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Heterogeneous Immuno-Virological Outcomes in the 81 HIV Controllers Enrolled in the ANRS HIV Controllers National Program.

Faroudy Boufassa[1], Asier Saez-Cirion[2], Jérome Le Chenadec[1], Azeb Tadesse[1], Véronique Avettand-Fenoel[3], Alain Venet[4], Christine Rouzioux[3], Jean-François Delfraissy[5], Olivier Lambotte[5], Laurence Meyer[1] for the ANRS EP36 HIV Controllers Study Group

[1] INSERM U1018; Univ Paris-Sud, Faculté de Médecine Paris-Sud, AP-HP, Hopital Bicêtre, Epidemiology and Public Health Service, Le Kremlin-Bicêtre, France. [2] Institut Pasteur, Unité de Régulation des Infections Rétrovirales, Paris, France. [3] Université Paris-Descartes EA3620, Hôpital Necker, Paris, France. [4] INSERM U802, Université ParisSud, Le Kremlin Bicêtre, France. [5] Service de Médecine Interne, Hôpital du Kremlin-Bicêtre, Le Kremlin-Bicêtre, France

Faroudy Boufassa, MD
Center for Research in Epidemiology and Public Health U1018
Inserm/Paris Sud 11
Hôpital de Bicêtre
94276 Le Kremlin-Bicêtre
France
Tel 33 1 45 21 23 65
faroudy.boufassa@inserm.fr

ABSTRACT

Background: HIV Controllers spontaneously maintain undetectable plasma viral loads (VL) for long periods of time. Because of the rarity of these patients, epidemiological data on large groups of HIV controllers are scarce. Here we detail the characteristics and evolution of 81 Controllers enrolled in 2006-2007 in the French ANRS National Observatory.

Methods: To be enrolled HIV controllers must have been HIV-1-infected for ≥10 years, asymptomatic, antiretroviral naïve, with >90% of plasma HIV-RNA measurements <400 copies/mL. At inclusion, all previously measured CD4 cell counts and VL, demographic, epidemiological, clinical and current biological data are collected. Mixed-effect linear models were used to assess CD4 cell count slope since HIV diagnosis.

Results: Out of 34 317 patients followed in 35 clinical centers, 81 Controllers patients were enrolled. Median age was 29 years [range: 0.8-65] at HIV diagnosis and 45 years [19-78] at enrollment. Women (43%) and patients infected through intravenous drug use (25%) were overrepresented and homosexual men underrepresented (15%) in controllers when compared to the ANRS SEROCO cohort of HIV-infected adults diagnosed at the same calendar time. Based on the history of viral loads, we identified 30 controllers (no blip group) in whom VL was always below the threshold, and compared them with other HIV controllers who had VL > threshold in less than 50% of measures (rare blip group; n=39) and those who had VL > threshold in more than 50% of measures (frequent blip group; n=12). No clinical, immunological or virological progression was observed in the no blip group, while 3 immunological (CD4<200/mm³) and/or virological (VL>1000 copies/mL) progression and 4 cancers were observed in the other groups. The estimated CD4 counts at HIV diagnosis were similar in the three groups and CD4 counts remained stable since HIV diagnosis in the no blip group (slope of 0.01 √CD4/mm³/year; p=0.89) while they significantly decreased in the other groups (respectively -0.26; p<0.005 in the rare blip and -0.28; p=0.02 in the frequent blip group). These results were not modified after adjustment on age at HIV-diagnosis, sex and geographical origin.

Conclusions: Spontaneous sustained HIV control is rare since the proportion observed of this phenomenon is here around 0.3%. Surprisingly, females and intravenous drug users are overrepresented, while homosexual male are underrepresented in Controllers. The role of immune inflammation in these patients should be investigated.

INTRODUCTION

HIV Controllers (HIC) are individuals in whom HIV-1 plasma viral load remains spontaneously undetectable without antiretroviral treatment whatever their CD4 levels. The definition of HIC is thus different from that of long-term non progressors (LTNP) who are defined by maintaining their CD4 cells count above 500 or 600/mm³. Patients who spontaneously control viral load on two consecutive measurements represent 7% of patients followed up during the first 5 years of infection in prospective cohorts of seroconverters. HIC, who durably keep undetectable viral loads, are rarer and generally estimated to be < 1% of routinely-followed up patients). Better understanding of the mechanisms responsible for spontaneous control of viremia may help to guide development of vaccines and therapies. Studies on HIC have so far focalized on pathophysiological aspects of HIV infection in these individuals. In contrast very few data are available on the clinical description, socio-demographic aspects and sexual behavior of these patients.

