Integrase S119P mutation correlates with disease progression in HIV-1 naïve patients

P-L4

D Armenia[1], MM Santoro[1], L Fabeni[2], D Di Carlo[1], C Gori[2], A Bertoli[1,4], A Latini[3], E Nicastri[2], R Bellagamba[2], R Libertone[2], A Cristaudo[3], M Andreoni[4], Z Debyser[5], A Antinori[2], CF Perno[2], F Ceccherini-Silberstein[1]

1 University of Rome Tor Vergata, Rome, Italy; 2 L. Spallanzani Hospital, Rome, Italy; 3 San Gallicano Dermatological Institute, Rome, Italy; 4 University Hospital Tor Vergata, Rome, Italy; 5 Katholieke Universiteit Leuven, Leuven, Belgium.

Background

To achieve productive infection, retroviruses such as HIV stably integrate their reverse transcribed RNA genome into a host cell chromosome. DNA integration of retroviruses is not random, instead each retroviral family favors DNA integration near a unique and specific subset of genomic features.

- **HIV integrase (IN) variants at positions 119, 122 and 231 show distinct local integration biases.** ***(Demeulemeester et al., Cells Host Microbe 2014)***
- **IN mutations at position S119 have been associated with HLA selection.** ***(Brockman et al., 2012)***
- **S119G and R231G are linked to disease progression in chronic HIV-1 infection in South-African patients with subtype C.** ***(Demeulemeester et al., Cells Host Microbe 2014)***

Aim

We characterized the prevalence of integrase polymorphisms at positions 119, 122 and 231 and their association with subtype, CD4 cell-count and HIV-RNA in a large cohort HIV-1 infected HAART-naïve patients.

Methods

625 HIV-1 infected individuals naïve to antiretrovirals with an available IN genotypic resistance test (GRT) have been analyzed.
The prevalence of polymorphisms at HIV-1 IN positions 119, 122 and 231 was evaluated.
Phi-coefficient correlation was calculated to evaluate potential associations between the polymorphisms at these positions. Potential associations between IN polymorphisms with CD4 cell count and plasma HIV-RNA at IN GRT have been evaluated by Mann-Whitney test.
In a subgroup of patients deferring the treatment after diagnosis and with at least 2 HIV-RNA/CD4 cell count measurements before starting HAART, the time to start treatment or to reach a CD4 cell count <350 cell/mm^3 was evaluated by Kaplan-Meier curves and Cox regression analyses. Linear mixed regression model was used to evaluate the decrease of CD4 cell count over time according with IN polymorphisms. The following variables were used as potential confounders in multivariable analyses: age, gender, subtype (B vs. non-B), CD4 cell count, plasma HIV-RNA at IN GRT and time from HIV-diagnosis.

Results

119P and 122I were the most prevalent polymorphisms at IN positions 119 and 122, while only 231K was rarely observed at position 231. 119P/T showed a significant higher prevalence in F subtype compared to B subtype, while 122I showed a higher prevalence in B subtype compared to CRF02_AG or other non B subtypes.

Prevalence of polymorphisms detected at IN position 119, 122 and 231 according to subtype in 625 HIV-1 infected individuals naïve to antiretrovirals

Mutation	Overall (N=625)	Subtype						P value[a] compared to B subtype				
		B (N=445)	CRF 02_AG (N=45)	F (N=41)	C (N=23)	G (N=16)	Other[b] (N=55)	CRF 02_AG	F	C	G	Other[b]
119S$_{wt}$	396 (63.4)	285 (64)	37 (82.2)	15 (36.6)	16 (69.6)	11 (68.8)	32 (58.2)	**0.014**	**0.001**	0.59	0.7	0.394
119P	120 (19.2)	76 (17.1)	5 (11.1)	13 (31.7)	7 (30.4)	4 (25)	15 (27.3)	0.304	**0.002**	0.155	0.497	0.065
119G	56 (9.0)	51 (11.5)	0 (0.0)	2 (4.9)	0 (0.0)	1 (6.3)	2 (3.6)		0.293	0.158	1	0.101
119T	26 (4.2)	11 (2.5)	2 (4.4)	9 (22.0)	0 (0.0)	0 (0.0)	4 (7.3)	0.339	**<0.001**	1	1	0.071
119R	23 (3.7)	19 (4.3)	1 (2.2)	2 (4.9)	0 (0.0)	0 (0.0)	1 (1.8)	1	0.695	0.615	1	0.713
119A	4 (0.6)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1	1	1	1	0.374
122T$_{wt}$	482 (77.1)	330 (74.2)	44 (97.8)	30 (73.2)	17 (73.9)	15 (93.8)	46 (83.6)	**<0.001**	0.89	1	0.085	0.125
122I	130 (20.8)	108 (24.3)	1 (2.2)	10 (24.4)	6 (26.1)	1 (6.3)	4 (7.3)	**<0.001**	0.986	0.843	0.134	**0.004**
122V	8 (1.3)	6 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1	1	1	1	0.216
122S	5 (0.8)	1 (0.2)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	3 (3.6)	1	0.162	1	1	**0.005**
231R$_{wt}$	614 (98.2)	434 (97.5)	45 (100)	41 (100)	23 (100)	16 (100)	55 (100)	1	1	1	1	1
231K	11 (1.8)	11 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1	1	1	1	1

