229 Geopolitical effects in the epidemiology of HIV-1 subtype B

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Introduction

HIV-1 was discovered in the early 1980's when the virus had already established a pandemic. For at least three decades the epidemic in the Western World has been dominated by subtype B infections, as part of a sub-epidemic that traveled from Africa through Haiti to the United States. However, the pattern of the subsequent spread still remains poorly understood. Here, we analyze a large global representative dataset of subtype B sequences aiming to uncover the subsequent spread pattern of the epidemic.

Material and Methods

We assembled a globally representative dataset of HIV-1 subtype B sequences (N=8,370), by pooling molecular data collected from patient-cohorts and systematically selected molecular epidemiology studies from around the world. The European dataset was comprised of sequences from SPREAD (Strategy to Control SPREAD of HIV Drug Resistance) and ESAR collaboration. We analyzed the sequences using statistical phylogeography run on 250 bootstrap trees. To date, this is the largest global phylogeographic study of subtype B.

Results

- Visual inspection of the global colored phylogeographic trees shows that European strains tend to cluster together, whereas North American strains are very dispersed among the global genetic diversity (Figures 1A,B). More specifically, HIV-1 sequences from Europe formed a large monophyletic cluster including 1,787 (44%) of the total European sampled population (N = 4,020) (Figure 1A). In contrast, North and Central & South American lineages were distributed across the global phylogeny suggesting thus that HIV-1 mobility is the highest between these areas and the rest of the world (Figure 1B). North American strains tend to have deeper roots than groups of sequences found in multiple other areas (Figure 1B).

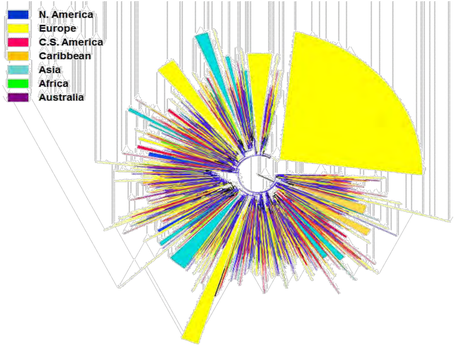


***Figure 1 A**. ML phylogeographic tree showing viral clades in different colors according to European, North, Central/South American, Caribbean, Asian, African and Australian sampling. Triangles indicate monophyletic clusters.*

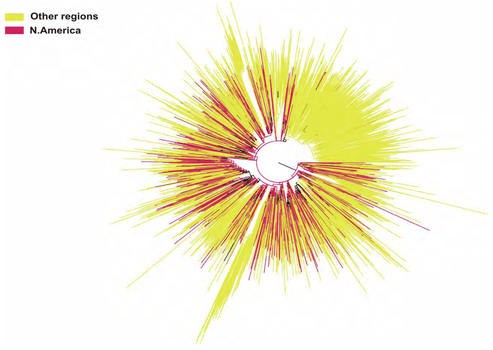


***Figure 1B**. ML phylogeographic tree showing viral clades in different colors according to North American and other regions sampling.*

- Regarding the global dispersal of HIV-1 subtype B between large geographical regions, Europe proved not to be a significant source of subtype B towards other regions. In contrast to the pattern of spread concerning Europe, we found that geographical regions of the Americas were the source of infections exported to the rest of the world. In detail, North America was a source of viral dispersal to all regions except Asia. Asia is the most isolated area having the least number of significant incoming and outgoing destinations, and having connections only with Oceania and Central/South America. The viral mobility among those large geographic regions is illustrated in Figure 2.

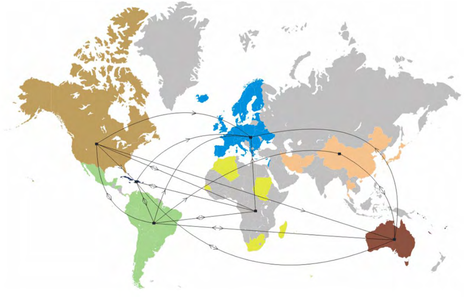


***Figure 2.** Global dispersal patterns of HIV-1 subtype B estimated by statistical phylogeography. Colors indicate different geographic regions (highlighted countries) from which HIV-1 sequences were available. Arrows indicate the direction of subtype B spread. Dots for different geographic areas are placed in the center of each area.*

- We repeated the statistical phylogeographic analysis by splitting Europe into two regions, Western and Central/Eastern Europe (C.E. Europe). We found no statistically significant viral dispersal towards C.E. Europe, but instead some significant mobility from C.E. Europe to Western Europe. So, apparently the high incoming viral mobility towards Europe is due to incoming mobility particularly to Western Europe rather than the whole continent.

