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# **Is long-term virological response related to CCR5 $\Delta$ 32 deletion in HIV-1-infected patients started on highly active antiretroviral therapy?**

Jean-Jacques Laurichesse <sup>1\*</sup>, Audrey Taieb <sup>2</sup>, Corinne Capoulade-Metay <sup>3</sup>, Christine Katlama <sup>4</sup>, Virginie Villes <sup>5</sup>, Marie-Christine Drobacheff-Thiebaud <sup>6</sup>, François Raffi <sup>7</sup>, Genevieve Chêne <sup>2</sup>, Ioannis Theodorou <sup>3</sup>, Catherine Lepout <sup>1</sup>, the ANRS C08 Aproco-Copilote study group

<sup>1</sup> Laboratoire de recherche en pathologie infectieuse AP-HP, Hôpital Bichat - Claude Bernard, Université Paris-Diderot - Paris VII, FR

<sup>2</sup> Centre épidémiologie et biostatistique INSERM : U897, Université Victor Segalen - Bordeaux II, FR

<sup>3</sup> Immunologie cellulaire et tissulaire INSERM : U543, IFR113, Université Pierre et Marie Curie - Paris VI, Gh Pitie-Salpetriere 83, Boulevard de L'Hopital 75013 PARIS,FR

<sup>4</sup> Service des maladies infectieuses et tropicales AP-HP, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie - Paris VI, 47-83, boulevard de l'Hôpital 75651 PARIS Cedex 13,FR

<sup>5</sup> Epidémiologie et Sciences Sociales Appliquées à l'Innovation Médicale INSERM : U379, Université de la Méditerranée - Aix-Marseille II, Institut Paoli-Calmettes 232, Boulevard Sainte Marguerite 13273 Marseille Cedex 09,FR

<sup>6</sup> CHU Besançon CHU Besançon, FR

<sup>7</sup> CHU Nantes CHU Nantes, Université de Nantes, 44035 Nantes, FR

\* Correspondence should be addressed to: Jean-Jacques Laurichesse <j-j.laurichesse@ch-mantes-la-jolie.fr >

## **Abstract**

### **Objective**

To examine whether CCR5  $\Delta$ 32 deletion is associated with long-term response to combination antiretroviral treatment (cART) in HIV-1 infected patients.

### **Methods**

The genetic sub-study of ANRS C08 APROCO-COPILOTE cohort included 609 patients who started a protease inhibitor-containing cART in 1997–99. Patients were considered to have a sustained virological response if all plasma HIV-RNA measurements between month 4 and years 3–5 were <500 copies/ml, allowing for a single blip. Virological response was compared between patients heterozygous for CCR5  $\Delta$ 32 ( $\Delta$ 32/wt) and wild-type patients (wt/wt) from month 4 to year 3 and month 4 to year 5. Logistic regression analysis was used to adjust for baseline demographical data, HIV-RNA, CD4 cell counts, antiretroviral naive status, time spent on antiretroviral therapy at year 3 and 5 and adherence to treatment (month 4 to year 3 and 5).

### **Results**

Sustained virological response was better in  $\Delta$ 32/wt than in wt/wt patients: 66% versus 52% up to year 3 ( $p=0.02$ ), nearly significant after adjustment to potential cofounders ( $p=0.07$ ).  $\Delta$ 32/wt patients had a better virological response, up to year 5, 48% versus 35% ( $p=0.01$ ), and remained significantly better, after adjustment, associated with a better virological response up to 5 years post initiation of cART ( $p=0.04$ ). There was no association with CD4 response.

### **Conclusion**

$\Delta$ 32/wt deletion is associated with a beneficial virological response to cART on the long-term. Whether this association can be a direct effect of  $\Delta$ 32/wt deletion remains questionable and needs confirmation in other observational studies.

**Author Keywords** HIV, antiretroviral therapy, CCR5  $\Delta$ 32 deletion, virological response

## **Introduction**

The CCR5 receptor for the  $\beta$ -chemokines RANTES (CCL5), MI-1 $\alpha$  (CCL3), and MIP-1 $\beta$  (CCL4) is the primary co-receptor for macrophage-tropic, non-syncytium inducing (NSI) strains of HIV-1 entry into CD4 cells [1]. The CCR5  $\Delta$ 32, an allele that contains a 32-base pair deletion encoding for a non-functional receptor, protects against infection in homozygotes patients and is associated with delayed disease progression and death in heterozygous untreated patients [2, 3, 4, 5].

