

# Diagnóstico da Infecção VIH – o que mudou em 10 anos

## *HIV infection diagnosis – What changed in 10 years*

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### Resumo

**Introdução:** A infecção VIH/SIDA mantém-se uma importante causa de morbidade e mortalidade nos países em vias de desenvolvimento, onde a terapêutica antiretroviral só está disponível para um número restrito de doentes. Nos países desenvolvidos, há tendência para estabilização da epidemia mas é ainda frequente o diagnóstico em fases tardias, com subaproveitamento dos benefícios do tratamento, aqui facilmente acessível. Em Portugal, país da Europa Ocidental com maior prevalência de infecção VIH, continua a verificar-se o aumento de novos casos.

**Objectivos e Métodos:** Avaliação retrospectiva com caracterização e comparação de dois grupos de doentes com infecção VIH acompanhados em consulta de um hospital central de Lisboa – um com diagnóstico em 1997/1998, outro com diagnóstico em 2007/2008 – com o objectivo de analisar possíveis diferenças de “perfil” demográfico, epidemiológico, clínico-laboratorial e terapêutico.

**Resultados:** Foram estudados 74 doentes com diagnóstico em 1997/1998 e 106 doentes com diagnóstico em 2007/2008. A idade média foi superior em 2007/2008. O sexo masculino predominou em qualquer dos períodos, sem diferença significativa. A raça negra e a origem não portuguesa tiveram maior representatividade em 2007/2008. Verificou-se um aumento da transmissão heterossexual e um menor número de casos associados ao uso de drogas endovenosas em 2007/2008. O estadio inicial não mostrou diferenças estatisticamente significativas nos dois períodos. Em 1997/1998 os esquemas terapêuticos envolveram maior número de comprimidos e maior número de tomas diárias.

**Conclusões:** Parece-nos fulcral o investimento em estratégias de redução de riscos e de diagnóstico precoce, em cuja definição devem ser contemplados múltiplos factores, individuais, comportamentais e sociais. Com uma prevenção mais efectiva e início atempado da terapêutica, que se objectiva progressivamente mais potente, mais simples e mais bem tolerada, e se aspira de acesso universal, talvez um dia se alcance o tão desejável controlo da epidemia.

**Palavras chave:** Infecção a VIH, SIDA, epidemiologia, transmissão, prevenção, comportamento, terapia antiretroviral.

### Abstract

**Introduction:** The HIV infection / AIDS is still an important cause of morbidity and mortality in developing countries, where only a restricted number of patients have antiretroviral therapy available. In developed countries there is a trend to stabilize the epidemics. Nevertheless, late stage diagnosis is still very frequent, overcoming the benefits of treatment early onset. Portugal is the Western European country with the highest prevalence of HIV infection, presenting an increasing number of new cases.

**Objective and Methods:** We retrospectively characterized and compared two groups of patients with HIV infection followed in an outpatient clinic of a Lisbon hospital. The first group included patients that had been diagnosed in 1997/1998, and the second group included patients diagnosed in 2007/2008. Our purpose was to ascertain any differences between the groups concerning demography, epidemiology, clinical presentation, laboratory parameters and therapy.

**Results:** We evaluated 74 patients diagnosed with HIV infection in 1997/1998 and 106 diagnosed in 2007/2008. The average age at the time of diagnosis was higher in 2007/2008 (37.8 vs 33.1 years). The male gender was predominant in both periods, without significant difference. There were more foreign patients in 2007/2008 (50% vs. 20.3%). There was an increase in heterosexual transmission (65.1% vs. 48.6%) and a decreased number of cases associated with injection drug use (3.8% vs. 32.4%) in 2007/2008. There were no significant differences of patients diagnosed on initial stage C between the two groups. In the 1997/1998 period, patients needed to take a higher number of pills distributed by a higher number of times per day.

**Conclusions:** The investment in strategies to reduce the risk of HIV transmission and early diagnosis is crucial. With a more effective prevention and an early institution of antiretroviral therapy, we expect to become more effective, easier and safer, day by day, and perhaps one day we will achieve the epidemic control.