OBJECTIVE

We describe here characteristics of 81 HIV Controllers enrolled in clinical centers in France in 2006-2007 and their CD4 trajectories since HIV diagnosis.

METHODS

STUDY POPULATION

All HIV controllers identified among HIV-1 infected patients followed-up in 35 clinical centers in France were enrolled for the ANRS HIV controllers national program after written informed consent.

Definition: HIV controllers had to be HIV-1-infected for ≥ 10 years, asymptomatic and never treated with antiretroviral drugs. In addition, HIV-1 RNA viral load had to be < 400 copies/ml in > 90% of the samples recorded since HIV diagnosis.

At the time of enrollement, all previously measured CD4 T-cell counts and HIV-1 RNA loads, demographic, epidemiological, clinical and current biological data are collected. Plasma HIV-RNA was measured on site (Cobas Amplicor HIV Monitor test [Roche Molecular Systems, Neuilly sur Seine, France; detection limits varying from 500 to 20 copies/mL] in 69% of cases; Quantiplex HIV-RNA (bDNA) [Bayer Diagnostics, Puteaux, France; detection limits varying from 10 000 to 40 copies/mL] in 27% of cases; and other techniques in 4% of cases [detection limits varying from 500 to 40 copies/mL]. Frozen total blood was stored at time of enrollement. Part of these samples were used to measure HIV DNA levels in a centralized laboratory using the ANRS real-time PCR assay. Quadruplicate tests were conducted by PCR in order to get numerical data values. Results are expressed as $\log_{10}$ copies/10^6 PBMC.

STATISTICAL ANALYSIS

Based on the history of viral loads since HIV diagnosis, patients were categorized in three groups:

-**No blip; n=30**: plasma HIV-RNA measurements always below the threshold of detection

-**Rare blips; n=39**: less than 50% of the HIV-RNA measurements above the threshold of detection (15.0% of the blips > 400 copies/mL)

-**Frequent blips; n=12**: more than 50% of the HIV-RNA measurements above the threshold of detection (12.4% of the blips > 400 copies/mL)

Qualitative variables were compared using chi-square or Fisher's exact tests, and continuous variables using the Kruskall Wallis test. Univariate and multivariate (after adjustment for sex, age and ethnicity) mixed-effect linear models were used to compare change overtime in square root CD4 cell counts between groups. This model was used in order to take into account the fact that subjects had repeated CD4 measurements; transformation of CD4 cell counts was used to fulfill the model assumptions.

SAS (Version 9.1, 2003; SAS Institute Inc., Cary, NC, USA) and STATA (Version 11.0, 2009; Stata Corp., College Station, Texas) were used for statistical analysis.

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RESULTS

Table 1: Main Baseline characteristics of the HIV controllers enrolled in the ANRS National Program (n=81)

Characteristics	HIV controllers N=81
Women	35 (43.1)
Caucasian	68 (84.0)
Homo/bisexual preference	12 (14.8)
Year of diagnosis Year of inclusion	1989 [1987-1994] 2006 [2006-2007]
Age at HIV diagnosis Age at inclusion	28 [24-32] 45 [40-50]
Median time since HIV diagnosis (yrs)	17.0 [13.0-19.1]
HCV +	31 (41.3)
Number of HIV-RNA measures/patient % HIV-RNA values>threshold	17 [12-20] 14.3 [0.0-31.9]
Number of CD4 measures/patient Median CD4 counts/mm³	21 [13-26] 777 [599-980]
No Blip group Rare Blip group Frequent Blip group	30 (37.0) 39 (48.2) 12 (14.8)

Data are median [25th-75th percentiles] or n (%)

Table 2: Main characteristics of HIV controllers according to whether they presented blips during control