Since 1996, the widespread use of combination antiretroviral therapy (cART) has improved the prognosis of HIV-1 infected patients [6, 7]. Several studies, whether immunological or virological, have focused on the association between CCR5 genotype and response to cART, at different time frames and have yielded controversial results [8, 9, 10, 11, 12, 13, 14, 15, 16, 17].

In the setting of the ANRS CO8 APROCO-COPILOTE cohort, we studied the association between the presence of the deletion and the virological response to cART up to 5 years.

## Patients and methods

### Patients

The ANRS CO8 APROCO-COPILOTE cohort is a prospective observational study that enrolled 1281 HIV-1 infected adults in 47 hospitals in France starting a protease inhibitor (PI)-containing antiretroviral regimen for the first time in 1997–1999 [18]. Patients had physical and laboratory examinations at enrolment, after one and four months of cART, and every four months thereafter. Sera and cells were collected at enrolment and at follow-up visits. A DNA bank was set up in 2002 to study genetic factors associated with response to treatment or tolerability of the antiretroviral drugs. The study was approved by the Ethics Committee of Hospital Cochin and informed consent was obtained from all participants.

### Methods

Polymerase chain reaction amplification of CCR5 sequences was done using genomic DNA extracted from cryo-preserved lymphocytes.  $\Delta$ 32 deletion in the CCR5 gene was detected by amplifying part (735 base pair) of the coding region [3]. CCR5  $\Delta$ 32 heterozygous ( $\Delta$ 32/wt) patients were compared to wild-type patients (wt/wt) for their baseline characteristics. Chi-square and Wilcoxon tests were performed to analyze categorical and quantitative variables, respectively. The study was performed in 2005.

CCR5  $\Delta$ 32 heterozygous ( $\Delta$ 32/wt) patients were compared to wild-type patients (wt/wt) for their long term virological and immunological response to cART. The long term virological response to cART was analysed up to year 3, then to year 5 by logistic regression. To be included in the year 3 and year 5 analyses, patients should have had respectively at least one data at year 3 +/- 4 months and one at year 5 +/- 4 months. First, a stable sustained virological response was defined as a plasma HIV-1 RNA measurement below the threshold of detection of 500 copies/ml at all measurements between month 4 (M4) and year 3, and between M4 and year 5. Patients experiencing only one plasma HIV-1 RNA above 500 copies/ml were considered as meeting the definition of sustained virological response in this analysis. Secondly, immunological response was assessed using the proportion of patients who achieved a CD4 cell count greater than 500/mm<sup>3</sup> at year 3 and at year 5 [19]. Both models were adjusted for the following baseline characteristics: HIV-1 RNA, CD4 cell count, history of antiretroviral treatment at baseline (naïve cART) and during the follow-up (month 4 to year 3 and 5) (median cumulative time under cART between M4 and year 3 or 5), adherence to treatment (month 4 to year 3 and 5) and demographical data (sex, age, country of birth and group of contamination). The portion of the follow-up spent without treatment was compared in the two groups:

- for the 3-year analysis, patients spent 2.5% of the follow-up without treatment (0.3% for CCR5  $\Delta$ 32 heterozygous patient and 2.9% for wild type patient p=0.18).
- for the 5-year analysis, patients spent 3.8% of the follow-up without treatment (2.1% for CCR5  $\Delta$ 32 heterozygous patients and 4.1% for wild type patients p=0.50).

Assessment of adherence was made by self-administrated questionnaire every year of follow-up defined in the cohort [20]. High adherence refers to patient who always declared being adherent, moderate adherence refers to patient who declared at least one moderate adherence, low adherence refers to patient who declared one time a non adherence and non adherence refers to patient who declared more than one time a non adherence.

Quantitative variables with clinically relevant threshold were analyzed as categorical variables, ie CD4 cell count categorized as  $\leq$ 200/200–350/350–500/ $>$ 500. Regarding other quantitative variables quartiles, median were considered. These potential confounding factors were used in virological and immunological analyses. Variables were included in the initial multivariable if they were associated with virological or immunological success in each univariable analysis separately with a  $P < 0.25$ . Reduced models resulted from stepwise selection retaining only variables associated with virological or immunological success at the 0.05 significance level.

Statistical analysis was performed using Statistical Analysis System software (SAS, version 8.2).

