

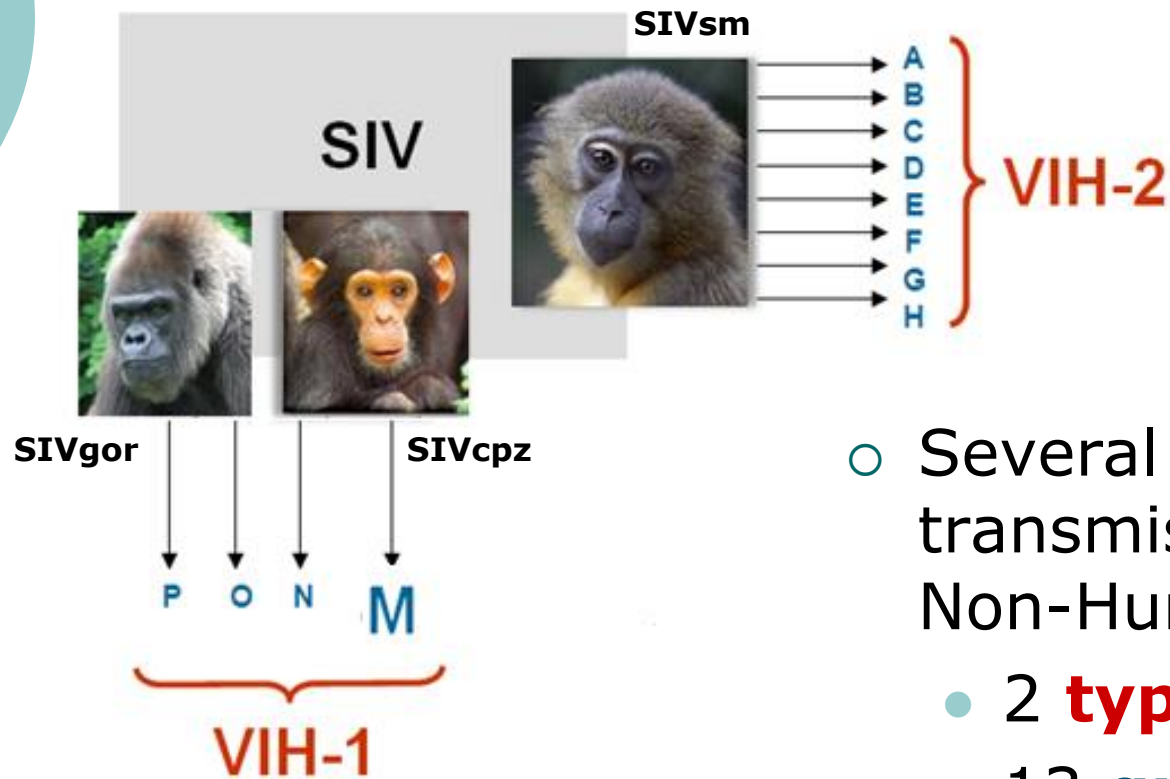


*The Political, Social and Cultural History of the
Emergence of HIV/AIDS in Africa
Workshop Coimbra - Apr, 16th 2015*

THE TWO PHASES OF HIV-1 GROUP O DIVERSIFICATION

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

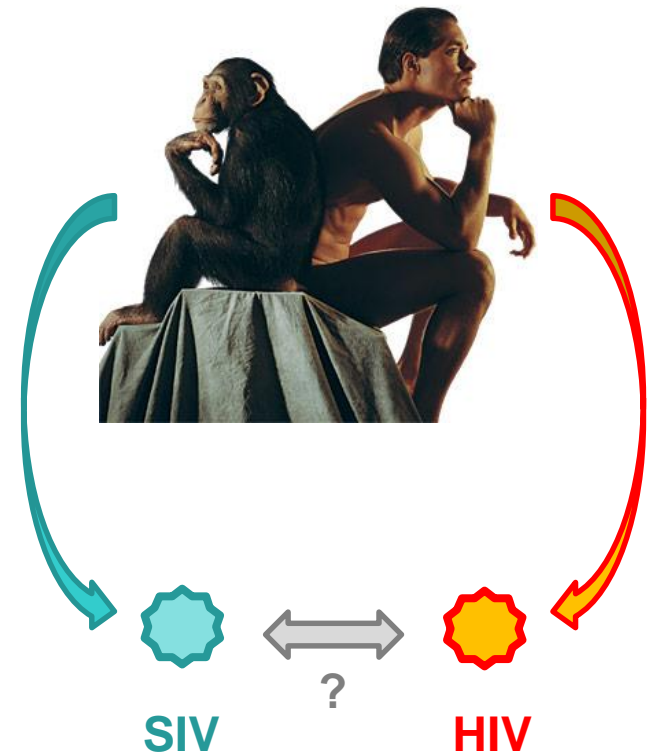
HIV origins in Non Human Primates



- Several cross-species transmissions from Non-Human Primates
 - 2 **types**
 - 13 **groups**

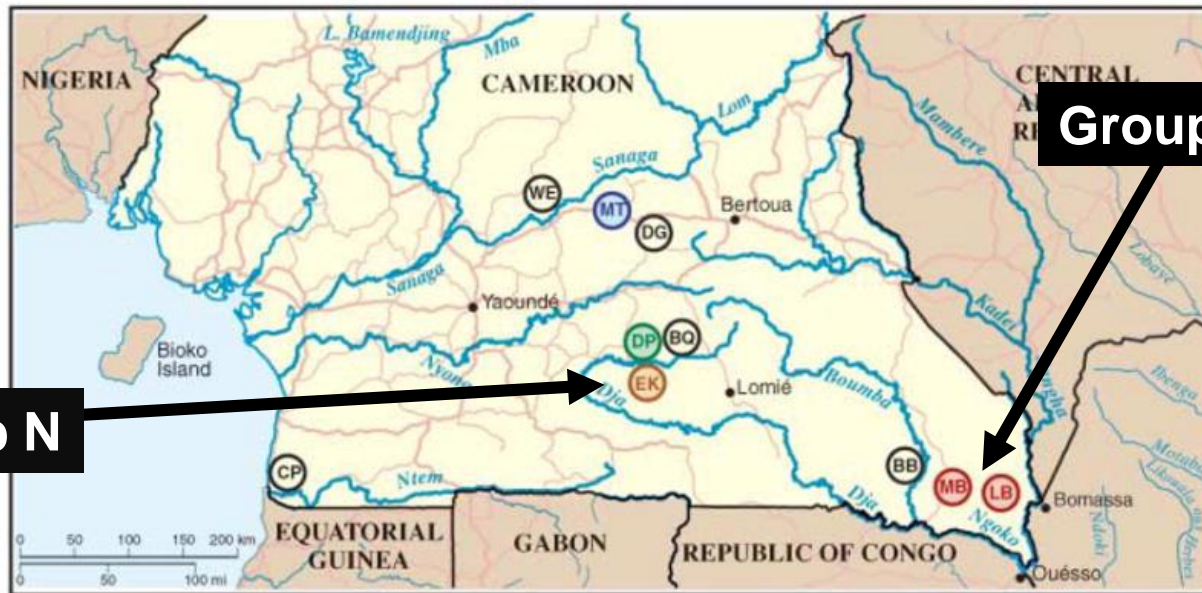
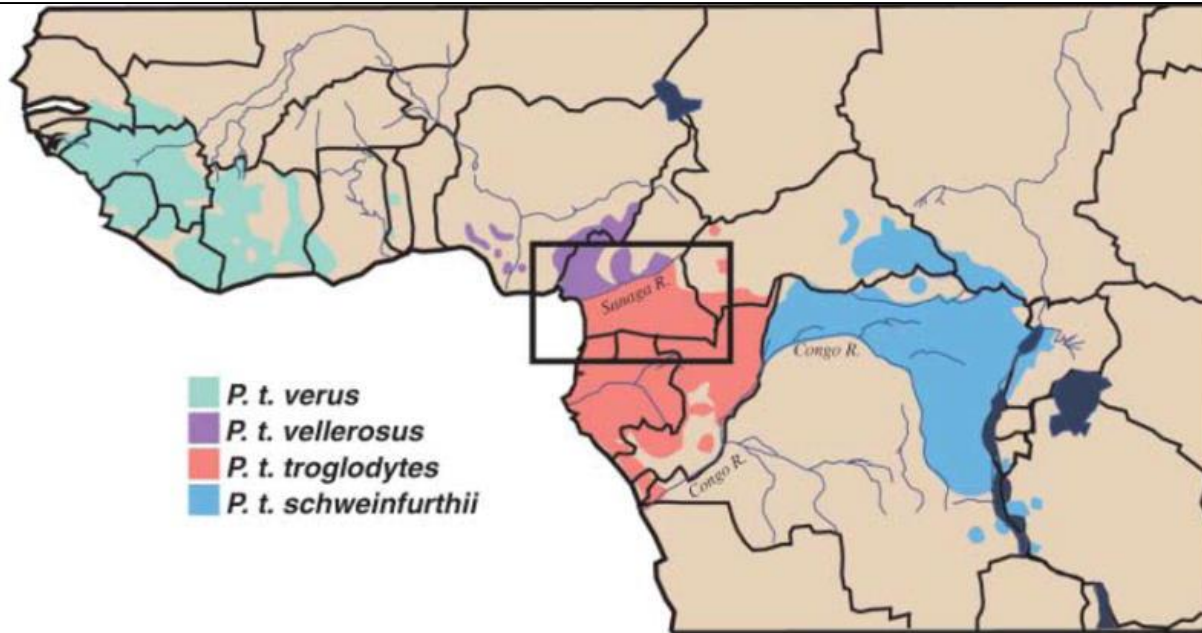
Finding the Simian Ancestors of HIV-1

- Sampling wild living Non Human Primates
- Identifying those SIV-infected
- Comparing the genetic sequence of these SIV to that of HIV



