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Evolution of HIV-1 groups M and O: genetic comparative analysis of 23 HIV-1/MO inter-group recombinant forms

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Background

HIVs are characterized by a **high genetic diversity**, due to their simian origins and their replication mode, enhanced by recombination events. Despite the great genetic divergence between pandemic **HIV-1/M** and **HIV-1/O** (endemic in Cameroon), **dual infections** between the two groups can **generate HIV-1/MO inter-group recombinants**. Only three cases were described until 2004 [1-3]. Emergence of such mosaic forms may have a strong impact on diagnosis and treatment due to the presence of highly divergent group O fragments in their genome. Between 2006 and 2017, the implementation of a **sero-molecular algorithm in Cameroon** and the **exploration of atypical HIV-1 infection reactivities** at HIV diagnosis or during follow-up in **France** allowed the description of **new HIV-1/MO infections** [4-6].

Aim

Analyze and compare the **recombination patterns** and **genetic peculiarities** of all HIV-1/MO recombinants currently characterized.

Materials and methods

- **Collection of available data** on infected patients and on all recombinant forms characterized between 1999 and 2017: geographic origin of patients, partial/whole genome sequencing, possible co-infection with parental strains.
- **Comparison of frequencies of their characteristics**: phylogenetic analysis, breakpoints numbers in each mosaic genome and location.

Results

- In addition to the first three cases described, **20 new recombinants or putative forms** were identified in Cameroon and France between 2006 and 2017. Thereby, **23 distinct, partially or completely sequenced, recombinant forms**, found in **22 patients**, were analyzed and compared, revealing a complexity of patterns [Fig.1].
- This work also highlighted a **variable degree of complexity** in profiles, with on average **two to three breakpoints** per recombinant genome [Fig.1].
- For the 23 MO recombinants, the **presence of HIV-1/M and/or HIV-1/O parental strains** was searched and results showed:
 - 12 recombinants with **no parental strains**
 - 10 recombinants **associated to one or two parental strains**
 - one case of **superinfection**, which led to the emergence of a recombinant form.
- Phylogenetic analysis showed that the 23 recombinant forms corresponded to **19 distinct unique recombinant forms (URFs)** [Fig.2]:
 - two URFs in two pairs of patients without any epidemiological link (BCF174/BCF212 and RBF222/RBF243 [6]),
 - one URF in two married patients (REC003/REC024 [4]),
 - one URF described by two different research teams, likely in the same patient (97CA.MP645MO [1]/YBF298),
 - two URFs in the same patient (RBF221-1 and RBF221-2),
 - no known link for the 13 other URFs.

