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Two Decades of Late Diagnosis in HIV Infection: Experience of a District Hospital (Late Study)

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Abstract

Background: Portugal has one of the highest incidence rates of HIV and AIDS and one of the highest percentages of late diagnosis in the European Union.

Objectives: Evaluation of late diagnoses between 1998-2018. Comparison of demographic, epidemiological and mortality data. Identification of risk factors to very late presentation.

Methods: Retrospective study of HIV patients with 1st visit between 1998-2018, divided into groups A: Lymphocyte TCD4+ count (TCD4+) <200 cells/µl; B: TCD4+ 200-350 cells/µl. Statistical analysis by Statistical Package for the Social Sciences® (SPSS) 24.0.

Results: From the data base, 613 patients met the TCD4+ cell count, but only 48% (n=533) fulfilled all inclusion criteria 65.5% of which (n=349) in group A. Group analysis (A *vs.* B): Male predominance 80.2% *vs.* 67.4% (p=0.001); age at 1st visit >40 yrs. 52.4% *vs.* 35.9% (p=0.001) increasing with time (p<0.001); heterosexual risk 55.3% *vs.* 52.7%, increasing with time (p<0.001); intra-hospital referral 50.4% *vs.*23.9% (p<0.001). Between-group comparison: 66.2% *vs.* 31.0% (p<0.001) had an AIDS-defining illness, most frequently tuberculosis (19.5% *vs.* 17.9%).

Mortality rate was higher in Group A (28.7%, p=0.020), with a lower survival time (1828 [433-3675] days, p=0.008).

Conclusion: Risk factors for very late presentation (TCD4+ <200 cells/µl) are as follows: Male gender (OR=2.00, CI 95% 1.25 to 3.20, p=0.004), age over 40 yrs. (OR=1.79, 95% CI 1.19 to 2.71, p=0.006) and intra-hospital diagnosis (OR=3.16, CI 95% 2.10 to 4.76, p<0.001). The increase in risk over 40 yrs was not observed in women (OR=0.90, CI 95% 0.40 to 2.07, p=0.809).

These results support the importance of early HIV diagnosis, with implications in global outcome and public health.

Keywords: AIDS; HIV; Late diagnosis

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Introduction

Despite the advances in early Human Immunodeficiency Virus (HIV) diagnosis and universal testing, from 2014 to 2016 a quarter of diagnoses were in an advanced stage of infection [1]. Thus in 2017, the European Union (EU) reported 25,353 new diagnoses [6.2 cases/10^5 inhabitants] [2] with 12.3% presenting with Acquired Immunodeficiency Syndrome (AIDS) at diagnosis [0.7 cases/10^5 inhabitants] [2,3].

In 2018, 37.9 million were living with HIV worldwide [4]; an incidence of 1.7 million [4] and 770,000 deaths due AIDS [4] that same year, accounting for 74.9 [58.3-98.1] millions of HIV patients (pts) and 32.0 million deaths due AIDS since the beginning of the epidemic [4].

In Portugal, between 1983-2017 the National Healthcare Institute Doctor Ricardo Jorge (INSA) [5] reported, 57,913 cases of HIV cumulatively, 38.16% of which presenting with AIDS. In fact, 2017 saw the highest incidence of HIV and AIDS [1-3,5] in all EU, with 1068 new cases [10.4 cases/10^5 inhabitants] [3], 68.1% of which asymptomatic at first clinical evaluation (visit). Analyzing TCD4+ counts (available in 84.7% of pts) 51.1% were late diagnoses (TCD4+ <350 cells/µl) of which 31.1% had advanced disease (TCD4+ <200 cells/µl) [1,2] and 14.8% with concomitant diagnoses of AIDS [1] at presentation. In that year, 261 deaths were reported, 134 due AIDS [1]. This situation was more prevalent in the heterosexual group [5].

Analyzing by district, Lisbon, Porto and Portimão presented the highest incidence of HIV between 2013-2017 [1], Lisbon being the highest [38.8 cases/10^5 inhabitants] [5].

The introduction of combined Antiretroviral Therapy (cART) in 1996, offered an effective recovery of the immunity [6,7] leading to an incidence drop of 40% [4] (since its peak in 1997 (16% since 2010 [4]), accounting for a decreased of more than 55% in mortality due to AIDS [4] since its peak in 2004 [3] (33% since 2010) in developed countries [3,4,6,8,9].

However, an increase in early diagnosis rates [10] in clinical practice was not observed and late diagnosis remains a problem both at individual and community levels [6].

Thus, the complete and accurate identification of at-risk populations allows more effective both preventive and therapeutic efforts.

The Local Healthcare Unit of Matosinhos was the first integrated unit in the Portuguese healthcare system to emerge and is the reference public health unit for the cities of Matosinhos, Póvoa de Varzim and Vila do Conde, providing healthcare for about 320000 inhabitants.