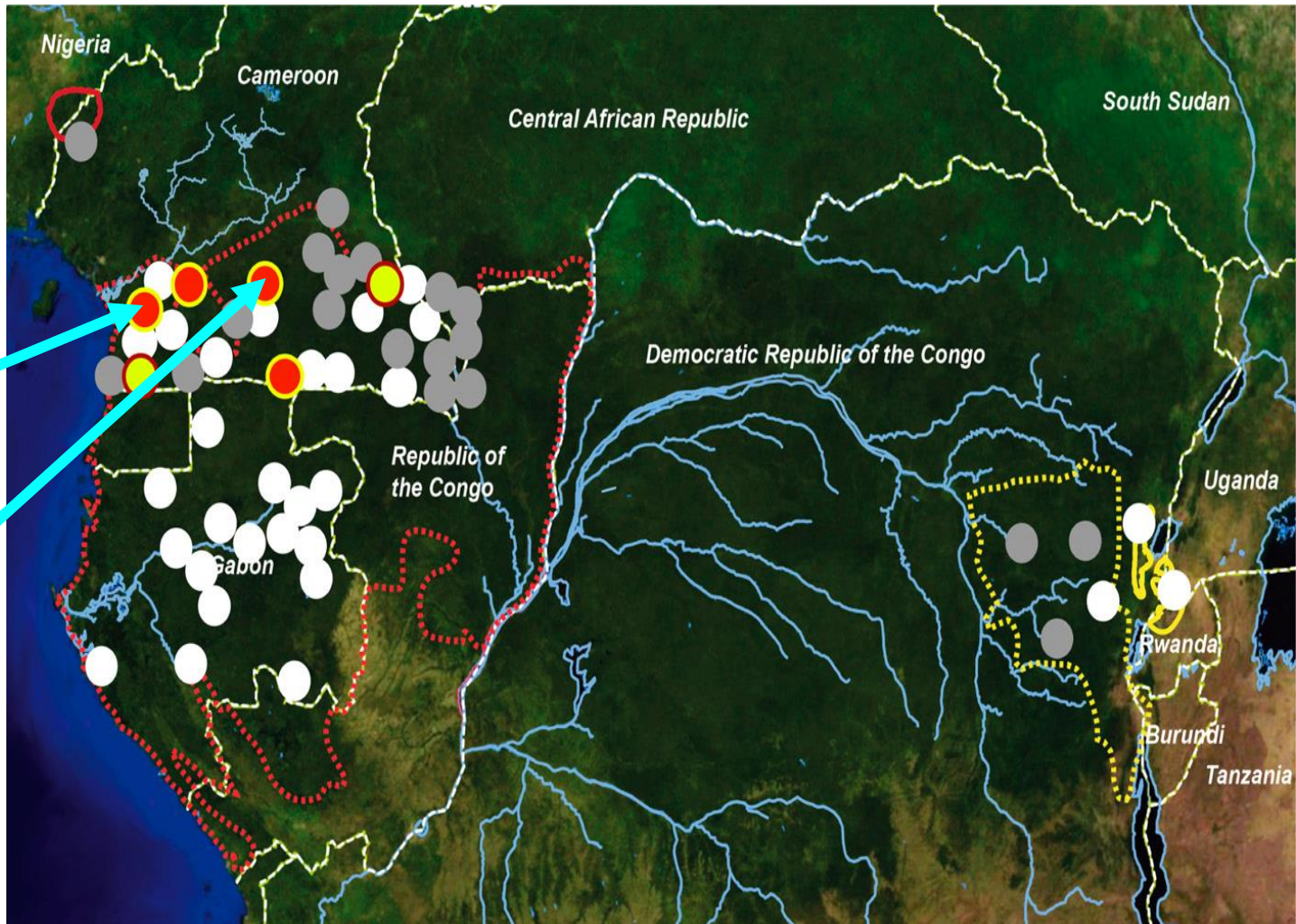
Chimpanzee Reservoirs of Pandemic and Nonpandemic HIV-1

Brandon F. Keele Science 2006



Origin of the HIV-1 group O epidemic in western lowland gorillas

Mirela D'arc PNAS 2015



Group P

Group O

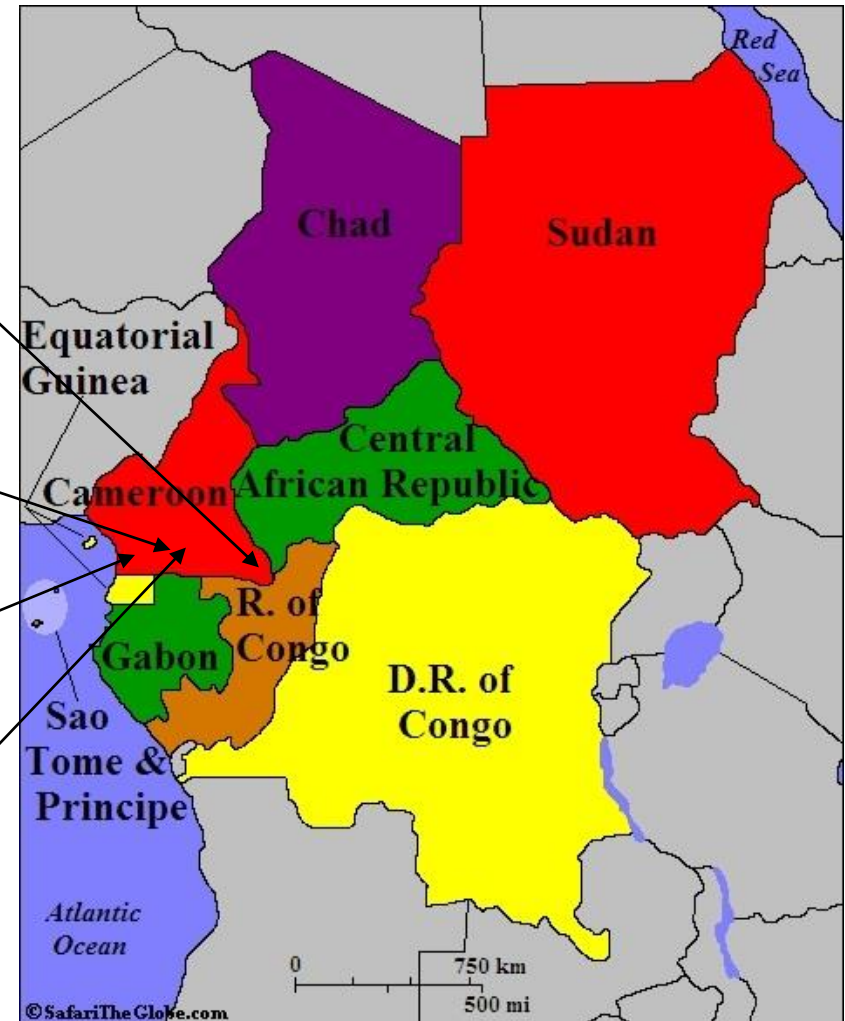
Mapping the Simian Ancestors of HIV-1

SIVcpz > group M

SIVcpz > group N

SIVgor > group P

SIVgor > group O

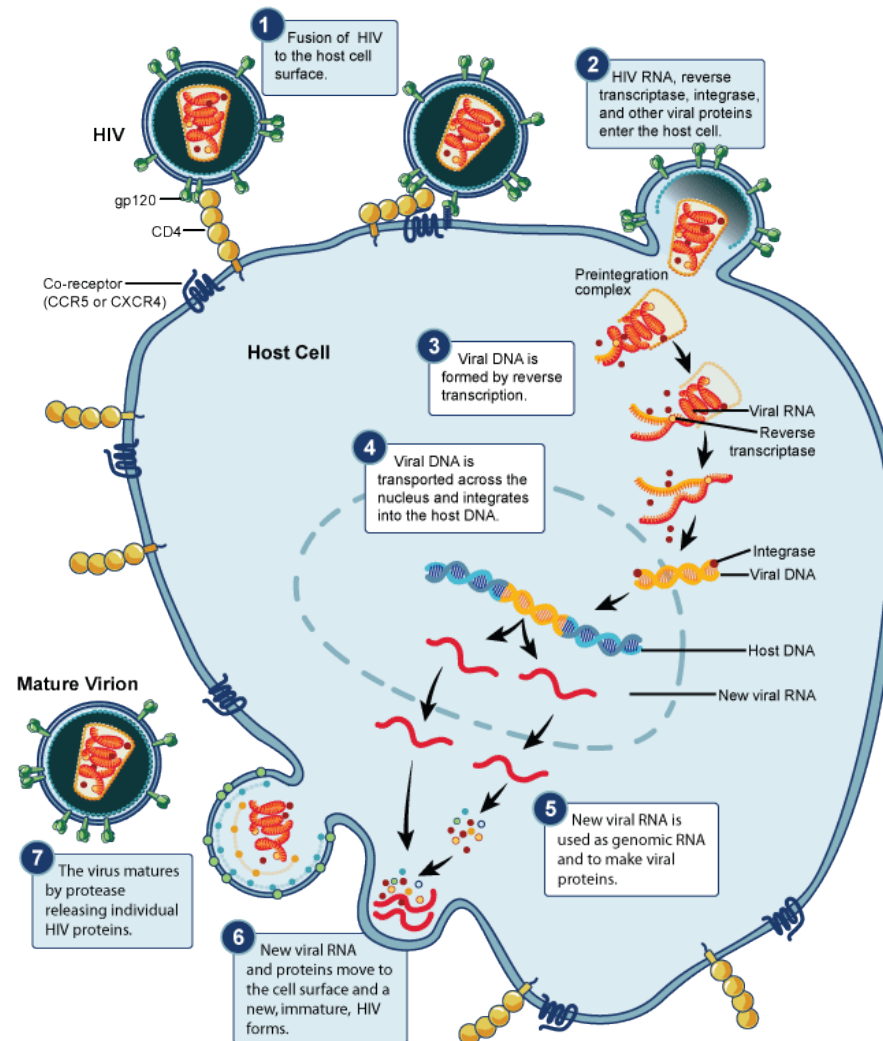


Four groups, one pandemic

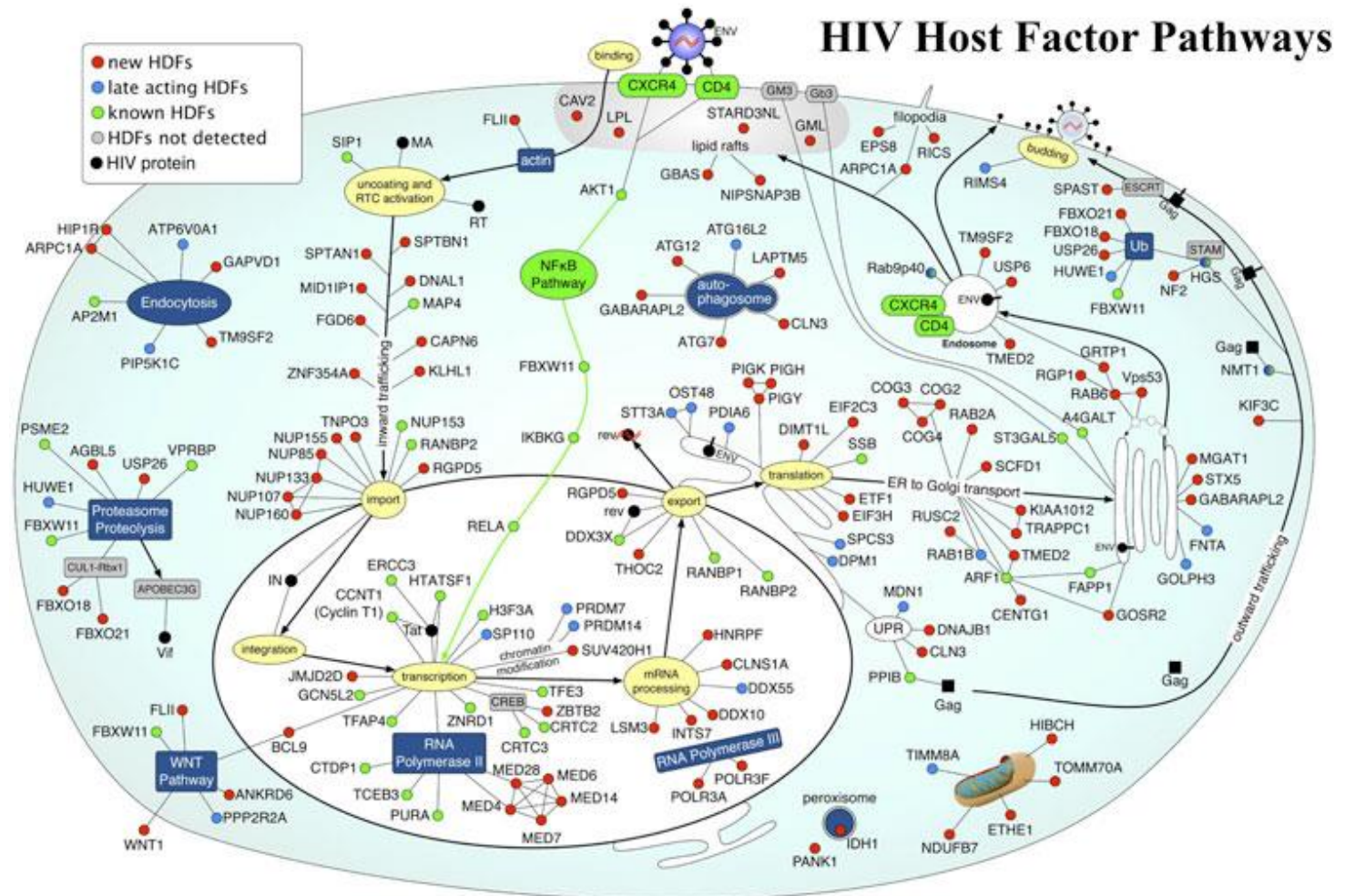
- Group M : pandemic, tens of millions infections worldwide
- Group P : 2 cases identified to date
- Group N : 15 cases identified to date
- Group O : endemic in Cameroon (10,000 to 30,000)



