

# HIV Dynamics and Evolution

May 8th 2014

## THE TWO PHASES OF HIV-1 GROUP O DIVERSIFICATION

Marie LEOZ, PhD student  
Laboratoire GRAM EA 2656  
Rouen, FRANCE



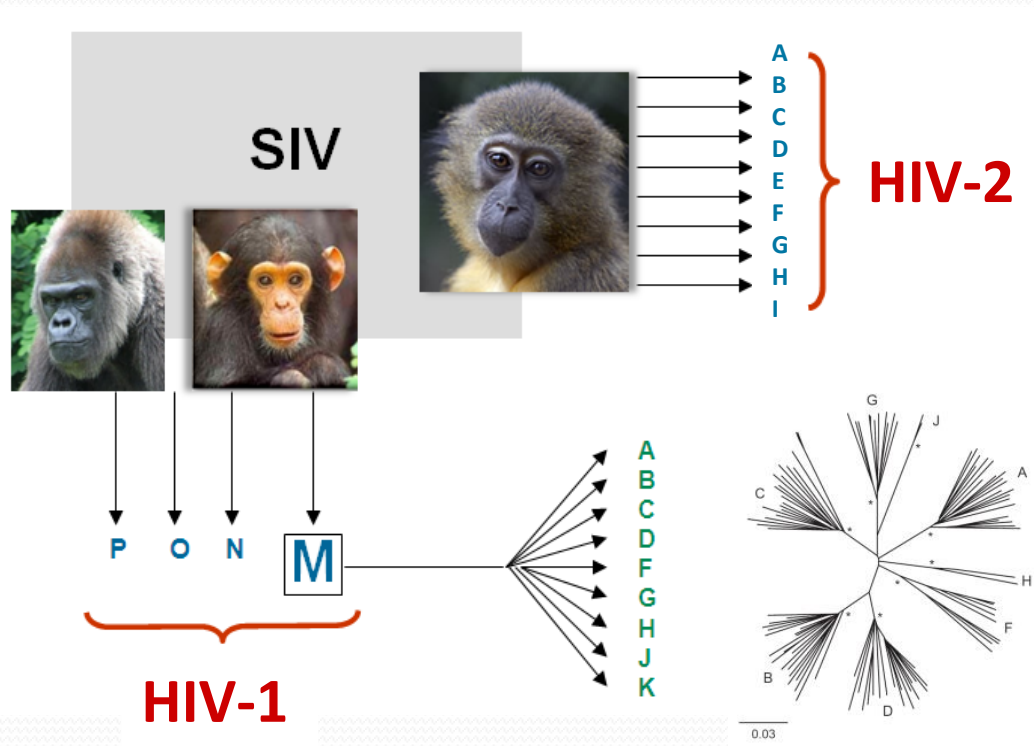
**BACKGROUND**

OBJECTIVES & METHODS

RESULTS

CONCLUSIONS

# Background : HIV genetic diversity



- Several cross-species transmissions of SIVs
  - 2 **types**
  - 13 **groups**
- Error prone RT + High replication rate + Selection pressures + Founder effects
  - HIV-1/M **subtypes**

# Background : HIV-1 molecular epidemiology

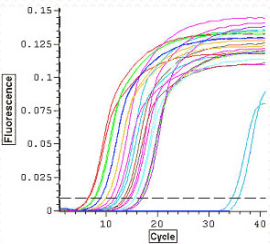
- M : pandemic > 34,000,000
- N et P : rares < 20
- **O : endemic in Cameroon** ~ 10,000 to 30,000
  - Also found in some geographically or historically linked countries
  - First exportations in Europe in the 1960's (Norwegian sailor and family)
- In France: 141 patients identified since 1992
  - Survey network : RES-O



# Background : HIV-1/O diagnosis, follow up and treatment



- High divergence between HIV-1/M and HIV-1/O
  - Impact on serodiagnosis and viral load quantitation
  - No specific algorithm available for interpretation of resistance mutations



