HIV-2 X4 Tropism is Associated with Lowest CD4 Cell Count in Treatment-experienced Patients

POSTER #828

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ABSTRACT

BACKGROUND: Genotypic tools for HIV-2 tropism determination have been recently established. In vitro studies have demonstrated maraviroc efficacy against HIV-2. Nevertheless, maraviroc use in HIV-2-patients is currently only considered in highly pre-treated patients. However, R5/X4 tropism distribution is still unknown during HIV-2 infection. The aim of this study was to describe HIV-2 tropism distribution in treatment-experienced patients and to assess the association between tropism and CD4 cell count and the presence of drug resistance mutations.

METHODOLOGY: All samples received for HIV-2 tropism in routine testing between April 2009 and June 2013 issued from ART treated patients experiencing virological failure were included. At time of tropism determination, CD4 cell count, HIV-2 viral load and genotypic resistance testing (protease, RT, integrase) results were collected. Genotypic resistance tests were interpreted according to the new European resistance algorithm (http://www.geno2pheno.org/). Associations between tropism and variables were tested by Mann-Whitney or Fisher exact tests.

RESULTS: 83 patients were included. Among them, CD4 cell counts, HIV-2 viral load, and genotypic resistance results were available in 67 samples (81%), 75 (90%) and 77 (93%), respectively. 35 (42%) viruses were predicted as R5 and 48 (58%) as X4. Median CD4 cells counts were 220 (IQR = 155-395) and 88 cells/mm3 (IQR = 52-171) in R5 and X4 groups, respectively (p<0.0001). Tropism distribution among CD4 cell counts strata is depicted in the table below.

CD4 cell count (cells/mm³)		0-50	51-100	101-200	201-350	>350
HIV-2 tropism distribution	% R5 *(n)*	17 *(2)*	7 *(1)*	41 *(7)*	75 *(9)*	64 *(7)*
	% X4 *(n)*	83 *(10)*	93 *(14)*	59 *(10)*	25 *(3)*	36 *(4)*

Among R5 and X4 groups, median HIV-2 viral load was 1417 (IQR = 417-11910) and 2187 copies/mL (IQR = 526-4730), respectively (p = 0.38). Patients with X4 viruses exhibited a significant higher number of drug resistance mutations in protease, RT, and integrase regions than patients with R5 viruses (median = 3 [IQR = 1-5] versus 1 [IQR = 0-4]; p = 0.01).

CONCLUSIONS: A high proportion of X4 tropic viruses was observed, particularly in patients with CD4 cell count below 100 cells/mm3. X4 tropism was associated with lower CD4 cell counts but also with higher number of drug resistance mutations, a longer therapeutic history in patients with X4 viruses. Thus, as in HIV-1, maraviroc use in HIV-2 salvage therapy may be compromised by a high proportion of X4 viruses. These results suggest that maraviroc use must be evaluated earlier in the infection in order to optimize the HIV-2 limited therapeutic arsenal.

BACKGROUND

- HIV-2 is naturally resistant to non-nucleoside reverse transcriptase inhibitors, fusion inhibitor, and displays a decreased susceptibility to some of protease inhibitors.
- HIV-2 susceptibility to maraviroc, a CCR5 inhibitor, has recently been evaluated by several *in vitro* phenotypic studies [1–3], and *in vivo* in case reports of salvage therapy [4-6] and genotypic tools for HIV-2 tropim determination are now established [7,8].
- Tropism distribution during natural history of HIV-2 infection is still unknown. When pooling findings of two previous studies of our team, conducted regardless clinical and therapeutic status, we found lower CD4 cells counts in patients harboring X4 viral strains (n=27; median=149 cells/mm^3; IQR=[66-301]) than in patients harboring R5 viral strains (n=52; median=304 cells/mm^3; IQR=[189-463]) (p=0.0003) [7,8].
- In our clinical practice and in case reports describing *in vivo* maraviroc use in HIV-2-infected patients [4-6], maraviroc is always used in salvage therapy in highly-experienced patients harboring multi-resistant viruses. However, this maraviroc usage may be compromised by a high prevalence of X4-tropic viruses in HIV-2 treatment-experienced patients.
- The aim of this study was to describe HIV-2 tropism distribution in treatment-experienced patients according to CD4 cell count.

