Transmitted drug-resistance in newly diagnosed HIV drug-naïve individuals in Portugal

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on behalf of the BEST HOPE Study Group

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Background

HIV infection cases: new cases per year of diagnosis

- 54,257 notified cases (1983-2015)
- 990 new diagnosis (in 2015)

HIV infection between 1983-2015 by transmission group and year of diagnosis

- 54.4% Hetero
- 40.5% MSM
- 4.6% IDUs

Relatório do Instituto Nacional de Saúde Doutor Ricardo Jorge, 2016

12th International workshop on HIV Transmission
PORTUGAL: Cases of HIV infection - distribution according to the geographic origin

Year of diagnosis

- 2005: 75.2%
- 2006: 75.2%
- 2007: 75.2%
- 2008: 75.2%
- 2009: 75.2%
- 2010: 75.2%
- 2011: 75.2%
- 2012: 75.2%
- 2013: 75.2%
- 2014: 75.2%
- 2015: 75.2%

Other regions: 24.8%
South America: 18.6%
Sub-Saharan Africa: 75.2%
East Europe: 18.6%
Western Europe: 75.2%
Portugal: 75.2%

Relatório do Instituto Nacional de Saúde Doutor Ricardo Jorge, 2016
In June 2016, 18.2 million people living with HIV had access to antiretroviral therapy.

Globally, the number of people receiving ARV treatment tripled between 2010 and 2015.
Background

Prevalence of TDR by transmission group

Background

2016
2.5% HIV prevalence
3.9% African-Americans
22.5% TDR

2013
In a rural HIV clinic in Kenya 1.1% TDR in ARV naïve adults

2014
Swiss cohort study
ART-naive MSM presented 8.4% TDR

It is extremely important to monitor TDR!!!
Objectives of the BEST HOPE project

- to construct a cohort of newly diagnosed HIV patients;

- to analyze the prevalence and characteristics of TDR on those patients;

- to know the socio-behavioral and risk factors that are associated with HIV infection, with or without TDR;

- to characterize HIV and TDR transmission chains and to identify risk factors associated to HIV and TDR transmission in specific vulnerable groups (Men who have Sex with Men (MSM) and Migrants);
**Methods**

- Prospective observational study

- Patients included in 19 Portuguese hospitals, covering the whole country

- **Collection of clinical data** (date of diagnosis, CD4, Viral load, etc.)

- **Collection of demographic and socio-behavioral data** (country of origin, city of residence, age, alcohol and drug use, condom use, number of sexual partners, sexually transmitted infections, etc.) for MSM and migrants by filling in a specific questionnaire

- **Collection of the genomic sequence** (Sanger sequencing) of the 1st ARV drug resistance test
Results

- Data collected from 301 patients until March 2017

Gender distribution:
- 1; 26.2%
- 2; 71.4%
- 3; 2.3%

Distribution by transmission group:
- 1; 56.5%
- 2; 39.5%
- 3; 1.3%
- 4; 2.6%
**Results**

**Figure 1- Distribution by patient groups**

- **MSM** (99, 32.9%)
- **Migrants** (54, 17.9%)
- **General population** (120, 39.9%)
- **Mig+MSM** (20, 6.6%)

**Total 301 patients**

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**Table 1- Distribution by geographic origin**

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>HIV-positive patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>73.4</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>13.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>8.3</td>
</tr>
<tr>
<td>Others</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Table 2- Patients originated from Sub-Saharan Africa distributed by country of origin**

<table>
<thead>
<tr>
<th>Sub-Saharan Africa</th>
<th>HIV-positive patients % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>4.0 (12)</td>
</tr>
<tr>
<td>Cape Verde</td>
<td>3.7 (11)</td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td>2.7 (8)</td>
</tr>
<tr>
<td>São Tomé and Príncipe</td>
<td>1.7 (5)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1.3 (4)</td>
</tr>
</tbody>
</table>
Results

More common subtypes:
• B (39.5%) and G (20.6%)

Compared to SPREAD (2002-2005)
• Subtype G decreased from 29.4% (SPREAD) to 20.6%
• Subtype A1 increased from 1.7% (SPREAD) to 9.6%
• Subtype F1 increased from 2.2% (SPREAD) to 7.3%
### Results

Table 3 - Prevalence of resistance mutations in the BEST HOPE study participants

<table>
<thead>
<tr>
<th></th>
<th>Patients % (n)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SDRM</td>
<td>12.3 (37)</td>
<td>9.0-16.5</td>
</tr>
<tr>
<td>Resistance to NRTIs</td>
<td>4.3 (13)</td>
<td>2.5-7.2</td>
</tr>
<tr>
<td>Resistance to NNRTIs</td>
<td>5.3 (16)</td>
<td>3.3-8.5</td>
</tr>
<tr>
<td>Resistance to PIs</td>
<td>4.3 (13)</td>
<td>2.5-7.2</td>
</tr>
</tbody>
</table>