## RESULTS

Among 1281 patients initially enrolled in the cohort, 609 (48%) participated in the genetic study set up in 2002. The reason for non-participation was lost to follow-up or withdrawal from the cohort (n=259), death (n= 84), refusal (n=51), inability to amplify (n=42) or unknown (n=236). As the selection was important, we compared baseline characteristics according to whether patients were selected or not for this study. Regarding CD4 cells count and undetectable HIV1-RNA at enrolment, no significant difference was noticed between these two groups. Regarding baseline CD4 cells count, participating patients had a median of 272/mm<sup>3</sup> vs 277/mm<sup>3</sup> among non participating patients (p=0.60). For HIV1-RNA, participating patients had a median of 4.5 copies/ml vs 4.5 copies/ml among non participating patients

( $p=0.13$ ). Among the 609 patients included in the analysis, 97 (16%) were heterozygous for the CCR5- $\Delta$ 32 deletion, 512 (84%) were wt/wt, and none were homozygous. At baseline, as compared to wt/wt patients,  $\Delta$ 32/wt patients were less frequently born in Africa and were older (table 1 ). They had a lower median HIV-1 RNA and a higher but not significant CD4 cell count (Table 1 ).

Patients were followed for a median duration of 76.3 months (Interquartile range 71.5–84.6) and experienced a median of 3 therapeutic new lines among heterozygous patients versus 4 among wt/wt ( $p=0.05$ ). 2679 episodes of treatment modification have been reported among 577 patients. 374 among 90  $\Delta$ 32/wt patients (93%) and 2305 among 487 wt/wt patients (95%). In the database, reasons are reported for 1975 of them. Among these, virological failure was mentioned in 165 cases whose 50 patients with at least one virological failure (4 for  $\Delta$ 32/wt patients (4%) and 46 for wt/wt patients (9%)).

601 and 576 patients were included respectively in the year 3 and year five analysis. Patients had a median of 9 available HIV-1 RNA measurements (IQR[8 –9 ]) between M4 and M36 and 15 available HIV-1 RNA measurements (IQR[13 –15 ]) between M4 and M60.

From M4 to year 3, 63 patients have a stable virological response (66%) among patients with the  $\Delta$ 32 deletion, and 264 (52%) among those without the deletion ( $p = 0.02$ ). When extended follow-up (M4 to year 5), respectively 44 patients (48%) and 168 patients (35%) have a stable virological response ( $p=0.01$ ).

At year 5, these differences were also noticed among  $\Delta$ 32/wt and wt/wt in the two subgroups adjusting for cART-naïve patients (51% vs 45% respectively) and pre treated patients (46% vs 27%) (this difference was significant  $p_{\text{Mantel Haentzel}}=0.02$ ). The proportion of patients with a CD4 cells count greater than 500/mm<sup>3</sup> at year 3 did not significantly differ between the  $\Delta$ 32 and wild type patients: 55% and 49 % respectively ( $p=0.26$ ), nor at year 5: 52% and 54%, respectively ( $p=0.73$ ).

After adjustment for confounding factors,  $\Delta$ 32 deletion significantly associated with a sustained virological response during the period M4 to 5 years post-enrolment ( $p=0.04$ ), and a near significantly associated with a sustained virological response during the period from M4 to 3 years post-enrolment ( $p=0.07$ )(Table 2 ).

For immunological response  $\Delta$ 32 deletion was not a significant factor associated with a CD4 count greater than 500/mm<sup>3</sup> at year 3 ( $p=0.78$ ), nor at year 5 ( $p=0.15$ ).

## DISCUSSION

Among 609 HIV-1 infected patients started on a PI containing treatment, the frequency of heterozygous patients for CCR5  $\Delta$ 32 was 16 %: it was 4% in patients born in Africa, and 19% in patients born in Europe, similar to previous studies carried out in similar populations [ 12 , 14 , 16 , 17 ]. The CCR5  $\Delta$ 32 deletion was associated to a better virological response to cART up to 3 and 5 years. Better virological response was not translated into a significantly better immunological response at any term of the study.

At baseline, patients with  $\Delta$ 32 deletion, were older, had higher CD4 cell count and lower HIV RNA than others. This might be explained by the effect of CCR5  $\Delta$ 32 deletion on the natural evolution of HIV infection before these patients started cART. Indeed, previous studies have shown that the presence of an allele with CCR5  $\Delta$ 32 confers a delayed progression to the HIV-1 disease in the absence of cART [ 3 , 4 ]. Furthermore, the effect of the deletion may have contributed to a possible selection bias [19 ]. Indeed, the patients who could be included in the genetic bank study were those who had survived from 1997 to 2002, and were younger. This bias limits the interpretation of our results, since only those with a better prognosis could be included.

