HIV late presenters in Denmark – need for increased diagnostic awareness among general practitioners

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ABSTRACT

INTRODUCTION: The study objective was to describe demographic and clinical characteristics among HIV late presenters in a Danish university hospital.

MATERIAL AND METHODS: Patients > 15 years of age were enrolled in this retrospective study. Data from the medical patient records were analyzed in accordance with the CD4 count at the time of HIV diagnosis.

RESULTS: Among 194 HIV patients (138 men and 56 women), 63 (33%) were diagnosed with a CD4 count below 200 cells/microlitre (late presenters). Heterosexuals constituted a larger proportion of patients in the late presenter group than did homosexual men (MSM) ($p = 0.02$), whereas a higher proportion of MSM than heterosexuals were diagnosed with HIV during primary infection ($p < 0.01$). Half of the late presenters had consulted a general practitioner three to 12 months prior to their HIV diagnosis. HIV antibody testing had not been performed although complaints consistent with possible underlying immune deficiency had been reported. Twenty percent of the late presenters had a persistently low CD4 count below 200 cells/micro litre at follow-up despite having received HAART therapy for more than two years.

CONCLUSION: One third of the HIV patients in this study were diagnosed as late presenters, and this group featured a higher proportion of heterosexuals than of MSM. The HIV antibody test should be performed more consistently on solid clinical ground by general practitioners.

Human immunodeficiency virus (HIV) is commonly diagnosed several years after the acute primary infection, even though patients commonly develop acute febrile illness at an early stage [1]. In most cases, the diagnosis is confirmed coincidentally by HIV antibody testing in an otherwise asymptomatic patient. Alternatively, the diagnosis is made late in the course of infection in connection with the occurrence of HIV-associated clinical manifestations or at the onset of AIDS-defining illness.

The ''dark figure'' is the group of currently undiagnosed HIV patients. It is estimated that the ''dark figure'' in Denmark equals approximately 1,000 persons [2]. The corresponding patients are generally unaware of their HIV-positive status and hence the risk of transmitting the infection. Early HIV diagnosis and initiation of highly active anti-retroviral therapy (HAART) are effective strategies to control the HIV-related morbidity and mortality [3, 4]. The group of HIV patients, known as late presenters, are diagnosed when clinical manifestations develop at a late stage of infection and the cluster of differentiation 4 (CD4) count has declined markedly to a level below 200 cells/microlitre [5].

This study describes demographic and clinical characteristics of HIV late presenters at a Danish university hospital to review the current HIV-test practice in Denmark.

MATERIAL AND METHODS

Eligible for the study were patients above 15 years of age who were diagnosed with HIV at the Department of Infectious Diseases at Aarhus University Hospital, Skejby, from 1 January 2003 through 31 December 2009.

Data on demographics and epidemiology, including age, sex, place of birth, mode of HIV transmission and the patient's medical history were retrieved from the medical records. We also collected information about patient risk behaviour obtained through partner notification by the HIV counsellor. CD4 count and serum HIV RNA (ribonucleic acid) concentration data were retrieved from the patient database (InfCareHiv, Health Solutions, Stockholm). Late presenters were defined as patients who had a recorded CD4 count below 200 cells/microlitre at the time of their HIV diagnosis. History of previous (negative) HIV tests was obtained from the patient notification report and from a review of patient-registered laboratory data.

To evaluate if the study group from Aarhus University Hospital, Skejby was representative for the HIV patient population nationwide and, in particular, for the

HIV late presenters in Denmark – there is a need for increased diagnostic awareness among general practitioners.

ORIGINAL ARTICLE

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TABLE 1

Demographic characteristics in accordance with the cluster of differentiation 4 count at the time of HIV diagnosis.

		CD4 count, cells/microlitre			
	Total (n = 194)	< 200 (n = 63)	200-349 (n = 37)	≥ 350 (n = 94)	p, CD4 < 200 vs CD4 ≥ 350
Median age, years	38	41	35	35	< 0.01
Sex, n (%)					NS
Men	138 (71)	42 (67)	24 (65)	72 (77)	
Women	56 (29)	21 (33)	13 (35)	22 (23)	
Risk group, n (%)					< 0.01
MSM	87 (45)	20 (32)	16 (43)	51 (55)	
Heterosexual men	51 (26)	22 (35)	8 (22)	21 (22)	
Women	56 (29)	21 (33)	13 (35)	22 (23)	
Place of birth, n (%)					NS
Denmark	129 (66)	39 (62)	23 (62)	67 (71)	
Africa	35 (18)	12 (19)	9 (26)	14 (15)	
Other	30 (16)	12 (19)	5 (12)	13 (14)	

CD4 = cluster of differentiation 4; MSM = men who have sex with men; NS = non-significant.