Intrinsic properties – viral fitness

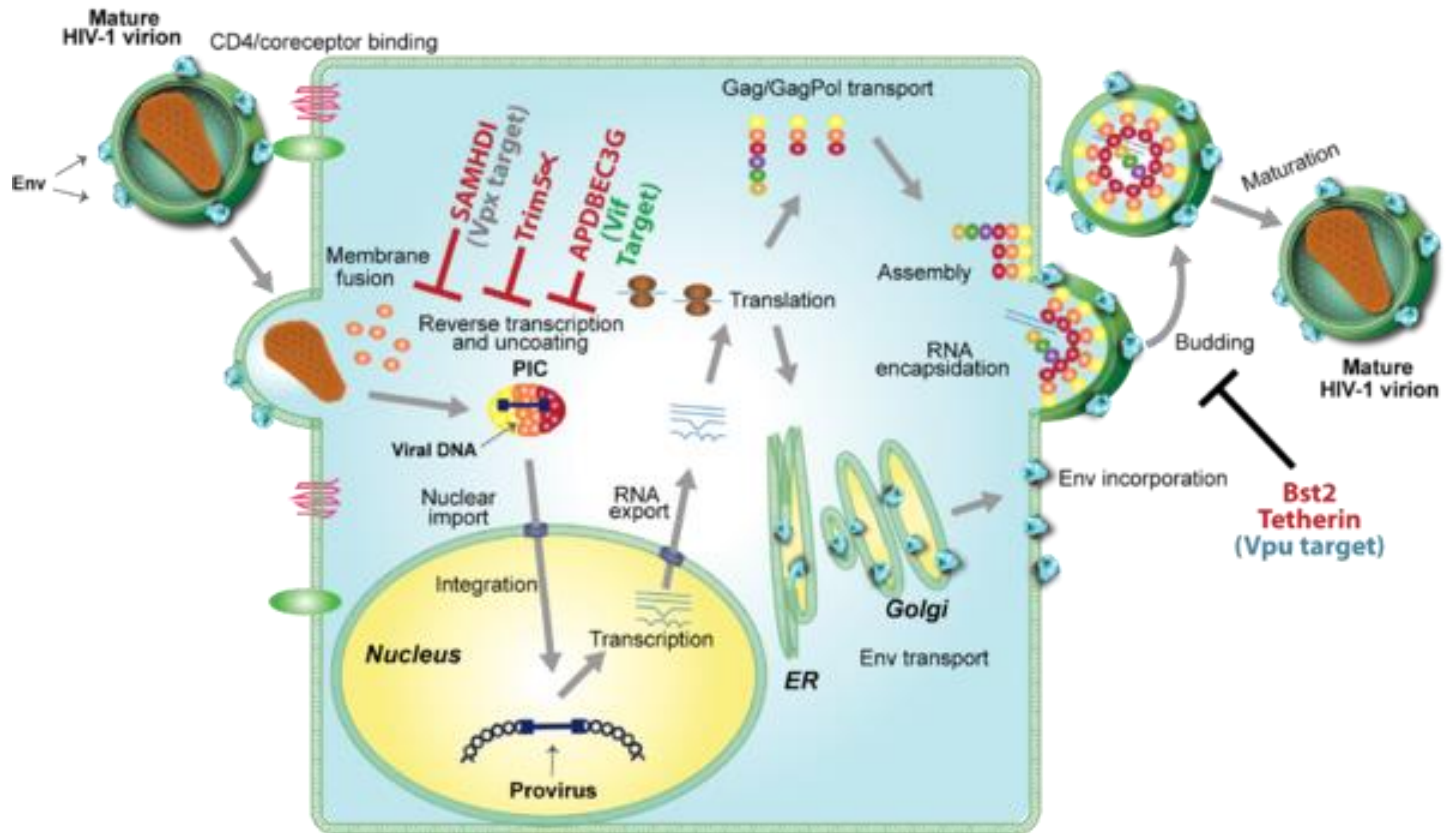


Virus – Host Interactions



Restriction factors

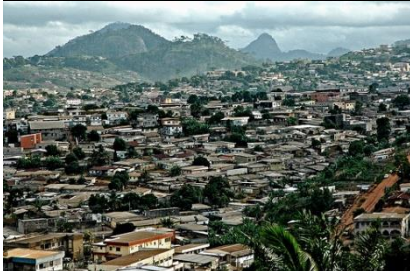
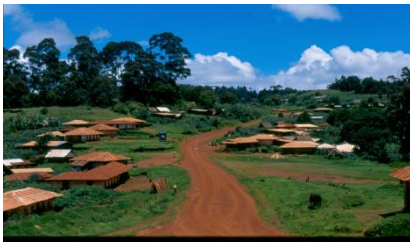
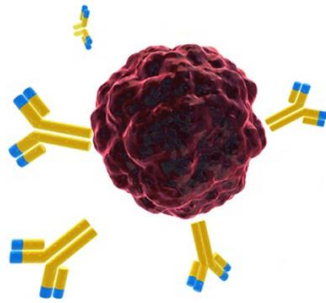
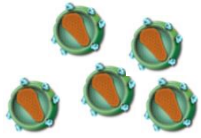
Cellular restriction factors



Viral adaptation to its host: consequences?

- Replication rate
- Viral load (viremia)
HIV-2 < HIV-1
- Pathogenicity (progression to AIDS)
- Transmission rate (Hum to Hum)
- Spread?
HIV-2 > HIV-1 group O

Many factors, many scales



- Intrinsic viral factors
- Host factors
- At risk behaviours
- Epidemiological context
- ... and more!!!

HIV-1 Group O : Epidemiology

- Endemic in Cameroon: 1% of HIV+ samples
 - 1,1% of 7.030 HIV+ samples from Yaounde, 2009 - 2010

J Acquir Immune Defic Syndr. 2010 Jan;53(1):107-10. doi: 10.1097/QAI.0b013e3181b97ec1.

Diagnosis and monitoring of HIV-1 group O-infected patients in Cameroun.

Vessière A¹, Rousset D, Kfutwah A, Leoz M, Depatureaux A, Simon F, Plantier JC.

- 1,0% of 1.469 HIV+ samples from Yaounde, 1996 - 2001

Biological and genetic characteristics of HIV infections in Cameroon
reveals dual group M and O infections and a correlation
between SI-inducing phenotype of the predominant
CRF02_AG variant and disease stage

Laurence Vergne,^a Anke Bourgeois,^a Eitel Mpoudi-Ngole,^b Rose Mougnotou,^b
Josephine Mbuagbaw,^b Florian Liegeois,^a Christian Laurent,^a Christelle Butel,^a
Léopold Zekeng,^c Eric Delaporte,^a and Martine Peeters^{a,*}

HIV-1 Group O : Epidemiology

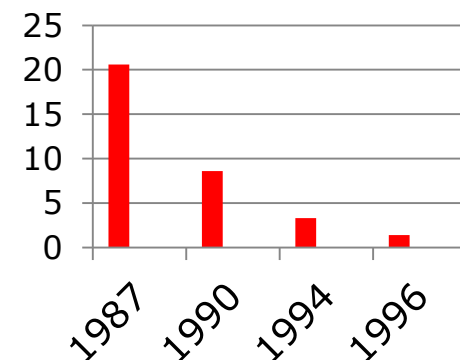
- Drop of relative Group O prevalence among HIV+ samples in the early 1990's

HIV-1 Group O Infection in Cameroon, 1986–1998

Ahidjo Ayouba,* Philippe Maucière,* Paul M.V. Martin,*
Patrick Cunin,* Jermie Mfoupouendoun,* Bernadette Njinku,*
Sandrine Souquière,† and François Simon†

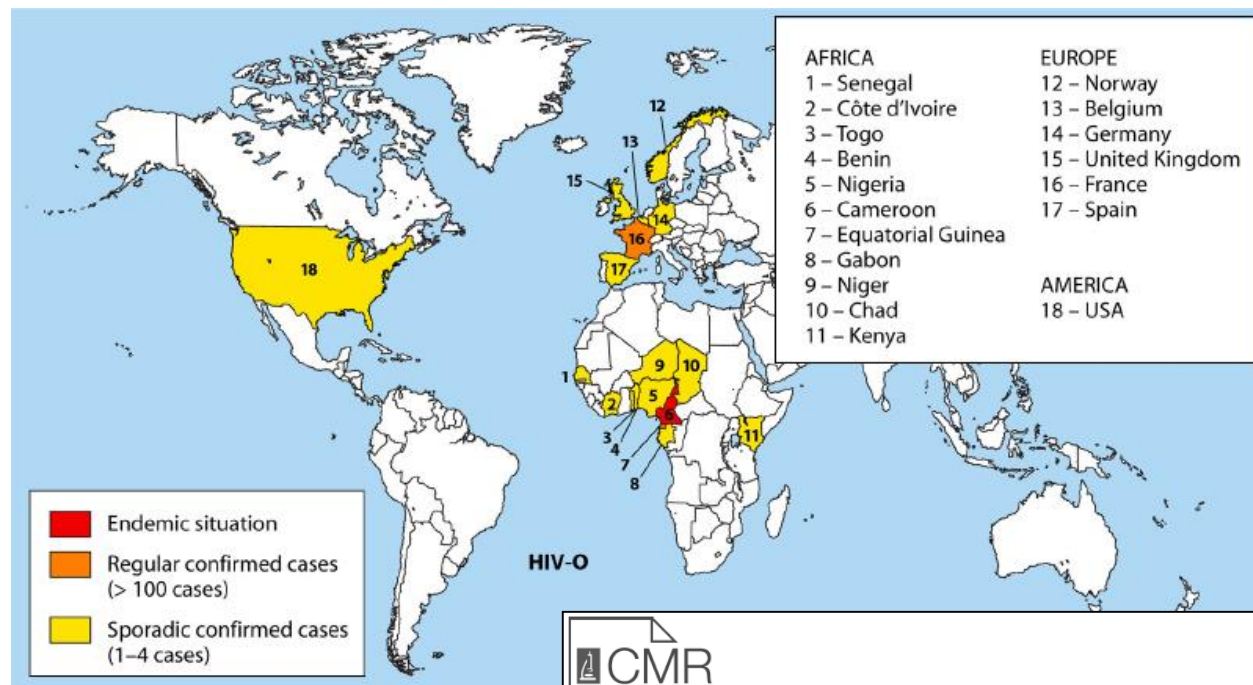
Table 2. Differentiation into group M and O of HIV-1 positive samples, 1986–1998

