Molecular analysis of HIV-1 subtype A1 and B dispersal patterns of persons with late presentation and advanced disease in Greece


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Introduction

Late presentation of human immunodeficiency virus (HIV) infection is a serious challenge for the management and prevention of HIV infection in Europe. Too many people throughout the European Region are diagnosed late (51%), increasing the risk of ill health, death and onward HIV transmission. The proportion of those diagnosed late (CD4 count < 350 cells/μL) was 58% in Greece in 2016 (ECDC).

Aim

We aimed to investigate the patterns of HIV transmission among late presenters in Greece using molecular epidemiology, in order to identify risk factors and gaps that need to be addressed at a national level.

Materials and Methods

Study samples included HIV-1 sequences isolated from 6,268 people living with HIV (PLHIV) diagnosed between 1999 and 2015 in Greece. Sequences were available in the PRT. We analysed 1,777 (28.4%) and 2,589 (41.3%) sequences of the subtype A1 and B, respectively, which are the most prevalent subtypes in Greece (Table 1).

Table 1. Characteristics of the study population

<table>
<thead>
<tr>
<th>HIV-1 subtype</th>
<th>A1 (N=1,777)</th>
<th>B (N=2,589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Nationality</td>
<td>Greek</td>
<td>Non-Greek</td>
</tr>
<tr>
<td>Risk group</td>
<td>MSW</td>
<td>MSM</td>
</tr>
<tr>
<td>HIV presentation status</td>
<td>Non-Late presenter</td>
<td>Late presenter</td>
</tr>
<tr>
<td>Age (in years)</td>
<td>38.6 (12.6)</td>
<td>37.8 (10.5)</td>
</tr>
</tbody>
</table>

Phylogenetic analysis was performed on subtypes A1 and B sequences from Greece along with a randomly selected global dataset of sequences (subtype A: N=1,500; subtype B: N=2,000). We used the reference database (RT). Phylogenetic trees were inferred by maximum likelihood method under the GTR model of nucleotide substitution including a gamma (Γ) distributed rates heterogeneity among sites as implemented in RAxML v8.2.10 program. Phylogenetic analysis was repeated in 5 replicates using a different set of randomly selected references.

Local transmission networks (LTNs) were considered as phylogenetic clusters including at least 2 sequences from the same geographic area (Greece) at a proportion higher than 70%. Only sequences belonged to clusters in the repeated replicates were considered as LTNs. Multivariable logistic regression models were applied for the statistical analysis in Stata 12. Late presenters were defined as persons with initial CD4 count between 200 and 350 cells/μL; those with advanced disease had an initial CD4 count < 200 cells/μL or clinical AIDS regardless of CD4 count.

Phylogenetic analysis revealed that:

- 93.8% (1,667 out of 1,777) of A1 sequences belonged to 38 LTNs, and specifically the largest one included 1,543 (86.8%) of the total subtype A1 sample (Figure 1A).
- 77.1% (1,966 out of 2,589) of B sequences belonged to 166 LTNs (Figure 1B).
- p<0.001

For subtype A, the percentage of PLHIV within LTNs was 95.2% (N=197) for late presenters, 96.1% (N=223) for those with advanced disease and 95.6% (N=446) for non-late presenters.

For subtype B, the corresponding figures were 85.8% (N=206) for late presenters, 71.8% (N=290) for those with advanced disease and 89.8% (N=569) for non-late presenters.

Multivariable logistic regression analysis showed that:

- Risk group (MSM vs heterosexuals; OR=6.07; p<0.001) and nationality (Greece vs non-Greek; OR=7.23; p<0.001) were associated with regional clustering of subtype A1 (Table 2).
- p<0.001

- Year of sampling (last sampling year; OR=1.17 per year; p<0.001) was associated with regional clustering of subtype B (Table 2).

- Late presentation or advanced disease status was not associated with regional clustering of subtype A1 (Table 2).

- PLHIV with advanced disease had a lower probability (OR=0.48 vs non-late presenters; p<0.001) of belonging to regional clusters of subtype B (Table 2).

Discussion

- Our study suggests that most HIV transmissions among PLHIV with late-presentation for subtypes A1 and B and those with advanced disease for subtype A1 occur locally (LTNs), calling for an intensification of testing.

- This is one of the few studies combining molecular and traditional epidemiology to study HIV dispersal patterns of PLHIV with late diagnosis and advanced disease.

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