0.0	1	0.7	0.53
Azithromycin	0	0.0	4	2.8	
Rifabutin	9	17.6	35	24.1	
Biological characteristics at HAART initiation					
Plasma HIV RNA (log ₁₀ copies/mL)	5.3	4.4 ; 5.6	5.1	4.2 ; 5.5	0.22
T Lymphocytes CD4+ count (cells/mm ³)	11	3 ; 38	16	8 ; 39	0.15
T Lymphocytes CD8+ count (cells/mm ³)	359	206 ; 576	386	215 ; 634	0.39
Total lymphocytes (cells/mm ³)	488	396 ; 858	688	410 ; 1065	0.09
Haemoglobinemia (g/dl)	11.5	9.8 ; 13.3	12.0	10.6 ; 13.0	0.23
Platelets (10 ³ /mm ³)	177	143 ; 230	157	119 ; 214	0.09

IQR: interquartile range; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor

* A modification of at least one drug defined a new regimen

Table 2. Univariable and multivariable analyses of factors associated with change in CD4+ level between baseline and 6 months after HAART initiation, adjusted for baseline CD4+. ANRS Co3 Aquitaine Cohort.

Characteristic	Univariable		Multivariable*	
	β	P	β	P
MAC exposure (vs. no exposure)	-25.5	<0.0001	-24.7	<0.0001
Age (for one year older)	0.3	0.53	–	–
Women (vs. men)	-5.8	0.64	–	–
Intravenous Drug Users (vs. other transmission groups)	-4.5	0.69	–	–
Naive of antiretroviral treatment (vs. experienced)	27.7	0.01	30.5	0.03
AIDS clinical stage (vs. other clinical stages)	13.6	0.32	–	–
Nadir of CD4+ count <50 cells/mm ³ (vs. \geq 50)	-16.6	0.25	-55.8	0.007
Baseline calendar period > 2000 (vs \leq 2000)	22.3	0.11	–	–
Baseline HIV RNA (for 1 log copies/mL higher)	21.2	0.0003	17.8	0.002

β : coefficient of the liner regression

MAC : Mycobacterium avium complex

* All listed characteristics included