- Natural presence of the Y181C mutation in the Reverse Transcriptase
  - Confers resistance to the 1st generation NNRTIs



# Background : HIV-1/O diversity and evolution

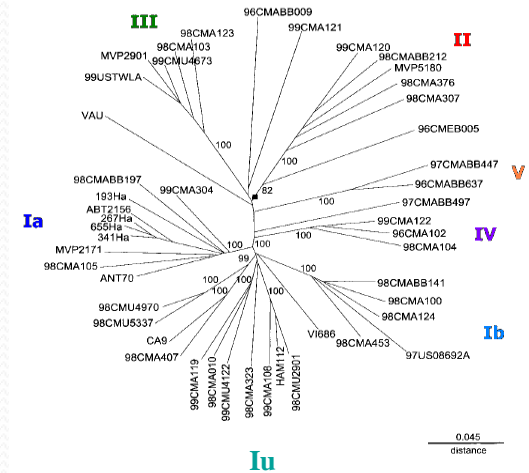
- Emergence

- HIV-1/O MRCA estimated around 1920 (1890 – 1940)

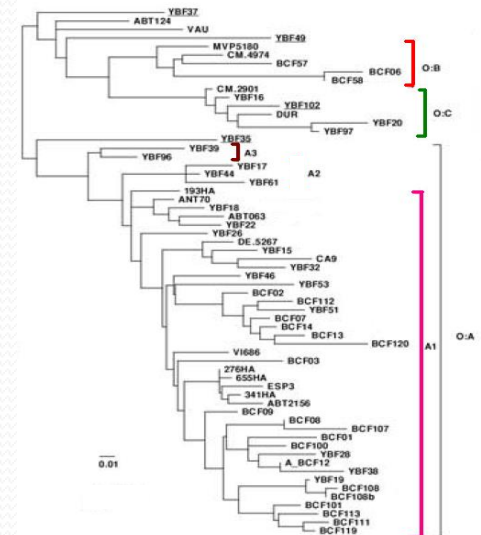
Lemey et al., 2004

- Genetic Diversity

- Several nomenclature proposals
    - Yamaguchi: 5 clusters
    - Roques: 3 clades
  - Few sequences available
  - > 10 years old studies



Yamaguchi et al., 2002 (*env* gp160)



Roques et al., 2002 (*env* gp41)



BACKGROUND

**OBJECTIVES & METHODS**

RESULTS




CONCLUSIONS

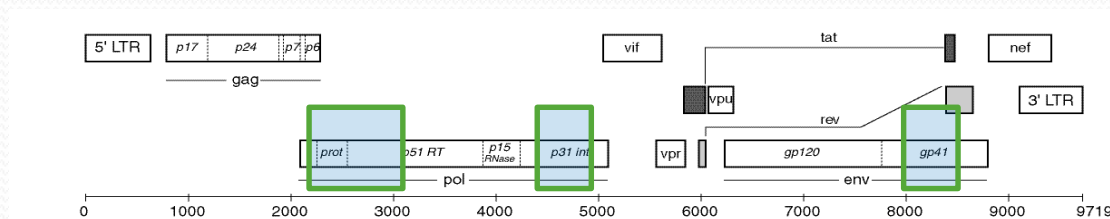
# Objectives:

- Use the largest series of HIV-1/O sequences to:
  - Investigate HIV-1/O genetic diversity in France and in Cameroon
  - Compare and evaluate the previous nomenclature systems
  - Re-estimate the tMRCA of HIV-1/O
  - Investigate the dynamics of HIV-1/O genetic diversity over time
  - Study the phylogenetic distribution of the Y181C resistance mutation



# Methods:

- Samples from 319 patients
  - Time of sampling ranging from year 1987 to 2012
  - In France (N=102)  Cameroon (N=87)  Gabon (N=1) 
- 190 strains were sequenced in three regions