Currently, it holds a total of 1112 pts with HIV/AIDS, 931 under steady follow-up by the Infectious Diseases Service (SI.HPH) with an incidence of 40 to 50 pts/yr. These pts are a part of Si. HPH database - Microsoft Access® created and registered at the National Data Protection Commission (Decree No. 67/1998 of 26 October) since 2007 and ASSOFT (Portuguese Software Association) since 2006.

Objective

To study the evolution of late diagnoses between 1998-2018, considering two TCD4+ cut-off groups at 1st visit: TCD4+ <200 cells/µl and TCD4+ 200 to 350 cells/µl; to compare demographic, epidemiological, AIDS-defining illnesses and mortality and to identify risk factors associated with very late presentation (advanced disease).

Methods

Observational and retrospective study; pts selected according to inclusion criteria - HIV pts with 1st visit at S. HPH between January 1998 and December 2018, aTCD4+ ≤ 350 cells/µl, and registered at the SI. HPH database. The exclusion criteria were pts with uncompleted data.

Microsoft Excel 365® was used for data collection from the database; variables under study are in Tables 1 and 2.

Statistical Analysis

Pts with TCD4+ <200 cells/µl were defined as very late presenters (advanced disease) (Group A) whereas those with TCD4+ 200 to 350 cells/µl as late presenters (Group B).

Evolution of the variables over time for the entire sample was made for equitable temporal periods in order to allow for a better statistical analysis; grouped in 1998-2004, 2005-2011 and 2012-2018.

To evaluate the normality of quantitative variables, the Kolmogorov-Smirnov test was applied and asymmetry, skewness and histograms were analyzed. After verification of non-normality ($p<0.05$), non-parametric tests were used: Mann-Whitney U test for analysis of two independent samples, for which r was used as an effect size measurement and the Kruskal-Wallis H test when analyzing more than 2 independent samples, for which the eta square test ($\eta 2$) was used as a measure of effect size.

Table 1: Quantitative variables under study.

Quantitative variables	- Age at 1st visit
	- Time HIV-1st visit*
	- Time HIV-AIDS
	- Time HIV-death
	- Time 1st visit-death§
	- Time AIDS-death**
	- TCD4+ lymphocyte count at the 1st visit

*time elapsed since HIV diagnosis and first medical visit with the HPH Infectious Diseases Service
†time elapsed between HIV diagnosis and the development of an AIDS-defining disease
‡time elapsed between HIV diagnosis and death
§time elapsed between the 1st consultation and death
**time elapsed between the development of an AIDS-defining disease and death

Table 2: Qualitative variables under study.

Qualitative variables	- Age group at the 1st visit*
	- Time interval of the 1st query†
	- Gender (male, female)
	- Race/ethnic (Caucasian, black, gypsy, unknown)‡
	- Nationalities (Portuguese, foreign, unknown)
	- Civil state (single, married, de facto marriage, widower, divorced, unknown)
	- HIV virus type (1, 2, 1 and 2)
	- Provenience (Health Centers-ULSM, HPH Emergency, HPH Internal Consultation, HPH Internment, Drug Addiction Care Center (CAT), Prison Establishment, External (i.e. out-of-hospital))§
	- Transmission risk (accidental/assault, heterosexual, conjugal, homosexual, bisexual, use of injectable drugs (IDU), vertical, transfusion)**
	- CDC stage in the 1st visit(A2, B2, C2, A3, B3, C3)
	- AIDS-defining illness¶
	- Death (yes, no)

In some analyses:
*age was categorized as less than or equal to 30, between 31 to 40, over 40 years
†the year of the first medical visit was categorized between 1998-2004, 2005-2011 and 2012-2018
‡the breed was categorized as Caucasian *vs.* others
§provenance was categorized into in-hospital *vs.* out-of-hospital
**the transmission route was categorized into heterosexual/conjugal, homosexual/bisexual, IDU, accidental/aggression, vertical/transfusion
¶grouped in esophageal candidiasis, cytomegalovirus infection (CMV), cryptococcosis, Progressive Multifocal Leukoencephalopathy (PML), neoplasic disease, tuberculosis (TB), pneumonia by *P. jirovecii*, others and without AIDS-defining disease

In case of normality violation, descriptive statistics of quantitative variables were report as median (interquartile amplitude). For qualitative variables, frequency was reported.

For categorical variables, the Chi-Square test (X^2) was used. When the percentage of cells with n<5 was higher than 20%, the Exact Fisher Test value was reported. The phi coefficient (ϕ) was used as an effect size measure for this test.

