

Characterisation of AIDS presenters and their response to antiretroviral therapy at Legnano general hospital (Italy) during the period 2000-2008

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SUMMARY

The aim of this study was to characterise the AIDS presenters diagnosed between 2000 and 2008 in Legnano (Italy), and describe their initial response to highly active antiretroviral therapy (HAART) and trends over time.

Seventy-six (48.7%) of 156 patients diagnosed as having AIDS in the period 2000-2008 were AIDS presenters. The proportion of AIDS presenters increased from 23.8% in 2000 to 70.6% in 2008 ($p=0.009$). The major risk factors were heterosexual transmission and a foreign place of birth, and did not significantly change over time. The median CD4+ cell count at diagnosis was 30 cells/ μ l and the median level of HIV RNA was 5.38 log copies/ml, with no differences between the transmission risk groups. Fifteen AIDS presenters died of AIDS-defining diseases; the others started HAART (72% with 2 NRTIs + boosted PI), and 40% after a drug resistance test. The median duration of the initial HAART was 107 days. After three months, 34% of the patients had undetectable HIV-RNA levels and the median CD4+ cell count was 140 cells/ μ l; the corresponding figures after 12, 24 and 48 months were respectively 84%, 82.3% and 94.1%, and 310, 370 and 380 cells/ μ l.

In conclusion, the AIDS presenters were mainly heterosexual men and immigrants. Their proportion increased significantly over time, and a substantial proportion maintained an immunovirological response to HAART.

KEY WORDS: AIDS presenters, HIV infection, Immunovirological response

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INTRODUCTION

Without highly active antiretroviral therapy (HAART), HIV-1 infection progressively destroys the immune system in the vast majority of infected patients, thus leading to opportunistic diseases and death. Although HAART and access to care is considered an important public health goal in industrialised countries (Levi, 2002), 10-39% of HIV-infected patients in Western coun-

tries still fail to benefit fully because they do not seek medical advice until their CD4+ cell counts are <200 cells/ μ l and/or they are already symptomatic. They are therefore more likely to be diagnosed as having opportunistic infections, are at higher risk of death, experience slower immunological improvement, and are more likely to transmit the virus to others (Chadborn *et al.*, 2006; Girardi *et al.*, 2004; Wolbers *et al.*, 2008).

The definition of "late presenters" or "AIDS presenters" varies depending on the study, and no consensus has yet been established. One clinical definition is "individuals presenting with a concomitant AIDS-defining opportunistic infection ('category C events' according to the classification of the Centers for Disease Control and Prevention) when HIV infection is first diag-

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nosed" (Battagay *et al.*, 2007; Boffito *et al.*, 2003), but other authors have used less restrictive definitions such as an opportunistic infection (OI) in the one (Castilla *et al.*, 2002) or two months preceding an HIV test (Hocking *et al.*, 2000). Late presenters have also been defined immunologically on the basis of CD4+ cell counts of <200 cells/ μ l (Krenz *et al.*, 2004; Manavi *et al.*, 2004), <100 cells/ μ l (Pulido *et al.* 2004), or 50 cells/ μ l (Sabin *et al.*, 2004), and other authors have used a mix of clinical and immunological criteria, with different levels of CD4+ cells (Gay *et al.*, 2006; Nelson *et al.*, 2006). Finally, a recently proposed definition is patients with a CD4+ count of less than 350 cells/ μ l or with AIDS at diagnosis (despite a CD4 count above 350 cells/ μ l) (Gatel, 2009), and the newer guidelines now recommend that all patients start HAART as soon as their CD4+ count falls to <350 cells/ μ l (DHHS, 2009; Gazzard - BHIVA 2008). Given these differences, it is not possible to compare the prevalence rates recorded by different studies.

The outlook of late presenters very much depends on their initial response to HAART, but even if the response is optimal their long-term prognosis may be compromised (Hogg *et al.*, 2001). The aim of this study was to characterise adult AIDS presenters diagnosed between January 2000 and December 2008 in Legnano (Italy), compare their clinical and immunovirological characteristics with those of non-AIDS presenters at diagnosis, evaluate their response to HAART, and describe trends over time.