**Key words:** HIV infection, AIDS, epidemiology, transmission, prevention, behaviour, antiretroviral therapy

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Received for publication on the 28th September 2010

Accepted for publication on the 17th August 2012

### INTRODUCTION

Almost 30 years after being identified the first few cases of Acquired Immunodeficiency syndrome (AIDS), the infection by the Human Immunodeficiency Virus

(HIV) is still representing an important cause of morbidity and mortality, mainly in developing countries, where it severely affects the population demographic development.<sup>1-4</sup>

The HIV/AIDS infection epidemics evolution overtime is closely related with behavioral and social changes, what seems to justify the gradual increase in the number of heterosexual transmission or the current trend of a growing incidence in the homosexual population.<sup>5-7</sup> On the other hand, the change of consumption pattern in recreational drugs and the strategies of risk reduction minimizing damages (replacement programs with methadone/syringe exchange /...) seem to explain, at least, partially a progressive decrease in parenteral transmission.<sup>8</sup>

The first AIDS case in our country was diagnosed in October 1983. At present, Portugal is the Western European country with a higher prevalence of HIV and AIDS,<sup>9</sup> still recording an increase on the number of new cases.<sup>10</sup> Similar to what happen in other European countries, the main transmission route has been until 2003 the use of endovenous drugs, and from that date onwards has been seen a gradual increase on the number of cases associated with sexual transmission, and at present, heterosexual transmission is remarkably higher than parenteral transmission (59.6% versus 23.6%) and the homo/bisexual transmission shows a growing trend to evolve.<sup>11</sup>

With the development of HAART – Highly Active Antiretroviral Therapy by the end of the 90ties, it was possible to transform HIV infection, from a past fatal condition in a chronic condition with a significant reduction in mortality and in reported cases of AIDS.<sup>12,13</sup>

However, even in regions with easy access to therapy, a significant number of infected individuals is not aware of their serologic condition and, as such, it is not under treatment, keeping the infection bring transmitted.

In Portugal, the National Program for the Prevention and Control of HIV/AIDS infection 2007-2010 is running focusing mainly on the early diagnosis and the timely start of treatment, only possible when making available the screening test for HIV in the healthcare routine.<sup>11</sup>

In spite of implementing awareness campaigns and prevention programs, even the sudden development in therapies and a better follow up of such patients, we are still before a worldwide pandemics, which is a severe public health issue all over the world.<sup>9,14,15</sup>

## OBJECTIVE AND METHODS

Our study aimed to compare two distinct periods of the HIV infection, in order to evaluate possible differences in the demographic, epidemiologic, clinic and laboratorial profile of the patient diagnoses in more recent years and the previous decade. The same way, we have evaluated some aspects regarding the therapeutic approach in such two periods, the initial coinciding with the beginnings of HAART and the second reflecting the current reality, with a wider pharmacological development.

We have selected a population of HIV infected patients followed in a clinic of a Lisbon central hospital, those with a diagnosis made in 1997/1998 and others with a diagnosis made in 2007/2008 and we proceeded with the retrospective analysis of the respective clinical files gathering the following data: gender, age, race, place of birth, type of transmission, reason for taking the test, source of reference to the clinic, initial staging, opportunistic diseases, anti-retroviral therapy in the first 12 months (emphasizing that in the analysis of the 5 last items it was only possible in patients whose follow-up was made by us since being aware of the HIV infection).

We defined as a limit date of gathering data the 31st March 2009.

In the statistics analysis the NCSS software for Windows was used. Descriptive statistic methods for demographic characteristics were used: distribution of frequencies for categorical variables and measurements of central trend and dispersion for the continuous variables. While comparing continuous variables the Mann-Whitney U test was used. A significant value of P lower than 0.05 was considered.

## RESULTS

From a total of 641 HIV infected patients enrolled in the clinic up to the 31st March 2009, 74 were identified in 1997/1998 and 106 with a diagnosis achieved in 2007/2008. From the first group, only 43 patients have started being followed up in this clinic immediately after being aware of being serum positive (the remaining did not have a previous follow-up or had already being followed in other sites); from the second group, all patients have been followed in this clinic since the diagnosis date.

The distribution by gender was overlapping in both periods, with higher representation of male patients (64.9% in 1997/1998 and 64.2% in 2007/2008) – *Table I*.