- Concatenated sequences submitted to:
  - Phylogenetic analyses (Maximum Likelihood)
  - Evolutionary analyses (Bayesian inference)



BACKGROUND

OBJECTIVES & METHODS

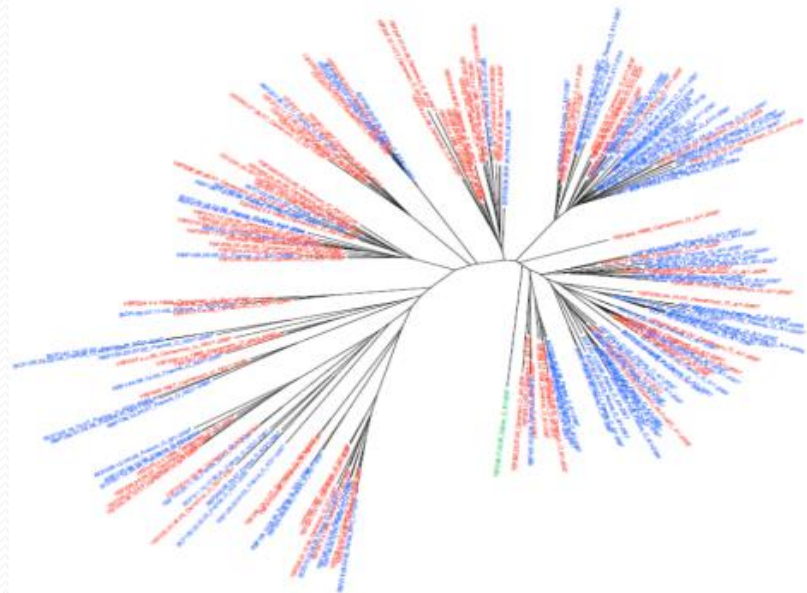
**RESULTS**

CONCLUSIONS

# Results: Country distribution

- Sequences sampled in France or in Cameroon are phylogenetically interspersed:

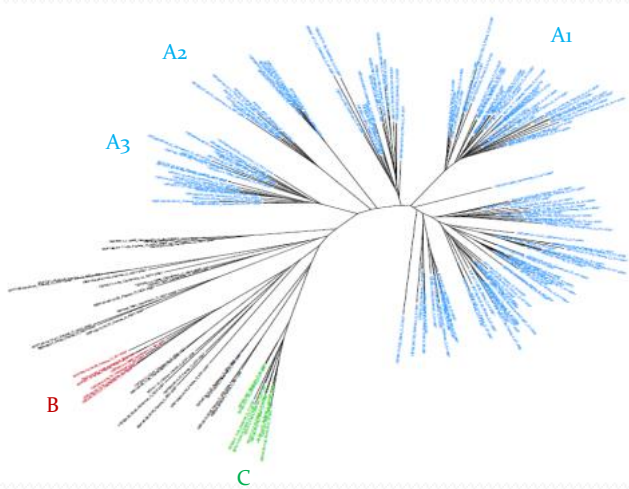
Sampling country:  
**Cameroon**  
France



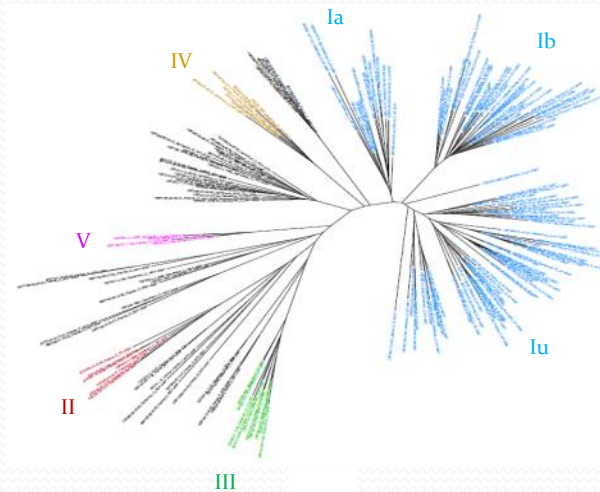
- Continuous strain importations from Cameroon to France rather than local epidemic