MATERIALS AND METHODS

AIDS presenters were defined as patients presenting with at least one AIDS-defining illness (Table 1) within one month preceding their first positive anti-HIV antibody test.

Their baseline data (gender, country and date of birth, HIV exposure category, time of HIV diagnosis, absolute CD4+ cell counts, HIV RNA levels, and clinical CDC classification at presentation) (Table 2) were taken from the AIDS notification forms completed for the Centro Operativo AIDS of Italy's Istituto Superiore di Sanità; the data concerning HIV subtypes, HAART and immunovirological analyses were collected from the patients' medical files. The data concerning gen-

TABLE 1 - AIDS-defining illnesses (CDC 1993).

Candidiasis of bronchi, trachea, or lungs
Candidiasis esophageal
Cervical cancer (invasive)
Coccidioidomycosis, disseminated or extra pulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal for longer than 1 month
Cytomegalovirus disease (other than liver, spleen or lymph nodes)
Encephalopathy (HIV-related)
Herpes simplex: chronic ulcer(s) (for more than 1 month); or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (for more than 1 month)
Kaposi's sarcoma
Lymphoma Burkitt's, immunoblastic or primary brain
Mycobacterium avium complex
Mycobacterium, other species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia (formerly Pneumocystis carinii)
Pneumonia (recurrent)
Progressive multifocal leukoencephalopathy
Salmonella septicemia (recurrent)
Toxoplasmosis of the brain
Tuberculosis, disseminated
Wasting syndrome due to HIV

der, age, country of birth (Italy / other country), exposure categories, absolute CD4+ cell counts and HIV RNA levels were compared with those of non-AIDS presenters before starting an antiretroviral therapy. The virological and immunological response of the AIDS presenters who started antiretroviral therapy was described by plotting the median HIV RNA log and CD4+ cell count before starting HAART, and after three, 12, 24 and 48 months of therapy.

TABLE 2 - CDC AIDS classification.

Category	CD4 count (cell/ μ l)		
	>500	200-500	<200
(A) Asymptomatic, primary HIV, PGL	A1	A2	A3
(B) Symptomatic, not (A) or (C)	B1	B2	B3
(C) AIDS-defining conditions	C1	C2	C3

CDC = Centers for Disease Control; PGL = persistent generalised lymphadenopathy.

HIV RNA load was determined using a signal amplification nucleic acid probe assay (Versant HIV-1 RNA 3.0, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Antiretroviral resistance was analysed using a nucleic acid sequencing test (Trugene HIV-1 Genotyping Kit, Siemens Healthcare Diagnostics), and the subtype was determined by comparing the viral sequence with the public database of the National Center for Biotechnology Information (NCBI, Bethesda, USA). T lymphocyte subsets were measured in whole blood by means of standard cytofluorimetry procedures.

The data were statistically analysed using the Mann-Whitney/Wilcoxon two-Sample test (Kruskal-Wallis test for two groups).

RESULTS

Seventy-six (48.7%) of the 156 adults diagnosed as having AIDS during the study period were AIDS presenters. Table 3 shows the epidemiological and clinical characteristics of the AIDS and non-AIDS presenters: there were statistically significant between-group differences in the country of birth (Italy / other country) and exposure categories, but no difference between males

and females. In particular, heterosexual men accounted for 53.9% of all of the AIDS presenters but only 22.5% of the non-AIDS presenters ($p=0.00001$).

Figure 1 shows that the proportion of AIDS presenters significantly increased over time, from 23.8% (5/17) in 2000 to 70.6% (12/17) in 2008 ($p=0.009$), but there was no significant variation in their gender, age, country of birth or behavioural risk factors over time (Figure 2; $p=0.4$). The median CD4+ cell count at the time of diagnosis was 30 cells/ μ l among the AIDS presenters, and 130 cells/ μ l among the non-AIDS presenters ($p=0.00001$); HIV RNA levels were 5.38 and 5.17 copies/ml respectively ($p=0.0008$), with no difference between the transmission risk groups. Forty percent of the patients underwent baseline drug resistance genotyping (systematically from May 2005) and the subtypes were 25 B (71.4%) and 10 non-B (28.6%).