Previous studies relating to the effect of virological response to cART according to CCR5- $\Delta$  32 deletion provided contradictory results: some found a protective role of the CCR5- $\Delta$ 32 deletion on virological response to cART [ 8 , 9 , 10 , 11 , 16 , 17 ] while others did not find any difference [12 , 13 , 14 , 15 ]. All have studied relatively short term response, no longer than 2 years. Moreover the characteristics of the patients, clinical and biological status of HIV infection, geographical origin, whether they were pretreated or naïve of cART, adherence to treatment, definition of the virological response (e.g 50 or 500 copies/ml) and time for assessment, varied among the studies.

Our study is probably the first to assess the impact of this deletion over a long follow-up of a large number of treated patients, and shows a significant better response after 5 years of treatment in the heterozygous patients. The longest follow-up was 24 months in the study of Bogner et al. [11 ], which found a better virological response to cART, among adherent caucasian patients, naïve of antiretroviral treatment.

The discrepancy between short-term and long-term virological response to cART in our study might explain some of the differences between previous studies. The interpretation of such a moderate effect of the deletion on response to cART would be in favour of either the absence of an effect among treated patients, or a limited effect only detectable after extensive follow-up.

In order to take into account differences existing at baseline or occurring during follow-up that might also influence response to cART, the multivariable analysis was adjusted for potential confounders. Yet, we found that long term virological response was more pronounced in the heterozygous patients, reflecting a true independent effect of the CCR5 Δ32 deletion in the context of a multifactorial determinism of long term virological response. Therefore, the potential disadvantage of the innate wild-type profile might be counterbalanced by the beneficial effect of high adherence level and appropriate time for starting cART.

In view of conflicting results in the previous studies, a meta-analysis including other observational cohorts would bring more evidence on the long-term effect of this mutation.

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## APROCO-COPILOTE ANRS CO8 study group Scientific Committee

**Steering Committee** : Principal Investigators : C. Leport, F. Raffi, Methodology : G. Chêne, R. Salamon, Social Sciences : J-P. Moatti, J. Pierret, B. Spire, Virology : F. Brun-Vézinet, H. Fleury, B. Masquelier, Pharmacology : G. Peytavin, R. Garraffo; **Other members** : D. Costagliola, P. Dellamonica, C. Katlama, L. Meyer, D. Salmon, A. Sobel ; **Events Validation Committee**: L. Cuzin, M. Dupon, X. Duval, V. Le Moing, B. Marchou, T. May, P. Morlat, C. Rabaud, A. Waldner-Comberoux; **Project coordination**: F. Collin-Filleul, **ANRS representatives** : Nadine Job-Spira, Marcia Trumeau, **Observers**: C. Perronne. **Clinical Research Group** : V. Le Moing, C. Lewden.

## Data monitoring and statistical analysis

J. Biemar, S. Boucherit, AD Bouhnik, C. Brunet-François, M.P. Carrieri, F. Couturier, J.L. Ecobichon,, V. Guiyedi, P. Kurkdji, S. Martiren, M. Préau, C. Protopopescu, C. Roy, J. Surzyn, A. Taieb, V. Villes, C. Wallet

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**Table 1**

Baseline characteristics of the 609 patients included in the APROCO-COPILOTE genetic sub-study according to CCR5 genotype

Characteristics		wt/wt (n=512)		Δ32/wt (n=97)	p
Male gender	N (%)	409 (80)		79 (81)	0.72
Age (years)	median (IQR)	37 (32–43)		38 (33–46)	0.05
Primary risks for HIV infection	N(%)				0.03
Injection drug use		87 (17)		8 (8)	
Place of birth	N(%)				0.0020
Europe		366 (71)		85 (88)	
Africa		68 (13)		3 (3)	
Other		24 (5)		-	
Missing data		54 (11)		9 (9)	
Year of first HAART	N (%)				0.68
1997		247 (48)		49 (51)	
1998–1999		265 (52)		48 (49)	
AIDS stage	N (%)	114 (22)		20 (21)	0.72
CD4+ cell count (/mm <sup>3</sup> )	median (IQR)	265 (119–403)		321 (156–466)	0.06
HIV-RNA (log <sub>10</sub> copies/ml)	median (IQR)	4.5 (3.7–5.2)		4.3 (3.6–4.7)	0.02
No prior antiretroviral treatment	N (%)	226 (44)		43 (44)	0.97

