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 Universitary Hospital of Reims (eastern France) in May 2008. Her biological and virological analyses indicated (*tab.1*):
-CD4 = 6/mm^3
- viral load = undetectable (Roche Cobas Taqman)
- viral load = 6.10^4 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 gp41 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-lengh 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.

	Target region	LTR	gag	protease	RT	integrase	gp120 V3	gp41
Viral Loads (log)	Roche Taqman		<1,6					
	Abbott M2000 in house LTRO	4,1				4,8		
	Abbott M2000 in house intO					5,0		
Serotyping	PLIA						HIV-M	
Group-Specific Amplification	VIH-O			+	+	+		-
	VIH-M			-	-	-		-

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.

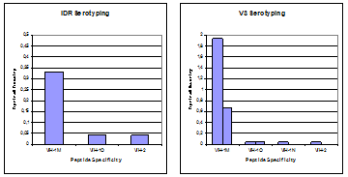

Figure 1:Optical densities observed using IDR peptides (a) or V3 peptides (b) of various HIV types and groups

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 (*fig1*).
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 amplication of M or O in the gp41, suggest that this young patient does not carry the parental HIV-O and HIV-M strains.

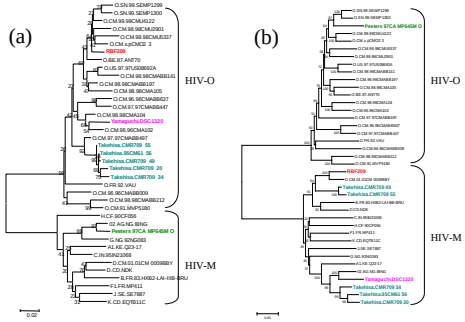

Figure 3: Phylogenetic analysis of the integrase region (a) and the vpr to gp120 region (b) of the RBF209 isolate together with the three previously described M/O recombinant forms. Method: Neighbor-Joining (1000 bootstraps tests), Distances Calculation: Kimura-2-Parameters model

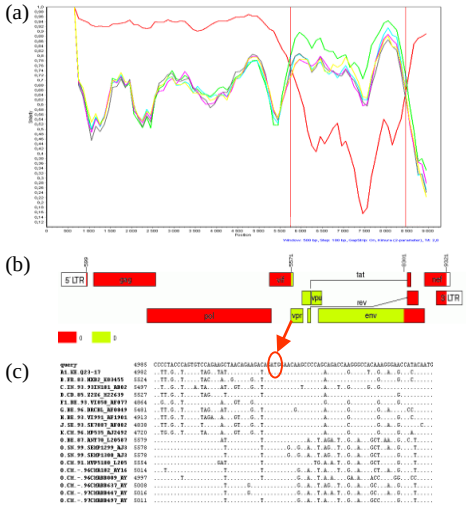

Figure 2: Characterization of the near full lenght O-M-O recombinant form. (a) Similarity plot indicating a HIV-O / HIV-M subtype D / HIV-O structure; (b) mapping the breakpoints on HIV-1 genome; (c) evidence of O/M recombination on the firs codon of vpr

CONCLUSION:

This fourth intergroup M/O recombinant form is the first described **outside Cameroon**.
Unlike the previously described cases witch 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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