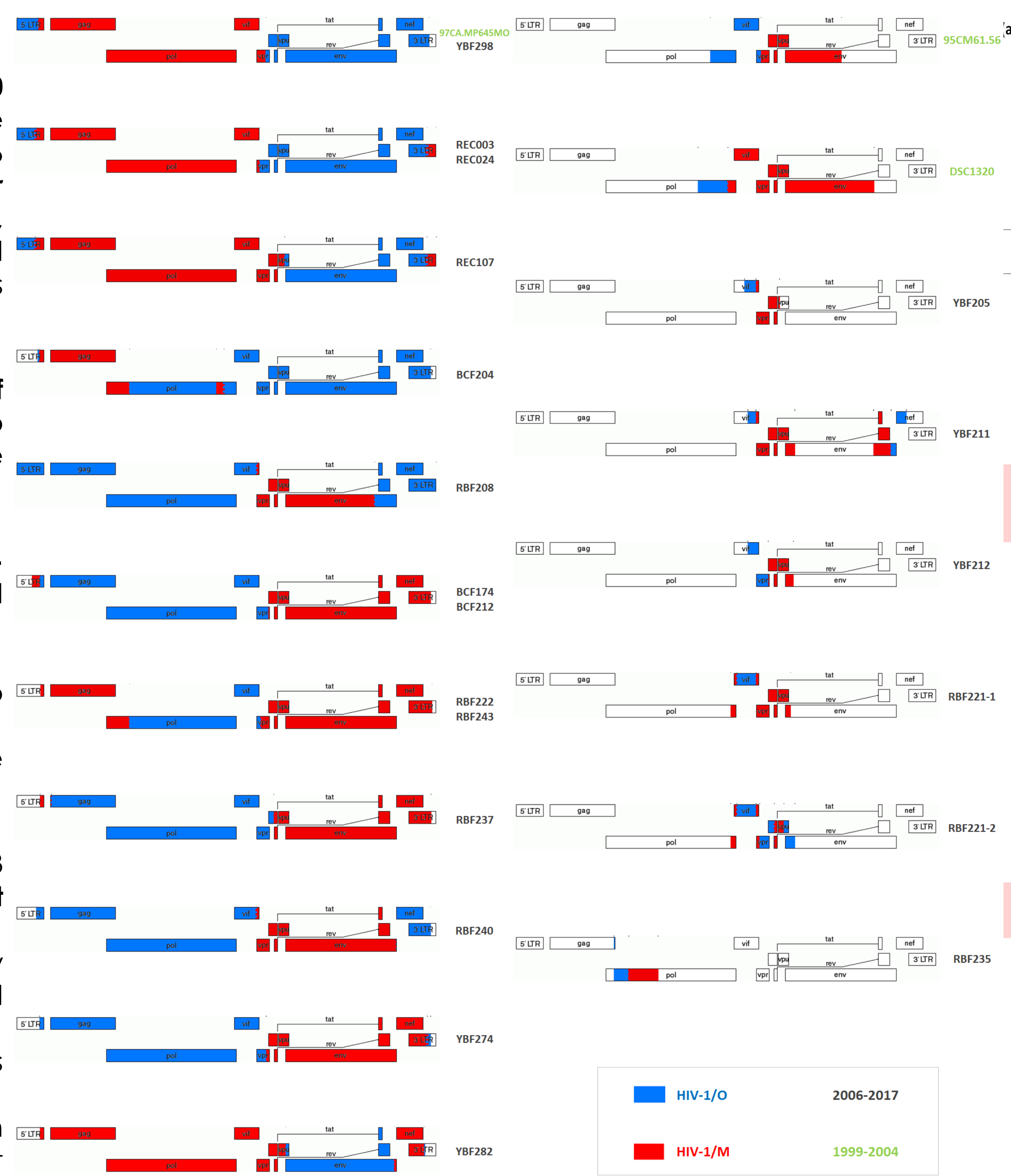


Fig. 1 Genomic profiles of the 23 described recombinants
Fragments belonging to HIV-1/O and /M are shown in blue and red respectively. Codes of recombinants described in 1999 and 2004 [1-4] are written in green and those of recombinants described between 2006 and 2017 in France and in Cameroon [4-6] are written in gray.

- These 23 recombinants were all found in **patients of Cameroonian origin** and genetic diversity of the mosaic fragments **matched the molecular epidemiology in Cameroon**. Indeed, a clear predominance of **HIV-1/M CRF02_AG** (53%) and of **HIV-1/O sub-group H** (87%) was observed [Fig.3].

- Analysis of the genomic profiles and of the breakpoints frequency in the 23 described recombinant forms revealed [Fig.4]:

- **hotspots in the "central" accessory genes** (*vif*, *vpr*, *vpu*), **reverse transcriptase**, **gp41** and **LTRs**
- **no recombination event in protease**, **gp120** and **nef**.

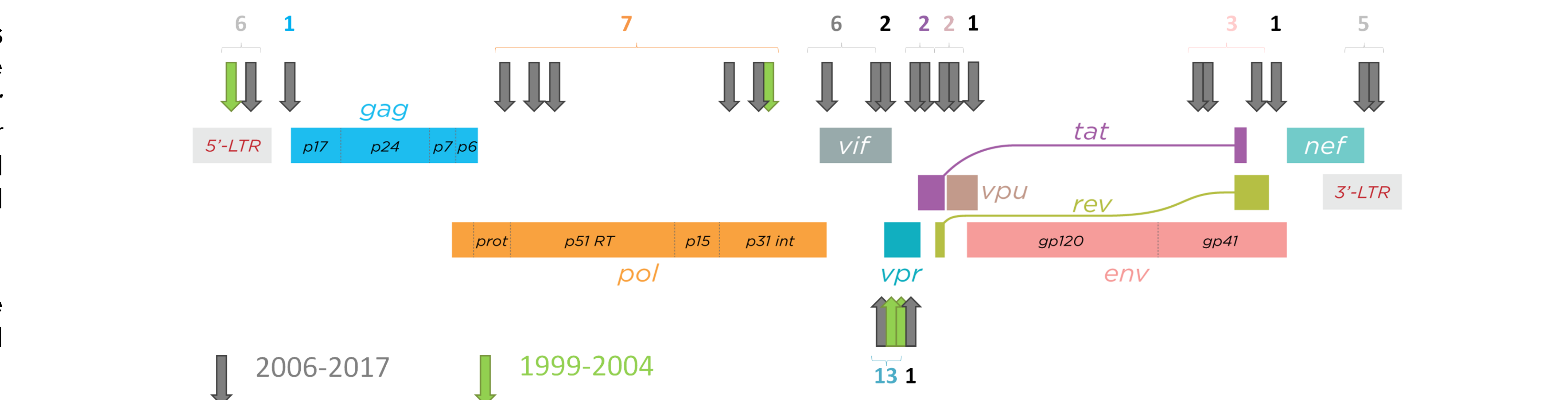


Fig. 2 Phylogenetic relationships of the HIV-1/MO fully sequenced Neighbour-joining trees of the PR-RT [899bp] (a) and gp41 [443bp] (b) regions were constructed with HIV-1/O and /M reference subset.

