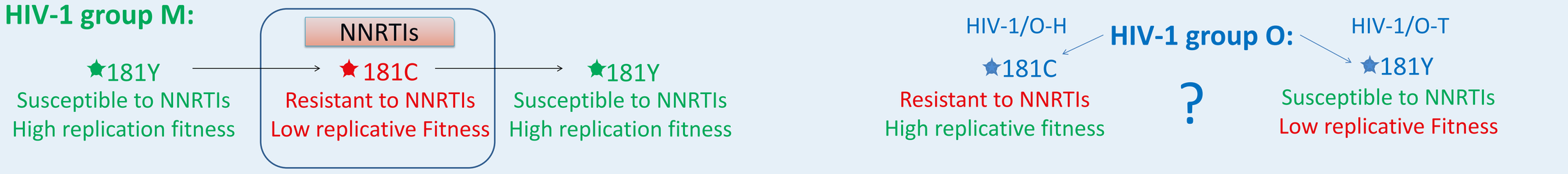
Next Generation Sequencing Analysis of HIV-1 Group O Reverse Transcriptase Residue 181C Prevalence and Evolution over Time, With or Without Antiretroviral Selection Pressure

Marie Leoz[1,2], Myriam Vezain[3], Elodie Alessandri-Gradt[1], Sophie Coutant[3], Guillemette Unal[1], Isabelle Tournier[3], François Simon[4], Jean-Christophe Plantier[1,2]

[1]Laboratoire GRAM EA2656, Université de Rouen, France; [2]Laboratoire de Virologie associé au CNR VIH, CHU de Rouen; [3]U1079, Service commun de génomique de l'Institut de Recherche et d'Innovation Biomédicale, Rouen, France; [4]Laboratoire de Virologie, Hôpital St Louis, Paris, France.

BACKGROUND

HIV-1 group O viruses are endemic in Cameroon and found sporadically in other countries. Their genetic divergence from pandemic HIV-1/M causes polymorphisms on residues associated to HIV-1/M antiretroviral resistance.



Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI) resistance mutation Y181C can be selected in HIV-1/M but naturally present in HIV-1/O, and associated to the recently emerged HIV-1/O-H subgroup[1]. A previous study suggested that residue 181C could confer a better replicative fitness to HIV-1/O *in vitro* and that signature residues were associated to 181Y-like or 181C-like lineages[2].

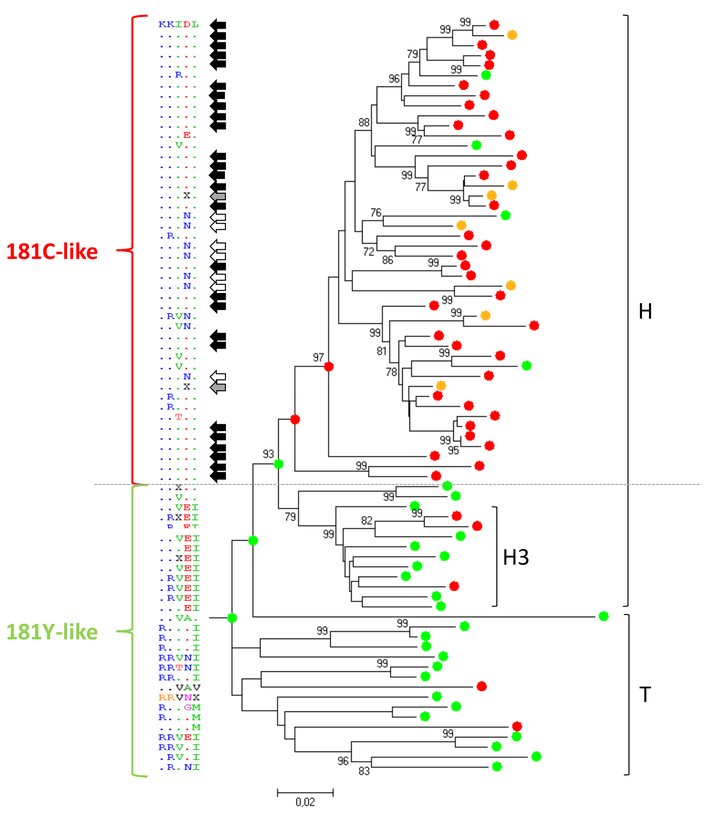
Here we aimed at exploring these hypotheses using *in vivo* samples and to investigate evolution of group O RT residue 181 under selection pressure due to NNRTI based treatment or not.

METHODS

We used Next Generation Sequencing to study residue 181 distribution and associated signature residue polymorphisms in 75 NNRTI-naïve HIV-1/O patients (1). Evolution of residue 181 over time – under selection pressure due to NNRTI based treatment or not – was investigated by Sanger and confirmed by NGS for some samples in 8 patients (2). We compared the viral loads from 59 untreated patients depending on residue 181 (3).

