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First Evidence of a HIV-1 M/O Recombinant Form Circulating Outside Cameroon

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INTRODUCTION:

HIV-O infection is endemic in Cameroon. Among these patients HIV-O positive (= 1% of all HIV infections), seroprevalence studies showed at least 10% of HIV-M/HIV-O dual infections, but only three O/M recombinant forms have been previously described [1, 2, 3]. In France, 119 patients have been yet identified with HIV-O infection, most of them originating from Cameroon. The suspicion of HIV-O infection often comes on the occasion of diagnosis difficulties or virological-clinical discordances due to their high genetic divergence compared to HIV-M, which can lead to poor or total lack of detection by certain commercial tests.

PATIENTS AND METHODS:

A 25years old Cameroonian woman (RBF209) living in France since 2000 had consulted at the University Hospital of Reims (eastern France) in May 2008. Her biological and virological analyses indicated (tab.1):

- CD4 = 6/mm³
- viral load = undetectable (Roche Cobas Taqman)
- viral load = 6.10⁴ cop/ml (Abbott Realtime)

Complementary analyses were performed using :

- in-house HIV-O specific viral loads, targeting the LTR and integrase regions
- serotyping assay using peptides that mimic the Immuno-Dominant Region (IDR) of the gp120 and the V3 loop of the gp120 specific to HIV-1 groups M, N and O and HIV-2
- HIV-O or M group-specific PCR in the Protease, Reverse Transcriptase (RT), Integrase and Gp41 regions

- near full-length genome characterization from viral RNA and intracellular DNA, using non specific XL-RT-PCR and XL-PCR, and sequencing with a set of 37 primers.

Viral Loads (log)	Target region		RT	Integrase	gp120 V3	gp41
	Roche Taqman	Abbott M2000				
	4.1	<1.6				
Serotyping	PLM					
Group-Specific Amplification	VHVO		+	+	+	HIV-M
	VHVM		-	-	-	-

Table 1: Viral loads, serotyping and group-specific amplifications results. Group O specific results are indicated in red, group M specific in green, and non specific in blue.

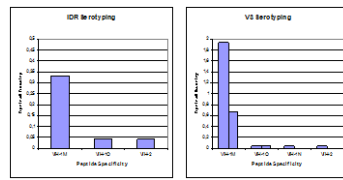


Figure 1: Optical densities observed using IDR peptides (a) or V3 peptides (b) of various HIV types and groups

RESULTS:

The viral loads results were firstly in favour of a group O infection. The HIV-M specific Roche Cobas Taqman test was undetectable while the HIV-O specific methods were positive as the non specific Abbott M2000 (tab.1). However, serotyping clearly indicated a specific group M reactivity (fig.1).

Group specific amplifications were positive only for HIV-O in the *pol* gene, and surprisingly no group-specific amplification was positive in the gp41 region (tab.1).

The near full length sequencing of the circulating viral RNA revealed a O-M-O recombinant form (fig.2) with a breakpoint in the gp41 region, explaining the negative results with group-specific primers. Another breakpoint was located on the first codon of *vpr*, where two of the three previously described M/O recombinants already shown a group switch.

Phylogenetic analyses indicated that RBF209 was not linked to the other M/O recombinants (fig.3).

The absence of HIV-O specific antibodies (fig.1) together with the negativity of group M specific PCR in the *pol* gene and no amplification of M or O in the gp41, suggest that this young patient does not carry the parental HIV-O and HIV-M strains.

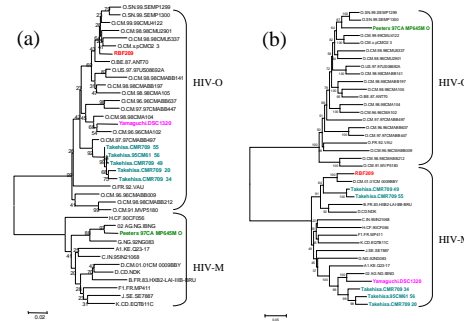


Figure 3: Phylogenetic analysis of the integrase region (a) and the *vpr* to gp120 region (b) of the RBF209 isolate together with the three previously described M/O recombinant forms. Method: Neighbor-Joining (1000 bootstraps tests), Distances Calculation: Kimura-2-Parameters model

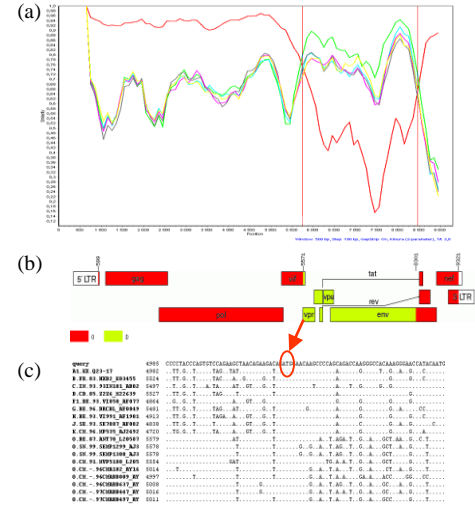


Figure 2: Characterization of the near full length O-M-O recombinant form. (a) Similarity plot indicating a HIV-O / HIV-M subtype D / HIV-O structure; (b) mapping the breakpoints on HIV-1 genome; (c) evidence of O/M recombination on the first codon of *vpr*

CONCLUSION:

This fourth intergroup M/O recombinant form is the first described outside Cameroon.

Unlike the previously described cases which emerged during a co-infection, this could be the first direct transmission by a M/O recombinant form ever described, emphasizing the dynamic and a possible spread of such strains.

This kind of genome structure has consequences for the follow up and treatment of the patient, as there are HIV-O related mutations in the *pol*-encoding protease, RT and integrase, but targets of the entry inhibitors are HIV-M.

With three intergroup recombinants switching in the *vpr* gene and the fourth at the end of the integrase, the hypothesis of a hotspot of intergroup recombination in *vpr* or around the accessory genes region has to be explored.

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