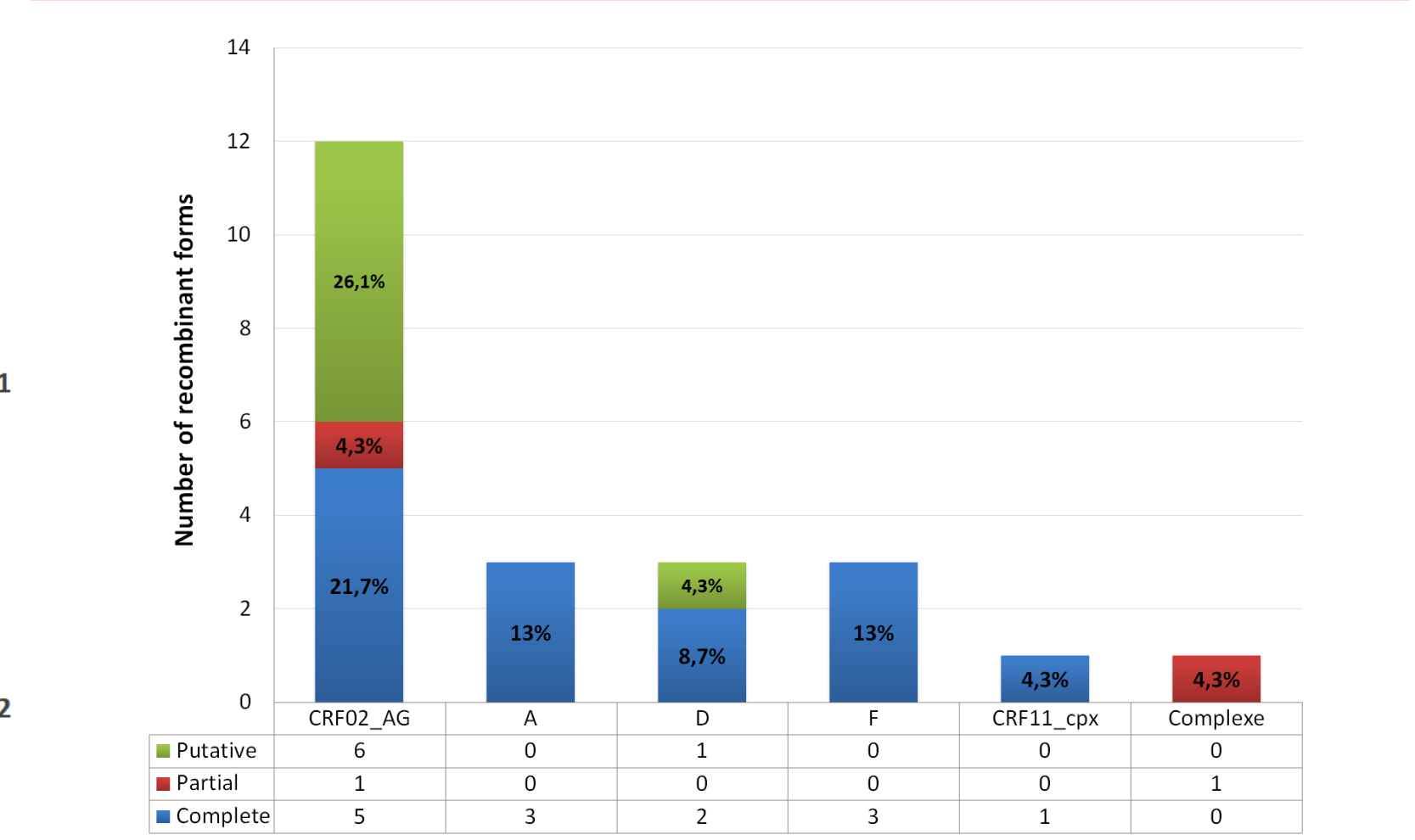


Fig. 3a Distribution of subtypes of HIV-1/M of the 23 described recombinants

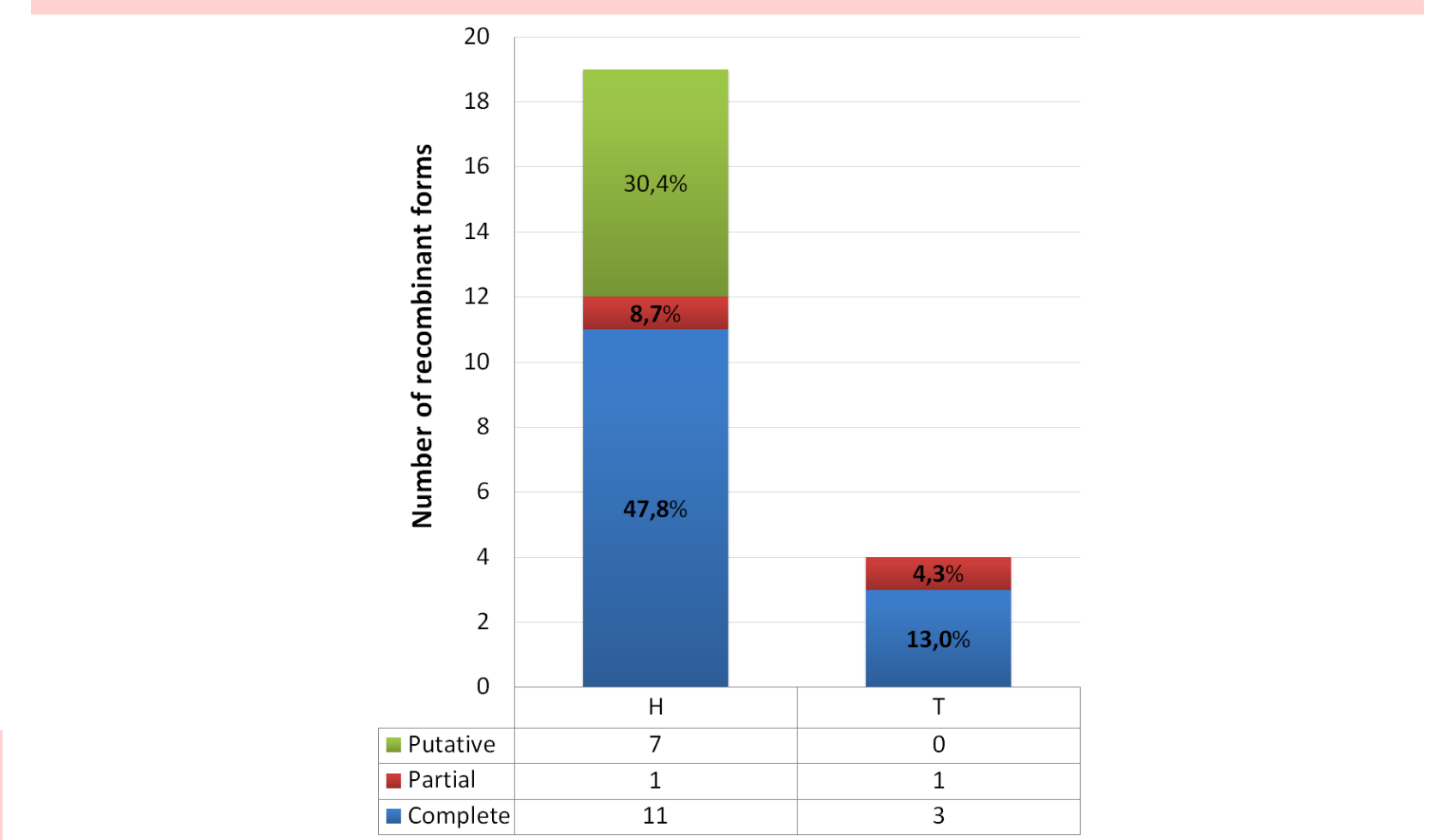


Fig. 3b Distribution of sub-groups of HIV-1/O of the 23 described recombinants [7]

Conclusions

- Despite the complexity of the recombination patterns, these recombinants could be detected with a **suitable sero-molecular strategy** or **following discordances** between detection and/or follow-up of results.
- The phenomenon of MO recombination is rare but **not anecdotal**, and **numerous situations** have been observed (single recombinants, or associated with one or two parental strains, or even a case of superinfection)
- **Inter-groups MO recombination hot/coldspot gradients** and the **location of breakpoints** were identified and remain to be compared with those in intra-group M recombinants.
- The analysis showed that recombinants were often single, with no parental strains, suggesting an **advantageous phenotype** of recombinant forms and a **possible better fitness** relative to parental strains, as observed by Peeters *et al.* [1].

In conclusion, this work allowed us to describe and analyze a unique series of HIV-1/MO recombinants, **highlighting a greater diversity and complexity than originally supposed**, and offering new research perspectives on the **conditions of emergence and virological properties of these recombinant forms**. Moreover, these multiple URFs-MO, single and transmitted in pairs of patients, could lead to **the diffusion and the emergence of a CRF_MO**.

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