RESULTS (1)

Residue 181C (red) was found in 40/75 NNRTI naive patients. Its association with HIV-1/O-H was confirmed (p<0.001). A 181C/Y mixture (orange) was found in 7 unlinked individuals.



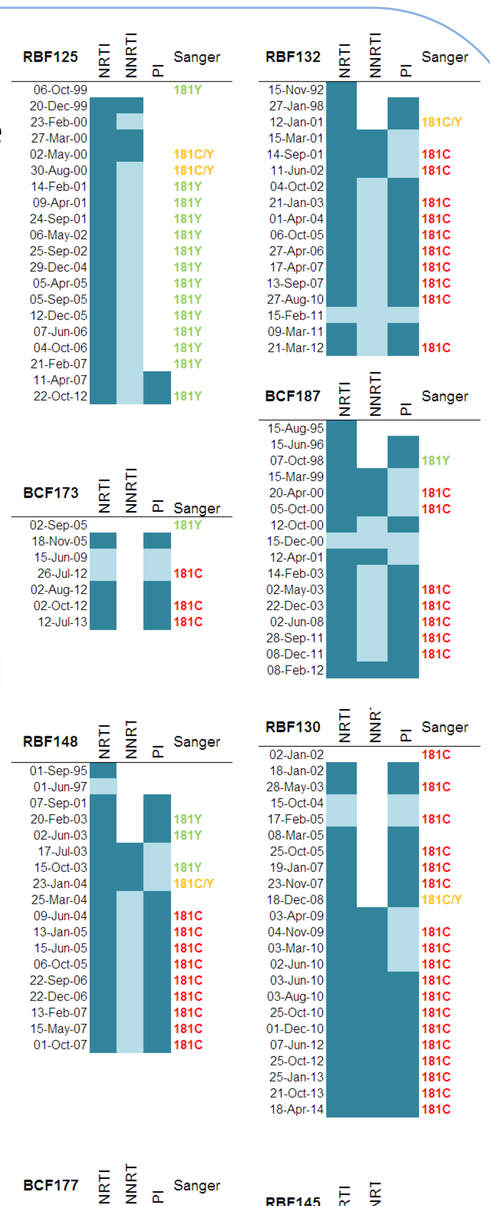
Residues at signature positions were diverse in 181Y viruses (green) but a 28K-103K-142I-174D-178L pattern was highly conserved in 181C viruses (black arrows).

RESULTS (2)

Evolution of residue 181 was similar to what observed under NNRTI in HIV-1/M for one 181Y HIV-1/O-T virus (RBF125).

Three HIV-1/O-H viruses selected 181C due to NNRTIs, but conserved it several years after NNRTI interruption (RBF132, BCF187, RBF148).

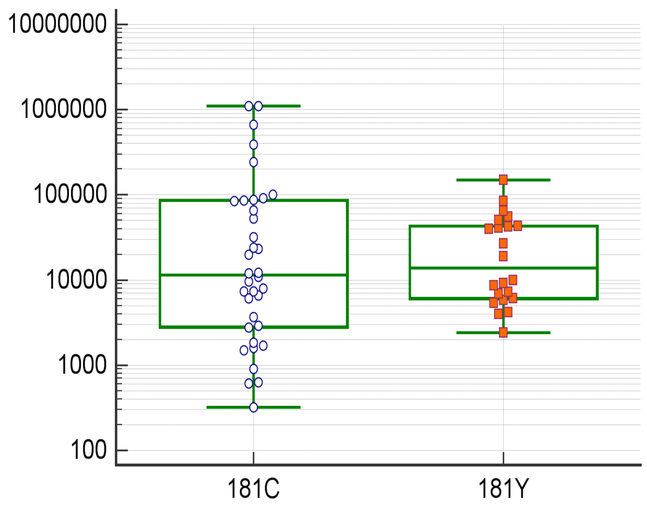
Four HIV-1/O-H viruses evolved without NNRTIs (C/Y => C, n=2, C => C/Y, n=2).



ARV naive
Under ARV treatment
Previously treated
*Confirmed by NGS

RESULTS (3)

The viral load range in untreated patients infected by 181C viruses (min: 2.5log cp/ml ; max: 6.0log cp/ml; N=37) was larger than that of 181Y virus infected patients (min: 3.4log ; max: 5.2log; N=22).



The mean viral load was higher in the 181C group (5.1log, median: 4.1log) than in the 181Y group (4.5log, median: 4.2log), but not significantly according to Student t test (p=014).

CONCLUSIONS

Mutation 181C presence and evolution in HIV-1/O is **linked to the virus genetic background**.

It is associated to the emergent HIV-1/O-H subgroup where it can be **naturally present, or conserved after NNRTI selection**, possibly due to a favourable pattern (28K-103K-142I-174D-178L) on **associated signature residues**.

However, **no replicative advantage** is observed for 181C viruses *in vivo*.

[1]Leoz et al., PLOS Pathogens 2015. [2]Tebit et al., AIDS Research and Human Retroviruses, 2016.