BEST HOPE - Cohort of HIV newly diagnosed patients in Portugal

Pingarilho M.[1], Pineda-Peña A.C.[1,2], Dias S.[1], Pimentel V.F.[3], Libin P.[4,5], Aleixo M.J.[6], Amaral-Alves D.[1], Ascenção B.[7], Azevedo F.[8], Baptista T.[9], Bredes C.[10], Brito P.[7], Cabanas J.[11], Cabo J.[12] ,Caixeiro M.[13], Caldas C.[14], Campos M.J.[15], Cardoso S.[12], Carvalho A.P.[11], Casella I.[7], Correia L.[16], Correia-Abreu R.[17],Côrte-Real R.[18], Costa I.[11], Costa O.[18], Cunha S.[16], Diogo I.[11], Faria D.[8], Faria T.[19], Feijó M.[7], Ferreira J.[10], Germano I.[21], Gomes A.[6], Gomes P.[11,20], Gonçalves F.[11], Gonçalves M.J.[22], Granado A.[6], Ivo M.S.[23], Jesus J.[21], Koch C.[24], Lino S.[12], Luís N.[7], Maio A.[25], Maltez F.[12], Mansinho K.[9], Marques N.[6], Marques S.[6], Martins S.[22], Mateus E.[7], Mendão.L.[15], Messias C.[7], Monteiro F.[24], Morais C.[26], Mota V.[26], Neves I.[17], Nunes S.[25], Oliveira J.[16], Pacheco P.[13], Pereira H.[26], Pereira-Vaz J.[26], Pessanha M.[11], Pimenta A.[10], Piñeiro C.[14], Pinheiro S.[27], Pinho R.[8], Poças J.[7], Proença P.[10], Ramos H.[28], Rocha M.[15],Rodrigues C.[21], Rodrigues P.[29], Rodrigues R.[26], Roxo F.[23], Sá J.[7], Salvado C.[6], Sarmento-Castro R.[22], Seixas D.[12], Serrão R.[14], Silva A.R.[29], Silva E.G.[19], Silva V.[7], Simão M.[8], Simões D.[15], Simões J.[21], Simões P.[12], Soares J.[14], Tavares R.[29], Teófilo E.[27], Trigo D.[13],Theys K.[5], Martins M.R.O.[1], Vandamme A.M.[1,5], Camacho R.J.[5], Abecasis AB.[1,5]

1-Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical/Universidade Nova de Lisboa (IHMT/UNL), Lisboa, Portugal; 2-Molecular Biology and Immunology Department, Fundación Instituto de Inmunología de Colombia (FIDIC), Basic Sciences Department, Universidad del Rosario, Bogotá, Colombia; 3-Universidade de São Paulo, Departamento de Microbiologia, São Paulo, Brasil; 4-Artificial Intelligence lab, Department of computer science, Vrije Universiteit Brussel; 5-Clinical and Epidemiological Virology, Department of Microbiology and Immunology, Rega Institute for Medical Research, KU Leuven, University of Leuven, Belgium; 6-Serviço de Infeciologia, Hospital Garcia da Orta, Almada, Portugal;7-Serviço de Infeciologia, Centro Hospitalar de Setúbal, 2910-446 Setúbal, Portugal; 8-Serviço de Doenças Infeciosas, Centro Hospitalar do Algarve, Hospital de Portimão, Portimão, Portugal; 9-Serviço de Doenças Infeciosas, Centro Hospitalar de Lisboa Ocidental, Hospital de Egas Moniz, Lisboa, Portugal; 10-Serviço de Infeciologia-Centro Hospitalar do Algarve, Hospital de Faro, Faro, Portugal; 11-Laboratório de Biologia Molecular (LMCBM, SPC, CHLO-HEM), Lisboa, Portugal; 12-Serviço de Doenças Infeciosas, Centro Hospitalar de Lisboa, Hospital Curry Cabral, Lisboa, Portugal; 13-Serviço de Infeciologia, Hospital Dr. Fernando da Fonseca, Amadora, Portugal; 14-Serviço de Doenças Infeciosas, Centro Hospitalar de São João, Porto, Portugal; 15-GAT - Grupo de Ativistas em Tratamentos, Lisboa, Portugal; 16-Serviço de Infeciologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; 17-Serviço de Infeciologia, Unidade de Local de Saúde de Matosinhos, Hospital Pedro Hispano, Matosinhos, Portugal; 18-Serviço de Patologia Clínica, Biologia Molecular, Centro Hospitalar de Lisboa Central, Lisboa, Portugal; 19-Unidade Local de Saúde do Baixo Alentejo, Hospital José Joaquim Fernandes, Beja, Portugal; 20-Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Superior de Ciências da Saúde Egas Moniz, Caparica, Portugal; 21-Serviço de Medicina 1.4, Centro Hospitalar de Lisboa Central, Hospital de São José, Lisboa, Portugal; 22-Serviço de Infeciologia, Centro Hospitalar do Porto, Porto, Portugal; 23-Hospital de Dia de Doenças Infeciosas, Hospital Distrital de Santarém, Santarém, Portugal; 24--Centro de Biologia Molecular, Serviço de Imunohemoterapia do Centro Hospitalar São João, Porto, Portugal; 25-Serviço de Infeciologia, Centro Hospitalar Baixo Vouga, Hospital de Aveiro, Aveiro, Portugal; 26-Serviço de Patologia Clínica, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; 27-Serviço de Infeciologia, Centro Hospitalar de Lisboa Central, Hospital de Santo António dos Capuchos, Lisboa, Portugal; 28-Serviço de Patologia Clínica, Centro Hospitalar do Porto, Porto, Portugal; 29-Serviço de Infeciologia, Hospital Beatriz Ângelo, Loures, Portugal.

