HIV transmission in the migrant population

D. Paraskevis
• Definitions
• Epidemiology of HIV in migrants
• Methods to estimate the origin of HIV acquisition
  ▪ Molecular epidemiology
  ▪ Bayes’ method based on CD4 and HIV-RNA
• aMASE study
• Origin of HIV infection for PWID in Greece
Definitions

- **Migrant**: any person who lives temporarily or permanently in a country where he or she was not born, and has acquired some significant social ties to this country (UN definition)
- **Immigrant**: someone who moves into a country with the intent to settle
- **Expatriate**: someone staying abroad temporarily or of an undetermined period, especially a white-collar professional or someone from a wealthy or English-speaking country
- **Refugee**: someone who has been forced to flee his or her country because of persecution, war, or violence (UN definition)
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THE GAP REPORT

UNAIDS
HIV/AIDS Surveillance 2017

2016 data

European Centre for Disease Prevention and Control
WHO Regional Office for Europe
In 2015, 37% of all newly-diagnosed cases of HIV in the EU/EEA were in people born outside of the reporting country.
Proportion HIV diagnoses in migrants* by country of report, EU/EEA in 2016

- New diagnoses in migrants from high-endemic countries
- New diagnoses in migrants from other countries

EU/EEA: 40% diagnosed in 2016 were born abroad

* Migrants are all persons born outside of the country in which the diagnosis was made.
New HIV diagnoses, by year of diagnosis, transmission and migration status, EU/EEA, 2007-2016

[Graph showing trends in new HIV diagnoses by transmission and migration status from 2007 to 2016.]
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Proportion of persons diagnosed late (CD4 cell count < 350 per mm$^3$ in 2016)
Molecular epidemiology studies
Estimates based on a query from the HIV sequence database for sequences sampled later than 2005

Beloukas and Psarris et al, IGE 2016
• Non-B transmissions in Western Europe have been associated with migrants from sub-Saharan Africa, and to a lesser extent from South East Asia and Eastern Europe
• Based on findings that migrants have been infected with non-B strains, we may hypothesize that they have been infected, at least at some proportions, pre-migration
• In Central Europe non-B clades are mainly linked with heterosexuals, and not with non-European origin.
• Non-Bs have a distinct pattern of epidemic spread in FSU countries associated with regional dispersal in drug injectors

Beloukas and Psarris et al, IGE 2016; Abecasis et al, Retrovirology 2013
Phylogenetic analyses revealed that domestic transmissions occur among immigrants between 16% and 28%, for several non-B clades, in Switzerland.

In Italy it was found that Italians, South Americans, and South-East Asians were detected at higher frequency (56.1%, 83.3%, and 100%) in phylogenetic clusters as compared to Africans (15%, p<0.001).

Subtype B transmissions were found at 23% and 3% of Africans and migrants from sub-Saharan Africa living in France and Spain, respectively, suggesting that these transmissions could have possibly occurred in Europe.

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Determining the likely place of HIV acquisition for migrants in Europe combining subject-specific information and biomarkers data

Nikos Pantazis,¹ Christos Thomadakis,¹ Julia del Amo,² Debora Alvarez-del Arco,² Fiona M Burns,³,⁴ Ibidun Fakoya,³ and Giota Touloumi¹; on behalf of the aMASE and CASCADE study groups*
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Pre and post-migration HIV acquisition

Advancing Migrant Access to Health Services in Europe

aMASE

European AIDS Treatment Group
Pre and post-migration HIV acquisition

2,249 interviews

UK
7 sites
420 interviews

The Netherlands
3 sites
124 interviews

Belgium
4 sites
264 interviews

Portugal
7 sites
192 interviews

Spain
18 sites
765 interviews

Italy
2 sites
81 interviews

Germany
2 sites
31 interviews

Switzerland
6 sites
188 interviews

Greece
8 sites
191 interviews
Geographic area of origin

Transmission mode:

- HET Female
- HET male
- MSM
- PWID
- Other/unknown

Transmission mode:

- Sub-Saharan African
- European migrants
- Latin America & Caribbean
- Others
Transmission mode

% 50,0

HET female  HET male  MSM  PWID  Other/unknown

Alvarez-Del Arco et al AIDS 2017
Post-migration HIV acquisition probability (95% CI)