**Table 2**

Factors associated with stable long-term virological response\* in 609 patients included in the APROCO-COPILOTE cohort assessed for CCR5 Δ32 deletion

Variables	Month 4 to year 3							Month 4 to year 5						
	Univariable analysis			Multivariable analysis				Univariable analysis			Multivariable analysis			
	%success	OR	95% CI	p	OR	95% CI	p	%success	OR	95% CI	p	OR	95% CI	p
CCR5 deletion				0.02			0.09				0.01			0.04
Δ32/wt	65	1.74	1.10–2.75		1.59	0.93–2.73		48	1.77	1.12–2.78		1.77	1.03–3.04	
wt/wt	52	1			1			35	1			1		
Sex				0.44			0.89				0.67			0.22
Male	55	1			1			37	1			1		
Female	51	0.85	0.57–1.28		1.04	0.61–1.76		35	0.91	0.59–1.40		1.42	0.81–2.48	
Age (years)				0.23			0.91				0.003			0.33
<37	52	1			1			31	1			1		
≥37	57	1.22	0.88–1.68		0.98	0.67–1.44		43	1.69	1.19–2.38		1.22	0.82–1.83	
Origin of birth				0.07			0.14				0.13			0.12
Africa	45	0.63	0.38–1.04		0.65	0.36–1.16		29	0.64	0.36–1.14		0.61	0.32–1.14	
Other	57	1			1			39	1			1		
Contamination group				0.58			0.69				0.15			0.27
Homo/bisexual	56	1.10	0.79–1.52		0.92	0.60–1.41		40	1.29	0.91–1.82		1.29	0.82–2.01	

CCR5 Δ32 in HIV treated patients

Other	54	1		1		34	1		1	
HIV-RNA at baseline(log <sub>10</sub> copies/ml)				0.17		0.09			0.32	0.56
<3,7	62	1		1		38	1		1	
[3,7 ;4,5[	49	0.60	0.38–0.94	0.57	0.34–0.98	31	0.72	0.44–1.17	0.68	0.39–1.20
[4,5 ; 5,2[	55	0.77	0.49–1.21	0.60	0.33–1.07	39	1.02	0.64–1.63	0.84	0.45–1.56
≥5,2	53	0.71	0.44–1.13	0.45	0.23–0.87	41	1.12	0.69–1.81	0.71	0.35–1.41
CD4/mm <sup>3</sup> at baseline				0.002		0.004			0.04	0.06
<200	52	0.46	0.27–0.78	0.36	0.19–0.69	39	0.77	0.45–1.29	0.52	0.27–1.00
[350–500[	46	0.36	0.20–0.62	0.33	0.17–0.62	28	0.46	0.26–0.81	0.40	0.21–0.79
[200–350[	59	0.61	0.34–1.10	0.51	0.26–1.01	38	0.72	0.41–1.27	0.54	0.27–1.06
≥500	71	1		1		46	1		1	
Time spent on cART** (months)				<0.0001		<0.0001			-	-
>35	62	3.70	2.47–5.52	3.57	2.24–5.69	-	-		-	-
≤35	31	1		1						
Time spent on cART** (months)				-	-				<0.0001	<0.0001
>55	-	-	-	-		44	5.91	3.34–10.46	6.15	3.28–11.53
≤55						12	1		1	
Adherence				0.001		0.02			0.0011	0.02
non adherence	30	0.27	0.12–0.62	0.25	0.09–0.68	14	0.20	0.06–0.61	0.28	0.08–0.94
low adherence	42	0.44	0.26–0.75	0.54	0.30–0.99	24	0.39	0.22–0.71	0.41	0.21–0.80
moderate adherence	56	0.78	0.54–1.13	0.84	0.55–1.30	36	0.70	0.48–1.02	0.68	0.44–1.04
high adherence	67	1		1		50	1		1	
Prior antiretroviral treatment				0.0003		<0.0001			0.0001	0.002
yes	63	1.84	1.32–2.55	2.98	1.85–4.79	46	1.95	1.38–2.75	2.18	1.33–3.55
no	48	1		1		30	1		1	

\* stable virological response defined as plasma HIV-1 RNA measurement below the threshold of detection of 500 copies/ml at all measurements except once between M4 and year 3 and 5.

\*\* cART: combination antiretroviral treatment