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GEOSPATIAL HIV DYNAMICS IN FRANCE: A GRAVITY EFFECT MODEL

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Background

- HIV epidemiology is constantly evolving and regular surveillance studies are needed to monitor the HIV genetic diversity shifts or global transmission patterns.
- Individuals during the primary HIV infection contribute disproportionately to the spread of the HIV epidemic due both to at risk behaviors and to high viral loads.
- Monitoring HIV epidemiology in this population is crucial in tracking the leading edge of HIV epidemics.

Objective

To characterize the geospatial dynamics of the HIV epidemics in France and identify factors associated with HIV dispersal for guiding prevention efforts

Methods

- **Sampling**. HIV-1 partial pol sequences from individuals diagnosed with primary HIV infection (PHI) in mainland France in ANRS AC43 network laboratories between 2014 and 2017.
- **Preliminary phylogenetic analysis and subsampling**. We first performed a phylogenetic analysis using combining all publicly available HIV pol sequences combined with our local dataset of HIV-1 sequences with known sampling location. The purpose of this preliminary analysis was to identify supported monophyletic clades ("clusters") sampled from the same administrative area (i.e. Mainland county). We then subsampled these supported monophyletic clades (> 3 sequences) by randomly keeping 1 sequence from each identified cluster. **Discrete phylogeographic inferences**. Phylogeographic inferences were performed using the discrete diffusion model[1] implemented in BEAST 1.10[2].
- **Generalized Linear Model (GLM) analysis.** GLM analyses were performed to investigate the potential contribution of a series of predictive variables to the dispersal rates among administrative areas. We included 9 predictors:
  - Four predictors were based on data directly associated with administrative areas: the number of recorded HIV-1 cases, the population count, the number of railway passengers, , and the number of sampled sequences (**Fig. 2**). For each of these local variables, we considered once the values at the administrative areas of origin and once the values at the destinations, leading to 10 distinct variables.
  - Four predictors were based on pairwise measures between administrative areas: a binary qualitative predictor specifying if administrative areas shared a common border, the driving time between location, and pairwise measures of geographic distance and inaccessibility among these areas[3].
  - Only Bayes Factors (BFs)[4] that remain significant after accounting for the sampling heterogeneity (i.e. BF adjusted) were taken into account to further reduce the false positive rate (see [5] for details).

Results

Fig. 1. Subsampling Workflow

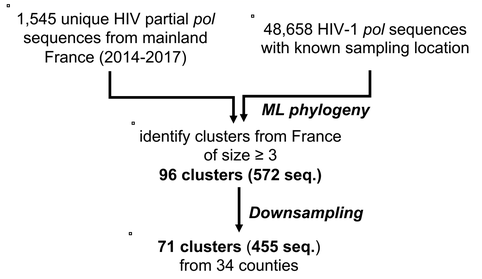
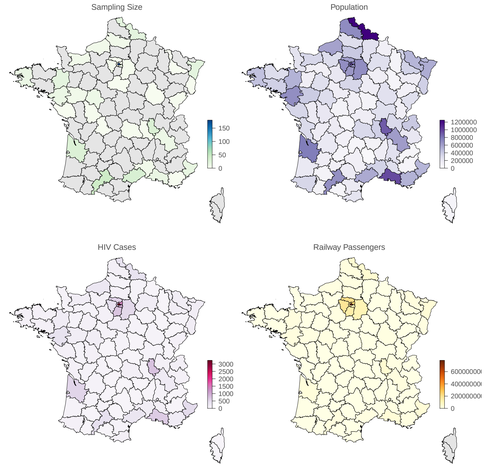


Fig. 2. Geospatial and Demographic Factors Included in the GLM Model



- Pairwise measures of geographic distance and inaccessibility among administrative areas were computed using an algorithm based on circuit theory implemented in the program Circuitscape 4.0.5[4].

Fig. 3. Intense Viral Exchange Between Counties

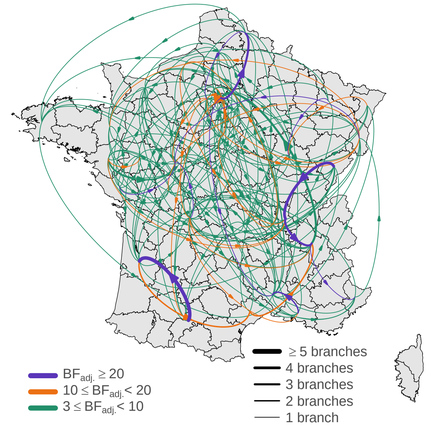


Fig.4. Key Role of Local Transmission in the Spread of the HIV Epidemic

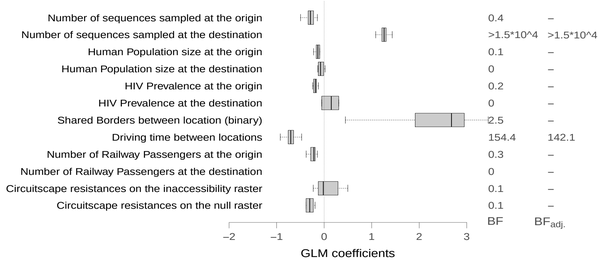


Fig 3. Number of dispersal events between Counties. Only transition curves that represent ≥2 transition events are shown. **Fig 4.** Box plots of the GLM coefficients for all tested predictors. Bayes factors (BF) support and adjusted BF ($BF_{adj.}$) accounting for the relative abundances of samples from each location are indicated on the right.

- **Population characteristics.** A total of 1,545 unique HIV-1 partial pol sequences were collected from 2014 to 2017 sampled across 37 French Counties (mainland).
- **Preliminary phylogenetic analysis and subsampling**. After combining our dataset with 48,658 publicly available HIV-1 B pol sequences with known sampling location, we identified 71 clusters of size ≥ 3 that represent 455 sequences from 34 counties (**Fig. 1**).
- **Discrete phylogeographic inferences** The discrete phylogeographic analysis based on these clades revealed high levels of virus exchange between the sampled counties with Paris and Lyon areas, the 2 largest cities ("Ile de France" and "Auvergne Rhone Alpes") being sources and recipients of viral dispersal (**Fig. 3**).
- **GLM analysis**. After investigating the potential contribution of predictive variables to the dispersal rates among counties in France (mainland), we showed that shorter driving time duration (BF>20) and in a lesser extend 'shared border' was supported by the results (BF=2.5) in addition to the sampling sizes at destination (**Fig. 4**).

Conclusions

- The combined use of phylogeography and GLM provides deeper insights into geospatial viral transmission patterns and factors associated with viral flows.
- Phylogeographic analyses confirm that highly populated areas could have a gravity effect on the French epidemic.
- These results may help to more efficiently allocate prevention resources and will allow to evaluate the impact of changes in demographic trends and policies.

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