Geographical origin

- Total: 63% (57, 67)
- European migrants: 71% (65, 76)
- LA & Caribbean: 71% (65, 76)
- Other: 71% (65, 76)

Mode of transmission

- HET female: 51% (45, 57)
- HET male: 72% (67, 76)
- MSM: 75% (63, 84)
- PWID: 60% (44, 75)
- Other/unknown: 45% (39, 52)

Alvarez-Del Arco et al AIDS 2017
Post-migration HIV acquisition probability (95% CI)

Sample size per country

Estimated probability (%)

Destination country

Belgium, n=232
Greece, n=175
Germany, n=29
Italy, n=55
Netherlands, n=109
Portugal, n=170
Spain, n=685
Switzerland, n=174
UK, n=380

Alvarez-Del Arco et al AIDS 2017
• Post-migration HIV acquisition was 63% (95% CI: 57%-67%)
• Factors associated with post-migration HIV acquisition among heterosexual women and MSM were age at migration, length of stay in host country and HIV diagnosis year and among heterosexual men, length of stay in host country, and HIV diagnosis year
A systematic review of post-migration acquisition of HIV among migrants from countries with generalised HIV epidemics living in Europe: implications for effectively managing HIV prevention programmes and policy

Ibidun Fakoya1*, Débora Álvarez-del Arco2,4, Melvina Woode-Owusu5, Susana Monge3,A, Yaiza Rivero-Montesdeoca2,A, Valerie Delpech5, Brian Rice5, Teymur Noori6, Anastasia Pharris6, Andrew J. Amato-Gauci6, Julia del Amo2,4 and Fiona M. Burns1,7
Proportion of infections among Africans acquired post-migration

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Country/City/Region</th>
<th>Profile</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valin, N (2008) [43]</td>
<td>Ile-de-France (France)</td>
<td>Sub-Saharan African</td>
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</table>
Proportion of infections acquired post-migration among people born in Caribbean or Asia or with Black Caribbean ethnicity

<table>
<thead>
<tr>
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<th>Country/City/Region</th>
<th>Profile</th>
<th>Proportion</th>
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<td>Pezzoli MC (2009) [12]</td>
<td>Italy</td>
<td>Sub Saharan African, Eastern Europe and Latin America</td>
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<tr>
<td>Staehelin C (2004) [42]</td>
<td>Switzerland</td>
<td>Southeast Asian</td>
<td>25</td>
</tr>
</tbody>
</table>
Limitations

• Data estimating the proportion of post-migration HIV acquisition from cross-sectional studies in different countries relied on samples that were either very small or unrepresentative

Fakoya et al, BMC Public Health 2015
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Molecular tracing of the origin of HIV-1 infection among persons who inject drugs in Athens: a phyloethnic study

D. Paraskevis*¹, E. Kostaki¹, GK. Nikolopoulos², V. Sypsa¹, M. Psichogiou³, J Del Amo⁴, I. Hodges-Mameletzis⁵, D. Paraskeva⁶, A. Skoutelis⁷, M. Malliori⁸, L. Williams⁹, SR. Friedman⁹, G.L. Daikos³, A. Hatzakis¹

¹Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece, ²Medical School, University of Cyprus, Nicosia, Cyprus, ³First Department of Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece, ⁴National Center for Epidemiology, Institute of Health Carlos III, Madrid, Spain, ⁵World Health Organization, Geneva, Switzerland, ⁶Hellenic Center for Disease Control and Prevention, Amarousio, Greece, ⁷Fifth Department of Internal Medicine and Infectious Diseases Evangelismos Hospital Athens, Greece, ⁸Medical School, National and Kapodistrian University of Athens, Greece, ⁹National Development and Research Institutes (NDRI), New York, USA
Molecular Tracing of the Geographical Origin of Human Immunodeficiency Virus Type 1 Infection and Patterns of Epidemic Spread Among Migrants Who Inject Drugs in Athens

Dimitrios Paraskevis, Evangelia Kostaki, Georgios K. Nikolopoulos, Vana Sypsa, Mina Psichogiou, Julia Del Amo, Ioannis Hodges-Mameletzis, Dimitra Paraskeva, Athanasios Skoutelis, Meni Mallion, Leslie Williams, Samuel R. Friedman, Georgios L. Daikos, and Angelos Hatzakis

1Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Greece; 2Medical School, University of Cyprus, Nicosia; 3First Department of Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Greece; 4National Center for Epidemiology, Institute of Health Carlos III, Madrid, Spain; 5World Health Organization, Geneva, Switzerland; 6Hellenic Center for Disease Control and Prevention, Amarouso; 7Fifth Department of Internal Medicine and Infectious Diseases Evangelismos Hospital Athens, and 8Medical School, National and Kapodistrian University of Athens, Greece; 9National Development and Research Institutes, New York, New York.
Newly diagnosed cases in Greece
Before 2011, the HIV epidemic in Greece was concentrated in MSM

In 2011, HIV cases among PWID rose sharply to > 250

The PWID outbreak peaked in 2012 (>500 cases)

Following interventions, cases have been decreasing since 2013

Majority of PWID have been infected within four PWID-specific clades (CRF14_BG, CRF35_AD, subtypes A and B)

The prevalence of HIV-1 infection was higher among male PWID originating from Asia (Afghanistan/Iran) and Balkan/Eastern Europe (ARISTOTLE study)

These findings prompted us to investigate in detail how HIV-1 epidemic spreads among migrant PWID
Aim

- To trace the geographic origin of infection
- To estimate potential geographical compartmentalization among PWID with different ethnicities, during the HIV-1 outbreak (2011-10/2014) in Athens
Methods (1)

- HIV-1 subtyping of sequences (N=2,274) derived from all HIV(+) individuals in Greece (sampled after 2010)
- Characterization of PWID specific local transmission networks (LTNs) by phylogenetic analysis
- Identification of the geographic origin of infection for sequences isolated from migrant (PWID) infected within the LTNs
- Estimation of the geographic origin of HIV-1 transmissions for migrant PWID infected outside the LTNs
- Phyloethnic analysis within each PWID-LTN in order to investigate geographic compartmentalization among the individuals with a non-Greek ethnicity (migrants)
Study population

Total Population* (N=2,274)

- PWID (N=874, 38.4%)
  - LTNs (N=746, 85.4%)
    - Greeks (N=585, 78.4%)
    - Non-Greeks (N=144, 19.3%)
  - Non-LTNs (N=128, 14.6%)
    - Greeks (N=81, 63.3%)
    - Non-Greeks (N=40, 31.3%)
    - Unknowns (N=7, 5.4%)

* Total HIV-1 infected population for whom sequences were sampled during January 2011 and October 2014
• HIV-sequences were available from 144, 312, 314 and 104 PWID sampled during 2011, 2012, 2013 and 2014 (until 31/10/2014), respectively.
• These numbers accounting approximately for 74.1% (874 out of 1,179) of all HIV-1(+) PWID diagnosed at the same period in Greece
• PWID local transmission networks (LTNs) were determined using phylogenetic analysis of all available sequences in our dataset (N=2,274) along with a large set of sequences from the Hellenic HIV-1 Sequence Database (N=2,216) and a globally sampled dataset used as references (N=6,276)
• Phylogenetic analyses were performed by maximum likelihood methods
Strategies on the reference dataset selection to identify the potential geographic origin of infection for the unclustered sequences

<table>
<thead>
<tr>
<th>HIV-1 Subtype/CRF</th>
<th>Reference dataset selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All the available globally sampled sequences¹</td>
</tr>
</tbody>
</table>

### Pure Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Reference dataset selection</th>
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<tbody>
<tr>
<td>A</td>
<td>✓</td>
</tr>
<tr>
<td>B</td>
<td>✓</td>
</tr>
<tr>
<td>F</td>
<td>✓</td>
</tr>
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</table>

### CRFs

<table>
<thead>
<tr>
<th>CRF</th>
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<td>CRF01_AE</td>
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</tr>
<tr>
<td>CRF03_AB</td>
<td>✓</td>
</tr>
<tr>
<td>CRF14_BG</td>
<td>✓</td>
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</table>

### URFs

<table>
<thead>
<tr>
<th>URFs</th>
<th>Reference dataset selection</th>
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<tbody>
<tr>
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</table>

### Unclassified sequences

<table>
<thead>
<tr>
<th>Unclassified sequences</th>
<th>Reference dataset selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

