Gp120 substitutions at "hot" positions associated with resistance to fostemsavir in naïve HIV-1 positive individuals

L. Lepore[1], C. Fabrizio[1], E. Milano[1], N. de Gennaro[1], A. Lagioia[1], A. Volpe[1], L. Scudeller[2]
A. Saracino[1], G. Angarano[1], L. Monno[1]

1.Clinic of Infectious Diseases, University of Bari, Italy; 2. Scientific Direction, Clinical Epidemiology Unit, IRCCS San Matteo Foundation, Pavia, Italy

BACKGROUND & AIM

- Fostemsavir (FTR), prodrug of Temsavir, is a novel attachment inhibitor under investigation, targeting the HIV-1 gp120. It is active regardless of viral tropism and subtype, except for the CRF01_AE, group O and HIV-2. Up to now, there is no evidence of *in vitro* cross-resistance with other classes of antiretroviral drugs, therefore FTR has the potential to be used in highly-treatment experienced population with unmet medical needs.
- So far, some substitutions of the highly variable HIV-1 gp120 were found to be associated with an altered susceptibility to FTR.
- The aim of our study is to investigate the presence of envelope (*env*) substitutions at "hot" positions associated with resistance to FTR in patients newly diagnosed with HIV-1 infection and to eventually correlate *env* substitutions according to HIV subtype and tropism (CRT).

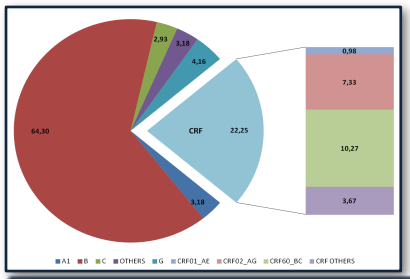
PATIENTS & METHODS

- In this single-center study (2008-2017), gp120 sequences from 409 patients (pts) with newly diagnosed HIV-1 infection were retrospectively analyzed. Clinical isolates were classified as either B and non-B subtypes (REGA-3 system). CRT was inferred with the g2p algorithm (FPR 10%) and duration of HIV infection estimated based on the proportion of ambiguous nucleotides in RT/PR (e.g. ≤0.2%: recent infection).
- The frequency of the following mutations for FTR resistance was assessed: L116P (325 sequences), A204D (370 seq), S375H/M/T (382 seq), M426L (282 seq), M434I (238 seq), M475I (112 seq). Other amino acid changes at the same positions were also recorded.
- Variability at each amino acid position of gp120 in C1-C4 subdomains of subtype B viruses was also evaluated using Shannon entropy. Entropy of R5 viruses versus non-R5 viruses was compared by means of Entropy-2 tool.

RESULTS

Baseline characteristics of the enrolled pts (N=409)

Age, median (IQR)	35.5 years (7.8-44.8)
Male, N (%)	346 (84.6%)
Italians, N %	357 (87.3%)
Infection < 1 year , N (%)	188 (46%)
Acute infection, N (%)	23 (5,6%)
Risk factor for HIV transmission, N (%)	
sexual route	368 (90.1%)
of whom MSM	213 (57,9%)
Baseline CD4 cell count, cell/mm^3 median (IQR)	364.0 (162.0-510.0)
Baseline log$_{10}$HIV-RNA , median (IQR)	4.72 (4.07-5.32)
Coreceptor tropism R5, N (%)	331 (81%)
Non-B strains, N (%)	149 (36.4%)
CRF01_AE, N	4 (1%)

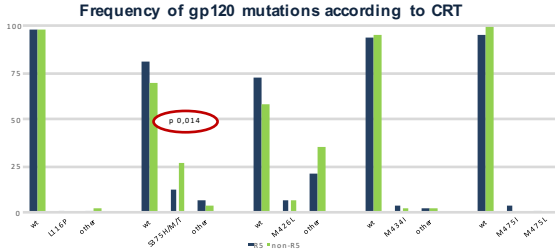


- **Subtype B** HIV-1, within the group M, is the most frequent subtype in the Americas, Western Europe and Australasia.
- **CRF60_BC**, is the most frequent in our area as a consequence of a recent outbreak among MSM. CRF02_AG is the second most prevalent subtype circulating in Italy after subtype B.