Nine of the 76 AIDS presenters (11.8%) had three simultaneous diagnoses of AIDS-defining illnesses, 14 (18.4%) had two, and 31 (40.8%) one. The three most frequent illnesses were *Pneumocystis jiroveci* pneumonia (27 cases), neurotoxoplasmosis (12 cases) and esophageal candidiasis (9 cases), with no significant differences between the risk groups.

TABLE 3 - Baseline characteristics of AIDS presenters and non-AIDS presenters between 1 January 2000 and 31 December 2008

	AIDS presenters	Non-AIDS presenters	<i>p</i>
No. of patients	76	80	
Median age (years)	41	41	NS
Gender			
Female (%)	19.7	21.3	NS
Male (%)	80.3	78.8	NS
Year of diagnosis	see Figure 1	see Figure 1	0.001
Exposure categories			
IVDU (%)	10.5	63.8	0.00001
MSM (%)	32.9	12.5	0.00001
Heterosexuals (%)	53.9	22.5	0.00001
Country of birth			
Italy (%)	82.9	97.5	0.0001
Other countries	17.1	2.5	0.0001

IVDU = intravenous drug user; MSM = men who have sex with men; NS = not significant.

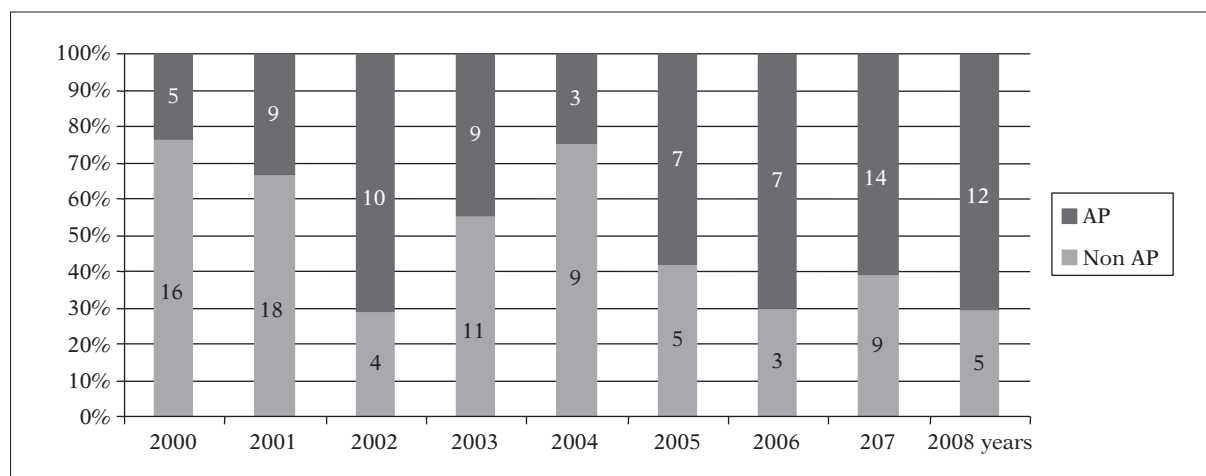


FIGURE 1 - AIDS presenters (AP) and patients with AIDS (non-AP) between 1 January 2000 and 31 December 2008.

Seven of the AIDS presenters dropped out within one month of diagnosis, and 14 died of AIDS-defining diseases within two months: eight cases of central nervous system diseases, three of mycobacteriosis, and three of *P. jiroveci* pneumonia. One patient died as a result of a non-Hodgkin lymphoma after nearly 24 months of efficacious HAART.