a. P value by Fisher test or Chi-Square test, where appropriate. b. A, D, K, BC, CRF01_AE, CRF02_AG, CRF03_AB, CRF06_cpx, CRF10_CD, CRF12_BF, CRF14_BG, CRF17_BF, CRF18_cpx, CRF18_cpx, B, CRF19_cpx, CRF31_BC, CRF37_cpx, CRF40_BF, CRF43_02G.

119P/G and 122I were strongly associated in HIV-1 naïve patients.

Mutation	N	Correlated mutation	N	Covariation Frequency N (%)	Pvalue	Phi
119P	120	122I	130	51 (42.5)	6.008599e-06	0.25
119G	56	122I	130	45 (80.3)	2.231324e-17	0.43

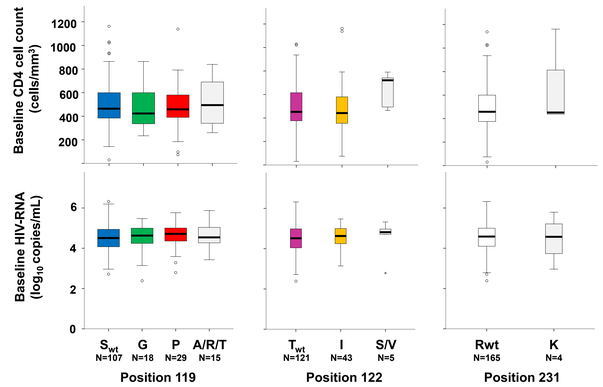
a. Polymorphisms 119A/R/T, 122S/V/T and 231K were not considered because their prevalence in the overall population was <5%.

Among 169 patients deferring HAART, no significant difference in CD4 cell count and/or plasma HIV-RNA was found at baseline according to IN polymorphisms at positions 119, 122 and 231.

Characteristics of the 169 patients deferring HAART for whom disease progression was evaluated

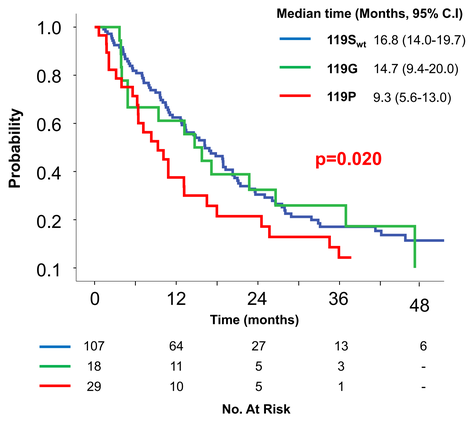
Male, n (%)	148 (87.6)
Age (years), median (IQR)	35 (29 – 42)
Viral load at IN GRT (log$_{10}$ copies/mL), median (IQR)	4.60 (4.10 – 4.99)
CD4 cell count at IN GRT (cells/mm^3), median (IQR)	458 (376 – 600)
Subtype, n (%)	
B	135 (79.9)
CRF02_AG	14 (8.3)
F	6 (3.6)
C	2 (1.2)
Other	12 (7.1)
No. of CD4 cell count measurments, median (IQR)	5 (2-7)
Follow-up duration (months), median (IQR)	13.1 (5.5-24.1)
Time from diagnosis (months), median (IQR)	2 (0-23)

CD4 cell count and plasma HIV-RNA at baseline according to IN substitutions at positions 119,122 and 231



Patients with 119P showed a shorted time to starting HAART or to reach a CD4 cell count <350 cell/mm^3 compared to those having 119G or 119S$_{wt}$.

