2015 CROI, Seattle, Washington, USA. Feb 23-26.
Session: Dissecting Pathogenesis Through In Vivo Studies, P-C14
Abstract number: 333

Immunological and Virological Progression in HIV Controllers

Nicolas Noel(1, 2); Nathalie Lerolle(1); Camille Lecuroux(2); Cécile Goujard(1, 5); Alain Venet(2); Asier Sáez-Cirión(3); Véronique Avettand-Fenoel(4); Laurence Meyer(5); Faroudy Boufassa(5); Olivier Lambotte(1, 2)
(1) AP-HP, Service de Médecine Interne et Immunologie Clinique, CHU Bicêtre; (2) Unité INSERM U1012, Université Paris Sud, Le Kremlin Bicêtre; (3) Unité de Régulation des Infections Retrovirales, Institut Pasteur, Paris; (4) AP-HP, Service de Virologie, CHU Necker-Enfants Malades, Paris; (5) Unité INSERM U1018, Université Paris Sud, Le Kremlin Bicêtre; FRANCE

Introduction

Some HIV controllers (HICs) eventually experience CD4+ T cell count loss and/or lose their ability to control HIV. We investigated the rate of immunologic and/or virologic progression (ImmP/VirP) and its determinants in the ANRS CO21/CODEX cohort.

Methods

- After enrolment in the CODEX cohort, ***suspected*** immunologic progression was defined as a CD4 T cell count < 350/mm^3 or a fall of > 200/mm^3 from an immediately preceding CD4 count of at least 600/mm^3. Suspected viral progression was defined as one HIV RNA measurement above 2000 copies/mL.
- Such cases were referred to as ***confirmed*** immunologic and/or virologic progression if the above criteria were met for two consecutive blood samples.
- Clinical characteristics, immune activation parameters (HLA-DR+CD38+ T cells and IP10 levels), ultrasensitive HIV VL and total HIV DNA were analyzed prior to and during progression.

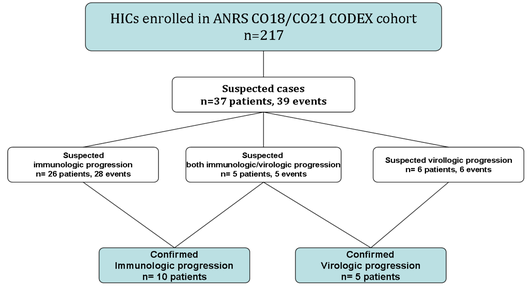

Figure 1. Study flow diagram.

Characteristics of the study population

- At the time of confirmed progression, the median [IQR] HIV RNA VL was 132 [39-858] copies/mL in immunologic progressors and 2210 [2119-3085] copies/mL in virologic progressors.
- The median [IQR] CD4 T cell count was 320 [301-336] in immunologic progressors and 725 [530-759] /mm^3 in virologic progressors.

Characteristics of the study population at enrolment into the cohort.

	HICs with immunologic progression (n=10)	HICs with virologic progression (n=5)	Non-progressor HICs (n=202)
Male gender, n (%)	3 (30)	3 (60)	98 (48,5)
Age (years)	48 [43-56]	34 [32-34]***	45 [39-50]
Duration of known HIV infection (years)	18 [13-23]	5 [5-8]***	13 [8-20]
HLA B57+ (%)	3/9 (33)	1/5 (20)	65/165 (39,4)
HCV+ status, n (%)	3 (30)	1 (20)	44 (22,8)
CD4 T cell nadir (/mm^3)	245.5 [220.3-259.8]***	433 [405.8-455.8]	496 [376-657.5]
CD4 T cell count (/mm^3)	416.5 [296-435]***	643 [527-1447]	763.5 [559.3-950.3]
Ultrasensitive HIV RNA (copies/mL)	117 [12-274]**	118 [78-1023]**	34 [11-89]
Total HIV DNA (/10^6 PBMCs)	11 [11-21]	42.5 [31.5-66.3]*	11 [10-46]
% of detectable VLs during history	35 [17-52]*	32 [17-47]	21 [18-25]

Results are quoted as the median [IQR] or as a percentage. All comparisons were performed relative to the group of non-progressor HICs. *: p<0.05, **: p<0.01, ***: p<0.001.

- When compared with non-progressors, **ImmP** had lower CD4 T cell counts prior to the progression. The us HIV RNA VL at enrolment and the frequency of blips prior to the enrolment in the CODEX cohort were higher in ImmP.
- The us HIV RNA VL and the total HIV DNA at enrolment were higher in **VirP** than in non-progressors.

Clinical events prior to progression were identified in 7 patients.

- 2 of the 5 patients with VirP reported unprotected sexual intercourses in the previous 3 months (also reported by 63 of the 197 non-progressors (31.9%) having provided information (*ns*).
- 3/10 patients displayed ImmP in the months following an infectious event (diarrhea and *Chlamydia trachomatis* infection in one patient, two episodes of bronchitis in a second patient, and the third patient experienced two episodes of prostatitis, an episode of gastro-enteritis and a whitlow).
- 1 patient underwent an epidural injection of corticosteroids in the month before immunologic progression. 1 patient was diagnosed with a B-cell lymphoma four months after immunologic progression.

Immune activation parameters prior to the progression events

- Markers of immune activation/inflammation were analyzed at enrolment (***ie 1-2 years before progression***) and compared with ART treated patients (VL < 40 copies during > 2 years stable cART) and viremic (VL>10000 cp/mL) patients
- The % of activated HLA-DR+CD38+ T cells and plasma IP10 levels were higher in ImmP than in non-progressors at inclusion in the cohort, and similar trends were observed for VirP.
- Interestingly, the proportion of activated T cells was (i) as elevated in progressor HICs as in viremic patients, and (ii) as low in non-progressor HICs as in ART-treated patients.

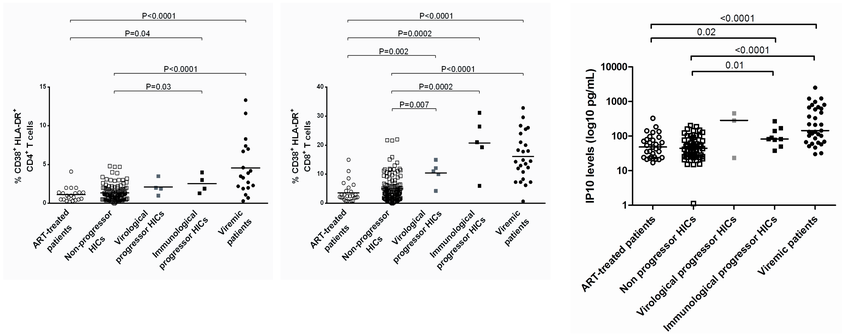

Figure 2. Immune activation parameters in immunologic or virologic progressor HICs and non-progressor HICs at inclusion in the CODEX cohort, compared with ART-treated patients and chronic viremic patients.

Discussion and conclusion

- The frequency of progression in our French cohort of HICs was 6.9% (considering only confirmed progressors) over a 5-year period
- The CD4 T cell count, a history of blips, and a higher us HIV RNA VL at inclusion are possible determinants for immunologic progression.
- The blood level of HIV DNA (reflecting the HIV reservoir) and a higher us HIV RNA VL at inclusion appear to be associated with virologic progression
- Patients with higher CD4+ or CD8+ T cell activation and IP10 levels at inclusion are at risk of progression
- All these parameters should be taken into account when stratifying at-risk patients, in order to adjust their follow-up and optimize the time at which cART is initiated.