TABLE 2

Background for HIV testing in accordance to cluster of differentiation 4 count at the time of HIV diagnosis.

		CD4 count, cells/microlitre			
	Total n (%) (n = 194)	< 200 n (%) (n = 63)	200-349 n (%) (n = 37)	≥ 350 n (%) (n = 94)	p, CD4 < 200 vs CD4 ≥ 350
Clinical assessment	93 (48)	50 (79)	18 (49)	25 (27)	< 0.0001
Patient's own initiative	35 (18)	2 (3)	8 (22)	25 (27)	< 0.0001
Partner notification	25 (13)	5 (8)	4 (11)	16 (17)	NS
Acute HIV infection	19 (10)	0	3 (8)	16 (17)	< 0.001
Immigration health examination	10 (5)	3 (5)	3 (8)	4 (4)	NS
Pregnancy/in vitro fertilisation	6 (3)	1 (2)	0	5 (5)	NS
Blood donor screening	6 (3)	2 (3)	1 (3)	3 (3)	NS

CD4 = cluster of differentiation 4; NS = non-significant.

HIV centres in Copenhagen, data from Aarhus were compared with similar data extracted from the Danish HIV Cohort Study (DHCS) for the same observation period (2003 through 2009).

Statistical analyses were performed using Fisher's test and χ^2, 2 × 2 for bivariate analyses and Mann-Whitney's test for continuous variables. The study was approved by the Danish Data Protection Agency.

RESULTS

In total, 194 HIV patients were enrolled in the study. Men constituted 71% (n = 138) and women 29% (n = 56) of the study population (**Table 1**). The median age was significantly higher for men (40 years) than for women (33 years), p < 0.001. Among men, 87 (63%) were homosexual (MSM) and 46 (34%) heterosexual, whereas five (3%) patients had a history of intravenous drug abuse.

In total, 32 countries of origin were represented in the study population. Patients born in Denmark constituted 66% (n = 129), followed by 18% (n = 35) from the African continent, 6% (n = 11) from Europe, 5% (n = 10) from Asia (six from Thailand), 4% (n = 7) from the Middle East and 1% (n = 2) of other or unknown origin. The patients from Africa were predominantly women: 28 (50%) and seven (5%), respectively (p < 0.0001). None of the African men were registered as MSM. A significantly higher proportion of MSM than heterosexual men was born in Denmark: 81 (93%) versus 33 (64%), p < 0.0001). Among the Danish male patients, 19 (15%) had had sex with someone from HIV high-risk areas (Thailand and Africa).

At the time of HIV diagnosis, 63 (33%) patients had a CD4 count below 200 cells/microlitre (late presenters). Among these, 27 patients had a CD4 count below 50 cells/microlitre (very late presenters). In the remaining group of patients, 37 (19%) were diagnosed with HIV when they had a CD4 count between 200 and 349 cells/microlitre, and 94 (49%) with CD4 counts above 350 cells/microlitre (Table 1). Heterosexuals constituted a larger proportion of patients in the late presenter group than in the MSM group: 43 (68%) versus 20 (32%), respectively (p = 0.02). Twenty-two (51%) of the heterosexual late presenters were Danish: 16 men and six women. There was no difference between the distribution of Danish patients and patients of another ethnic origin with regard to the three CD4 count categories. In the group of late presenters, only one patient had a history of intravenous drug abuse.

In almost half of the cases, an HIV antibody test had been performed as part of the clinical assessment (n = 93; 48%) with the highest occurrence among late presenters (**Table 2**). In this group, 15 patients had been identified as HIV positives in conjunction with the diagnosis of another sexually transmitted infection. Tests performed at the patient's own initiative was the second most common test reason (n = 35; 18%), followed by tests in relation to partner notification by the HIV counsellor (n = 25; 13%) and acute HIV infection (n = 20; 10%). In the latter category, significantly more MSM than heterosexuals had been diagnosed with acute HIV: 16 (18%) and four (4%), respectively; p < 0.01. Other reasons for performing an anti-HIV antibody test were immigration health examination (5%), pregnancy/in vitro fertilization (3%) and blood donor screening (3%).

Analysis of former HIV antibody test data showed that 38 (20%) patients had been tested (with a negative result) during the period preceding the date of the positive antibody result. A higher proportion of men than women had previously been tested: 26% and 4%, respectively, p < 0.0001. The same trend was observed when comparing MSM with heterosexual men: 32% and

TABLE 3

Laboratory findings and clinical manifestations in accordance with cluster of differentiation 4 count at the time of HIV diagnosis.