A binary logistical regression was drawn to analyze the predictive variables of presentation with advanced disease based on the significant variables previously analyzed between groups. The result was presented in Odds Ratio (OR) followed by 95% Confidence Interval (95% CI). The Odds Ratio (OR) is an effect size measure,

Table 3: Characteristics of HIV-infected patients at the first visit in Group A and B.

Characteristics	Frequency (%) in Group A	Frequency (%) in Group B
Gender		
Female	69 (19.8%)	60 (32.6%)
Male	280 (80.2%)	124 (67.4%)
Type of HIV		
HIV 1	339 (97.1%)	182 (98.6%)
HIV 2	5 (1.4%)	1 (0.5%)
HIV 1 e 2	5 (1.4%)	1(0.5%)
Age		
≤ 30 years	66 (18.9%)	55 (29.9%)
30-40 years	100 (28.7%)	63 (34.2%)
>40 years	183 (52.4%)	66 (35.9%)
Civil Status		
Single	139 (39.8%)	93 (50.5%)
Marital union	16 (4.6%)	4 (2.2%)
Married	133 (38.1%)	60 (32.6%)
Divorced	23 (6.6%)	8 (4.3%)
Widower	17 (4.9%)	8 (4.3%)
Unknown	21 (6.0%)	11 (6.0%)
Race/ethnic		
Caucasian	244 (69.9%)	125 (67.9%)
Black	7 (2.0%)	9 (4.9%)
Gypsy	3 (0.9%)	0 (0.0%)
Unknown	95 (27.2%)	50 (27.2%)
Nationality		
Portuguese	243 (69.6%)	123 (66.8%)
Foreign*	9 (2.6%)	11 (6.0%)
Unknown	97 (27.8%)	50 (27.2 %)
Transmission Route		
HSH†	27 (7.7%)	15 (8.2%)
Heterosexual	168 (48.1%)	79 (42.9%)
Conjugal (heterosexual)	25 (7.2%)	18 (9.8%)
Bisexual	8 (2.3%)	5 (2.7%)
Use of inject able drugs	117 (33.5%)	65 (35.3%)
Vertical	1 (0.3%)	1 (0.5%)
Accidental/Assault	2 (0.6%)	1 (0.5%)
Transfusion	1 (0.3%)	0 (0.0%)
Provenance		
Local health centers	60 (17.2%)	60 (32.6%)
Exterior‡	90 (25.8%)	51 (27.7%)
CAT§	9 (2.6%)	15 (8.2%)
Prison establishment and teaching	14 (4.0%)	14 (7.6%)
HPH Internal Consultation	19 (5.4 %)	17 (9.2%)
HPH Internment	134 (38.4 %)	14 (7.6%)
HPH Urgency	23 (6.6 %)	13 (7.1%)
AIDS defining condition	231 (66.2%)	57 (31.0%)

*includes 2 individuals from Guinea-Bissau, 3 from Brazil, 3 from Mozambique and 1 from Ukraine, in Grupo A and 2 from Guinea-Bissau, 2 from Mozambique and 1 from Angola, Cape Verde, Ghana, Nigeria, Uruguay and Ukraine, in Group B

†men who have sex with men

‡includes self-diagnosis center (CAD), Portuguese Blood Institute (IPS), other health centers and other hospitals

§Drug treatment center for drug addicts

whereas the Wald value indicates the contribution of each variable to the model in question.

The variables were then compared between Group A and B and the significance level established for all analyses was 0.05.

Statistical analysis was made by Statistical Package for the Social Sciences® (SPSS Inc®. Chicago, Illinois, EUA) version 24.0.

Ethical Considerations

Submitted and approved by the Subcommittee on Ethics for Life Sciences and Health of the University of Minho and by the Council of The Ministry and Ethics and Health Committee of ULSM.

The ethical requirements of secrecy, anonymity and confidentiality were met during the process of collection, storage and processing of data.

Results

Of the 1112 HIV pts registered at the SI.HPH database, with 1st visit between 1998-2018, 613 (55%) presented with TCD4+ ≤ 350 cells/µl. Of those, 80 were excluded due to misinformation in the database. Therefore, 533 pts were included: 349 (65.5%) in Group A and 184 (34.5%) in B with a median TCD4+ of 62 cells/µl [23-119] in A *vs.* 287 cells/µl [247-314] in B (Figure 1).

Between 2001-2013 the incidence was higher than 25 cases/yr., with a maximum of 42 in 2012. In a grouped temporal analysis, the distribution was as follows: 31.0% (n=165) in 1998-2004, 44.8% (n=239) in 2005-2011 and 24.2% (n=129) in 2012-2018. Between 2003-2011, with early screening already underway, 55.8% (n= 297) of all pts were late diagnoses at 1st visit.