Fifty-four of the AIDS presenters (71%) are still receiving HAART and being regularly followed up: 11 (20%) on first-line therapy (the first combination of antiretroviral drugs), 18 (33%) on second-line, 16 (30%) on third-line, eight (15%) on fourth-

line, and one (2%) on fifth-line. Thirty-nine patients (72%) started on two nucleoside reverse transcriptase inhibitors (NRTIs) + one boosted protease inhibitor (PI) at the time of diagnosis (Figure 3). The most frequent therapeutic combinations in each line are summarised in Table 4. The median duration of the initial HAART was 107 days; the switches to other therapies were mainly due to adverse events or simplification. Seven patients experienced virological failure (>1000 copies/ml), five of whom received a successfully redesigned HAART on the basis of the results of a drug resistance genotyping test; the re-

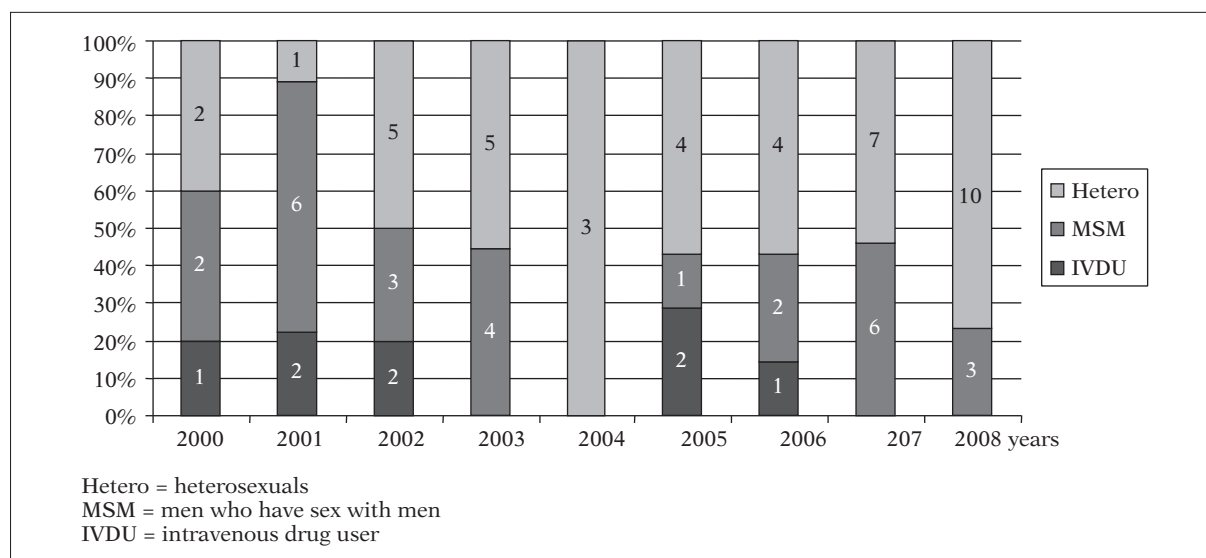


FIGURE 2 - AIDS presenters by behavioural risk factor.