BACKGROUND

Every day, around 7000 people still get infected with HIV worldwide. Antiretroviral (ARV) therapy reduced morbidity and mortality, and while early ART is expected to reduce incidence, transmission of HIV infection is still ongoing. Transmission investigations shed light on how to prevent HIV spread and on the origin of transmitted drug resistance (TDR). Clinical, socio-behavioral and therapy adherence factors influence the transmission of HIV and the efficacy of interventions.

In Europe, the latest estimates of TDR in newly diagnosed patients were around 9.4%[1], however, some regions in Sub-Saharan Africa have a prevalence as high as 11.6%[2]. Recently, several LMIC reported levels of HIV Drug Resistance (HIVDR) at or above 10% amongst antiretroviral (ARV) Therapy (ART) naïve patients and up to 37% among individuals re-starting ART. Particularly, a recent study indicated a prevalence of 57% of HIVDR to tenofovir, the most used first line drug, in patients on virological failure from Sub-Saharan Africa[3].

The HIV epidemic has been shown to present highly compartmentalized epidemics[4]. Furthermore, patterns of TDR in Europe have been shown to vary between risk groups. This could be explained by the fact that Men who have Sex with Men (MSM) originate from resource-rich countries and are mostly infected with subtype B, for whom ARVs have been available for longer. In contrast, heterosexually infected patients in Europe are mostly immigrants from Sub-Saharan Africa where the use of ART has been initiated more recently[5].

No studies on newly diagnosed HIV patients exist to understand recent patterns of TDR in Portugal.

OBJECTIVES to construct a cohort of newly diagnosed HIV patients in Portugal

- to analyze the prevalence and characteristics of TDR in newly diagnosed HIV patients
- to describe and analyze risk factors associated with HIV infection and transmission of drug resistance in Portugal.

MATERIAL AND METHODS

Study Population

- **Recruitment of patients:**
  - Patients recruited in 18 Portuguese hospitals
  - Recruitment of participants done by clinicians and clinical staff
    - **Inclusion criteria**:
      - ✓ at least 18 years old
      - ✓ new HIV diagnosis since September 2014
      - ✓ baseline drug resistance test
    - **Exclusion criteria:**
      - ✓ compromised understanding /not-imputable

Drug resistance testing

- Drug resistance testing with population-based Sanger sequencing of protease (PR) and partial reverse transcriptase (RT) (ViroSeq HIV-1 Genotyping System or TRUGENE HIV-1 genotyping kit)
- TDR mutations defined according to the 2009 list of Surveillance Drug Resistance Mutations (SDRM) from the World Health Organization
- Nucleotide sequences submitted to the Calibrated Population Resistance tool -HIV drug resistance database version 6.0 (http://cpr.stanford.edu/cpr.cgi)
- Clinical impact of TDR evaluated with HIVdb v7.0 and Rega v 9.1.0. (https://hivdb.stanford.edu/hivalg/by-mutations/)

HIV-1 Subtyping

- HIV-1 subtypes and circulating recombinant forms (CRF) determined using two different HIV-1 subtyping tools:
  - Rega version 3 (http://www.bioafrica.net/typing-v3/hiv)
  - COMET version 3.0 (http://comet.retrovirology.lu/)

Data Collected:

- 248 patients included until November 2016
- For each patient:
  - ✓ clinical form filled in by the clinicians
  - ✓ HIV genomic sequence obtained from the first drug resistance test
  - ✓ Socio-behavioral data obtained through a questionnaire for patients of specific vulnerable groups (MSM and Migrants)

Data management:

- Relational Access database, constructed to store and manage the data collected

Data analysis:

RESULTS

Table 1 -Prevalence of resistance mutations in participants of the BEST HOPE study

	Patients n (%)	95% CI
Sequences with **any** SDRM	34 (13.7)	9.9-18.6
RT Sequences with any **NRTI** SDRM	12 (4.9)	2.8-8.3
RT Sequences with any **NNRTI** SDRM	14 (5.7)	3.4-9.3
PR Sequences with any **PI** SDRM	13 (5.3)	3.1-8.8

Nucleoside Reverse transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs)

- Primary drug resistance detected in 13.7% of individuals
  - ✓ Resistance to NNRTIs presented the highest values of SDRM (5.7%)
  - ✓ Resistance to NRTIs found in 5.3% and on PIs in 4.9%
- 12.1% [95% CI: 8.6-16.7] of the patients presented single class resistance, while 1.2 % [95% CI: 0.4-3.5] presented double class drug resistance and only one patient presented triple class drug resistance.