# Results: Topology & Nomenclature

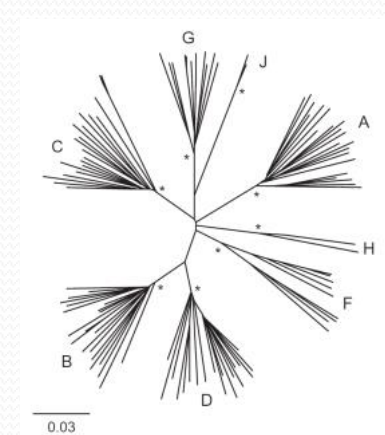
- A continuum of diversity with few clusters
- An asymmetrical shape (comet vs HIV-1/M double star)



Roques et al., 2002 (*env gp41*)



Yamaguchi et al., 2002 (*env gp160*)

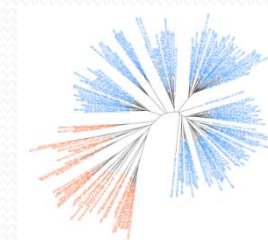
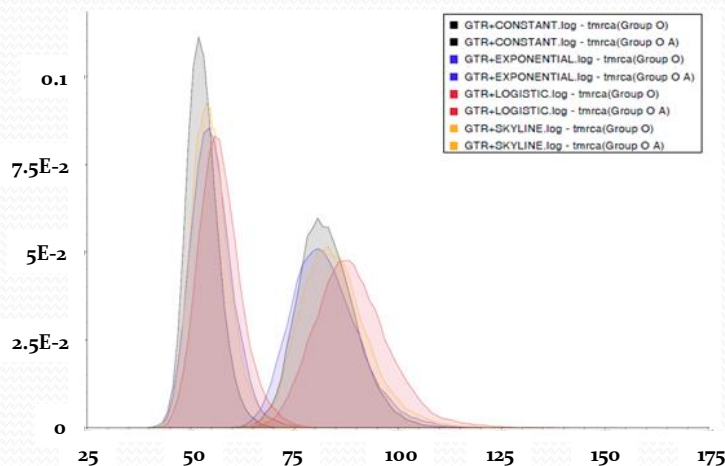


HIV-1/M

- The previous nomenclatures were partially discordant but already shown a predominant clade (A or I : blue)

# Results: MRCA new estimates

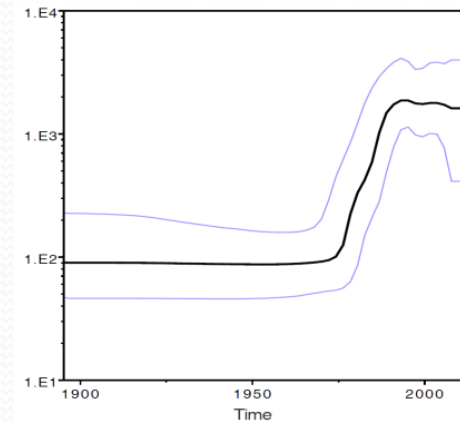
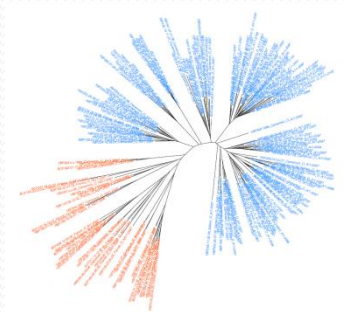
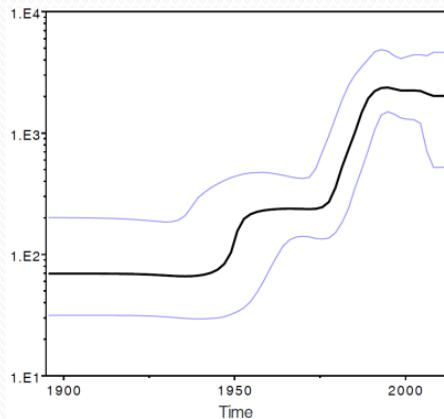
- Dataset = 157 concatenated sequences with a single known sampling time for the 3 regions
  - Several growth models tested gave consistent estimates