In a grouped analysis, the incidence in A ranged from 31.2% (n=109) in 1998-2004 to 43.8% (n=153) in 2005-2011 to 24.9% (n=87) in 2012-2018. However, 58.0% (n=202) of the diagnoses were made between 2004-2012. In B, the variation went from 30.4% (n=56) in 1998-2004 to 46.7% (n=86) in 2005-2011 to 22.8% (n=42) in 2012-2018. In this group, 55.4% (n=102) were diagnosed between 2003-2011.

Regarding TCD4+ count at 1st visit, no significant differences were observed over time ($H(2)=1,640$, $p=0.440$, $\eta^2=0.003$). The proportion of pts in Group A was always higher than in B with a ratio of 1.9:1, which remained constant over time ($X^2(2)=0.471$, $p=0.790$, $\phi=0.030$). However, over the last 3 years (2016-2018), the annual incidence reached its lowest, only comparable to that of 1998-1999, with a total of 8 cases in 2018, 7 of which with advanced disease in both groups.

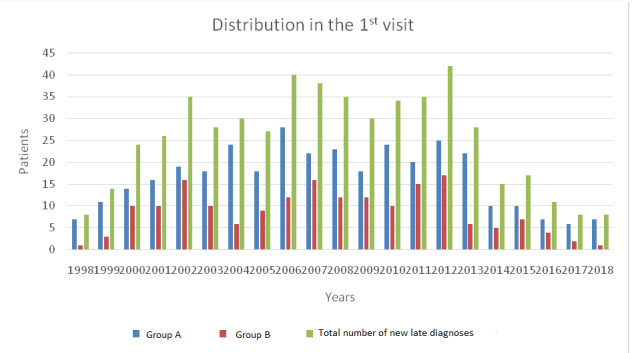

Figure 1: Distribution of the total number of new late diagnoses per year of the 1st medical visit.

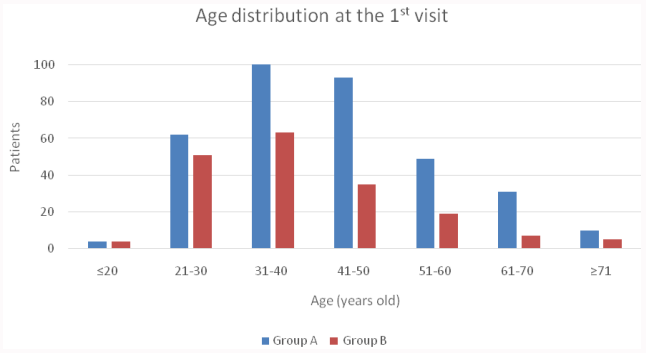

Figure 2: Patients distribution by age at the 1st medical visit.

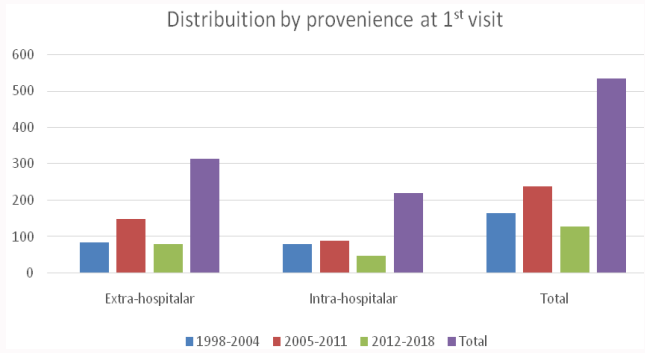

Figure 3: Distribution of late diagnoses by time intervals according to provenance.

The epidemiologic distributions of pts are shown in Table 3.

Regarding HIV type, no significant association was observed across the groups (Fisher Test =1.316, p=0.573, ϕ=0.057). In an overall gender analysis, 75.8% (n=404) of patients were male and 24.2% (n=129) female, with a significant association between males and the risk of advanced disease at presentation ($X^2(1)=10.824$, p=0.001, ϕ=-0.143). This predominance was observed in both groups with a significantly higher prevalence in Group A, with 80.2% (n=280) of cases *vs.* 67.4% (n=124) in B.

In a detailed gender analysis, 69.3% (n=280) of men presented with advanced disease at 1st visit *vs.* 53.5% (n=69) of women ($X^2(1)=10.824$, p=0.001, ϕ= -0.143).

This predominance of the male gender remained constant over time, as well as a male:female ratio of 3.13:1 for all of late diagnoses ($X^2(2)=0.666$, p=0.717, ϕ=0.035). The median TCD4+ at 1st visit was higher in women (186 cells/µl [59-289]) when compared to men (105 cells/µl [38-232]) (U=20977, p=0.001, r= -0.145).