- Primary resistance to ARVs was detected in 12.3% of the participants
  
  - 10.9% [n=33, 95% CI: 7.9-15.0] of participants presented **single class resistance to ARVs**
  - 1.0% [n=3, 95% CI: 0.34-2.9] of participants presented **double class resistance to ARVs**
  - Only one participant presented **triple class resistance to ARVs**
### Table 4- ARV resistance mutations identified in the BEST HOPE study population

<table>
<thead>
<tr>
<th>NRTI</th>
<th>Patients n (%)</th>
<th>NNRTI</th>
<th>Patients n (%)</th>
<th>PI</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M41L</td>
<td>7 (2.3)</td>
<td>K103N</td>
<td>9 (2.9)</td>
<td>L90M</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>V75M</td>
<td>2 (0.7)</td>
<td>G190S</td>
<td>3 (1.0)</td>
<td>N88D</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>L210W</td>
<td>2 (0.7)</td>
<td>K101E</td>
<td>1 (0.3)</td>
<td>M46I/L</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>T215D/E</td>
<td>4 (1.3)</td>
<td>L100I</td>
<td>1 (0.3)</td>
<td>I54V</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>K65R</td>
<td>1 (0.3)</td>
<td>Y188L</td>
<td>1 (0.3)</td>
<td>D30N</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>4 (1.3)</td>
<td>Y181C</td>
<td>1 (0.3)</td>
<td>I84V</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>K70E</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L74V/I</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NRTIs:** most frequent mutation M41L  
**NNRTIs:** most frequent mutation K103N  
**PIs:** most frequent mutation L90M

**NRTIs:** most frequent major mutation M184V  
**NNRTIs:** most frequent major mutation K103N  
**PIs:** major mutation I84V

*Pls, Protease inhibitors; NRTIs, Nucleoside Reverse Transcriptase Inhibitors; NNRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors*
**Results**

Guidelines for 1st line ARV therapy in Portugal (without using integrase inhibitors):

- TDF/FTC or ABC/3TC (NRTI) with RPV or EFV (NNRTI) or TDF/FTC or ABC/3TC (NRTI) with DRV/r or ATV/r (PI)

As alternative regimen:
- NVP as NNRTI
- LPV/r as PI

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### Table 5 - Number of patients and mutations causing resistance to ARVs used as 1st line therapy

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>Drug</th>
<th>Patients High-Level Resistance</th>
<th>Patients Intern Resistance</th>
<th>Patients Low-Level Resistance</th>
<th>Identified mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td>Tenofovir (TDF)</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>K65R, M41L, L210W, T215rev</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine (FCT)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>K65R, M184V/I</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>K65R, M184V/I, K70E</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>Efavirenz (EFV)</td>
<td>13</td>
<td>1</td>
<td>2</td>
<td>K103N, K101E, Y181C, G190A</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine (RPV)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>L100I, Y188C</td>
</tr>
<tr>
<td></td>
<td>Nevirapine (NVP)</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>L100I, K103N, Y181C, Y188L, G190S/A</td>
</tr>
<tr>
<td><strong>PI</strong></td>
<td>Atazanavir (ATV/r)</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>I84V, I54V, L90M</td>
</tr>
<tr>
<td></td>
<td>Darunavir (DRV/r)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>I84V</td>
</tr>
<tr>
<td></td>
<td>Lopinavir (LPV/r)</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>I54V, M46I/L, L90M</td>
</tr>
</tbody>
</table>
Results

Table 6 - % TDR by patient group

<table>
<thead>
<tr>
<th>Groups</th>
<th>TDR % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migrants</td>
<td>9.3 (5/54)</td>
</tr>
<tr>
<td>MSMs</td>
<td>11.1 (11/99)</td>
</tr>
<tr>
<td>MSM-Migrants</td>
<td>15.0 (3/20)</td>
</tr>
<tr>
<td>General population</td>
<td>12.5 (15/120)</td>
</tr>
</tbody>
</table>

MSM-Migrants presented the highest level of TDR

Table 7 - % TDR by country of origin

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>TDR % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>12.2 (27/221)</td>
</tr>
<tr>
<td>Brazil</td>
<td>12.0 (3/25)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>4.9 (2/41)</td>
</tr>
</tbody>
</table>

Patients from Portugal and Brazil presented higher levels of TDR

Table 8 - % TDR by subtype

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>A1</th>
<th>B</th>
<th>C</th>
<th>CRF02_AG</th>
<th>F1</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDR % (n)</td>
<td>10.3 (3/29)</td>
<td>11.8 (14/119)</td>
<td>30.8 (8/26)</td>
<td>14.3 (2/14)</td>
<td>4.5 (1/22)</td>
<td>8.1 (5/62)</td>
</tr>
</tbody>
</table>