Periods	No. of samples	HIV-1/M (%)	HIV-1/O (%)
1986-1988	301	239 (79.4)	62 (20.6)
1989-1991	625	571 (91.4)	54 (8.6)
1994-1995	2,458	2,376 (96.7)	82 (3.3)
1997-1998	4,160	4,100 (98.6)	60 (1.4)
Total	7,544	7,286 (96.6)	258 (3.4)



HIV-1 Group O : Epidemiology

- Also found in some geographically or historically linked countries



HIV-1 Group O : Epidemiology

- Oldest HIV-1 group O infection ever reported: Norway in the 1960's

VIROLOGY 231, 43–47 (1997)
ARTICLE NO. VY978510

Sequence Analysis of HIV-1 Group O from Norwegian Patients Infected in the 1960s¹

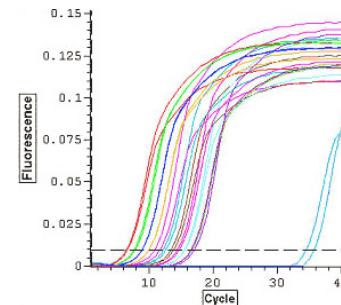
Tom Ø. Jonassen, Kathrine Stene-Johansen, Einar S. Berg, Olav Hungnes, Christian F. Lindboe,*
Stig S. Frøland,† and Bjørn Grinde²

- In France: 142 patients identified since 1992
 - Survey network : RES-O



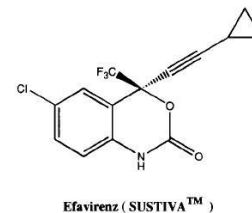
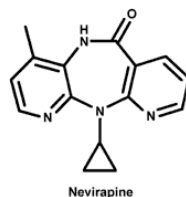
Group O infections: diagnosis, follow up and treatment?

- High divergence between HIV-1/M and HIV-1/O
- Assays designed to detect group M can be less sensitive
 - Impact on serodiagnosis and viral load quantitation

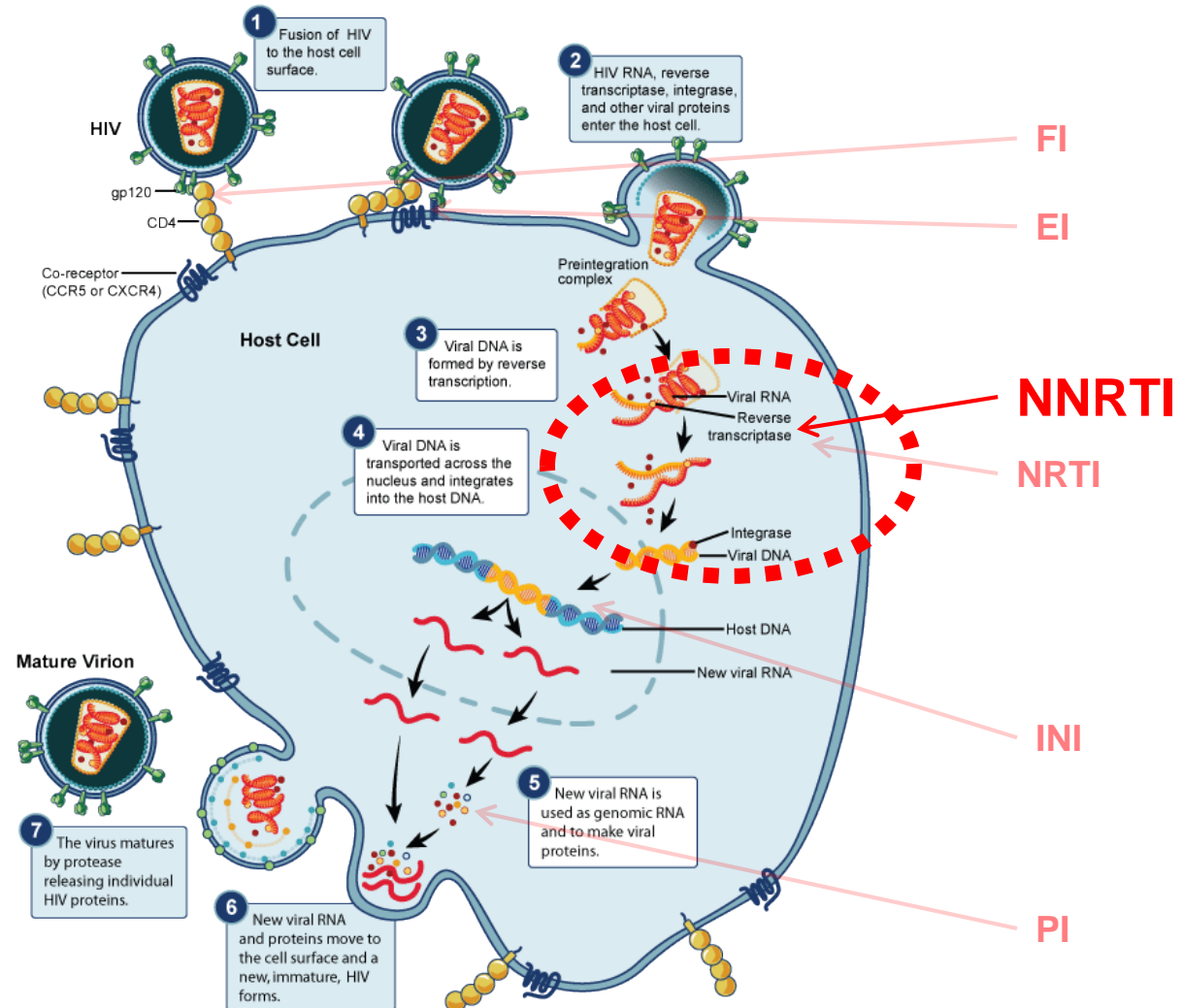


Group O infections: diagnosis, follow up and treatment?

- Non-specific tools: group O is detected but not identified as such
- 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

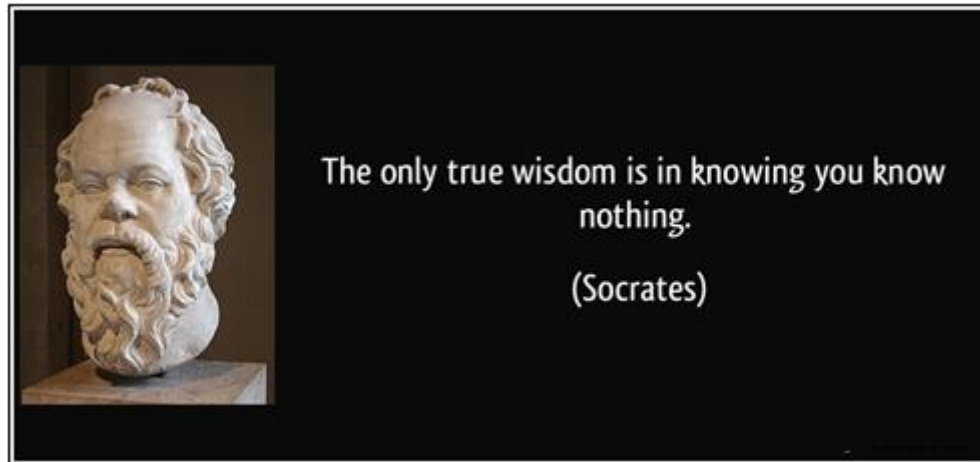


Reverse transcriptase



HIV-1 Group O Diversity and Evolution

- What evolution dynamics?
- What factors involved?



- No exhaustive sequential testing
- No prevalence data before the 1980's

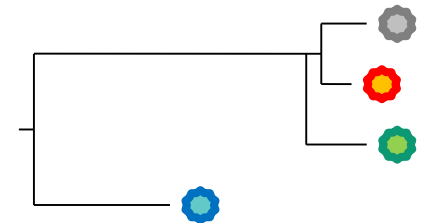
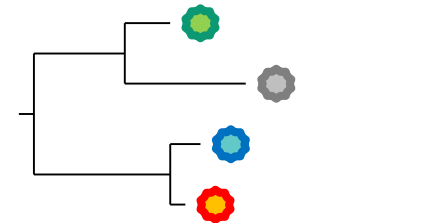
Data, tools, and hypotheses

 **ATCGATCGATCG**

 **TTCGAACGATCC**

 **TACGTACGATTC**

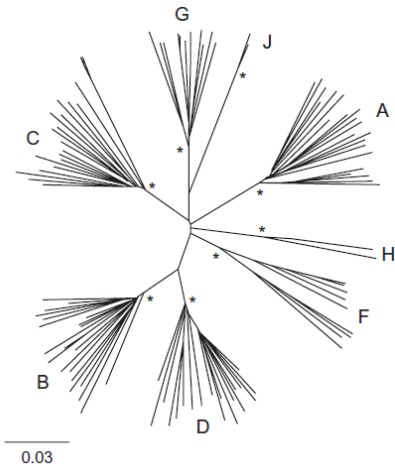
 **GACTTACCATGC**



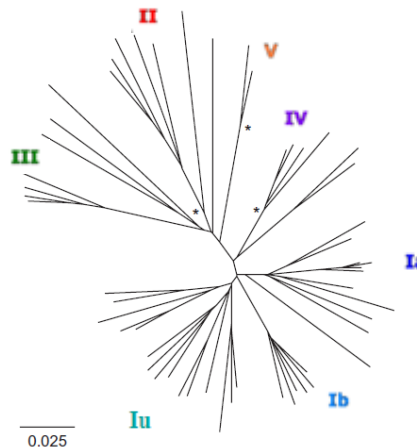
(...)
(....!)
(.....!!!)
(.....!!!!)
(.....!!!!!)