Age at1st visit was significantly higher in Group A (U=25939, p<0.001, r= -0.158), with a median of 41.22 yrs. [31.96-50.94] *vs.* B of 36.02 yrs. [29.23-45.62]. The age group 31 to 40 yrs accounted for the highest number of diagnoses, 30.6% (n=163). However, the majority of cases, 54.8% (n=291), were diagnosed between 31 to 50 yrs.

In group A, 52.4% (n=183) were over 40 yrs of age, 28.7% (n=100) between 31 to 40 yrs. and 18.9% (n=66) ≤ 30 yrs. *vs.* 35.9% (n=66) over 40 yrs, 34.2% (n=63) between 31 to 40 yrs and 29.9% (n=55) ≤ 30 yrs in B. Older age (>40 yrs.) was associated with advanced disease at 1st visit ($X^2(2)=14.705$, p=0.001, ϕ=0.166).

For all of late diagnoses, age at 1st visit increased significantly overtime (H(2)=52.005, p<0.001, η^2=0.098). From 1998-2004 the median age was 32.89 yrs. (28.35 to 41.31); in 2005-2011, 40.42 yrs (32.57 to 48.66) and from 2012-2018, 46.02 yrs (37.53 to 55.82).

Analysis by age groups showed, in 1998-2004, 33.9% (n=56) were younger than 30 yrs. and 26.1% (n=43) were over 40 yrs.; in later years (2012-2018), 13.2% (n=17) were below 30yrs old and 67.4% (n=87) over 40 yrs., attaining a statistically significant difference ($X^2(4)=52.563$, p<0.001, ϕ=0.314).

Both group A and B saw a predominance of the male gender across all age groups, with significantly more men over 40 yrs with advanced disease ($X^2(2)=7.853$, p=0.02, ϕ=0.150) at presentation. In group A, 84.2% (n=154) of those over 40 yrs were men and of those, 79.4% (n=154) presented with advanced disease at 1st visit. In group B there is no significant association between gender and age at 1st visit ($X^2(2)=2.362$, p=0.307, ϕ=0.113) (Table 4). Identical results were obtained in logistic regression analysis where male pts over 40 yrs had a higher chance of having advanced disease (OR=3.25, CI 95% 1.87 to 5.66, p<0.001) at presentation (Figure 2 and Table 4).

Table 4: Frequency of late diagnoses by age according to gender in Group A and B.

Age (years old)	Frequency (%) in Group A		Frequency (%) in Group B	
	Female	Male	Female	Male
≤ 30	21 (31.8%)	45 (68.2%)	17 (30.9%)	38 (69.1%)
31-40	19 (19.0%)	81 (81.0%)	17 (27.0%)	46 (73.0%)
>40	29 (15.8%)	154 (84.2%)	26 (39.4%)	40 (60.6%)

Table 5: CDC status in the 1st medical visit.

	CDC Status	Total (%)	Female (%)	Male (%)
Group A	**A3**	30.9 (n=108)	24.1 (n=26)	75.9 (n=82)
	B3	14.6 (n=51)	17.6 (n=9)	82.4 (n=42)
	C3	54.4 (n=190)	17.9 (n=34)	82.1 (n=156)
Group B	**A2**	66.3 (n=122)	32.8 (n=40)	67.2 (n=82)
	B2	17.4 (n=32)	50 (n=16)	50 (n=16)
	C2	16.3 (n=30)	13.3 (n=4)	86.7 (n=26)

This association between advanced disease at presentation and age >40 yrs observed in males ($X^2(2)=19.965$, p<0.001, ϕ=0.222), was not observed in females ($X^2(2)=0.068$, p=0.966, ϕ=0.023).

Regarding transmission route and TCD4+ count, no significant differences were reported (H(3)=0.767, p=0.857, η^2=0.001).

In a global analysis, there were significant differences in transmission route over the years (Fisher Test= 45,650, p<0.001, ϕ=0.289). In 1998-2004, injection drug use was the highest (Fisher Test =45,650, p<0.001, ϕ=0.289) accounting for 49.7% (n=82) of infections acquired during this period. Subsequently, it decreased to 32.2% (n=77) in 2005-2011 and to 17.8% (n=23) in 2012-2018. The heterosexual route increased over time, from 46.7% (n=77) in 1998-2004 to 56.1% (n=134) in 2005-2011 and to 61.2% (n=79) in 2012-2018 in which period it was the transmission route with the highest statistical significance (Fisher Test= 45.650, p<0.001, ϕ=0.289). Homosexual risk increased from 3.0% (n=5) in 1998-2004 to 19.4% (n=25) in 2012-2018. Transmission associated with other risks (Accidental/Aggression, Vertical, Transfusion) increased from 0.6% (n=1) in 1998-2004 to 1.6% (n=2) between 2012-2018.