Subtype C presented the highest level of TDR

p=0.889

p=0.387

p=0.048
## Results

### Table 8- Simple Binary logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sig</th>
<th>OR Crude</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population*</td>
<td>0.890</td>
<td>0.910</td>
<td>0.453-1.828</td>
</tr>
<tr>
<td>Migrants</td>
<td>0.537</td>
<td>1.19</td>
<td>0.59-2.42</td>
</tr>
<tr>
<td>MSM</td>
<td>0.752</td>
<td>1.14</td>
<td>0.491-2.612</td>
</tr>
<tr>
<td>MSM-Mig</td>
<td>0.757</td>
<td>1.15</td>
<td>0.491-2.612</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male*</td>
<td>0.016</td>
<td>0.226</td>
<td>0.067-0.760</td>
</tr>
<tr>
<td>Female</td>
<td>0.973</td>
<td>0.66</td>
<td>0.283-1.575</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low*</td>
<td>0.712</td>
<td>0.993</td>
<td>0.963-1.025</td>
</tr>
<tr>
<td>High</td>
<td>0.147</td>
<td>0.461</td>
<td>0.162-1.313</td>
</tr>
<tr>
<td><strong>Geographic region of origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portugal*</td>
<td>0.184</td>
<td>0.368</td>
<td>0.084-1.614</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>0.185</td>
<td>0.980</td>
<td>0.275-3.495</td>
</tr>
<tr>
<td>Brazil</td>
<td>0.975</td>
<td>4.790</td>
<td>0.765-29.979</td>
</tr>
<tr>
<td><strong>Subtype A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td>0.737</td>
<td>0.808</td>
<td>0.232-2.813</td>
</tr>
<tr>
<td>Yes</td>
<td>0.871</td>
<td>2.06</td>
<td>0.908-4.707</td>
</tr>
<tr>
<td><strong>Subtype B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td>0.822</td>
<td>0.922</td>
<td>0.454-1.872</td>
</tr>
<tr>
<td>Yes</td>
<td>0.005</td>
<td>3.770</td>
<td>1.506-9.436</td>
</tr>
<tr>
<td><strong>Subtype C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td>0.163</td>
<td>7.306</td>
<td>0.447-119.372</td>
</tr>
<tr>
<td>Yes</td>
<td>0.005</td>
<td>3.770</td>
<td>1.506-9.436</td>
</tr>
<tr>
<td><strong>Subtype D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td>0.163</td>
<td>7.306</td>
<td>0.447-119.372</td>
</tr>
<tr>
<td>Yes</td>
<td>0.005</td>
<td>3.770</td>
<td>1.506-9.436</td>
</tr>
</tbody>
</table>

### Table 9- Multiple binary logistic regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sig</th>
<th>OR Adjust</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype F1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.275</td>
<td>0.321</td>
<td>0.042-2.463</td>
</tr>
<tr>
<td><strong>Subtype G</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.261</td>
<td>0.567</td>
<td>0.211-1.523</td>
</tr>
<tr>
<td><strong>CRF02_AG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.816</td>
<td>1.200</td>
<td>0.258-5.587</td>
</tr>
<tr>
<td><strong>Viral Load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.640</td>
<td>1.097</td>
<td>0.744-1.618</td>
</tr>
<tr>
<td><strong>Stage of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A and B*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.034</td>
<td>2.442</td>
<td>1.067-5.586</td>
</tr>
<tr>
<td><strong>STI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.191</td>
<td>1.645</td>
<td>0.780-3.470</td>
</tr>
</tbody>
</table>

*Reference category
Final Considerations

• The Portuguese epidemic is changing;

• Incidence of subtype G has decreased, while the incidence of other non-B subtypes is increasing, specially A1;

• The % of TDR (12.3%) is higher compared with the last estimate of 2005 (7.8% - SPREAD); suggesting that TDR is increasing;

• The NNRTIs class presented the highest values of TDR (5.2%);

• Subtype C presented high values of TDR compared to other subtypes, due to the highly prevalent L90M mutation.
Final Considerations

- Gender, subtype C and advanced disease (stage C) are correlated with TDR in the univariate analyses;

- Only gender and subtype C remained associate with TDR in the multivariate analysis.
Perspectives

• To increase the number of patients included in the study population;

• To analyze socio-behavioral and demographic factors and correlate them with the genomic data and with transmission chains;

• To characterize Portuguese transmission chains of HIV and of TDR;

• To identify mutations transmitted in these transmission chains.
**Funding**

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Catarina Rodrigues
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Célia Morais
Celina Bredes
Cláudia Salvado

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Telo Faria
Teresa Baptista
Vanda Mota
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THANK YOU!!!