LATE PRESENTATION AMONG PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN TURKEY

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SUMMARY

Objective: Late presentation of the patients with human immunodeficiency virus (HIV) infection is associated with less favourable treatment responses, more accelerated clinical progression, and a higher mortality risk. Although HIV prevalence is low in Turkey, it is steadily increasing and the information about late presentation among HIV-positives is limited. We aimed to analyze the status of late presentation among HIV-positive patients in Turkey.

Methods: All newly diagnosed HIV/AIDS patients from 2003 to 2016 were enrolled in this study by five dedicated centres in Istanbul, Turkey. Demographic data, CD4+ counts, and HIV RNA were collected from medical records and were transferred to a HIV database system. Late presentation was defined as presentation for care with a CD4 count < 350 cells/mm^3 or presentation with an AIDS-defining event, regardless of the CD4 cell count. A medical literature search was done for the analysis of late presentation in Turkey.

Results: The cohort included 1,673 patients (1,440 males, median age 35 years). Among them, 847 (50.6%) had an early diagnosis, with a CD count of more than 350 cells/mm^3. The remaining 826 were late presenters. Among late presenters, 427 (25.5% of all, 51.7% of late presenters) presented with advanced HIV disease. Late presenters were more elderly and less educated. The gender seemed comparable between groups. Late presentation was more likely among married patients. Early presenters were more likely among homosexuals, those diagnosed in screening studies, and in lower HIV-RNA viral load category. There has been a decreasing trend among late presenters in 2011–2016 when compared to 2003–2011 period.

Conclusion: Current data suggest that half of HIV-infected patients present late in Turkey. In our cohort, those presented late were more elderly, less educated, married and had heterosexual intercourse. On admission, late presenters had more HIV-related diseases and were more likely in higher HIV-RNA category. In the cohort, men having sex with men were less likely late presenters. Efforts to reduce the proportion of late presentation are essential for almost every country. The countries should identify the risk factors of late presentation and should improve early diagnosis and presentation for HIV care.

Key words: late presentation, human immunodeficiency virus infection, acquired immunodeficiency syndrome

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INTRODUCTION

Human immunodeficiency virus (HIV) infection is generally diagnosed years after the primary infection (1). It is either diagnosed by HIV-antibody testing in an otherwise healthy person or the patient presents late with an adult immune deficiency syndrome (AIDS) defining illness. There is increasing evidence that early diagnosis and initiation of effective antiretroviral therapy control the HIV-related morbidity and mortality (2, 3). Late presentation is associated with less favourable treatment responses, more accelerated clinical progression, and a higher mortality risk. In addition, late presenters produce a significant burden to the healthcare systems: they may have transmitted the virus to others since they are unlikely to be aware of their infection and they require more healthcare resources than those diagnosed earlier (4).

The recent evidence from the Strategic Timing of Antiretroviral Treatment (START) trial determined when to start antiretroviral

therapy (ART) in people with asymptomatic HIV infection. In START, HIV-positive individuals with a CD4 count < 500 cells/mm^3 were randomized to immediate ART initiation or deferral until their CD4 count declined to 350 cells/mm^3. The interim analysis showed that immediate initiation of therapy was associated with a reduction in the incidence of serious AIDS-related, serious non-AIDS-related events and death from any cause compared with deferring ART until the CD4 count declined to less than 350 cells/mm^3. These events decreased by 57% among those starting ART immediately compared to the deferred ART arm. The overall reduction included a reduction in tuberculosis, lymphoma and Kaposi's sarcoma. Considering the results of the START trial, guidelines of the World Health Organization (WHO), European AIDS Clinical Society (EACS) and British HIV Association (BHIVA) recommended that ART should be initiated in all HIV-positive adults with any CD4 cell count (5–7). Further, randomized clinical trial data were also available from the Temprano trial recruiting 1,600 participants in Ivory Coast, which also demonstrated a reduced risk of death associated with earlier ART initiation (8). However, despite efforts to provide ART to all HIV-positive patients, around one third of the patients with HIV infection continue to present late (9). Late presentation for HIV infection remains an unresolved challenge.

Turkey is among low-prevalence countries in Europe in HIV infection. The information about late presentation among HIV-positives in the country is limited. We aimed to analyze the status of late presentation among HIV-positive patients in Turkey.

