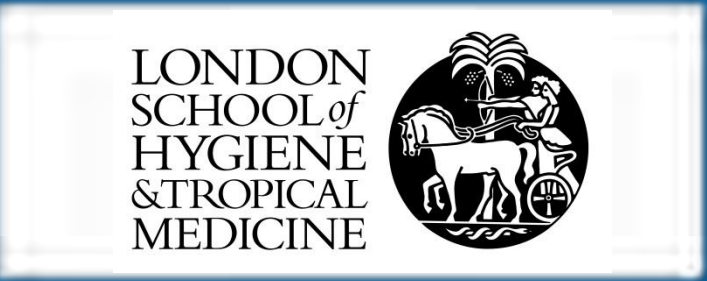
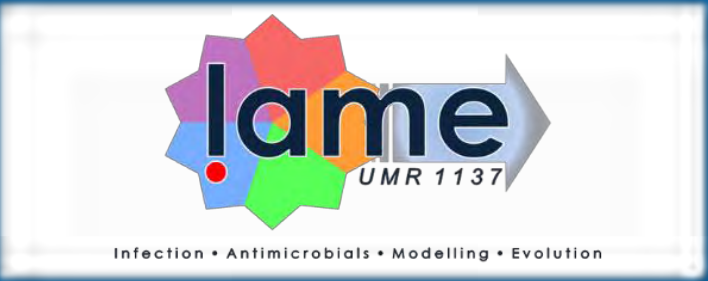




HIV-2 Group A in France Displayed Two Clades with Distinct Geographical Origins

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BACKGROUND

- To date nine distinct lineages of HIV-2 have been identified and appear to represent independent host transfers. By analogy to HIV-1 these lineages have been termed groups A-I , but only groups A and B have spread into humans (Gao et al 1994, Damond et al. 2004).
- HIV-2 group A is mainly found in Western Africa and seems to have originally spread from Guinea-Bissau during the independence war (1963-1974) (Lemey et al. 2003).
- HIV-2 group B mainly predominates in Ivory Coast (Pieniazek et al. 1999)

- In France, HIV-2 represents 1 to 2% of all newly diagnosed HIV infections and more than 1048 HIV-2 infected patients have been included in the French ANRS CO5 HIV-2 cohort since 1994.
- Among these patients, the HIV-2 diversity is higher than in other northern countries, with a higher representation of HIV-2 group B (a third of all identified viruses) than group A. This is mainly explained by local immigration patterns with a strong representation of patients from Ivory-Coast, Mali, Burkina-Faso or Ghana (Damond et al. 2001).

- HIV-2 group A was originally subdivided in three different clades, based on whole *env* gene sequences (Breuer 1995). However, these clades were not retrieved when analysing the N-terminal portion of gp41 alone. In another study using the *env* gene, group A was divided in two distinct clades, reflecting possible geographical divisions (Damond et al. 2001).

OBJECTIVES

- In this study, we aimed to describe HIV-2 diversity observed in France, to confirm the existence of two clades among HIV-2 A group and to explore their geographical locations.

METHODS

- A total of 446 partial *pol* (PR and RT area, 1350 nt), 130 partial *env* (encompassing the V3 loop, 525 nt) and 155 complete *vif* (655 nt) sequences obtained among 386, 118 and 155 patients sampled in France, were analyzed.
- 207, 374 and 22 publically available sequences from GenBank were also included for *pol*, *env* and *vif* analyses. Available SIVsmm and SIVmac sequences were also included (n=63).

- Maximum likelihood phylogenetic trees were constructed using FastTree 2.1 under the GTR evolutionary model. Branch support was estimated with the SH-Like test method (ref).
- Possible recombinant sequences inside each genes were checked and removed before phylogenetic analysis using RPD4.

- Patient's country of birth was retrieved for 272 patients sampled in France and included in the French ANRS CO5 HIV-2 cohort.

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RESULTS

- In all trees, HIV-2 group A formed two distinct and strongly supported clusters (branch support > 80%), herein called A1 and A2, in all trees (cf. **figure 1**).
- Overall our three trees, 68.1, 14.0 and 17.9% sequences belonged to cluster A1, A2 and B, respectively (cf. **table 1**).
- The genetic diversity of HIV-2 sequences was significantly higher in the French cohort than among publically available sequences, as depicted by the higher representation of sequences belonging to the A2 clade (24.9 vs 7.3%, p<0.001) and B group (34.7 vs 7.6%, p<0.001).
- Median genetic distance between clades A1 and A2 were 0.12 [IQR=0.11-0.14], 0.12 [0.11-0.13] and 0.15 [0.12-0.18] substitutions/site for *pol*, *vif* and *env*, respectively.