The average age of diagnosed patients in 1997/1998

Table I

Patients distribution by gender, age, race, country of origin and transmission route

Characteristics	1997/1998 (n=74)		2007/2008 (n=106)		p
	N	%	N	%	
<b>Gender</b>					
Male	48	64,9	68	64,2	P=0,921
Female	26	35,1	38	35,8	
<b>Age</b>					
≤19 years	8	10,8	—	—	P=0,765 P=0,158 P=0,335
20-39 years	47	63,5	65	61,3	
40-59 years	16	21,6	33	31,1	
≥ 60 years	3	4,1	8	7,6	
<b>Race</b>					
Caucasian	67	90,5	71	67,0	P= 0,001
Black	7	9,5	35	33,0	
<b>Country of origin</b>					
Portugal	59	79,7	53	50,0	P<0,001
Western Europe	2	2,7	1	0,9	
Eastern Europe	—	—	4	3,8	
Africa	7	9,5	37	34,9	
South America	6	8,1	11	10,4	
<b>Route of transmission</b>					
Heterosexual	36	48,6	69	65,1	P= 0,03
Homosexual	13	17,6	31	29,3	P= 0,07
Drug addiction	24	32,4	4	3,8	P< 0,001
Vertical	1	1,4	—	—	
Transfusion	—	—	1	0,9	
Unknown	—	—	1	0,9	

was 33.1 years, lower than the average age of patients diagnosed in 2007/2008 which was 37.8 years ( $p=0.005$ ). In any of those periods there was a higher number of patients in the age group from 20 to 40 years old – 63.5% in 1997/1998 and 61.3% in 2007/2008 - Table I.

The Caucasian race was predominant in both periods assessed, and it was seen however an increase of black patients in the period 2007/2008 (33.0% vs 9.5% -  $p=0,001$ ) - Table I.

Most patients were born in Portugal (79.7% in 1997/1998 and 50.0% in 2007/2008), although it was seen an increase on the number of foreign patients in 2007/2008 ( $p<0,001$ ), mainly those from Portuguese speaking African countries, namely Angola, Cape

Verde, Guinea-Bissau and Mozambique - Table I.

In 2007/2008 it was seen a number of cases associated with heterosexual transmission (65.1% vs. 48.6% -  $p=0.03$ ) with a decrease on the number of cases associated with the use of endovenous drugs (3.8% vs. 32.4% -  $p<0,001$ ). Regarding homosexual transmission, in spite of having seen a higher number of cases in 2007/2008 (29.3% vs 17.6%), such difference was not statistically significant - Table I.

In the assessment of the following endpoints only patients we followed were considered, since the date of diagnosis (43 in 1997/1998 versus 106 in 2007/2008).

In 1997/1998, the most frequent reason to carry out a serum screening was the presence of opportunistic disease (30.2%) or the sexually transmissible diseases (23.2%). In 2007/2008, the main diagnoses contexts were the existence of risk behavior/infected partner (26.4%) and the appearance of an opportunistic disease (17.9%) - Table II.

Regarding the patients origin, it was identified as more prevalent in 1997/1998 the Dermatology/Venereology clinic (39.5%), followed by hospitalization in Medicine awards (20.9%) and the Medicine Clinic (14.0%). In 2007/2008 the main sources of reference were hospitalization (19.0%), the Emergency Service (16.0%) and the infected partner followed in the clinic (12.2%) - Table III.

Regarding the initial classification, a higher increase on the percentage of patients in the C stage in the period 1997/1998 (30.2% vs 17.9%), but without statistical significance was recorded – Table IV. Among the diseases defining AIDS and with particular relevance and an overlapping expression in both periods, tuberculosis was particularly relevant (52.9% in 1997/1998 and 52.6% in 2007/2008); the Kaposi Sarcoma was the second more frequent opportunistic disease (35.3% in 1997/1998 and 15.8% in 2007/2008).

Regarding the immunologic characterization there were no significant statistics either, being overlapping the percentage of patients with T lymphocytes CD4

Table II

## Reason for performing the HIV infection serum test

Reason for the test	1997/1998 (n=43)		2007/2008 (n=106)	
	N	%	N	%
Adenopathies	—	—	6	5,7
Pre-surgical evaluation	—	—	6	5,7
Oral Candidiasis	—	—	2	1,9
Risk behavior/Infected Partner	4	9,3	28	26,4
Unknown	2	4,7	1	0,9
Opportunistic Disease	13	30,2	19	17,9
Sexually transmitted diseases	10	23,2	7	6,5
Infected son	—	—	4	3,8
Pregnancy	2	4,7	10	9,4
Other	—	—	2	1,9
Cutaneous pathology	5	11,6	6	5,7
Pneumonia	3	7	—	
Detox programme	—	—	1	0,9
Constitutional complaints	—	—	4	3,8
Seroconversion	1	2,3	6	5,7
Febrile syndrome	1	2,3	4	3,8
Thrombocytopenia	2	4,7	—	