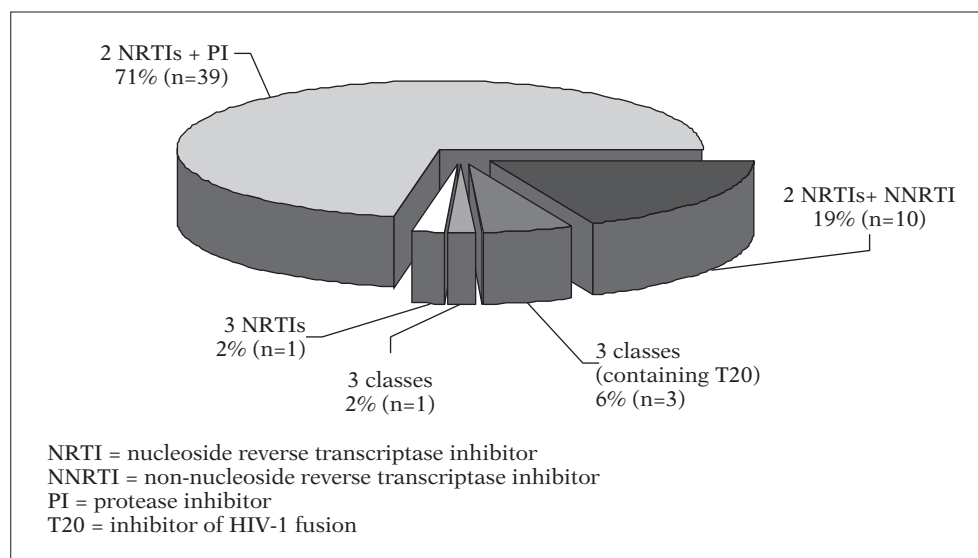


FIGURE 3 - First-line antiretroviral therapy.

TABLE 4 - Most frequently used therapeutic combinations for each line of treatment.

	2NRTIs+PI	2NRTIs+NNRTI	Other
1st line	39	10	5
2nd line	19	14	10
3rd line	11	11	3
4th line	4	5	
5th line		1	

NRTI = Nucleoside reverse transcriptase inhibitor; NNRTI = Non-nucleoside reverse transcriptase inhibitor; PI = Protease inhibitor.

remaining two patients experienced new failures due to lack of compliance.

After three months of therapy, 34% of 45 patients had undetectable HIV RNA levels (<50 copies/ml) and 75% had <400 HIV RNA copies/ml; the median HIV RNA log and CD4+ cell counts were respectively 2.24 copies/ml and 140 cells/ μ l. After 12 months, 84% of 39 patients had undetectable HIV RNA levels, and their median CD4+ cell count was 310 cells/ μ l. Thirty-four patients were followed up for 24 months: 82.3% had undetectable HIV RNA levels, and their median CD4+ cell count was 370 cells/ μ l. Of the 17 patients followed up for 48 months, 94.1% had undetectable HIV RNA levels and their median CD4+ cell count was 380 cells/ μ l.

DISCUSSION

Our data show that about half of all of the patients diagnosed as having AIDS during the study period were AIDS presenters. Similar results were obtained in the ANRS-EN12-Vespa study (Delpierre *et al.*, 2007), which found that 42.6% of patients became aware of their HIV infection at the time of an AIDS-defining event. It is alarming that, despite measures to encourage HIV testing, there are still patients in Italy who are diagnosed as having AIDS when they are still unaware that they have HIV infection. There is clearly still a lack of understanding of the risk behaviours that should lead to HIV testing. This is even more serious as the prevalence of AIDS presenters increased during the study period, from 24% in 2000 to 71% in 2008. Other studies have not observed such an increase (Sabin *et al.*, 2004), but this is probably due to differences in the definition of AIDS presenters.

Unlike other studies indicating that AIDS presenters are more likely to be older and female (Sabin *et al.*, 2004; van Lunzen *et al.* 2009) or male (Castilla *et al.*, 2002), we did not find any differences in gender or age between our AIDS presenters (although 80% were men) and non-AIDS presenters. As found in other Western countries (Sabin *et al.*, 2004; van Lunzen *et al.* 2009), our late presenters were mainly heterosexual men. HIV is being acquired by a decreasing number of injecting drug users (IDUs) in England and Wales