Group O genetic diversity: background

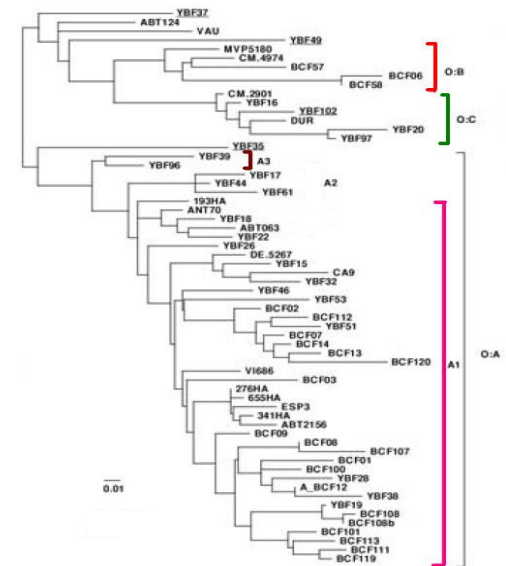
- Several nomenclature proposals
 - Yamaguchi: 5 clusters
 - Roques: 3 clades
- Few sequences available
- > 10 year old studies



HIV-1 Group M
Archer et al., 2007 (*env* gp160)



HIV-1 Group O
Yamaguchi et al., 2002 (*env* gp160)



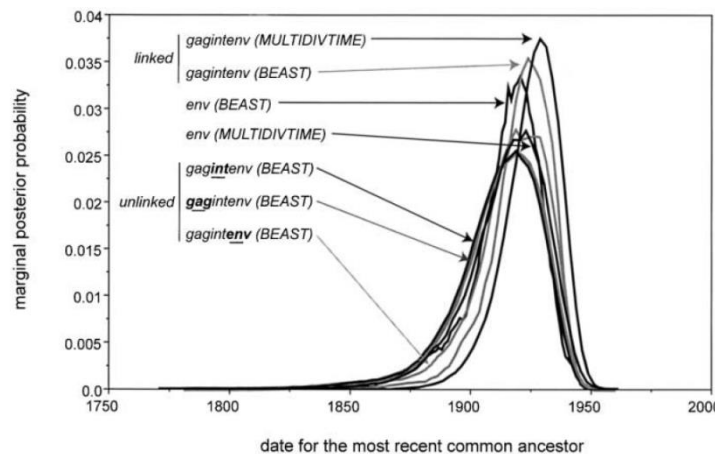
HIV-1 Group O
Roques et al., 2002 (*env* gp41)

Group O tMRCA: background

- Most Recent Common Ancestor (MRCA) estimated to have existed around 1920 (1890 – 1940)

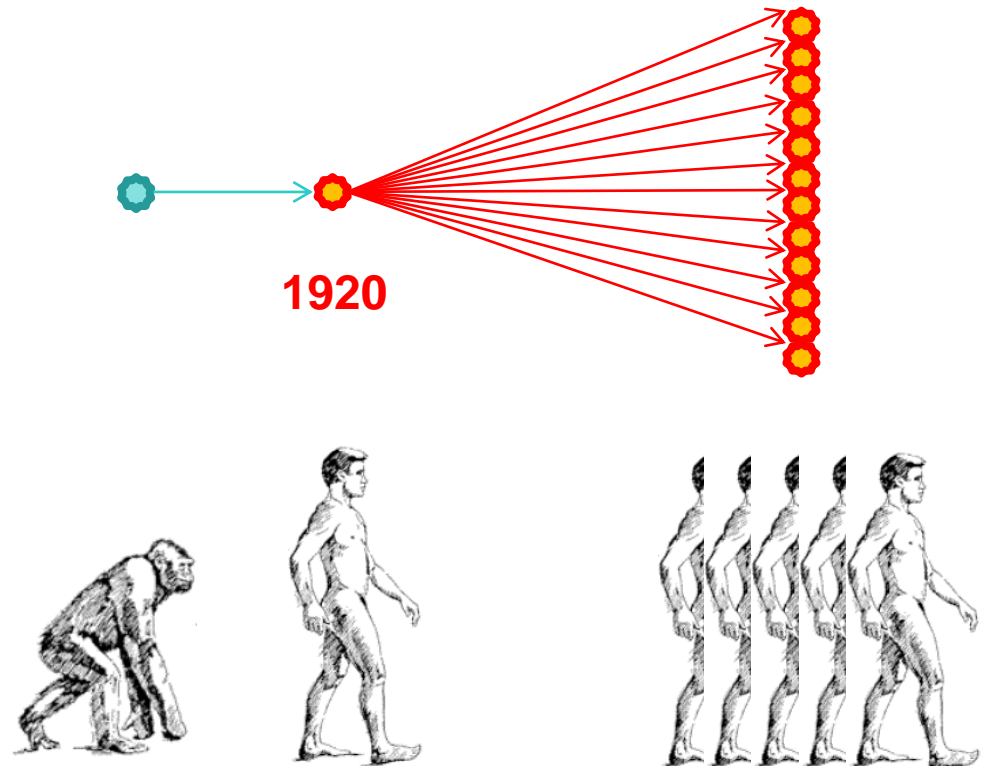
The Molecular Population Genetics of HIV-1 Group O

Philippe Lemey,^{*,1} Oliver G. Pybus,[†] Andrew Rambaut,[†] Alexei J. Drummond,[†]
David L. Robertson,[‡] Pierre Roques,^{§,**} Michael Worobey,^{††}
and Anne-Mieke Vandamme^{*}



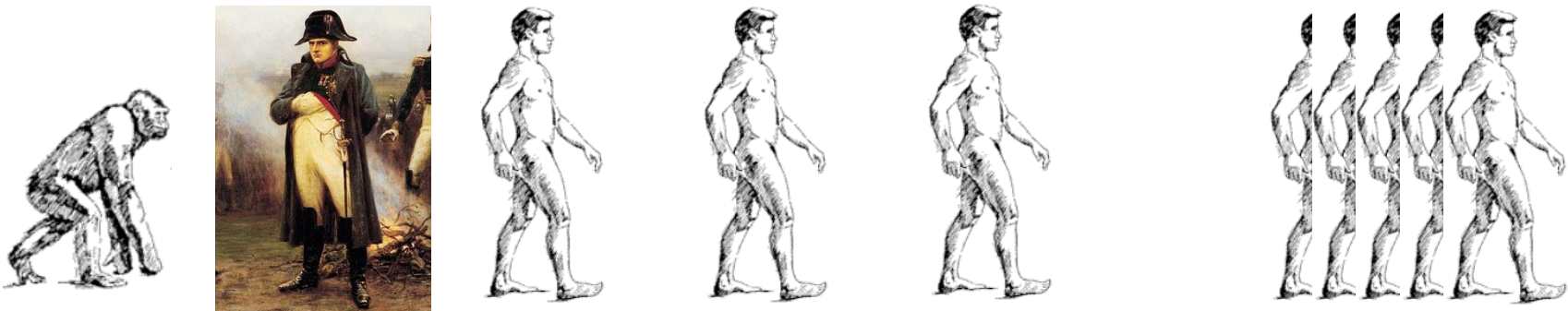
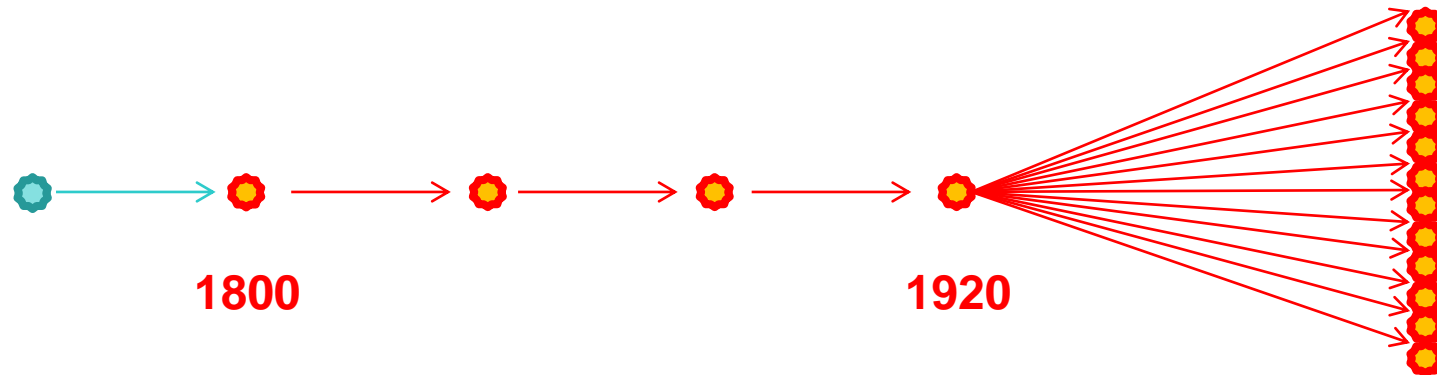
Group O tMRCA: background

- Most Recent Common Ancestor (MRCA) in 1920 **does not mean** crossing the barrier species in 1920

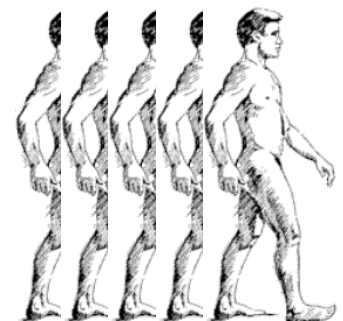
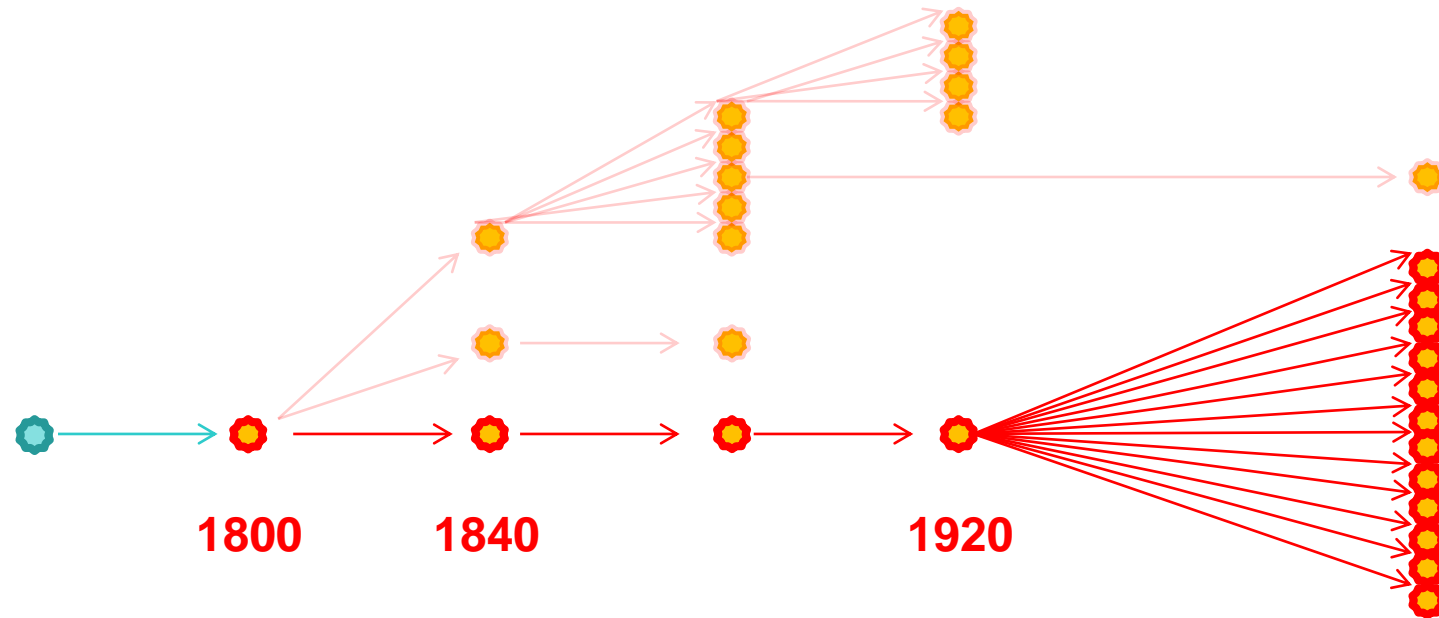