Table III

## Patients origin/reference

Characteristics	1997/1998 (n=43)		2007/2008 (n=106)	
	N	%	N	%
Hospitalization	9	20,9	20	19,0
Emergency Dept.	1	2,3	17	16,0
Health Centre / CAT	1	2,3	4	3,8
Medicine Appointment	6	14,0	3	2,8
Surgery Appointment	—	—	5	4,7
Dermatology/Venereology Ap.	17	39,5	7	6,6
Maternity/Pediatrics	2	4,7	9	8,5
Partner	3	7,0	13	12,2
Other	4	9,3	28	26,4

count lower than 200/mm<sup>3</sup>, on the date of diagnosis on both periods assessed (27.8% in 1997/1998 vs 30.9% in 2007/2008) - Table IV.

In 1997/1998, from the 43 patients followed in the

clinic since the infection awareness, 38 started antiretroviral therapy (ARVT) in the first year after diagnosis, according to the recommendations of the time. In the remaining 5 patients, therapy was not started as the due compliance was not assured. The more often used nucleoside reverse transcriptase inhibitors (NRTI) in such period were the stavudine (44.8%) and zidovudine (28.9%), associated with lamivudine. In 3 (7.9%) patients was implemented therapy with 3 NRTI, including abacavir (in association with zidovudine and lamivudine) in the context of a clinical trial. 28 (73.7%) patients were prescribed a regime based on a protease inhibitor (PI), being indinavir the most used (75.0%). In the reminder 7 (18.4%) patients ARVT was started with a NRTI, nevirapine (Figure 1). Such therapeutic regimes demanded that a high number of pills was taken – 73.7% patients were taking daily from 10 to 16 pills, divided in two or three takes. Even the simplest regime implied to take at least 6 pills

per day. During the first 12 months, the therapy was modified/interrupted in 11 (28.9%) patients due to: adverse events (5 cases), therapy failure (4 cases) and drop outs (2 cases). The adverse events found were: gastrointestinal intolerance (2 cases) and renal lithiasis (2 cases), both associated with therapy with indinavir and a possible hypersensitivity reaction associated with abacavir (1 case).

From the 106 patients diagnosed in 2007/2008, ARVT was started during the first years after diagnosis, with schemes appropriate to the current recommendations, in 59 patients. In the reminder 47 patients, the following reasons were identified of non-inclusion in the therapy: absence of

criteria up to the date established for limiting the study (36 cases), clinic drop outs (10 cases) and death (1 case). Within the prescribed NRTI, the most often used was tenofovir (86.4%), followed by abacavir

**Table IV**  
Initial count of T lymphocytes DC4 count and initial clinical stage

Caracteristics	1997/1998 (n=43)		2007/2008 (n=106)		P
	N	%	N	%	
<b>Initial CD4</b>					
≤49	3	6,9	14	13,2	
50-199	9	20,9	19	17,9	
200-349	11	25,6	22	20,8	
≥350	18	41,9	47	44,3	
Unknown	2	4,7	4	3,8	
<b>Estadio Inicial</b>					
Stage A	28	65,1	80	75,5	P=0,199
Stage B	2	4,7	4	3,8	P=0,804
Stage C	13	30,2	19	17,9	P=0,09
Unknown	—	—	3	2,8	

(10.2%) and then zidovudine (3.4%), associated with emtricitabine or lamivudine. Regarding the third drug of the scheme, in 38 (64.4%) patients it was one NRTI, being efavirenz the most used (94.7%) and in 21 (35.6%) patients in a PI, namely atazanavir (57.1%) and lopinavir (42.9%), potentiated with ritonavir (Fig. 1). The current regime includes a smaller number of pills – 83.1% patients took 3 or less pills daily, and in less daily takes – 79.7% of patients in one only take. From the 59 patients started in ARVT, on the time limit for gathering data only 31 had finished 12 months of therapy – which was modified/interrupted in 8 (25.8%) patients. The reasons given were: adverse events (3 cases), therapy failure (2 cases), therapy simplification (1 case), drug interactions (1 case) and drop out (1 case).