	Total (n = 194)	CD4 count, cells/microlitre < 200 (n = 63)	200-349 (n = 37)	≥ 350 (n = 94)	p, CD4 < 200 vs CD4 ≥ 350
Positive screening results, n (%)					
Syphilis antibody test	15 (8)	4 (6)	3 (8)	8 (9)	NS
HBsAg	9 (5)	5 (8)	2 (5)	2 (2)	NS
anti-HCV	9 (5)	2 (3)	2 (5)	5 (5)	NS
Median HIV RNA level at the time of HIV diagnosis, 10^3 copies/ml serum (95% CI)	80 (1-4,152)	210 (18-5,279)	66 (4-703)	42 (1-650)	< 0.0001
Clinical manifestations prior to the time of HIV diagnosis, n (%)					
Weight loss	58 (30)	41 (65)	8 (22)	9 (10)	< 0.0001
Oral candidiasis	34 (18)	28 (44)	3 (8)	3 (3)	< 0.0001
Chronic diarrhoea	33 (17)	22 (35)	3 (8)	8 (9)	< 0.0001
Recurrent respiratory tract infections	32 (17)	27 (43)	2 (5)	3 (3)	< 0.0001
Lymphadenopathy	30 (16)	14 (22)	5 (14)	11 (12)	NS
Herpes zoster dermatitis (shingles)	22 (11)	20 (32)	2 (5)	0	< 0.0001
Seborrhoic dermatitis	13 (7)	6 (10)	3 (8)	4 (4)	NS
Pneumocystis jirovecii pneumonia	8 (4)	8 (13)	0	0	< 0.01
Mycobacterium tuberculosis infection	8 (4)	5 (8)	2 (5)	1 (1)	NS
Lymphoma	7 (4)	4 (6)	0	3 (3)	NS
Toxoplasmosis	2 (1)	2 (3)	0	0	NS

anti-HCV = hepatitis C antibody; CD4 = cluster of differentiation 4; CI = confidence interval; HBsAg = hepatitis B surface antigen; RNA = ribonucleic acid.

16%, respectively, p < 0.05. In 15 (17%) MSM and seven (14%) heterosexual men, two or more previous (negative) HIV antibody tests had been performed.

In total, 15 (8%) patients had a positive syphilis antibody test, nine (5%) patients were hepatitis B surface antigen (HBsAg) positive and nine (5%) patients were hepatitis C antibody positive (anti-HCV) positive (**Table 3**). It was noted that among seven patients, three of whom were *late presenters,* there had been a positive syphilis and/or hepatitis laboratory result two to five years prior to the positive HIV antibody test result. Mean HCV RNA serum concentration was highest among patients with a CD4 count below 200 cells/microlitre. Among the late presenters, clinical manifestations such as weight loss, lymphadenopathy, oral candidiasis, chronic diarrhoea, recurrent respiratory infections and herpes zoster rash had been significantly more frequently reported compared with the groups with CD4 counts above 200 cells/micro litre. It was documented in the medical records and by the HIV counsellor that in a minimum of 32 (51%) of the late presenter patients, a general practitioner (GP) had been consulted three to 12 months prior to the time of the HIV diagnosis with complaints that were consistent with a possible underlying immune deficiency without an HIV antibody test being performed.

Pneumocystis jiroveci pneumonia (n = 8), tuberculosis (TB) infection (n = 8), lymphoma (n = 7) and toxoplasmosis (n = 2) had been diagnosed in 24 patients among whom 18 (29%) were late presenters compared with six (5%) patients with a higher CD4 count (p < 0.0001). It should be noted that among the eight patients with a TB infection, five had tested HIV positive one to five years after the TB infection had been diagnosed and treated.

During the seven-year observation period, 1,615 HIV patients had been registered in the DHCS Thus, the Aarhus study population constituted 12% of the total national figure. There was no significant difference between patient characteristics in Aarhus and Copenhagen with respect to median age (38 years versus 37 years), intravenous drug abuse (3% versus 7%) and non-Danish ethnicity (34% versus 30%). By contrast, a significantly larger proportion in the Copenhagen patient population was men (81% versus 71%) in general and MSM (56% versus 45%) in particular (p < 0.01 and p < 0.05), whereas a higher proportion in the Aarhus study group was late presenters (33% versus 26%; p < 0.05).