Env substitutions

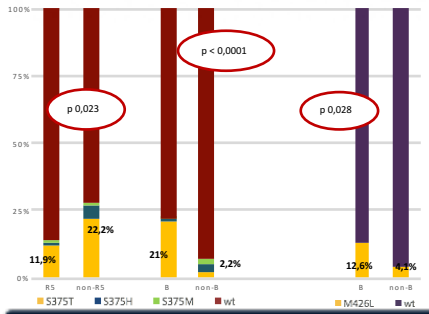
In descending order of frequency, mutations were: **S375T** (13.0%); **M426L** (6.74%); **M434I** (2.94%); **M475I** (2.68%); **S375H** (1.57%) **S375M** (0.79%) and **L116P** (0.31%). A204D was never detected.

Frequency of gp120 mutations according to CRT



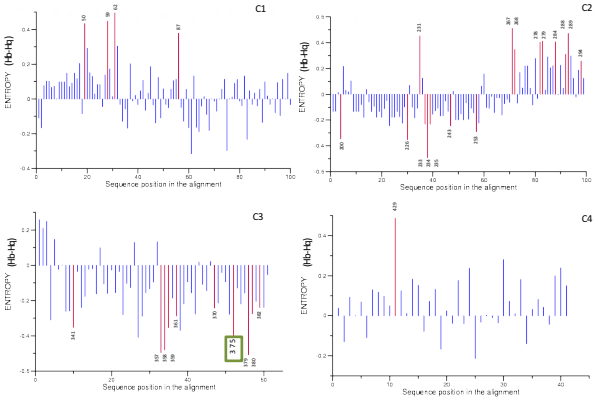
Frequency of gp120 mutations according to subtype

post hoc analysis for positions 375 and 426 *p<0,025*



- For position 375, significance was steered by S375T, comparing both R5 vs non-R5 and B vs non-B viruses.
- A trend of significance was present at position 426 in B vs non-B viruses comparison.

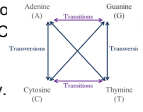
Entropy difference in subtype B: R5 variants vs non-R5 (Hb= non-R5, Hq= R5)



- For each subdomain, entropy difference was diversified: only in C2, significance was observed in both populations, while for the 3 remaining portions, it seemed that the entropy difference was significant only in one group compared to the other one.
- No significant difference in the amino acid variability was observed for any of the substitutions previously studied, with the only exception of position 375 in the C3 domain where a significant variability was demonstrated in R5-viruses.

S375T
The most frequent detected substitution

- It was also found in C subtype, unlike previous study.



- Reasonable explanation of S375T > S375H/M:
  Ser → 1 transversion → Thr
  Ser → 1 transversion + 1 transition → His
  Ser → 2 transversions → Met

- C4 domain showed a lower variability possibly because C4, being buried into a hydrophobic pocket, stays in a safe place against the selective pressure of the host immune response.

CONCLUSIONS

- Gp120 substitutions that may prejudice susceptibility to FTR were detected in different subtypes and in both R5 and non-R5 variants.
- Despite the great variability of gp120, the overall frequency of known mutations for FTR resistance was low.
- In B subtype, the predominant mutation was S375T, whose role in reducing FTR efficacy is much less substantial than L116P, S375H and M426L, which, conversely, were detected in a smaller proportion of subjects.
- We believe that FTR might be considered a promising therapeutic option for a large target of patients. It would be worthwhile to investigate additional mutations potentially reducing FTR efficacy in a larger scale.

References:

- Kozal M, Aberg J, Pialoux G, et al. PS 8/5 - Phase 3 Study of Fostemsavir in Heavily Treatment Experienced HIV-1 Infected Subjects: Day 8 and Week 24 Primary Efficacy and Safety Results (BRIGHTE Study, Formerly AI438-047). [Abstract Number: PS 8/5]. *16th European AIDS Conference*, October 25-27/2017. Milan, Italy
- Zhou N, Nowicka-Sans B, McAuliffe B, et al. Genotypic correlates of susceptibility to HIV-1 attachment inhibitor BMS-626529, the active agent of the prodrug BMS-663068. *Journal of Antimicrobial Chemotherapy*, 2013, *69*(3), 573-581
- Monno L, Brindicci G, Lai A, et al. An outbreak of HIV-1 BC recombinants in Southern Italy. *Journal of Clinical Virology*, 2012, *55*(4), 370-373