Kaplan Meyer estimates to evaluate the time of starting HAART or of reaching CD4 cell count <350 cell/mm^3 in HAART naïve patients



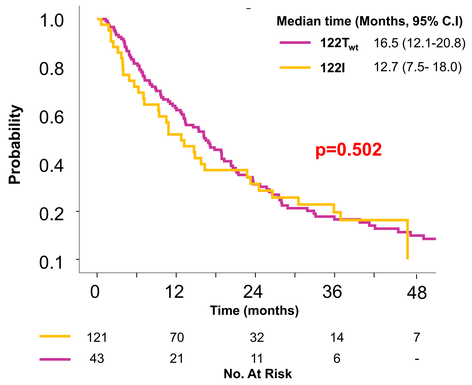
By Cox multivariable analysis, 119P and a higher baseline viremia were independent predictors of HIV-1 disease progression. Conversely, a higher baseline CD4 cell count was associated to a lower probability toward disease progression.

Relative adjusted hazard of starting HAART or reaching CD4 cell count <350 cell/mm^3

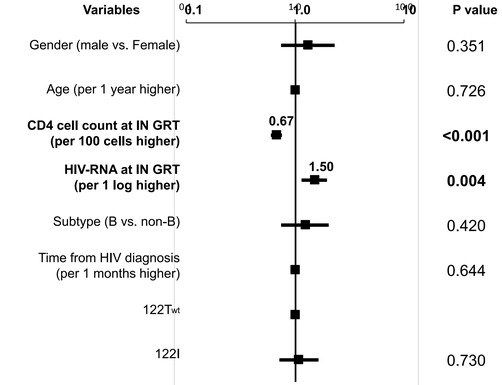
Even though 119P and 122I were significantly associated (see above), the impact of 119P on disease progression was independent from the co-presence of 122I mutation.

By Kaplan Meyer estimates and multivariable Cox regression, substitutions at position 122 were not associated with the probability of starting HAART or achieving CD4 cell count <350 cells/mm^3.

Kaplan Meyer estimates to evaluate the time of starting HAART or of reaching CD4 cell count <350 cell/mm^3 in HAART naïve patients

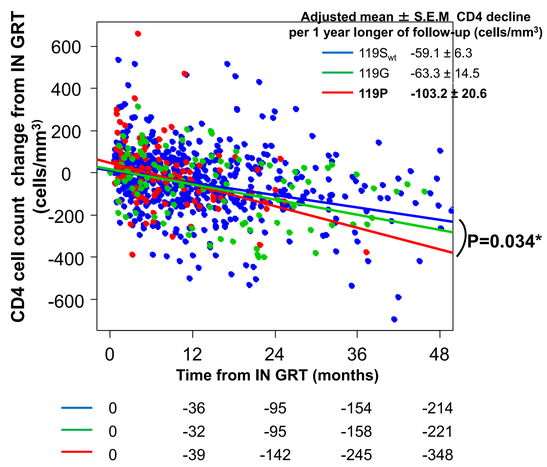


Relative adjusted hazard of starting HAART or reaching a CD4 cell count <350 cell/mm^3



Patients with 119P mutation showed a higher CD4 cell count decline compared to those with 119G or 119S$_{wt}$.

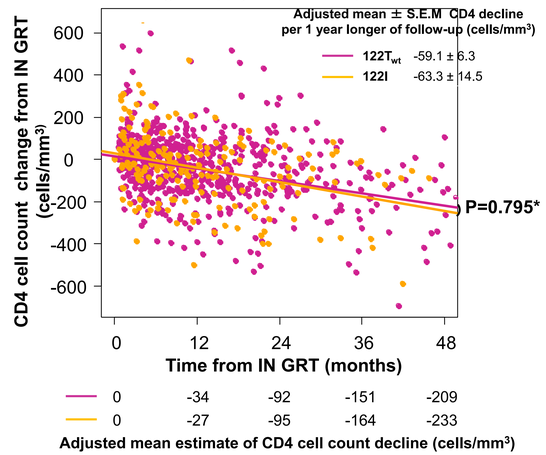
Scatter plot of CD4 cell count decline over time stratified according to IN polymorphisms at position 119



*Pvalue for comparison of 119P vs. 119S$_{wt}$

Patients with 122I mutation showed a similar CD4 cell count decline compared to those showed 122T$_{wt}$

Scatter plot of CD4 cell count decline over time stratified according to IN polymorphisms at position 122



*Pvalue for comparison of 122I vs. 122T$_{wt}$

CONCLUSIONS

Integrase position S119, beyond the observed correlations with integration site targeting and host immune response, might define patients with accelerated disease progression. Further investigations on polymorphisms at position S119 are necessary to understand this observation.

contact: daniele.armenia@gmail.com