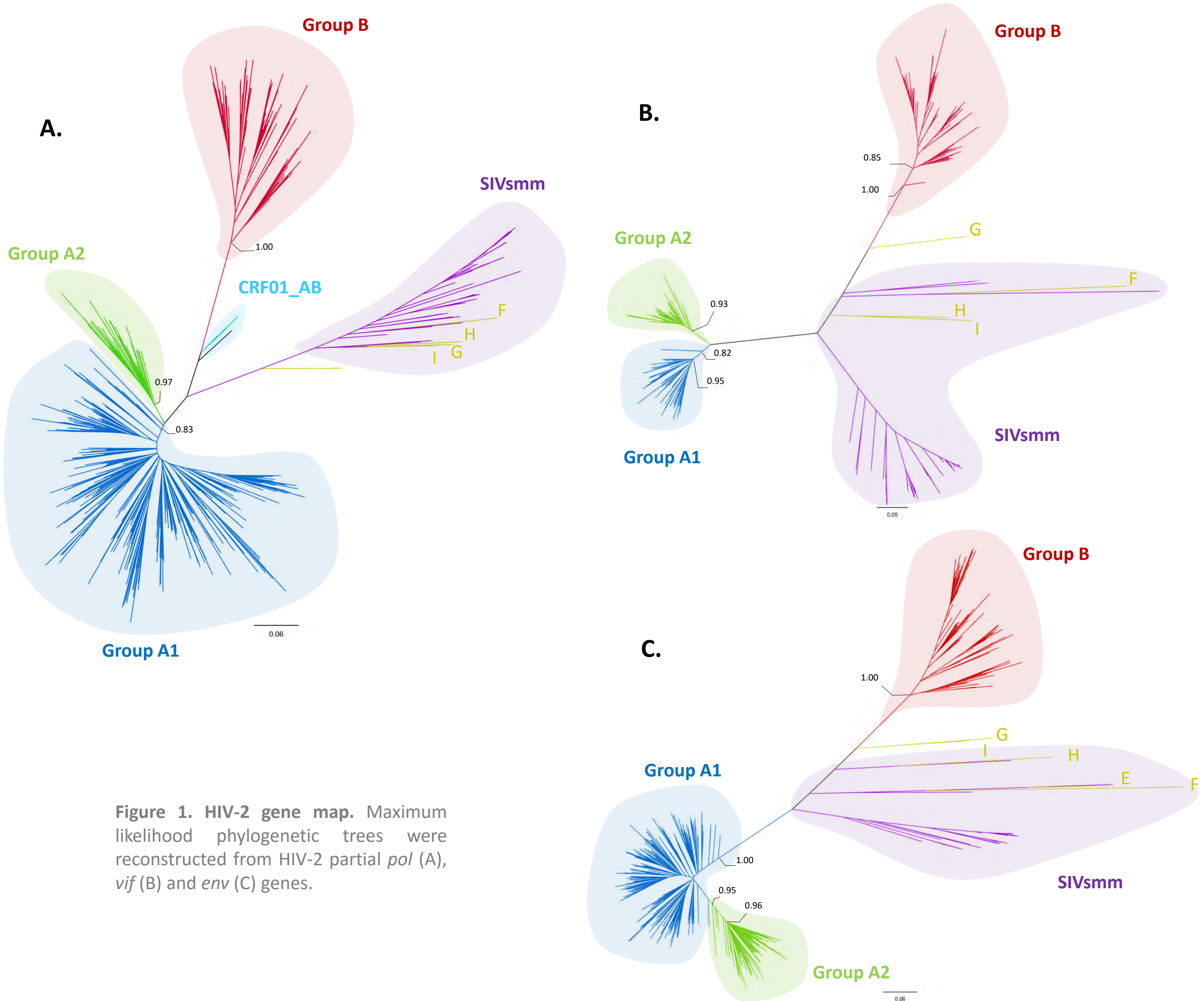


Figure 1. HIV-2 gene map. Maximum likelihood phylogenetic trees were reconstructed from HIV-2 partial *pol* (A), *vif* (B) and *env* (C) genes.

- As expected, all sequences obtained from CRF01_AB clustered together. Only one patient from the French dataset clustered together with CRF01_AB sequences. Interestingly this patient was born in Ivory Coast as the patient at the patient source of the Japanese patients contamination. Among the 85 patients born in Ivory Coast and sampled in France, only 1 seemed to belong to the CRF01_AB.
- Among the 183 sequences with at least two different genes available in this analysis, 17 (9%) presented inconsistent clade assignments across trees. This may suggest the existence of some other recombinant events and need to be explored further by whole genome sequencing.

- When analysing the country of birth of patients from the French ANRS CO5 HIV-2 cohort, 197 (73%) were born in Western Africa. Patient's country of birth according to the virus's clade, are depicted in **figure 2**.
- HIV-2 clade A1 was most prevalent amongst patients born in coastal Western African countries (i.e. Senegal, Gambia, Guinea Bissau and Guinea) with 40 (83%) A1- and 8 (17%) A2-infected patients. Inversely, A2 strains were predominantly found among patients originating from inland western countries such as Mali and Burkina Faso with 8 (22%) A1- and 29 (78%) A2-infected patients. This suggests distinct geographical origins of the two clades, followed by founder effects. Sequences issued from patients born in Ivory Coast displayed a balanced prevalence of these clades with 13 (45%) A1- and 16 (55%) A2-infected patients.

| | A1 | A2 | B |
|-----------------------------|------------|------------|------------|
| French Database | 141 | 87 | 121 |
| Sequences | (40.4%) | (24.9%) | (34.7%) |
| Publically available | 481 | 41 | 43 |
| sequences | (85.1%) | (7.3%) | (7.6%) |
| Total | 622 | 128 | 164 |
| | (68.1%) | (14.0%) | (17.9%) |

Table 1. Distribution of each HIV-2 clades among French database sequences and publically available sequences.