Group O tMRCA: background

- **Most Recent** Common Ancestor (MRCA) in 1920 rather means crossing the barrier species in 1920 or before

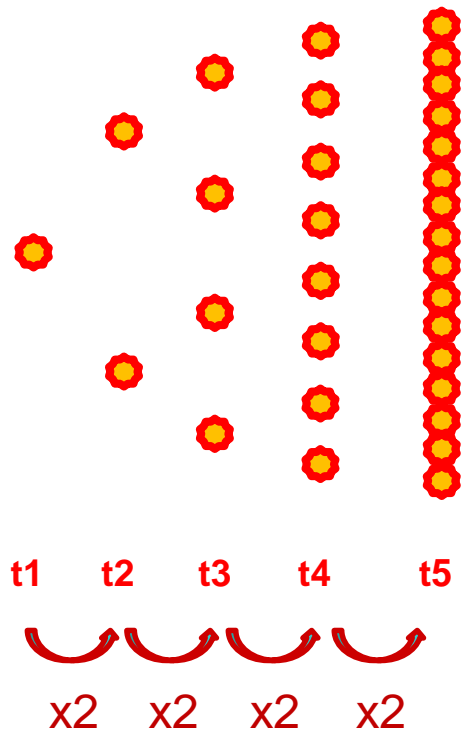


Group O tMRCA: background

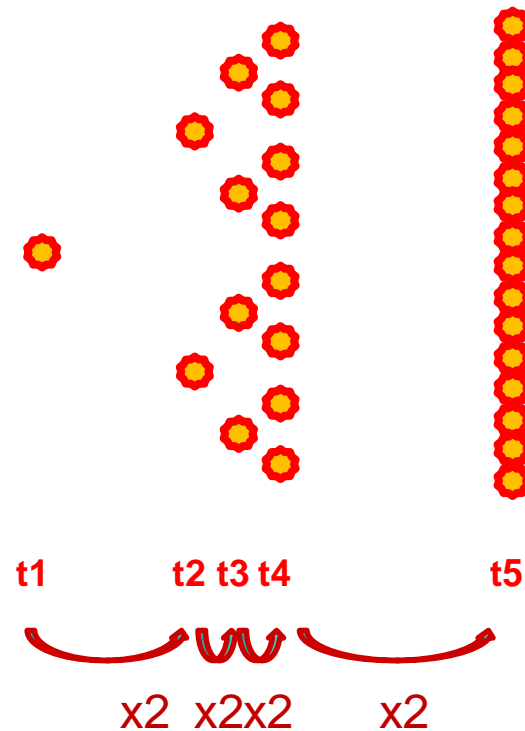


Group O dynamics: background

Exponential growth



Viral population dynamics?



Group O dynamics: background

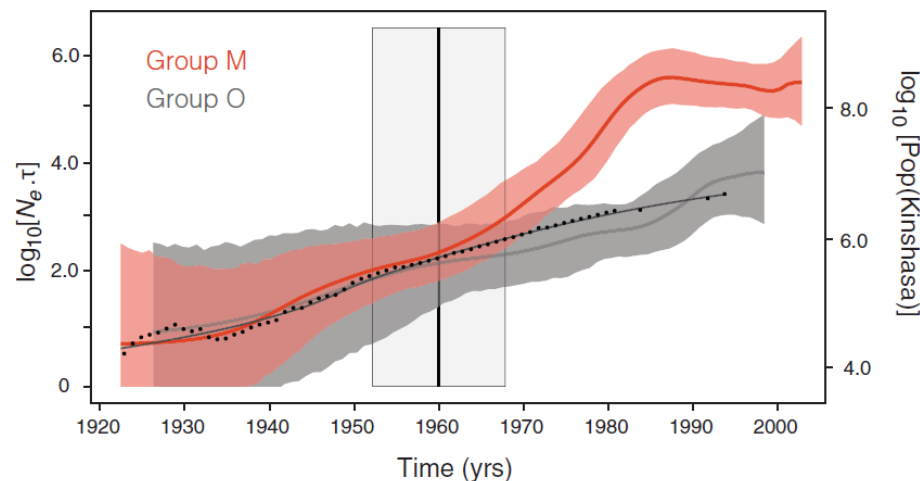
- *'The effective number of Group O infections has been increasing exponentially with a slower growth rate than group M'*

The Molecular Population Genetics of HIV-1 Group O

Philippe Lemey,^{*,1} Oliver G. Pybus,[†] Andrew Rambaut,[†] Alexei J. Drummond,[†]
David L. Robertson,[‡] Pierre Roques,^{§,**} Michael Worobey,^{††}
and Anne-Mieke Vandamme^{*}

The early spread and epidemic ignition of HIV-1 in human populations

Nuno R. Faria *et al.*
Science **346**, 56 (2014);






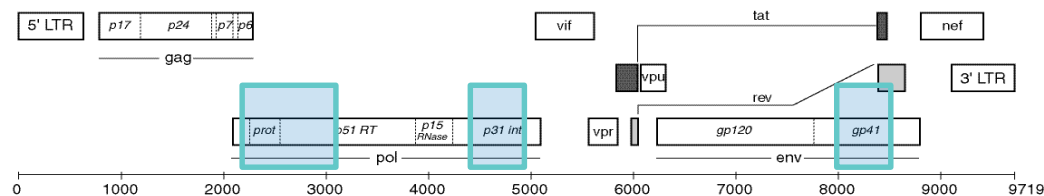


Objectives of the study

- 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 190 patients
 - Time of sampling ranging from year 1987 to 2012
 - In France (N=102) 
 - Cameroon (N=87) 
 - Gabon (N=1) 
- Sanger sequencing in three genome regions

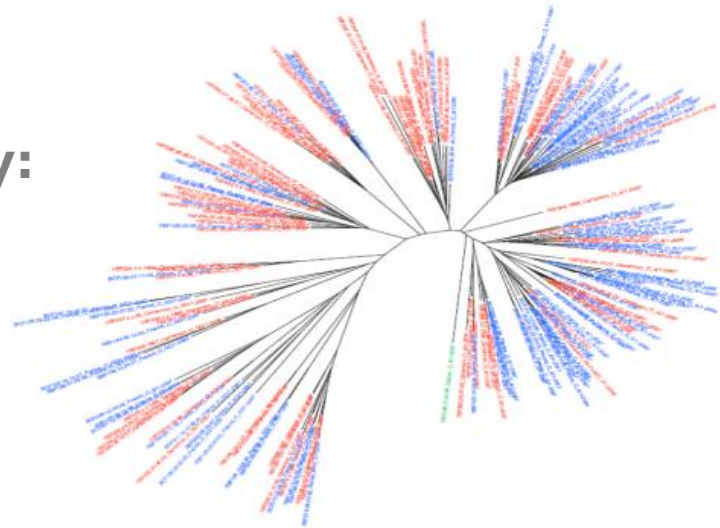


- Concatenated sequences submitted to:
 - Phylogenetic analyses (Maximum Likelihood)
 - Evolutionary analyses (Bayesian inference)

Results: Country distribution

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

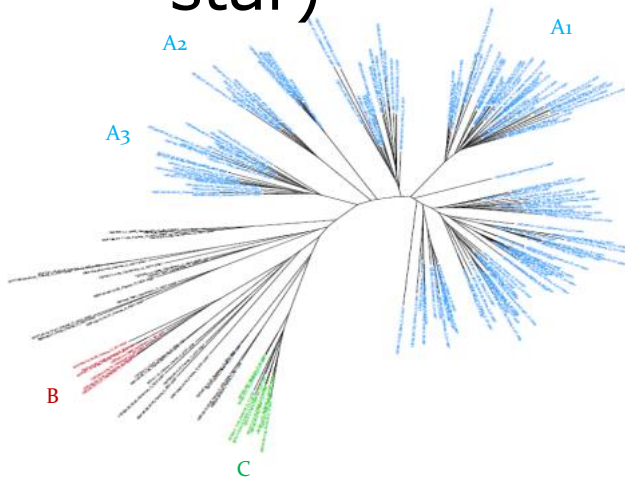
Sampling country:
Cameroon
France



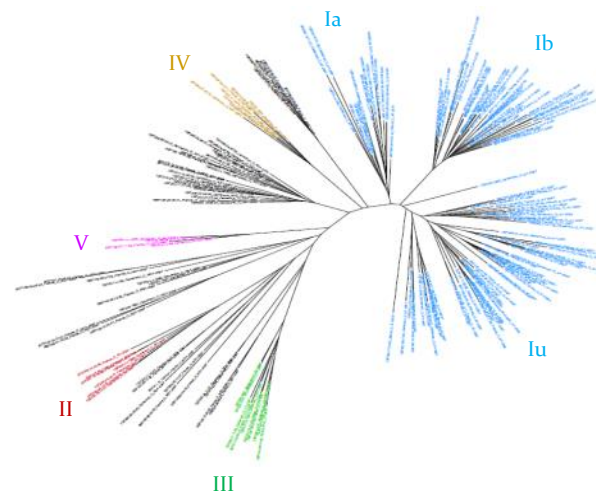
- Continuous strain importations from Cameroon to France rather than local epidemic

Results: Topology & Nomenclature

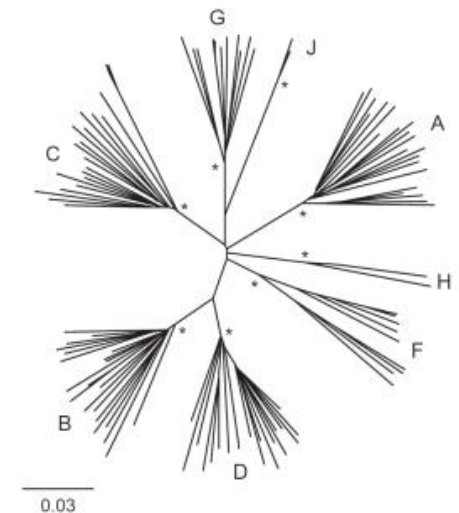
- A continuum of diversity with few clusters
- An asymmetrical shape (comet vs HIV-1/M double star)