MATERIALS AND METHODS

The HIV-positive patients were enrolled in this study by the Action against HIV in Istanbul (ACTHIV-IST) Study Group, which consists of five dedicated HIV centres in Istanbul, Turkey. Three of these centres are located in university hospitals and two are in public training hospitals. All newly diagnosed HIV/AIDS patients with confirmed diagnosis were tested using Western Blot verification test (HIV BLOT 2.2, MP Biomedicals Asia Pacific, Singapore). The CD4+ cell counts were obtained by standard flow cytometry (FACScalibur, Becton Dickinson, New Jersey, USA) and HIV viral load was measured by PCR (COBAS Ampliprep/COBAS TaqMan HIV-1 Test, Roche Molecular Systems, USA). Demographic data including age, sex, transmission routes, education level, marital status, and history of imprisonment, CD4+ counts, and HIV RNA were collected from medical records and were transferred to the HIV database system.

Late presentation was defined as presentation for care with a CD4 count below 350 cells/mm^3 or presentation with an AIDS-defining event, regardless of the CD4 cell count.

Presentation with advanced HIV disease was defined as presentation for care with a CD4 count below 200 cells/mm^3 or presentation with an AIDS-defining event, regardless of the CD4 cell count (10).

An analysis of late presentation in Turkey was searched in PubMed (Medline) using the key words of "late presentation", "HIV", and "Turkey". Only recently diagnosed, treatment-naive cohorts were determined. Those describing the patients by CD4 count were included. Meeting presentations were excluded. Additional publications were proposed by the authors.

All analyses were performed using SPSS 15 (SPSS Inc, Chicago, IL, USA). Data were described using mean ± standard deviation (SD) (or median and range) and as an absolute number and percentage when indicated. The student t test was used to analyze quantitative data. The chi-square test was used to analyze categorical variables. A p value < 0.05 was considered as statistically significant.

RESULTS

The cohort included 1,673 patients (1,440 males, median age 35 years). The characteristics of the patients are given in Table 1. Among them, 847 (50.6%) had an early diagnosis, with a CD count of more than 350 cells/mm^3. The remaining 826 were late-presenters (Table 2). Among late presenters, 427 (25.5% of all, 51.7% of late presenters) presented with advanced HIV disease. The characteristics of late and non-late, "early" presenters are given in Table 2. Late presenters were more elderly and less educated. The gender seemed comparable between the groups. Late presenters were more likely among married patients. Early presenters were more likely among homosexuals, those diagnosed in screening studies, and in lower HIV-RNA viral load category. There has been a decreasing trend among late presenters in 2011–2016 when compared to 2003–2011 period.

Six previous studies of treatment-naive patients from Turkey reported the patient number by CD4 count (11–16). Four studies (12–15) used the classification of CD4 counts < 200/mm^3, 200–350/mm^3, 350–500/mm^3, > 500/mm^3, one study (11) used < 100/mm^3, 100–350/mm^3, 350–500/mm^3, > 500/mm^3 and another study (16) used < 200/mm^3, 200–500/mm^3, > 500/mm^3. The patients by CD4 count in the studies and in the current study are shown in Table 3.

DISCUSSION

In Turkey, the first case of HIV/AIDS was reported in 1985. According to the survey conducted by the Turkish Ministry of Health, there were 13,181 cases of HIV infection out of a population of 78.9 million people in Turkey between October 1985 and July 2016 (17). Among these patients, the transmission route was unknown in 46%, heterosexual contact in 38% and homosexual

Table 1. *Characteristics of patients included in cohort*

Patient number	1,673
Sex (male/female)	1,440/233
Transmission route	
Heterosexual intercourse	639
Homosexual intercourse	572
Intravenous drug use	9
Blood/blood product use	20
Other	5
Unknown	368
Median CD4 cell (count/mm^3)	353
Median HIV RNA level (copies/mL)	98,150

contact in 13%, and injecting drug use in 2%. In a recent study of 829 untreated HIV-1 positive Turkish patients, the male patients reached 84% and the probable route of transmission was heterosexual intercourse in 437 (53%) patients and homosexual intercourse in 256 (31%) patients (14). In the largest series (n = 1,292) of HIV-positive patients from Turkey, we reported that there was a male predominance (85%) and that men having sex with men (MSM) accounted for 40% of all patients with available sex preference data (18).