- We found that the number of exporting countries significantly correlates with the number of subtype B infections in the source country, suggesting that areas with high number of HIV prevalent cases are more likely to spill over infections to other countries (Figure 3). The scatter plot suggested that UK and France lie far from the regression line, which means that they do not provide as many spillovers within Europe as it would be expected for their high number of prevalent cases. Removal of UK and France from the analysis dramatically improves the correlation ($R^2 = 0.69$, $p < 0.0001$) suggesting that UK and France had a different spillover pattern than the rest of the European countries. We found no significant correlation between the number of prevalent cases within a country/region and the number of countries which are source of viral introduction to that country/region.

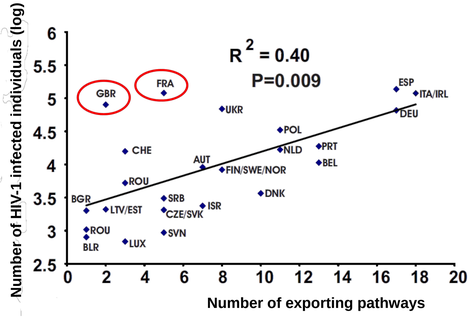


***Figure 3.** Scatter plot of the total number of HIV-1 subtype B infected individuals per country/region versus the number of exporting pathways for each country/region (Europe only). The solid line is the fitted regression line. R^2 is the coefficient of determination and P is the p-value of the regression model.*

- We made an index that is equal to the ratio of the observed total migration events (importing and exporting) to non-European divided by the expected total migration events to non-European regions. This ratio if larger than 1 indicates that a country is more connected to non-European countries. Three countries were found to have the largest significant ratio, specifically the United Kingdom (ratio = 1.8), Switzerland (ratio = 1.6) and France (ratio = 1.5) (all having $p < 0.001$, significant for multiple comparisons) (Figure 4).

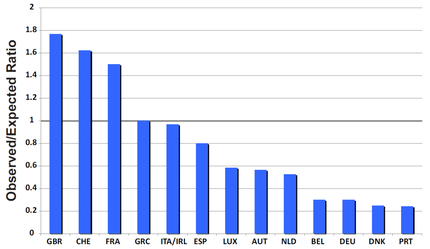


***Figure 4.** Ratio of observed versus expected out-of-Europe migration index for migration events between geographic areas and specific Western European countries. Only Western European countries with significant migration events with at least one non-European geographic area are reported*

Discussion

- Our study shows that the American continent has been influential in driving the Western epidemic, not only at the initial random dispersal event, but also through constant subsequent mobility to the rest of the world. The striking role of America in disseminating subtype B infections was probably a consequence of the early introduction and propagation of this clade in North America remaining silent for almost a decade. At that time numerous spill overs may have occurred to several geographic areas through blood transfusions, intravenous drug use or unprotected sexual intercourses. The role of North America as a hub for subtype B, therefore, was probably unpreventable during the silent initial phase of the epidemic in seventies and beginning of eighties. Dispersal events from C.S. America to other areas probably occurred subsequently to the initial spill overs from N America and they can be explained due to the popularity of the former as a touristic destination and the high population mobility from and to S. America.
- In striking contrast, the role of Europe for this subepidemic with respect to the rest of the globe was secondary and the incoming infections spread mainly among regional populations. It is also surprising that C.E. Europe did not import more than expected from West Europe even though West Europe had historically higher levels of subtype B infection. The low population mobility in C.E. Europe versus Western Europe might explain the low levels of viral dispersal between the two areas.
- The highest mobility between any European country and non-European regions was observed for the UK, Switzerland and France. UK and France saw similar patterns with connections to Americas and Africa and we have also found that for the correlation between number of prevalent cases and number of significant migratory routes, UK and France had a striking deviation. This is in accordance with our findings that both these countries provide major sources of viral mobility from outside Europe (North, Central & South America and Caribbean), suggesting the distinct nature of these countries with regard to epidemic spread in Europe.
- We show that the global viral phylogeography of HIV subtype B was not random and suggest that, since major landmarks of the last part of the 20th century influence human (hence virus) mobility, the virus spread around the globe is largely the result of natural virus-host ecological dynamics.

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