- HIV-1/O MRCA around 1930 (95% HPD: 1914 – 1944)
- Predominant clade MRCA around 1945 (1933 – 1955)

# Results: Genetic Dynamics

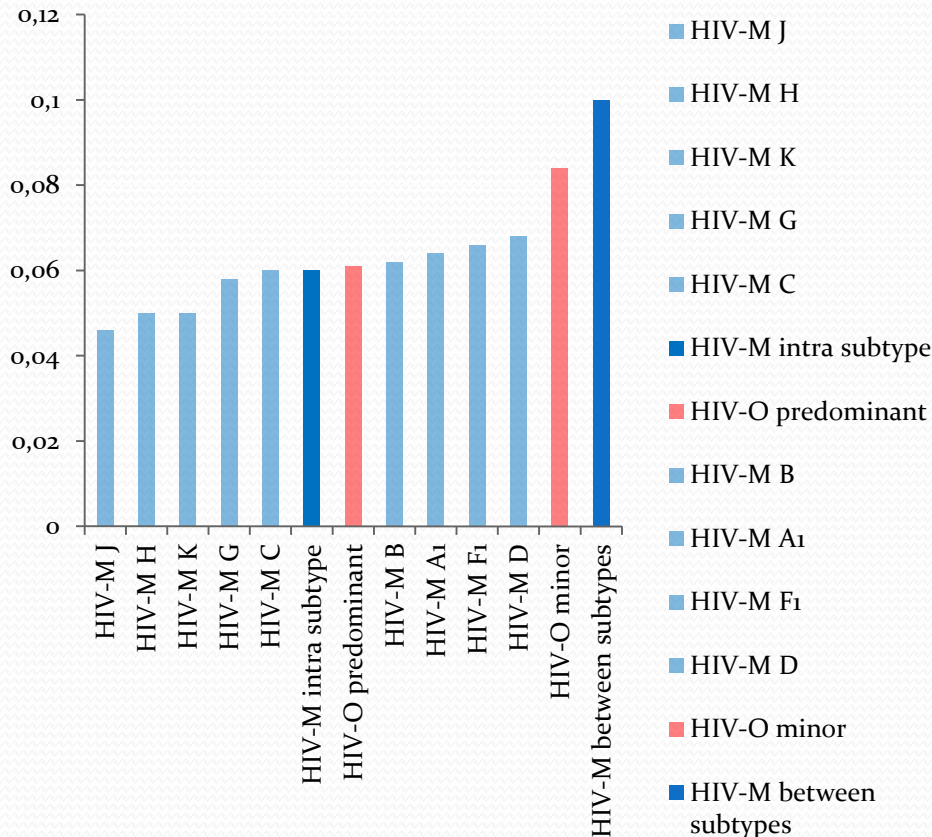
- 2 phases of exponential growth of HIV-1/O genetic diversity
- The predominant clade only displays the 2nd wave



- First one in the 1950's
- Second one, more extensive, in the 1980's
- The predominant clade (blue) emerged in the 1980's from a now minor population (orange)

# Results: comparing the two populations

- Mean pairwise distances



- Mean evolutionary rate

predominant > minor  
 Evolve significantly faster ( $p > 10^{E-5}$ )

- Mean growth rate

predominant > minor  
 Grow significantly faster ( $p > 10^{E-5}$ )