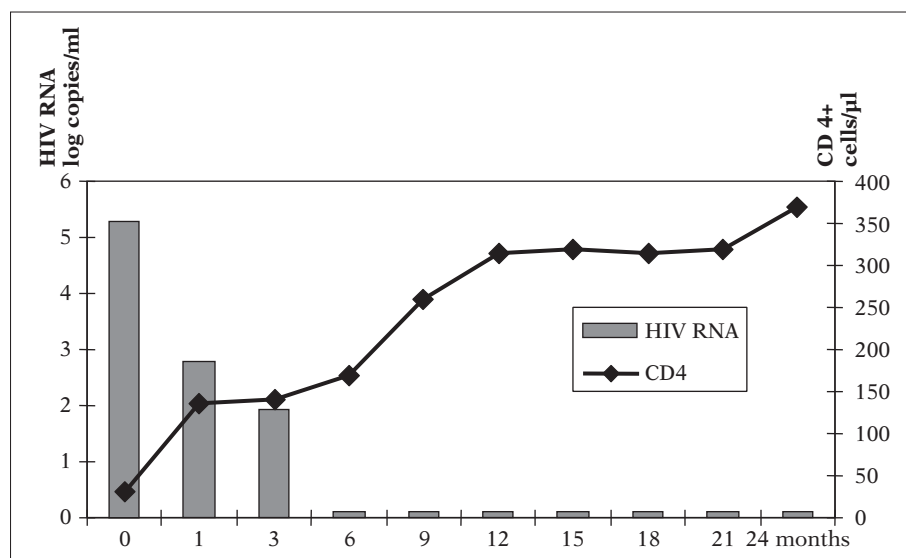


FIGURE 4 - Median HIV RNA levels and CD4+ cell counts in AIDS presenters over time.

(Gupta *et al.*, 2000), France (Baratin *et al.*, 2004) and Italy (Suligo *et al.*, 2003), but by an increasing number of older heterosexual males. Various factors have changed IDU epidemiology in Italy: national information campaigns, the availability of therapeutic opportunities such as methadone, free syringe exchange programmes, and the greater availability of non-injected drugs (Borghi *et al.*, 2008). On the other hand, intravenous drug users (IVDUs) are less compliant with follow-up and therapy, and were prevalent in our non-AIDS presenter group.

Data from the Italian Ministry of Health show that the percentage of AIDS cases among heterosexuals increased from 14.8% before 1997 to 44.7% in 2007-2008 (Notiziario dell'Istituto Superiore di Sanità, 2009). One possible explanation of this is that at the start of the HIV epidemic heterosexuals felt that they were less at risk than IVDUs and men who have sex with men (MSM), and their self-exclusion from HIV screening led them to be the main reservoir of AIDS presenters.

As pointed out in a recent study of the Italian National System for New HIV Diagnoses of HIV Infection (Camoni *et al.*, 2007), increasing numbers of new HIV diagnoses were observed among foreign people living in Italy during the period 1992-2004, and the incidence of new diagnoses among immigrants was 69/100,000 of those with residence permits against 8.7/100,000 Italian-born inhabitants. This suggests that the immigrant

population has relatively higher circulation of HIV infection and, like other authors (Sabin *et al.*, 2004; van Lunzen *et al.* 2009), we found that being an immigrant was a determinant of being an AIDS presenter. The late presentation of HIV infection in this population may reflect a breakdown in family ties and their exclusion from society due to language, cultural and/or socioeconomic barriers.

Finally, although late AIDS presenters may be very difficult to treat (because of the negative impact on adherence of combined therapy for opportunistic diseases and HIV infection, the adverse affects on efficacy of interactions between these treatments (Dean *et al.*, 2002), the severity of AIDS events at diagnosis, etc.), the rates of antiretroviral therapy and adherence to it have been found to be good in various studies (Mocroft *et al.*, 2003; Sabin *et al.*, 2004; van Lunzen *et al.* 2009). We also found that a substantial proportion of our AIDS presenters retained an immunovirological response during the study period (Núñez *et al.*, 2003) despite initial difficulties such as the fact that adverse events and the need to simplify planned HAART were the most frequent reasons for changing therapy. Although the virological and immunological data before starting antiretroviral therapy were worse than those relating to the non-AIDS presenters, the response to therapy was very good as can be expected in the HAART era.

In conclusion our data suggest that the principal

determinants of being a AIDS presenter are being a heterosexual man and being an immigrant, and so particular attention should be paid to increasing early HIV testing among these categories. Moreover, although AIDS presenters represent a disadvantaged group, their response to anti-retroviral therapy is very good.

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