Heterosexual contact was the highest transmission route

registered in both groups. In A, it accounted for 55.3% (n=193) (7.2% (n=25) marital) - 89.9% (n=62) of which were women and 46.8% (n=131) men with a male:female ratio of 2.11:1 and 52.7% (n=97) in B (9.8% (n=18) marital) - 81.7% (n=49) women *vs.* 38.7% (n=48) men, at a ratio of 0.98:1. This was followed by IDU at 33.5% (n=117) in A *vs.* 35.3% (n=65) in B. IDU were mainly male with 44.4% (n=55) (Fisher Test= 35,977, p<0.001, ϕ=0.423). However, age at 1st visit was lower in IDU - median of 34.42 yrs [29.85-40.47] - and higher in cases of heterosexual transmission (H(3)=78,679, p<0.001, η^2=0.148) - median of 46.32 yrs [33.53-55.82], 36.92 yrs [28.83-50.61] in women and 48.60 yrs [40.74-58.14] in men.

Homosexual/bisexual transmission represents 10.0% (n=35) in Group A and 10.9% (n=20) in B (Fisher Test= 0.465, p=0.948, ϕ=0.026).

In Group A, there is a significant association between gender and transmission route (Fisher Test= 46,090, p<0.001, ϕ=0.348). In Group B, the association between females and heterosexual transmission remains. Women IDU present at earlier stages than heterosexual men do.

Regarding marital status, there was no significant association between this and the groups (X^2(5)=7.163, p=0.209, ϕ=0.116). Singles accounted for 39.8% (n=139) in Group A and 50.5% (n=93) in B.

No significant association was observed between the groups and nationality (X^2(2)=3.863, p=0.145, ϕ=0.085) nor race/ethnicity (X^2(1)= 1.455, p=0.228, ϕ=0.061). Portuguese nationality was the most prevalent in both groups, so was Caucasian race.

In group A, there was a higher origin from hospitalization in this hospital (38.4%, n=134), while in B the majority came from local healthcare centers (32.6%, n=60). This association was statistically significant (X^2(6)=67.902, p<0.001, ϕ=0.357).

In a grouped analysis, intra-hospital provenance (Emergency, Outpatient Clinic and Hospitalization) was 50.4% (n=176) in A *vs.* 23.9% (n=44) in B. When compared, this association was significant, with 76.1% (n=140) of all diagnoses in Group B made on an extra-hospital basis (X^2(1)=34.950, p<0.001, ϕ= -0.256). Of all intra-hospital diagnoses, 80% (n=176) belonged to Group A.

In a global analysis over time, 27.8% (n=148) of late diagnoses came from hospitalization in this hospital; in fact, 58.7% (n=313) stemmed from an extra-hospital basis and 41.3% (n=220) from an intra-hospital basis. The percentage of intra-hospital diagnoses underwent variations over time (X^2(2)=6.025, p=0.049, ϕ=0.106), decreasing over the last 14 years. Thus, from 2005-2011, extra-hospital diagnoses were significantly more prevalent, with 62.3% (n=149), corresponding to 47.6% of all extra-hospital diagnoses made over time (X^2(2)=6.025, p=0.049, ϕ=0.106).

Intra-hospital diagnoses were associated with a higher risk of advanced disease (OR=3.16, 95% CI 2.10 to 4.76, p<0.001). In fact, it holds the greatest statistical significance of all risk factors analyzed by logistic regression. A patient with an intra-hospital diagnosis had a 3.2 (95% CI 2.1 to 4.8) times higher chance of having advanced disease at diagnosis. Similarly, males had a 2.0 (95% CI 1.3 to 3.2) times higher chance of advanced disease at 1st visit (OR=2.00, 95% CI 1.25 to 3.20, p=0.004), compared to females. Age over 40 yrs was associated with a risk of advanced disease at presentation 1.8 (95% CI 1.2 to 2.7) times higher (OR=1.79, 95% CI 1.19 to 2.71, p=0.006). IDU (OR=1.20, 95% CI 0.64 to 2.25, p=0.576) and heterosexual transmission (OR=1.12, CI 95% 0.58 to 2.15, p=0.736) were not associated with advanced disease at 1st visit.

Regarding staging at 1st visit, according to CDC criteria adopted by Si.HPH, in A, 54.4% (n=190) of pts were at stage C3, 82.1% (n=156) being male. In B, 66.3% (n=122) were at stage A2, 67.2% (n=82) of which male. In Group A, 54.4% (n=190) had an AIDS-defining illness at 1st visit while in B only 16.3% (n=30) did.

Within each group, stage at 1st visit was not associated with gender (X^2(2)=1.827, p=0.401, ϕ=0.072). Both men and women were most commonly at stage C3 in Group A, 55.7% (n=156) and 49.3% (n=34) respectively. Also, in Group B, 66.1% (n=82) of men and 66.7% (n=40) of women presented at stage A2.