Even if the percentage of patients that modified or stopped ARVT in the period 1997/1998 has been higher, such difference did not have a statistic significance ( $p=0,062$ ).

## DISCUSSION

In our analysis, the mean age of the diagnosed patients in 2007/2008 was higher than the average age of diagnosed patients in 1997/1998, what is probably related with a higher number of cases of heterosexual transmission, as demonstrated in other studies.<sup>16</sup>

On the other hand, it was not found a difference in the distribution by gender between both periods studied, what contrasts, somehow, with the worldwide reality and even national, where, in spite of being kept a higher representation of the male gender, it is

described a gradual increase of the number of cases of the female gender.

We have seen an increase of patients of non Portuguese origin, as well as of Black race, in the last period assessed, what is surely related with the wide immigrant community, mainly coming from African countries, namely of the former Portuguese colonies.

Heterosexual transmission had an important weight in both periods, mainly in 2007/2008, where it was responsible for a higher percentage of new infections, and these data agree with the national data.<sup>17</sup>

Like other studies carried out, we have also seen a decrease on the number of infection cases associated with the use of endovenous drugs, what is probably due to the efficacy of the information and awareness campaigns

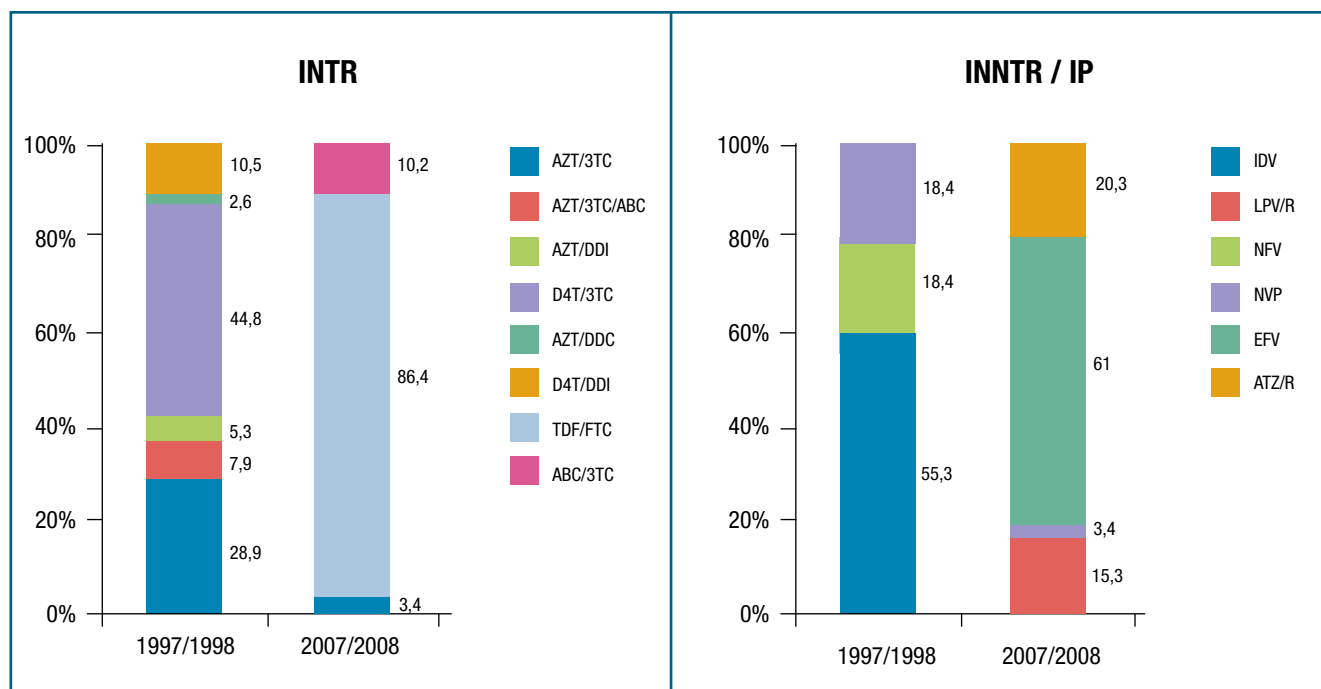
addressed to this group and to the institution of replacement programs with methadone and syringe swap.