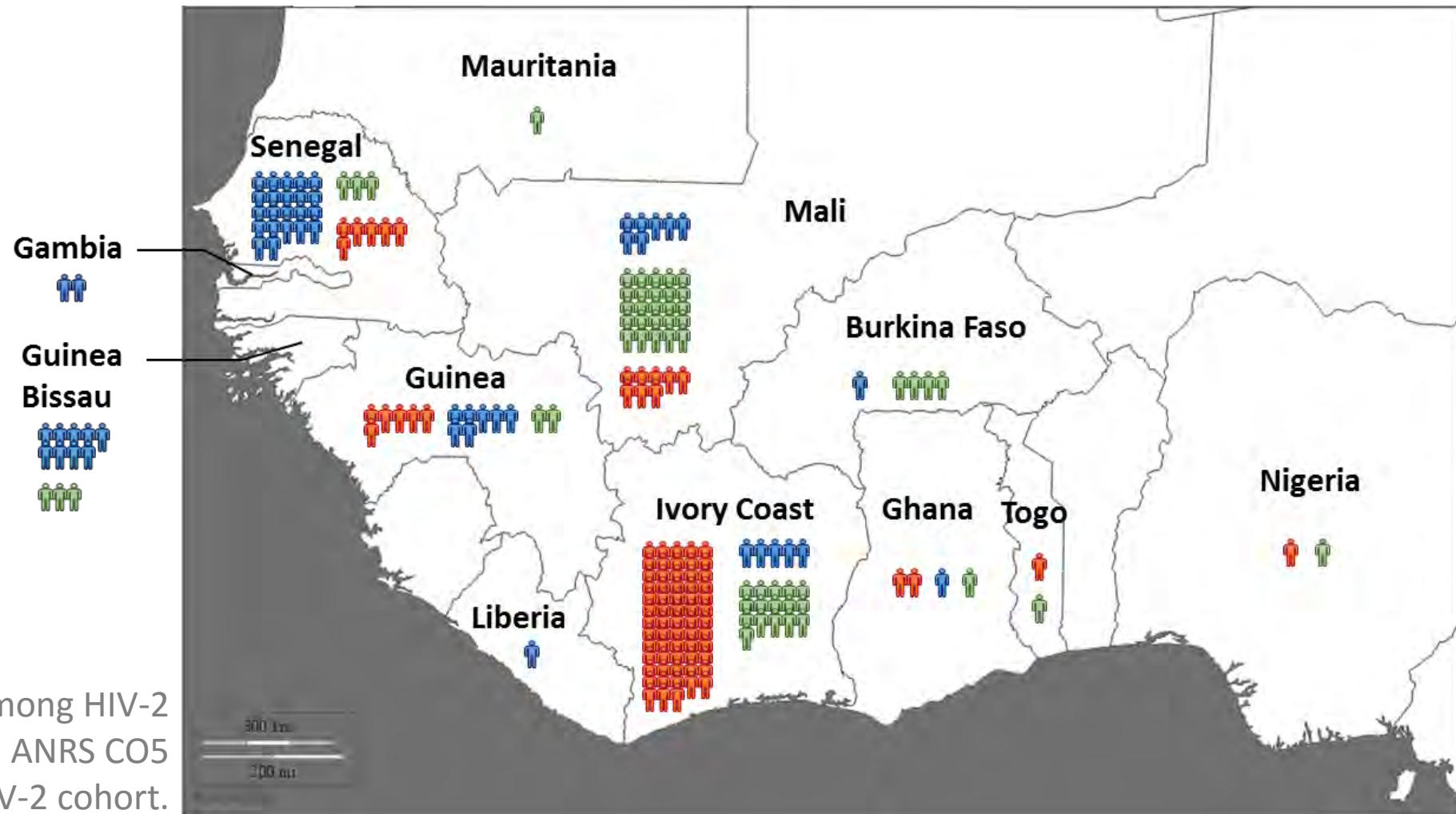


Figure 2. Distribution of country of birth among HIV-2 clades for patient included in the French ANRS CO5 HIV-2 cohort.

DISCUSSION

- This study provides an enhanced understanding of the geographical and genetic diversity of HIV-2. It highlights the co-circulation of two distinct group A clades in France.
- HIV-2 A1 clade seems to be strongly linked to the countries present along the western coasts of Africa, while A2 clade and B groups seem to have emerged in Mali and Ivory Coast. This is likely explained by an ancient divergent event, followed by founder effects.
- These findings need to be further explored using dated phylogenies and phylogeographic analysis through molecular inference analyses.