In the entire sample, presentation at AIDS stage (A3, B3, C1, C2 and C3) at 1st visit was significantly higher in males, with 75.7% (n=306) of men at AIDS stage (X^2(1)=17.459, p<0.001, ϕ=0.181), which accounts for 80.2% of all AIDS stages at 1st visit. However, the association between presentation at AIDS stage at 1st visit and transmission route was not verified (Fisher's Test=1.483, p=0.703, ϕ=0.055).

Comparing the groups, 66.2% (n=231) in Group A and 31.0% (n=57) in B developed an AIDS-defining illness throughout the study course. The association between the development of an AIDS-defining illness and the presentation with advanced disease was statistically significant (X^2(1)=60.140, p<0.001, ϕ=-0.336), with Group A responsible for 80.2% of all AIDS-defining illnesses developed over time. The AIDS-defining illness developed showed significant differences between groups (X^2(9)=77.545, p<0.001, ϕ=0.381).

Tuberculosis (TB) was the most prevalent in both groups, with 19.5% (n=68) in A *vs.*17.9% (n=33) in B. However, in Group A, pneumonia by *P. jiroveci* with 10.9% (n=38) ensued, seconded by cryptococcal meningitis with 5.2% (n=18) while in B, non-Hodgkin lymphoma followed with 3.8% (n=7).

No significant differences were observed between the time of HIV diagnosis and the 1st visit (HIV-1st visit time) between groups (U=30417, p=0.317, r= -0.04). In a global analysis, HIV-1st visit time had a median of 47 days [8-292] and increased significantly over time (H(2)=15,694, p<0.001, η^2=0.03), from 43 days [4-100] in 1998-2004 to 68 days [24-1181] in 2012-2018. It should be noted that 65.1% (n=347) of patients were observed at 1st consultation up to 90 days after diagnosis.

In Group A, there was a variation between -16 and 8221 days with a median of 43 days [8-212] and in B, between -86 and 9414 days, with a median of 63 days [8-563]. Negative values correspond to observed pts who were later diagnosed with HIV. The maximum times observed correspond to those tracked but lost to follow-up, returning several months to years later in a symptomatic phase.

The time between HIV diagnosis and the development of a AIDS-defining illness (HIV-AIDS time) was significantly lower in Group A, with a median of 9 days [0-418], than in B whose median is 435 days [5-1763] (U=4310, p<0.001, r= -0.235). In A, the concomitant diagnosis of an AIDS-defining illness with HIV (-180 to 180 days) occurred in 70.2% of cases (n=160) while in B in 36.8% (n=21).

In a global analysis, HIV-AIDS time had a median of 21 days (0-742) and did not undergo significant changes over time (H(2)=1.691, p=0.429, η^2=0, 006).

In a global analysis, there was a total of 136 deaths (25.5%), 73.5% (n=100) of which attributable to Group A ($X^2(1)=5.236$, p=0.020, ϕ= -0.099). In this case, 79.4% (n=108) had a AIDS-defining illness ($X^2(1)=47.346$, p<0.001, ϕ=0.298). In group analysis, significant differences were observed in mortality rate between the two; 28.7% (n=100) in A *vs.* 19.6% (n=36) in B ($X^2(1)=5.236$, p=0.020, ϕ= -0.099).

Over time, the percentage of deaths decreased significantly, ranging from 37.6% (n=62) in 1998-2004, to 25.5% (n=61) in 2005-2001 and to 10.1% (n=13) in 2012-2018, considering all late diagnoses ($X^2(2)=28,805$, p<0.001, ϕ=0.232).

Regarding time from HIV diagnosis to death (HIV-death time), in a global analysis, HIV-death time has decreased significantly over the years (H(2)=7.682, p=0.021, η^2=0.06). In1998-2004, it corresponded to a median of 2623 days (1496-3834), 1808 days (400-3750) in 2005-2011, and 342 days (89-4284) in 2012-2018. In a group analysis, a significantly lower HIV-death time was observed in Group A, with a median of 1828 days [433-3675] compared to B with a median of 2623 days [1815-53239 (U=1252, p=0.008, r= -0.227).

Time from1st visit to death (1st visit-death time) was significantly lower in Group A, with a median of 830 days [220-2440], than in B, with a median of 2503 days [1623-3364] (U=947, 50, p<0.001, r= -0.357). It experienced a significant decrease over time (H(2)=31.679, p<0.001, η^2=0.236), undergoing a reduction from 2453 days [1073-3460] in 1998-2004 to 647 days [210-2180] in 2005-2011 to 180 days [53-921] in 2012-2018.