In spite of not having a statistic significance, it seems to exist a trend to an increase on the number of cases of HIV infection acquired in the context of homosexual contacts, similar to what has been registered in the national program.<sup>17</sup> Contributing to such fact it should be an increase on risk behavior, promoted on one hand for decreasing the fear of being infected and, on the other hand, for the growing infection prevalence resulting of a higher survival and consequently a higher opportunity of transmitting the disease.<sup>7,18</sup>

In 2007/2008, the main reason for carrying out the HIV infection screening was the risk behavior infecting partners, what could reflect a higher risk perception, although not always translated in behavior.

A higher number of patients referred to the clinic from the Emergency Service in 2007/2008, has revealed surely a more adequate valuing, on the part of doctors, of risk behavior and clinical, laboratorial and imaging “alarming signs”.

Although no statistically significant differences had been found regarding the initial C stage and the T lymphocytes CD4 count lower than 200/mm<sup>3</sup> between these two periods, we verified that in 2007/2008 there was a high proportion of diagnosed patients with AIDS criteria and low counts of T lymphocytes and CD4, i.e., at later stages of the infection (“late presenters”). It is, in fact, necessary to test more often the individuals who do not belong to the groups classically identified as of risk. A study carried out from 1992 to 2006 has



Initial antiretroviral therapy

FIG. 1

verified that in the more recent period, around a third of cases were diagnosed in an advanced stage of immunodeficiency, being mainly male patients, heterosexuals, foreigners and older.<sup>16</sup>

Complying with the then guidelines recommended,<sup>19</sup> antiretroviral therapy was started in all patients diagnosed in 1997/1998 who could guarantee an adequate compliance. In 2007/2008 only 55.7 % of diagnosed patients have started therapy, as the recommendations at the time were more conservative, recommending therapy to be started later.<sup>20,21</sup> However, the current trend seems to be, once again, to start the therapy in its earlier stages, advocating its benefit mainly in patients with cardiovascular pathology and in those co-infected with B and/or C hepatitis virus.<sup>22</sup>

Regarding the choice of drugs, there are clear differences between the two periods, related to the therapy guidelines and available drugs in each period.<sup>19-21</sup> Therefore, in the 1997/1998 biennium most therapeutic regimes (73.7%) started based on the PI, considered of higher potency comparatively to the NNRTI class, at the date with nevirapine as only representative; already in 2007/2008 the scheme instituted in a higher number of cases (64.4%) has included a NNRTI, with a special highlight to efavirenz, being the choice dictated by an

overlapping efficacy, easier to take dosages and a lower cost regarding the PI. Regarding the NRTI backbone, while in 1997/1998 the hypotheses were diversified and randomized, in the more recent period the options are more limited and well defined, being the potency and tolerance the features making preferential (86.4%) the tenofovir/emtricitabine co-formulation.

In the last few years we have been seeing the emergence of new drugs and fixed/co-formulations associations, resulting in posologic simplification of the current therapeutic schemes, as it has been evident in our assessment. This surely will be reflected in the compliance and in a more adequate observation of the antiretroviral therapy.

The reduced number of assessed patients does not allow to draw conclusions on the change rate/therapeutic interruption (which did not show a statistically significant difference between these two periods), or on the underlying causes.

## CONCLUSIONS

In our assessment we have seen that in 2007/2008 patients presented a higher average age. The heterosexual transmission had a higher contribution in the new diagnosis of HIV infection, seeing a lower number of

cases associated to the use of endovenous drugs. We also verified that is still high the number of diagnosed patients in later stages, raising the awareness to the need of an early diagnosis.

In the last few years we have seen a simplification of the therapeutic schemes, with a lower number of pills and takes, with a higher tolerance as made evident through our analysis.

In spite of the data gathered being in accordance with the recorded at national level, we studied a small population, making difficult to generalize to the country reality.

**Note:** Work presented by the authors during the “IX Master de SIDA” in the Medical School of Barcelona University.

### Acknowledgements

The authors acknowledge the Service of Infectious Diseases of the Hospital Clinic, Barcelona, in special to Dr. Josep Gatell, Dr. Josep Mallolas and Dr. Josep Miró, as well as to the group of the Outpatient Clinic of Medicine/Immunodeficiency in the Medicine 1.4 Service of the Central Lisbon Hospital Centre, EPE, namely Dr. Isabel Germano, Dr. Fátima Lampreia and Dr. Umbelina Caixas. ■

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