Current data showed that half of HIV-infected patients present late in Turkey. In recently diagnosed patient cohorts, mean (or median in some studies) CD4 counts were reported in a range of 236 to 441/mm^3 (Table 4) (19–24). In the first analysis of late presenters in the country, we noted that late presenters corresponded to 66% of 209 newly diagnosed HIV-positive individuals (13). Among late presenters, 58% of them (38% of all) presented with advanced HIV disease. In a recent study of 237 patients, > 500/mm^3 was 23%, 200–500/mm^3 was 37% and < 200/mm^3 was 40%

Table 2. *Characteristics of early and late presenters (N=1,673)*

Characteristics	Late presenters CD4 ≤ 350/mm^3 (n = 826)		Early presenters CD4 > 350/mm^3 (n = 847)		p-value
	n	%	n	%	
Age					
< 18 years	4	0.5	9	1.1	< 0.001
18–35 years	369	44.7	493	58.2	
36–50 years	318	38.5	262	30.9	
> 50 years	135	16.3	83	9.8	
Sex (male/female)	698/128		742/105		0.039
Marital status*					
Married	321	38.9	245	28.9	< 0.001
Unmarried	322	39.0	436	51.5	
Widowed	69	8.4	46	5.4	
Education					
Illiterate	273	33.1	254	30.0	0.001
Literate	5	0.6	3	0.4	
Primary school	119	14.4	86	10.2	
Secondary school	83	10.0	63	7.4	
High school	143	17.3	155	18.3	
University	199	24.1	285	33.6	
Risk group*					
Heterosexual intercourse	405	49.0	234	27.6	< 0.001
Homosexual intercourse	257	31.1	315	37.2	
Intravenous drug use	8	1.0	1	0.1	
Blood/blood product use	5	0.6	15	1.8	
Other	3	0.4	2	0.2	
Diagnosis*					
Screening tests	393	47.6	541	63.9	< 0.001
HIV-related diseases	330	40.0	180	21.3	
Years of admission					
1993–2000	4	0.5	1	0.1	
2001–2005	21	2.5	14	1.7	< 0.001
2006–2010	208	25.2	136	16.1	
2011–2016	593	71.8	696	82.2	
HIV RNA level category*					
> 100,000 copies/mL	417	50.5	273	32.2	< 0.001
≤ 100,000 copies/mL	289	35.0	459	54.2	

*The total does not reach 100% because of data in "unknown" category.

Table 3. *CD4 counts and patients by CD4 count among treatment-naive HIV-infected patients from Turkey**

Reference	Year	Number of patients	Mean/median CD4 count/mm^3	Patients by CD4	
				count/mm^3	n (%)
Aydin et al. (11)	2011	164	NR	> 500	27 (16.5)
				350–500	31 (19)
				100–350	70 (42.5)
				< 100	36 (22)
Karaosmanoğlu et al. (12)	2011	136	Median (range): 302 (9–1,270)	> 500	20 (15)
				350–500	22 (16)
				200–350	41 (30)
				< 200	53 (39)
Karaosmanoğlu et al. (13)	2013	209	NR	> 350	72 (34)
				200–350	58 (28)
				< 200	79 (38)
Yemisen et al. (14)	2014	788	Mean ± SD: 358 ± 271	> 350	347 (44)
				200–350	189 (24)
				< 200	252 (32)
Aydin et al. (15)	2015	306	Mean (range): 394 (4–1,270)	> 500	67 (22)
				350–500	56 (18)
				200–350	82 (27)
				< 200	101 (33)
Çerçi et al. (16)	2016	237	Mean: 260 (240 before 2006; 375 after 2006)	> 500	54 (23)
				200–500	88 (37)
				< 200	95 (40)
Current study	2017	1,673	Median: 353	> 350	847 (50.5)
				200–350	399 (24)
				< 200	427 (25.5)

*The patients may overlap in the cohorts.
NR – not reported

Table 4. *CD4 counts of treatment-naive HIV-infected patients from Turkey**

Reference	Year	Number of patients	CD4 count/mm^3
Aydin et al. (19)	2013	120	Mean ± SD: 441 ± 216
Sayan et al. (20)	2013	394	Median (range): 340 (1–1,660)
Yalçınkaya et al. (21)	2014	190	Median (range): 280 (0–1,000)
Aydin et al. (22)	2015	308	TPHA(−) group, mean ± SD: 336 ± 16
			TPHA(+) group, mean ± SD: 324 ± 32
Sayan et al. (23)	2016	1306	Median (range): 361 (4–1,351)
Sayan et al. (24)	2016	78	Median (range): 236 (6–626)

SD – standard deviation, TPHA – *Treponema pallidum* hemagglutination
*The patients may overlap in the cohorts.