# Results: Distribution of the Y181C mutation in the RT

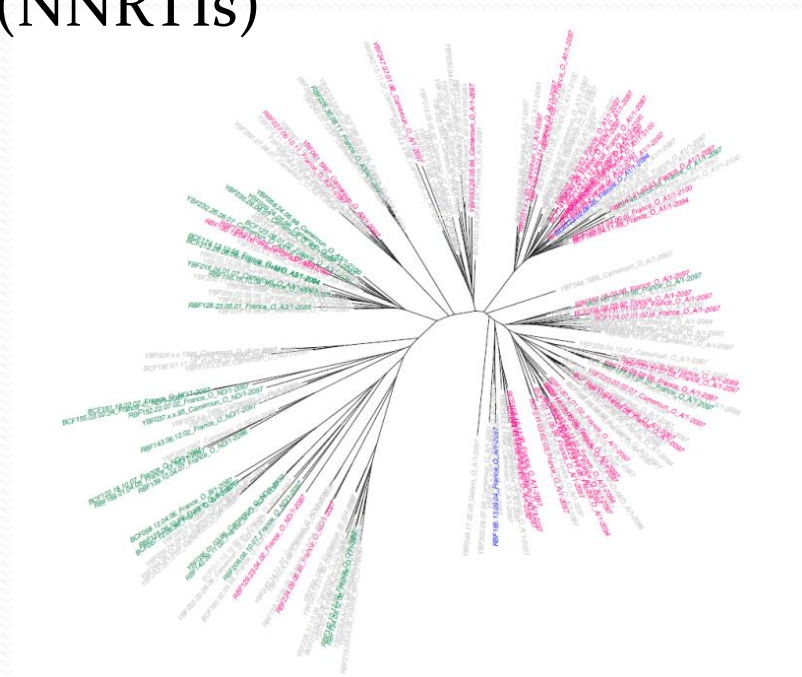
- Confers natural resistance to the Non Nucleotide Reverse Transcriptase Inhibitors (NNRTIs)

Residue in 80  
NNRTI-naive  
patients:

181Y

181C/Y

181C



- Found in 62,5% sequences sampled from NNRTI-naive patients
- Statistically associated to the predominant clade





BACKGROUND

OBJECTIVES & METHODS

RESULTS

**CONCLUSIONS**

# Conclusions: Genetic Diversity

- No local spread of HIV-1/O in France despite some local transmissions and continuous importations
  - Why? HIV-1/M non-B subtypes did
- Broad genetic diversity but few clusters
  - Due to local diversification
  - Previous discordant nomenclatures do not fit
- Existence of a predominant clade
  - Selective advantage?
  - NNRTI resistance mutation Y181C



# Conclusions: Dynamics

- HIV-1/O MRCA around 1930, close to HIV-1/M
  - HIV-1/M originated in Cameroon but only spread in the 1990's
  - Genetic diversity of HIV-1/O reached a plateau in the 1990's
- The predominant population emerged recently, stemming from a first level of ancient genetic diversity
  - What context and/or intrinsic factors involved?
- HIV-1/o still circulate and thus diversify
  - Opportunities for a third wave...?



# Aknowledgements



- **Marie Leoz**

- Laboratoire GRAM EA 2656, Université de Rouen
- Laboratoire de Virologie, CHU de Rouen
- Rouen, France



- **Felix Feyertag**

- Computational and Evolutionary Biology, Faculty of Life Science, University of Manchester  
Manchester, UK



# Aknowledgements

- **CHU de Rouen**



- Marie Leoz
- Fabienne De Oliveira
- Jean-Christophe Plantier

- **Direction Interarmées du Service de Santé**

- Philippe Mauclère

- **APHP CHU Bichat**

- Florence Damond

- **APHP CHU St Louis**

- François Simon



- **University of Manchester**



- Felix Feyertag
- David Robertson

- **Centre Pasteur du Cameroun**



- Jude Kfutwah

*AND ALL THE PATIENTS*