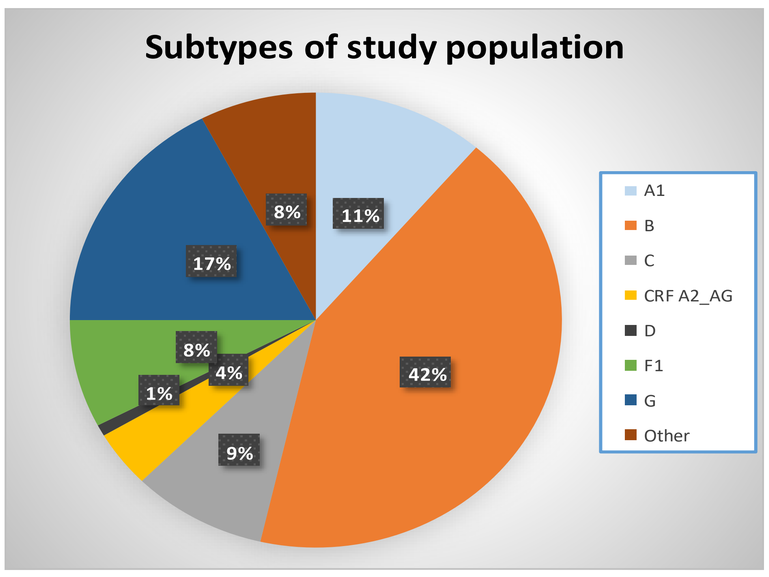

Figure 1- HIV-1 subtypes identified in the BEST HOPE study population

- The most common pure subtypes were **B (42%)** and **G (17%)**, followed by subtypes A1 (11%), C (9%), F1 (8%) and D (1%).
- The recombinant form CRF02_AG represented 4% of the samples

- Until November 2016, the **BEST HOPE population** included 248 patients, of which **40.8%** (101/248) were **MSM** and **14.5%** (36/248) were **migrants.**
- **59.4% of the MSMs** were infected with **subtype B**, followed by subtype A1 (17.8%), subtype C and F1 (5%) and with subtype G (4%).
- **25% of the migrants** were infected with **subtype C**, followed by subtype B (16.7%), subtype G and F1 (11.1 %) and subtype A1 (8.3%).
- 11.9% of MSMs and 11,1% of migrants presented any SDRM

Table 2- Drug resistance mutations identified in the recruited BEST HOPE patient population

NRTI	Patients n(%)	NNRTI	Patients n(%)	PI	Patients n(%)
M41L	7 (2.8)	**K103N**	9 (3,6)	L90M	8 (3,2)
V75M	2 (0,8)	**G190S**	2 (0,8)	N88D	2 (0,8)
L210W	2 (0,8)	K101E	1 (0,4)	M46I/L	2 (0,8)
T215D	3 (1,2)	**L100I**	1 (0,4)	I54V	1 (0,4)
K65R	1 (0,4)	**Y188L**	1 (0,4)	D30N	1 (0,4)
M184V/I	4 (1,6)	**Y181C**	1 (0,4)	**I84V**	1 (0,4)
T215E	1 (0,4)				
L74V/I	1 (0,4)				

Nucleoside Reverse transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs)
Bold: major mutations, as defined by the 2009 list of SDRMs from the World Health Organization.

- **5.2%** [n=13; 95% CI: 3.1-8.8] of patients presented mutations causing high level resistance to NNRTIs, **1.6%** [n= 4; 95% CI:0.6-4.1] high level resistance to NRTIs and only **0.4%** (n=1) high level resistance to PIs.
- NRTIs: the more frequently identified ARV resistance mutation was M41L
- NNRTIs: the more frequently identified ARV resistance mutation was K103N, which confers resistance to Efavirenz (EFV) and Nevirapine (NVP)
- PIs: the more frequently identified ARV resistance mutation was L90M.
- Cross resistance - T69 insertion or Q151M - was not found.
- High level resistance to Truvada (Tenofovir + Emtricitabine) was found in 4 patients (4/248, 1,6%) (K65R and M184V/I).

CONCLUSIONS

- **Primary drug resistance** was detected in **13.7%** of individuals. This value almost doubled compared to the last study performed in Portugal (SPREAD), where 7.8% of patients were identified as carrying resistance associated mutations[6]
- Primary drug resistance to **NNRTIs** is worrying, with **5.2%** of patients presenting high level resistance to EFV or NVP and 0,8% to Rilpivirine (RPV)) at baseline.
- Primary drug resistance was found in 11.9% of MSMs and in 11.1% of migrants.
- The **most common subtypes** were **B (42%)** and **G (17%).** The incidence of subtype G decreased substantially when compared to the estimate of SPREAD (29.4%). Conversely, the incidence of subtype A1 increased from 1.7% to 11%.
- **Subtype A1** is circulating in Portuguese **MSMs (18%)**, concordantly to what has been found in other European countries.
- The subtypes circulating in MSMs compared to migrants are very different, suggesting the existence of compartmentalized epidemics.

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