Characteristics	No Blip N=30	Rare Blips N=39	Frequent Blips N=12	p
Women	15 (50.0)	14 (35.9)	6 (50.0)	0.44
Caucasian	23 (76.7)	34 (87.2)	11 (91.7)	0.45
Homo/bisexual preference	4 (13.4)	8 (20.5)	0 (0.0)	0.25
Age at diagnosis	28 [26-32]	29 [23-33]	28 [24-35]	0.89
Age at inclusion	45 [40-49]	45 [39-49]	48 [42-50]	0.56
Positive HCV serology	12 (44.4)	14 (38.9)	5 (41.7)	0.91
Number of measures of HIV-RNA	14 [9-19]	17 [14-22]	17 [11-19]	0.09
Number of blip (HIV-RNA value>threshold)	0 [0-0]	4 [2-6]	11 [9-14]	<0.001
% of blip (HIV-RNA value>threshold)	0.0 [0.0-0.0]	23.5 [14.3-29.4]	75.0 [67.9-83.3]	<0.001

Data are median [25th-75th percentiles] or n (%)

Table 3: Characteristics at first measurement at HIV diagnosis and at inclusion

Characteristics	No Blip N=30	Rare Blips N=39	Frequent Blips N=12	p
At HIV diagnosis				
Time from HIV diagnosis to first CD4/mm³ (yrs)	2.8 [0.3-6.5]	1.3 [0.01-4.3]	3.0 [0.1-9.6]	0.16
First CD4/mm³	813 [610-1090]	795 [641-1000]	782 [624-916]	0.73
Time from HIV diagnosis to first HIV-RNA (yrs)	5.9 [3.0-10.2]	7.8 [2.9-8.9]	9.7 [7.4-12.1]	0.11
At inclusion				
Time from HIV-diagnosis to inclusion (yrs)	15.1 [11.9-19.1]	16.9 [13.9-19.1]	18.5 [17.2-20.3]	0.13
CD4/mm³	819 [668-992]	644 [445-890]	628 [569-906]	0.02
$\log_{10}$ HIV-DNA/10^6 PBMC	1.78 [1.34-2.18]	1.70 [1.45-2.00]	1.90 [1.62-2.09]	0.73

Data are median [25th-75th percentiles] or n (%)

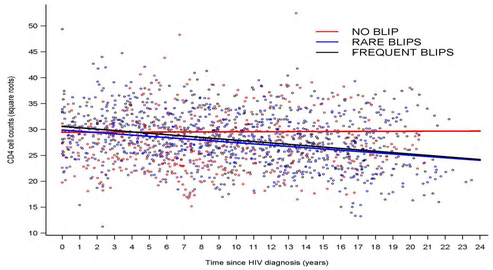
VIROLOGICAL and/or CLINICAL PROGRESSION

Table 4: Clinical or virological progression after inclusion

Characteristics	No Blip N=30	Rare Blips N=39	Frequent Blips N=12	p
Cancer	0 (0.0)	3 (7.7)	1 (8.3)	0.26
HIV-RNA value>1000 cop/mL	0 (0.0)	1 (2.6)	2 (16.7)	0.06
Deaths	1 (3.4)	1 (2.6)	0 (0.0)	0.99

Data are median [25th-75th percentiles] or n (%)

Fig. 1: Predicted trajectories of mean √CD4 cell counts according to whether HIC presented blips during control (81 HIV controllers, 1668 CD4 measurements)



MAIN RESULTS

- Compared to patients from the ANRS SEROCO Cohort who were diagnosed at the same calendar period than HIC (i.e. 1988-1989 in median):
  - The proportion of women among HIC (43%) is higher than expected (30%)
  - MSM patients (26%) are under-represented among male HIC
  - Intravenous drug users (25%) are over-represented (7% in the SEROCO cohort)

- Estimated CD4 counts at the time of HIV diagnosis did not significantly differ between blippers and never blippers. Conversely, estimated mean slopes of √CD4 in the rare blips group and frequent blips group significantly differed from zero (-0.25√CD4/mm³/year; p=0.005 and -0.28 √CD4/mm³/year; p=0.02) while √CD4 slope in the no blip group did not differ from zero. Slopes in the rare and frequent blips did not statistically differ. These results were not modified after adjustment for age at diagnosis, sex and geographical origin.

CONCLUSION

We are currently implementing a prospective cohort of HIV controllers in France and analysing data in the two large European CASCADE and COHERE collaborations. This longer follow-up of a large number of HIC will help us to better describe long-term prognosis of HIV controllers, including CD4 decrease, frequency of immuno-virological escapes or clinical progression.