(16). The other studies reported the rate of patients presented with < 350/mm^3 as 56% to 69% (11–15). Those with a CD4 of < 200/mm3 were available in 5 studies and it ranged from 32% to 40% (12–16). In the current study, which represents the largest HIV-positive population reported from the country, half of the patients were late presenters and a quarter of the patients presented with advanced HIV disease.

The definition of late presentation is debateful and more than 20 different definition were cited in the literature (4, 9, 10, 25–31). Although the most common definitions have been based on CD4 count, there has been no consistency among definitions, making the estimate of epidemiology of late presentation more challenging. Definitions based on the presence of AIDS at diagnosis or on very low CD4 cell counts (< 50/mm^3 for example) estimates

10–15% (26, 27), whereas definitions based on higher CD4 counts (< 200–350/mm^3) report 30–40% (28–31). The Late Presentation for HIV Treatment in Europe programme was initiated in 2008. In 2011, the initiative released a consensus definition to identify the persons at particularly increased risk of disease progression and provide improvement in surveillance and public health needs (10). Two definitions were agreed: late presentation (CD4 count < 350/mm^3, or presentation with an AIDS defining event regardless of CD4 count) and presentation with advanced HIV disease (CD4 count < 350/mm^3, or presentation with an AIDS defining event regardless of CD4 count).

In our cohort, those presented late were more elderly, less educated, married and had heterosexual intercourse. On admission, late presenters had more HIV-related diseases and were more likely to be in higher HIV-RNA category. In the cohort, relatively less MSM patients were diagnosed as late presenters. (257/826, 31% vs. 315/847, 37%). This finding was in accordance with other cohorts (29, 32) and can be explained by increased awareness of HIV infection among MSM compared with heterosexuals. A higher proportion of MSM are tested for HIV suggesting a selection bias towards MSM and HIV tests either on routine screening or during the course of acute infection.

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study including 30,454 patients from 34 countries reported that the median CD4 count at presentation was 368/mm^3 (33). In 2010, 47.5% of the patients had CD4 < 350/mm^3, while this figure was 48.7% in 2013. There was significant increase in male and female patients who inject drugs and a significant decline in late presenters in northern Europe. Across Europe, certain groups carry increased risk for late presentation including intravenous drug use, older age, foreign birth, and non-White ethnicity (34). Beside this big scale cohort across Europe, several European countries reported their cohorts determining the status of late presentation and the factors determining it. In Swiss HIV cohort study including 1,366 patients late presenters were more likely to be females or from sub-Saharan Africa and less likely to be highly educated or MSM (32). Among the 20,496 patients, 53.9% presented late and 31.2% had advanced HIV disease (including 2,253 patients with AIDS) in a big scale French cohort (35). MSMs were less likely than all other transmission groups to present late, and the risk of late presenters increased with age. The frequency of late presenter decreased from 57.1% among patients enrolled in 2003–2004 to 49.7% in 2007–2009 (35). In Danish cohort, 3,027 patients were diagnosed with HIV from 1995–2009; 34.7% had advanced HIV disease and 51.2% were late presenters. Age > 50 years, heterosexuals of non-Danish origin, 'other' route of transmission, and diagnosis before 2002 were associated with an increased risk of presenting with advanced HIV, whereas a negative HIV test prior to diagnosis was associated with a significantly reduced risk (36).

In an Asian cohort, among 3,744 patients, 2,681 (72%) were late presenters. Older patients and injecting drug users were more likely to be late presenters. Homosexual HIV exposure and females were less likely to be late presenters (37). In an African cohort of 14,487 eligible patients, 85.6% were late presenters and 63% presented with advanced HIV disease. Late presentation decreased from 88.9% in 2005 to 80.1% in 2010 and advanced HIV disease from 67.8% in 2005 to 53.6% in 2010.

Male sex, older age and hepatitis B virus and hepatitis C virus coinfections were associated with late presentation. Male sex, older age, unemployment and hepatitis B virus coinfection were among the predictors of advanced HIV disease (38). In contrast to the recent efforts to determine all HIV-infected patients and to treat them to control the disease burden, many individuals present to the clinical care in an advanced stage.

CONCLUSION

The late presentation is a challenge for the given patient since it goes with a significantly higher morbidity and mortality. It is also a challenge for the healthcare services. Efforts to reduce the proportion of late presentation are essential for almost every country. The countries should identify the risk factors of their late presenters and should use targeted public health interventions to improve early diagnosis and presentation for HIV care. Improvements in HIV testing policies emphasizing vulnerable groups are crucial.

Conflict of Interests

None declared

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