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



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

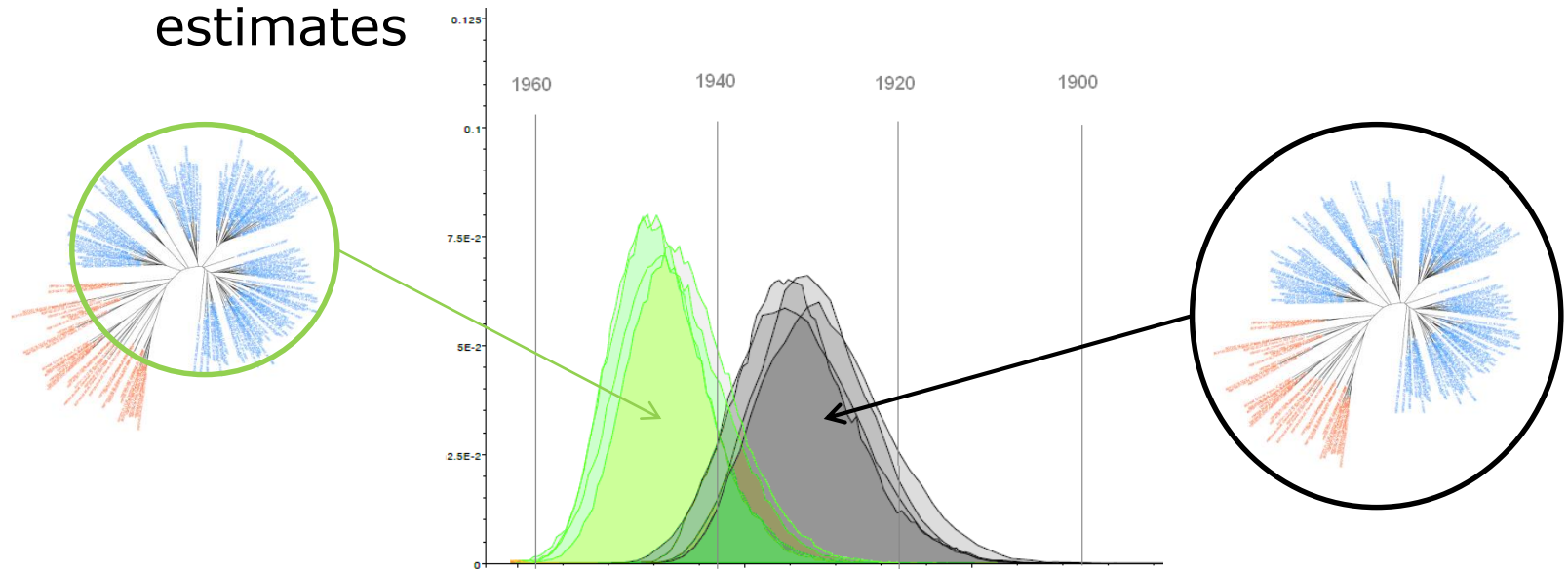


HIV-1/M

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

Results: MRCA new estimates

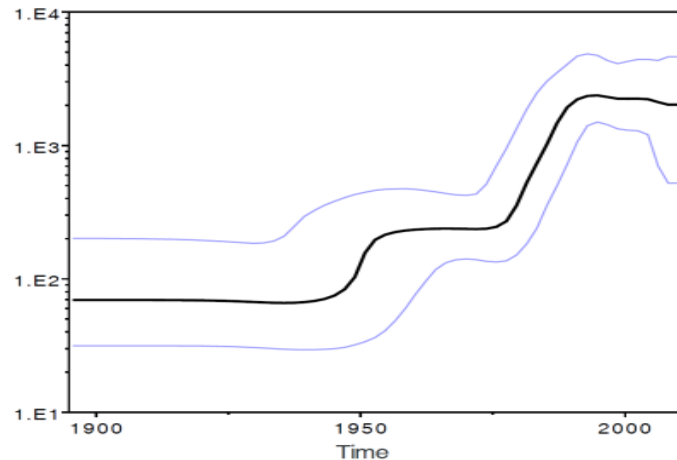
- Dataset = 157 concatenated sequences with a single known sampling time for the 3 regions
 - Several growth models tested gave consistent estimates



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

Results: Population Dynamics

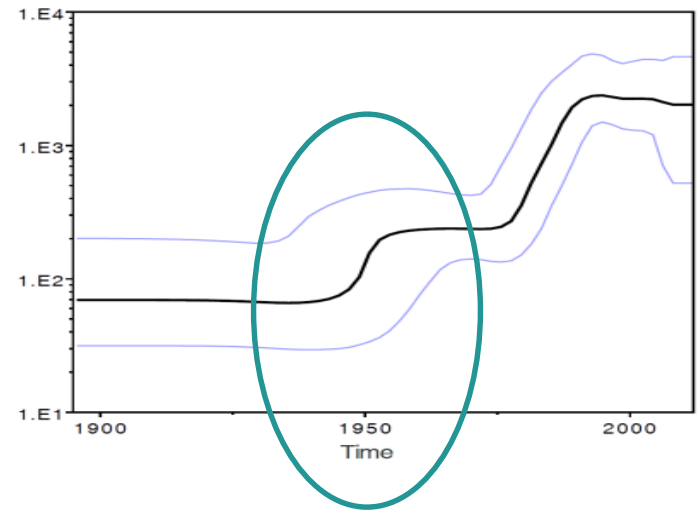
- 2 phases of fast exponential growth of HIV-1/O genetic diversity



- First one in the 1950's
- Second one, more extensive, in the 1980's

Results: Population Dynamics

- What factors involved?



Hepatitis C Virus Infection in Cameroon: A Cohort-Effect

Eric Nerrienet,^{1*} Régis Pouillot,¹ Guillaume Lachenal,² Richard Njouom,¹ Jermie Mfoupouendoun,¹
Catherine Bilong,¹ Philippe Mauciere,¹ Christophe Pasquier,³ and Ahidjo Ayouba¹

¹Centre Pasteur du Cameroun, Yaoundé, Cameroun

²Laboratoire d'Histoire des Sciences (REHSEIS), CNRS-Université Paris VII, Paris, France

³Laboratoire de virologie, CHU de Toulouse Purpan, Toulouse, France

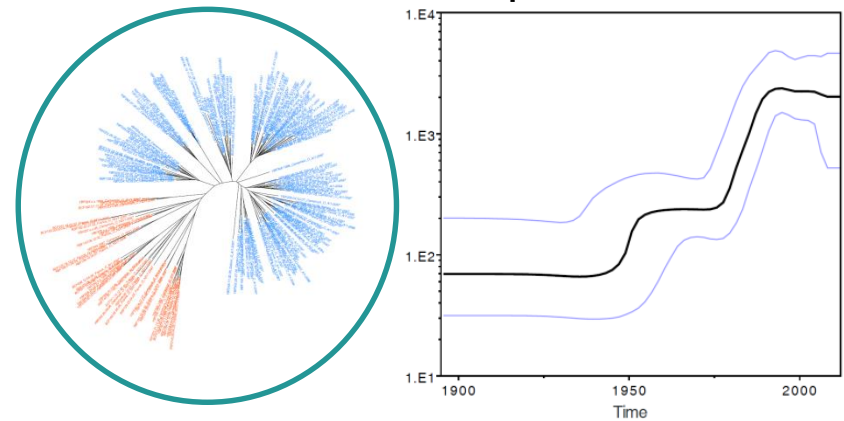
- *'Parenteral infection on the occasion of mass medical campaigns during the 1920 to 1960 period is the most likely explanation'*

Results: Population Dynamics

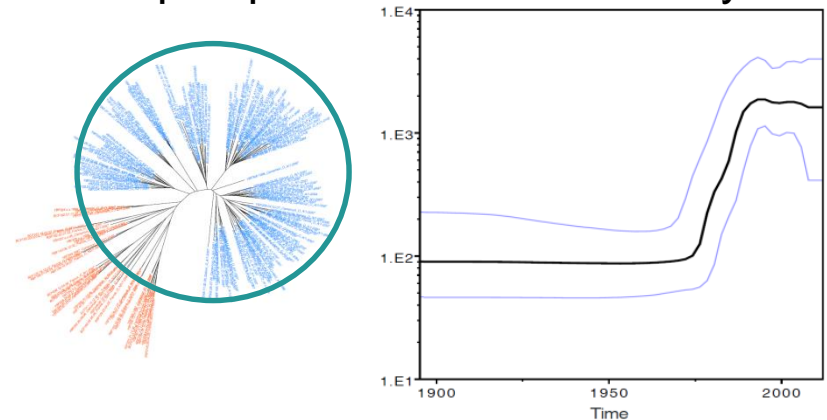
The predominant clade (blue) only displays the 2nd fast growth phase

- The predominant clade emerged in the 1980's from a now minor population (orange)

Overall Group O



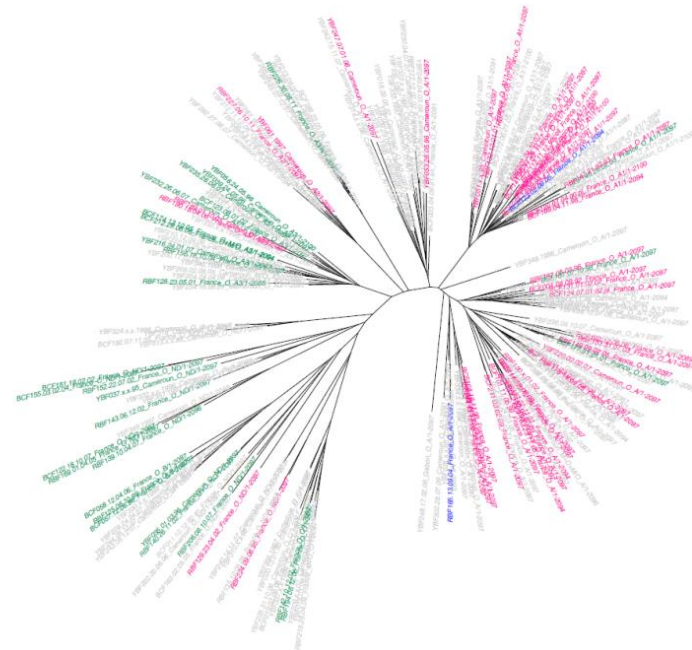
Group O predominant clade only



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

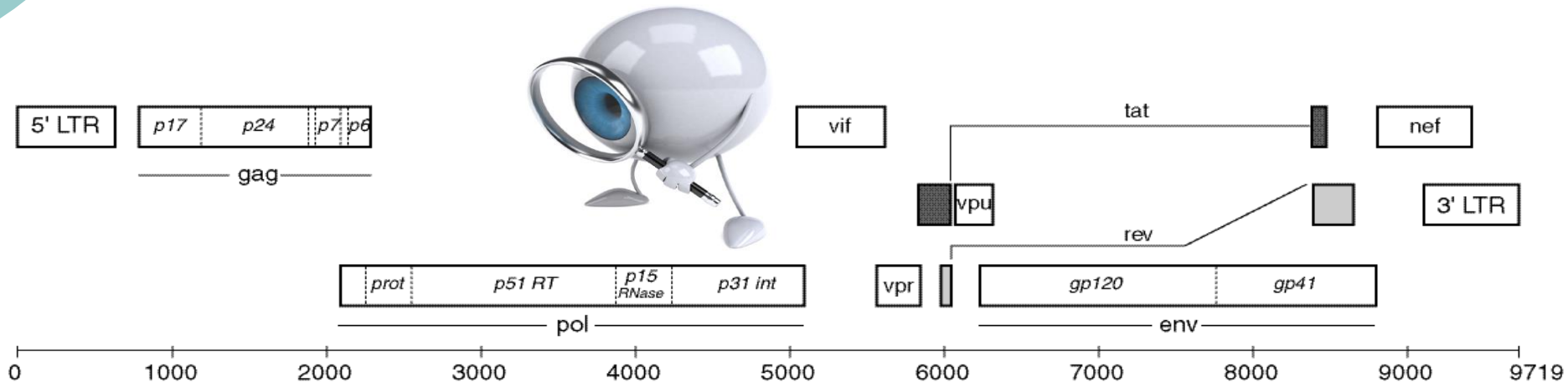


- Found in 62,5% sequences sampled from NNRTI-naive patients
- Statistically associated to the predominant clade