There were no significant differences between time from diagnosis of an AIDS-defining illness to death (AIDS-death time) between groups (U=872, p=0.429, r= -0.076).

Conversely, AIDS-death time has decreased significantly over the years (H(2)=14,776, p=0.001, η^2=0.138), from a median of 1071 days [432-2568] in 1998-2004 to 435 days [232-1589] in 2005-2011 and to 67 days [9-312] in 2012-2018.

Discussion

As seen in the remainder of the country [1], there is a high prevalence of late diagnoses in this hospital (55%), with 65.5% of patients under study presenting with advanced disease at 1st visit, results that have remained stable over time despite all/new screening measures implemented by the Portuguese government [7]. This is a higher estimate than that from published European data [2,5,6,9].

In this sample, there was a predominance of late diagnoses in men, between 31 to 50 years, with heterosexual infection-risk, in singles, Caucasian and with extra-hospital provenance, which probably reflects lost screening opportunities. It is also important to note that in 2017, late diagnoses in the EU occurred mostly in women (52%), 63% in people over 50 years, 52% of cases in IDU, 52% by heterosexual transmission and 56% from sub-Saharan Africa [2]. However, in our analysis, late diagnoses in women remained constant over time around 24%, a lower value than the European reality [2].

The number of late diagnoses at older ages (>40 years) increased over time (67.4% in the 2012-2018 period), which may be associated with increased heterosexual transmission and decreased IDU over time (61.2% and 17.8% respectively in the last period). However, this may also be due to the pressure of stigma or low risk perception between older men and their health care providers. The low prevalence of homosexual cases reported in this sample compared to other studies [2,4] may also be due to the social stigma of affirmation of homosexual practices, a fact for which this study does not allow a more detailed coverage.

It should be emphasized that despite the overall decrease in the percentage of intra-hospital diagnoses, 41.3% of them had this provenance (50.4% of cases of advanced disease), with implications in health status, response to therapy, overall prognosis and transmission [6].

The risk factors for presentation with advanced disease found in this study, which were the male gender, age >40 years (particularly in men) and in-hospital diagnosis, suggests that this subgroup failed all the screening opportunities thus far. The fact that age does not constitute a risk factor for women may be due to the widespread screening of HIV infection in the first and third trimester of each pregnancy.

The absence of statistical significance regarding marital status, nationality and race/ethnicity may be due to an insufficient number of cases or sexual transmission amongst individuals with divergent civil states in the former. However, risk factors such as ethnic minorities, emigrants and low literacy [2,6,7] should be subject of subsequent studies.

Regarding the transmission route, none presented a significant association. Contrary to what was observed in the EU where, in 2017, 59% of AIDS cases occurred after immediate diagnosis of HIV in IDU [2], in this sample the presentation at AIDS stage at 1st visit was not associated with transmission route.

It should also be noted that 54.4% of patients with advanced disease had an AIDS-defining illness at 1st visit, with a shorter 1st visit-death time (as well as HIV-AIDS and HIV-death time) and significantly higher number of deaths, highlighting the prognostic implications of a late diagnosis [6].

The most commonly diagnosed AIDS-defining illness was *Mycobacterium tuberculosis* (TB) infection, which reflects the high/moderate prevalence of this disease in Portugal, especially in this region (25.3 cases/10^5 inhabitants in Porto district in 2018 [11-18]). This association leads to the recommendation of HIV screening in all TB cases [19].

Time from HIV to1st visit increased over time. A value of 65.1% observed up to 90 days after diagnosis contrasts with European data (92% of those diagnosed in 2017 were linked to health care up to 90 days after diagnosis [2]). However, the difficult adherence of patients to health care due to non-perception of illness is one of the most important contributing elements, which coupled with the stigma caused by the disease, makes them diverge from care centers.

The number of deaths also experienced a decrease over time, as well as HIV-death time, 1st visit-death time and AIDS-death time, which indicates that despite the severe immunosuppressive status at arrival, cART still manages to recover many situations through strict control of the virus [13].

Conclusion

The results show that despite the campaigns instituted at national

level encouraging early screening, the percentage of late diagnoses and in particular of advanced disease still remains high, which has serious prognostic implications, for both patients and the community, due to the transmissibility of the infection. This reflects the need for implementation of new warning mechanisms, at both patient, physician and population level, of surveillance and screening, in particular in those groups strongly represented by late presentation. Thus, a better knowledge of the features of the epidemic at local levels will allow for a better adequacy of control and prevention strategies to the specificities of each geographical area, in order to complement the national strategy in achieving the 90-90-90 goals [1,5].

These results also show the importance of timely HIV diagnosis, with rapid availability of evaluation and follow-up visits in a treatment center for initiation of cART as early as possible as well as counseling and prophylaxis (if indicated), in order to reduce morbidity and mortality.

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