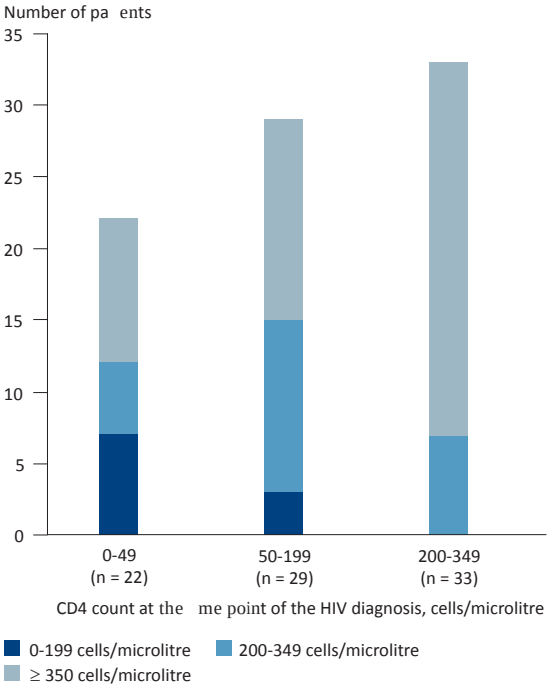
Figure 1 shows the CD4 counts that were available at follow-up in 2010 from the 94 (90%) of the 104 patients found originally with a CD4 below 350 cells/microlitre. Ten patients (20%), all from the late presenter group (n = 51), had a persistent CD4 count below 200 cells/micro litre. Among the ten patients, eight had been receiving HAART therapy for more than two years.

DISCUSSION

This study showed that one third of the HIV patients

FIGURE 1

Cluster of differentiation 4 (CD4) count in 2010 following the observation period 2003-2009 in accordance with nadir CD4 count below 350 cells/microlitre at the time the HIV diagnosis.



were diagnosed as late presenters with a CD4 count below 200 cells/micro litre. Similar observations have been made in other European countries [5, 6]. The patient characteristics of the Aarhus HIV study population were slightly different from the patient characteristics of the Copenhagen HIV population. In the latter group, the proportion of male patients – including MSM – was higher, whereas the proportion of late presenters was lower. This observation was in accordance with our results from the Aarhus study population which showed that although MSM represents the largest group among the HIV infected [7], relatively more heterosexually infected patients are diagnosed as late presenters. This finding could be explained by a higher awareness of HIV infection among MSMs compared with heterosexuals which translates into a practice of more frequent HIV antibody tests among MSM patients. Previous (negative) HIV antibody testing had more frequently been performed in the MSM group than in the heterosexual male group. It cannot be ruled out that there is a higher attention level among health care professionals towards HIV antibody testing of MSMs than of heterosexuals. A significantly higher proportion of MSM had been tested and found HIV positive during the course of acute infection. This suggests a possible selection bias towards MSM and HIV testing.

The study revealed that late presenters had suffered symptoms consistent with a condition of a possible underlying severe immune deficiency for a longer period prior to the HIV diagnosis. Three to twelve months prior to the HIV diagnosis, a minimum of half of the late presenters had consulted a GP with complaints, including weight loss, lymphadenopathy, recurrent respiratory infections, chronic diarrhoea, candidiasis and/or herpes zoster rash without undergoing an HIV antibody test at the GP.

Several barriers are involved in the process of delayed HIV diagnosis in late presenters [8]. The first barrier is constituted by the patient. The patient may have personal motives to avoid being tested for HIV while seeking medical care, the patients may simply not consider themselves to be at risk of HIV infection, or they may be anticipating spontaneous clinical recovery in cases where symptoms are present. Another barrier is rooted at the level of the health care professional, as the overall decision about when and in which patients to perform an HIV antibody test may be biased. Although clarification of possible sexual exposure is important in the overall risk assessment, the HIV antibody test should be performed on a broader indication and more consistently as advocated by the Danish National Board of Health.

Late presenters with a low CD4 count and a correspondingly compromised immune system are at significant risk of developing severe HIV-associated disease manifestations [9]. In relation to immune constitution after initiation of HAART therapy, late presenters are also at a potential risk of having a poor CD4 count. In general, a decline in serum HIV RNA after initiation of therapy to a non-detectable level is followed by an increase in CD4 count. However, late presenters are commonly observed to have a persistently low CD4 count for a long period after initiation of therapy. This tendency was also observed in the present study. Most of the late presenters had a persistently low CD4 count of less than 200 cells/micro litre despite HAART therapy for more than two years. As a result, late presenters will continuously be at risk of developing AIDS-defining illness and overall morbidity despite an efficient therapeutic outcome in terms of an undetectable HIV RNA load.

In conclusion, one third of the HIV patients in this study were late presenters with a CD4 count below 200 cells/micro litre at the time of their HIV diagnosis. A high proportion of late presenters were heterosexual; MSM patients are more prevalent among HIV patients diagnosed at an early stage of infection. Part of the HIV diagnostic delay in late presenters seems to be a lack of HIV antibody test initiatives on the part of the GPs. There is thus a need to raise awareness among health care professionals about risk groups with a possible undiagnosed HIV infection.

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