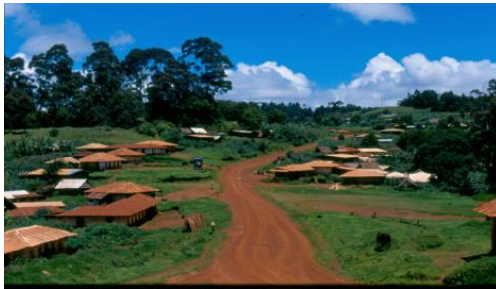
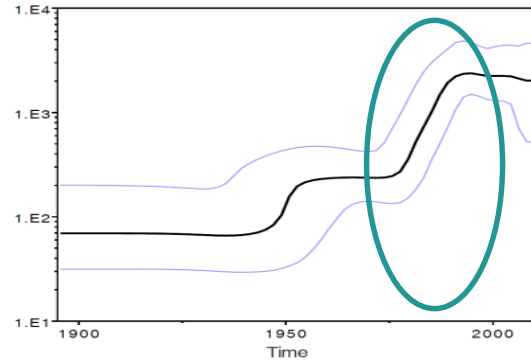
Results: Distribution of the Y181C mutation in the RT

Divergent Evolution in Reverse Transcriptase (RT) of HIV-1 Group O and M Lineages: Impact on Structure, Fitness, and Sensitivity to Nonnucleoside RT Inhibitors[∇]

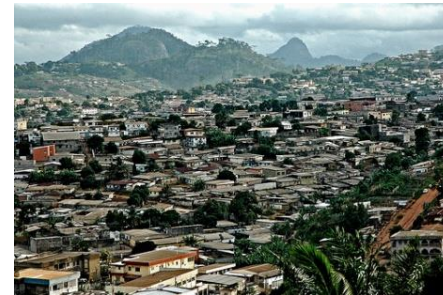
Denis M. Tebit,¹ Michael Lobritz,¹ Matthew Lalonde,¹ Taina Immonen,¹ Kamendra Singh,² Stefanos Sarafianos,² Ottmar Herchenröder,³ Hans-Georg Kräusslich,⁴ and Eric J. Arts^{1*}



From Rural to Urban areas?

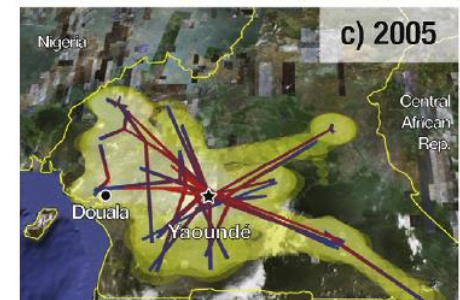
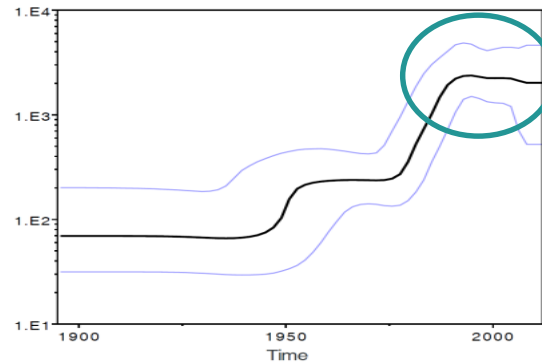
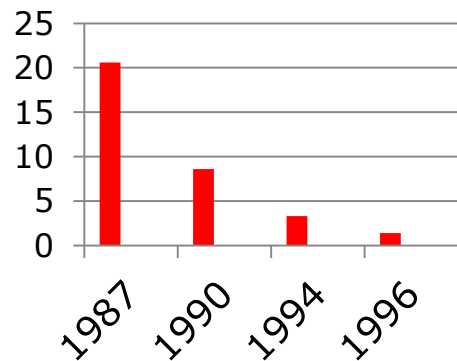


???



Slowing down again

Group O relative prevalence among HIV+ samples

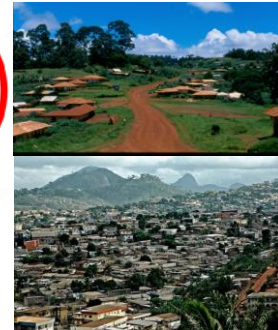
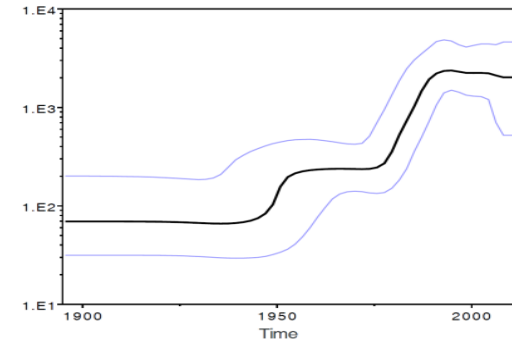
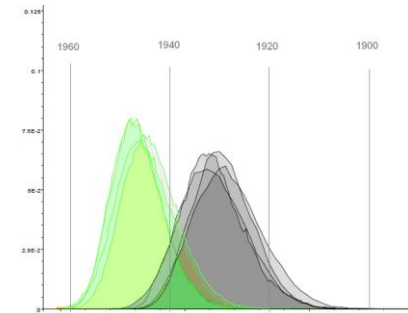


Phylodynamics of the HIV-1 CRF02_AG clade in Cameroon

Nuno R. Faria ^{a,*}, Marc A. Suchard ^{b,c,d}, Ana Abecasis ^e, João D. Sousa ^a, Nicaise Ndembi ^{g,h}, Idalina Bonfim ^e, Ricardo J. Camacho ^{e,f}, Anne-Mieke Vandamme ^a, Philippe Lemey ^a

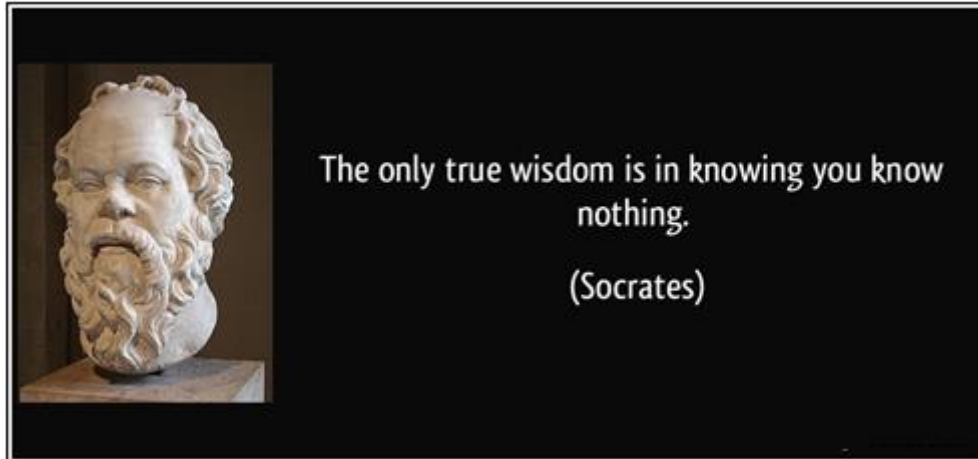
Take home messages

- Group O MRCA estimated in **1920 - 1930**
 - Close to Group M
- Despite limited spread, group O growth had been through **slow and fast phases**
- **Intrinsic as well as contextual** factors might have been involved



To conclude

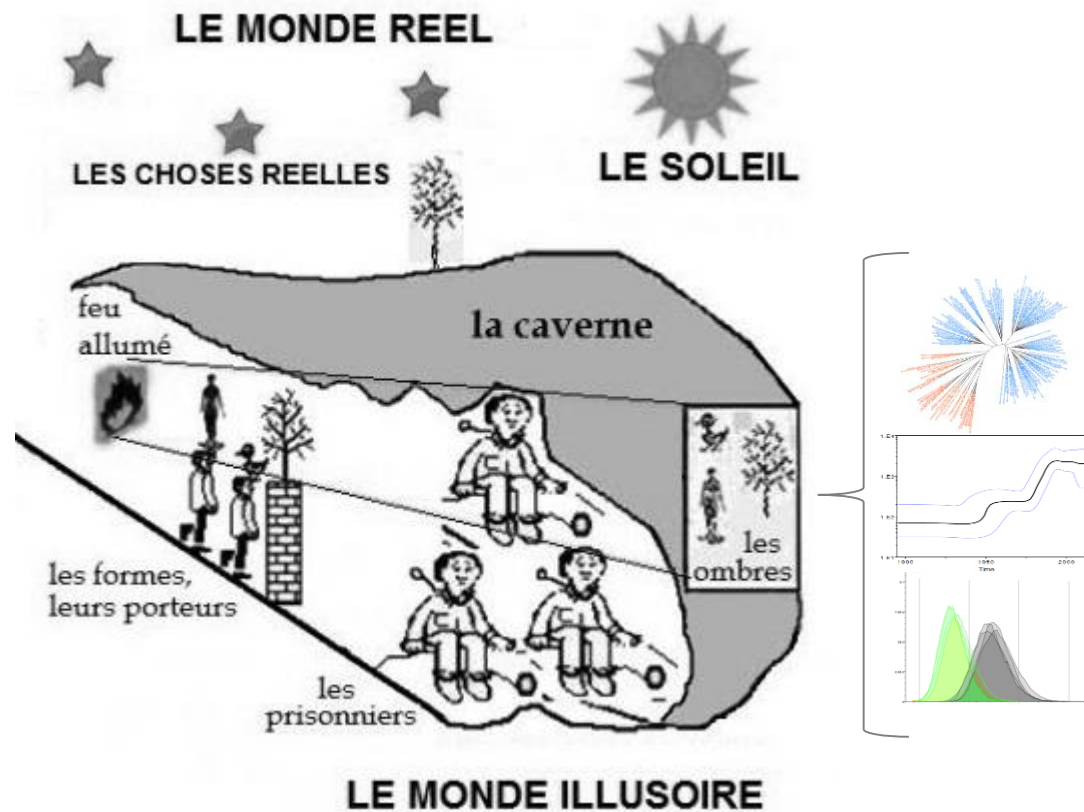
Don't forget wise Socrates...



- Sampling still limited
- Need for a more exhaustive study in Cameroon

To conclude

Let's put a little philo in our phylo 😊



Aknowledgements

○ **CHU de Rouen**

- Fabienne De Oliveira
- Jean-Christophe Plantier



○ **Direction Interarmées du Service de Santé**

- Philippe Mauclère

○ **Université Paris Diderot**

- Guillaume Lachenal

○ **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