PATIENTS AND METHODS

INCLUSION CRITERIA

Retrospective study

- Antiretroviral treated patients presenting virological failure
- Routine HIV-2 tropism testing performed on physician request
- Period study: April 2009 to June 2013

COLLECTED DATA (at sampling time)

- CD4 cell count
- HIV-2 viral load
- Genotypic resistance test
- Genotypic tropism test

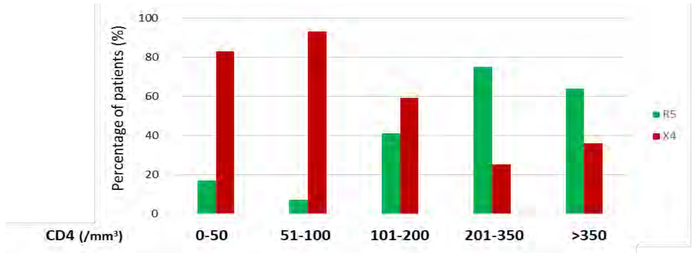
TROPISM AND DRUG RESISTANCE DETERMINATION

- Tropism determination was performed by V3 loop sequence interpretation as previously described [7]
- Genotypic resistance tests were performed using in-house methods and interpreted according to the recent European resistance drug resistance mutations list [9]

STATISTICAL ANALYSIS

- Associations between tropism and variables were tested by Mann-Whitney or Fisher's exact tests using R software

FIGURE. HIV-2 tropism distribution among CD4 cells counts strata in 67 antiretroviral-treated patients with available CD4 cells counts.



CD4 (/mm³)	0-50	51-100	101-200	201-350	>350
R5 tropism :					
%	17	7	41	75	64
(n)	*(2)*	*(1)*	*(7)*	*(9)*	*(7)*
Med. of DRM	*4,5*	*1*	*1*	*2*	*0*
X4 tropism :					
%	83	93	59	25	36
(n)	*(10)*	*(14)*	*(10)*	*(3)*	*(4)*
Med. of DRM	*1*	*3*	*4*	*0*	*6*

RESULTS

PATIENTS

- 83 patients were included, CD4 cell count, HIV-2 viral load, and genotypic resistance results were available in 67 (81%), 75 (90%) and 77 (93%) of samples, respectively
- 48 patients (58%) were infected with HIV-2 group A, 35 (42%) with HIV-2 group B.

Tropism group	% *(n)*	Median HIV-2 viral load *(copies/mL)*	Median CD4 cell counts *(cells/mm^3)*	Median drug resistance mutation count
R5	**42%** *(35)*	**1,417** [IQR=417-11,910]	**220** [IQR=155-395]	**1** [IQR=0-4]
X4	**58%** *(48)*	**2,187** [IQR=526-4,730]	**88** [IQR=52-171]	**3** [IQR=1-5]

HIV-2 TROPISM RESULTS

- HIV-2 tropism was predicted as R5 in 35 patients (42%) and as X4 in 48 (58%) patients. No significant difference between HIV-2 groups A and B (p=0.65).

TROPISM AND HIV-2 VIRAL LOAD

- Viral load not different in R5 group and X4 (p=0.75).

TROPISM AND CD4 COUNTS

- CD4 counts were higher in R5 than X4 group (p<0.0001)

TROPISM AND DRUG RESISTANCE

- X4-tropic viruses displayed more drug resistance mutations than R5-tropic viruses (p=0.02). 29 (71%) and 12 (29%) of the patients with X4 and R5 virus, respectively, exhibited viruses with more than 2 drug resistance mutations (p=0.03).

CONCLUSION

- In the present study, based on 83 antiretroviral-experienced HIV-2-infected patients, we reported :
  - A high proportion of X4-tropic viruses (58% versus 34% in our previous studies conducted regardless therapeutic and clinical status of patients, data not shown)
  - X4 tropism was particularly predominant in patients with CD4 cell count below 100/mm^3 (88%).
  - X4 tropism was also associated with a higher number of drug resistance mutations, suggesting a more advanced therapeutic history in these patients.
- Further studies are needed in order to determine HIV-2 tropism distribution in antiretroviral-naïve population and during natural history of HIV-2 infection.
- However, our results highly suggest that maraviroc use in HIV-2 salvage therapy in severely immunocompromised and antiretroviral-experienced patients may be compromised by a high proportion of X4 viruses. Maraviroc need to be evaluated in earlier stages of HIV-2 infection, in order to optimize the HIV-2 limited therapeutic arsenal.

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