¹ Los Alamos HIV-1 sequence database

² 55 sequences were found available worldwide
Results
## Distribution of ethnicity in PWID

<table>
<thead>
<tr>
<th>Country/Region of origin</th>
<th>PWID</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Central Asia</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>29 (3.3)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>41 (4.7)</td>
</tr>
<tr>
<td>Greece</td>
<td>666 (76.2)</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>46 (5.3)</td>
</tr>
<tr>
<td>South Asia</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td>South &amp; Southeast Asia</td>
<td>14 (1.6)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24 (2.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>874 (100)</strong></td>
</tr>
</tbody>
</table>
### Geographic origin of infection

<table>
<thead>
<tr>
<th>Geographic origin of infection</th>
<th>HIV-1 Subtype/CRF</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Greece</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A (LTN)</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td></td>
<td>B (LTN)</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td></td>
<td>CRF14_BG (LTN)</td>
<td>100 (54.4)</td>
</tr>
<tr>
<td></td>
<td>CRF35_AD (LTN)</td>
<td>18 (9.9)</td>
</tr>
<tr>
<td></td>
<td>URFs including LTN</td>
<td>24 (13.1)</td>
</tr>
<tr>
<td></td>
<td>Subtype A (non-LTN)</td>
<td>5 (2.7%)</td>
</tr>
<tr>
<td></td>
<td>Subtype B (non-LTN)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>CRF01_AE (non-LTN)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal</strong></td>
<td><strong>173 (94.3)</strong></td>
</tr>
<tr>
<td><strong>Not in-Greece</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Putative origin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greece/Israel</td>
<td>CRF03_AB</td>
</tr>
<tr>
<td></td>
<td>Romania</td>
<td>CRF14_BG (non-LTN)</td>
</tr>
<tr>
<td></td>
<td>Romania</td>
<td>Subtype F</td>
</tr>
<tr>
<td></td>
<td>Turkey/Bulgaria</td>
<td>URF</td>
</tr>
<tr>
<td></td>
<td>Turkey</td>
<td>Unclassified</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>CRF14_BG (LTN)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>CRF35_AD (LTN)</td>
</tr>
<tr>
<td></td>
<td>Unspecified</td>
<td>Unclassified</td>
</tr>
<tr>
<td></td>
<td><strong>Subtotal</strong></td>
<td><strong>11 (5.7)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>184 (100)</strong></td>
</tr>
</tbody>
</table>
Subtype F

- Greece
- Romania
- Brazil
- Spain
- Other areas
Multiethnic study
• Our analysis revealed evidence for significant compartmentalization according to ethnic origin for subtype A and CRF14_BG, whereas we didn’t find significant differences for subtype B and CRF35_AD
Subtype A

Greek
Non-Greek
Unknown

0.002
Subtype B

Greek
Non-Greek
Unknown
CRF14_BG

Trees randomly reshuffled at tips (N=300)  Original Trees (N=300)

Number of trees

Cross-Ethnic Group Transmissions

0 5 10 15 20 25 30 35 40 45 50

86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117

Original Trees (N=300)
CRF35_AD

Trees randomly reshuffled at tips (N=408) vs Original Trees (N=408)

Number of trees

Cross-Ethnic Group Transmissions
Conclusions (I)

- We showed that the majority (94.3%) of infections among migrants (PWID and non-PWID) clustered within PWID-LTNs originated in Greece.
- Our findings suggest that across different ethnic groups, HIV infections are more likely to have been locally acquired.
- We also showed the existence of significant transmission networking between migrants. These findings could have public health implications, especially in PWID-related epidemics.
Conclusions (II)

• The proportions of post-migrations differ greatly across different ethnic and risk groups in Europe

• Baye’s method based on CD4 and HIV-RNA measurements and molecular epidemiology are preferred for the estimation of the putative origin of HIV-1 infection

• Pervious methods have several limitations and require different type of data
Acknowledgments

• Julia del Amo

Funding:
• US National Institute on Drug Abuse (NIDA) (Grant: DP1 DA034989)
• Hellenic Scientific Society for the Study of AIDS and STDs
• National Strategic Reference Framework 2007–2013
• European Social Fund and Greek national resources (MIS 365008)