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ORIGINAL PAPER

Lack of awareness in both patients and physicians contributes to a high rate of late presentation in a South West German HIV patient cohort

J. M. Kittner · L. von Bialy · J. Wiltink · T. Thomaidis · B. Gospodinov · A. Rieke · F. Katz · T. Discher · K. Rath · B. Claus · G. Held · G. Friese · B. Schappert · M. Schuchmann · P. R. Galle

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Abstract
Purpose To assess rate of late presentation with HIV in Southwestern Germany and to identify patient characteristics correlated with CD4 nadir.
Methods Patients with primary diagnosis who presented to one of ten participating clinics rated on knowledge and behavior towards HIV testing on a self-developed questionnaire, whereas clinical data was assessed by the physician.
Results 161 patients were included. Risk factors were homosexual (59.5 %) or heterosexual contacts (26.8 %), drug use (2.0 %), migration (3.9 %), or others (7.8 %). 63.5 % had a CD4 T cell count < 350/µl. 52.5, 17.4, and 31.1 % were diagnosed in CDC stadium A, B or C, respectively. 209 disease episodes were reported, from whom 83.7 % had led to the diagnosis of HIV. 75.2 and 68.3 % said to have been well-informed about ways of transmission and testing offerings, respectively, and 20.4 % admitted to have psychologically repressed the possibility of being infected. 48 patients rated their personal behavioral risk as "high" or "very high". Of these, however, only ten had performed at test in the precedent year. Performing a regression analysis, younger age and previous testing were correlated with a higher CD4 T cell nadir ($p = 0.005$, and 0.018, resp.).
Conclusion The rate of late presentation in this region was even higher compared to national or European surveys. Most infected patients perceived to have had only a low risk. Several disease episodes did not lead to the initiation of HIV testing by the physician.

Keywords HIV · Late presentation · Missed diagnosis · Personal risk · Testing behavior

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J. M. Kittner (✉) · L. von Bialy · T. Thomaidis · M. Schuchmann · P. R. Galle
1st Medical Department, University Medical Centre Mainz, Langenbeckstr. 1, 55131 Mainz, Germany
e-mail: jenskittner@yahoo.de

J. Wiltink
Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre Mainz, Mainz, Germany

B. Gospodinov
Private Practice, Saarbrücken, Germany

A. Rieke
Kemperhof Koblenz, Koblenz, Germany

F. Katz
St. Josefs Hospital, Wiesbaden, Germany

T. Discher
II. Medical Department, University Medical Centre, Giessen/Marburg, Germany

K. Rath
Westpfalz-Klinikum, Kaiserslautern, Germany

B. Claus
Klinikum Ludwigshafen, Ludwigshafen, Germany

G. Held
1st Medical Department, University Medical Centre, Homburg/Saar, Germany

G. Friese
Private Practice, Giessen, Germany

B. Schappert
Private Practice, Mainz, Germany

Introduction

The availability of a highly efficient antiviral therapy (ART) enables HIV-infected patients to experience an almost normal life expectancy [1]. However, if ART is started only after a significant damage to the immune system had occurred, morbidity and mortality are increased in comparison to the general population [2]. Beside the individual harm, late presentation is disadvantageous on an epidemiological level: it not only increases costs for medical care in the affected patients [3], but also the likelihood of transmission events until the patient becomes aware of the infection and receives ART [4]. Observational studies have demonstrated that the median of patients reaching a nadir < 200 CD4 T cells/µl was infected for more than 9 years [5].

The term "late presentation" was recently defined as first presentation for specific medical care with less than 350 CD4/µl or with an AIDs-defining illness but it is already subject of discussion of whether this threshold has to be increased to 500 cells/µl [6, 7].

Unfortunately, approximately half of the patients worldwide are diagnosed late [8], and the situation in Western countries does not substantially differ with a rate of 53.8 % in an European survey [9]. In Germany, data from a large cohort is available showing a rate of 49.4 % [10].

Efforts to decrease the rate of late-presentation have led to different concepts: in the United States, every citizen who gets into contact with any healthcare facility is offered HIV testing (USPSTF, [11]). In Europe, the concept of "client initiated counseling and testing" is widely accepted, asking persons who perceive an increases risk of HIV infection to decide whether a test should be performed [12], This is added by "provider initiated testing" performed in routine settings like pregnancy or known i.v. drug use, or if symptoms suggestive for an HIV infection were observed. However, several studies showed that even symptomatic patients were not offered an HIV test [13–15], and therefore, it is one emerging strategy to provide a list of "marker diseases" whose appearance gives rise to testing [16, 17].

Individual testing behavior may depend on knowledge and awareness on HIV, on easy access to testing facilities, but may be also influenced by several social, psychological and legal aspects [18]. The general German public repeatedly was shown to be well informed about ways of transmission [19], and several testing opportunities are available. However, persons may be reluctant to testing since it can have several negative consequences: patients may fear the negative emotions associated with an incurable disease, especially if they are not well-informed about treatment possibilities [20]. In addition, persons may be afraid of social discrimination [21], or may want to avoid the obligation to inform sexual partners [22].

Aim of the current study

It is the aim of the current study to characterize patients who first present with HIV in to reveal the rate of late presentation, disease episodes that preceded the diagnosis, and whether patients' knowledge and behavior towards testing are associated with CD4 T cell counts at the time point of first presentation.

Methods

This is an epidemiological study on patients with a recent diagnosis of an HIV infection presenting to one of ten outpatient clinics or private practices cooperating in the "Arbeitsgemeinschaft HIV Rhineland-Palatinate, Saarland, Giessen" covering the southwestern region of Germany.

Recruitment took place between 1st of March 2011 and 30th of June 2012. Adult patients could be included if they presented with a first diagnosis in one of the participating outpatient clinics, or if they re-attended this clinic for regular care and their primary diagnosis was less than 2 years ago. Patients were asked to participate during routine visits. Prior to inclusion, written informed consent was obtained from all participants.

The questionnaires were developed by an expert panel of physicians with long-term clinical experience who collected, discussed and consented factors which might influence the state of CD4 T cells at the point of first presentation.

The physician's questionnaire comprised the following parameters as assessed at the time point of first presentation: CD4 and CD8 T cell counts, viral load, and who initiated the first positive HIV test (patient, health care professional, or routine examination), and whether and with which substances antiviral therapy was planned respectively initiated within 6 weeks after diagnosis. Physicians were asked to tick whether diseases from the following list had occurred recently or in the past: Pneumocystis pneumonia, candida esophagitis, oral candidiasis, herpes zoster, CMV infection, oral hairy leukoplakia, cerebral toxoplasmosis, condyloma, syphilis, gonorrhea, bacterial pneumonia, lymphadenopathy persistent for more than 3 months, tuberculosis, malignant lymphoma, weight loss of more than 10 % of body weight, acute retroviral syndrome, viral hepatitis, Kaposi´s sarcoma, skin changes, or HIV encephalopathy. Free lines were given if the disease was not listed. Further on, physicians were asked to state whether the respective disease had led to the diagnosis of HIV. Symptoms and diseases were planned to be categorized to be either strongly or moderately associated with HIV, to be epidemiologically associated, or whether no direct association with HIV could be seen. The diagnosis of HIV was not

counted as "missed" if the disease episode had occurred prior to a reported negative test.

The patients' questionnaire comprised data on age, sex, the time point of first diagnosis, the way of transmission (heterosexual or homosexual contacts, intravenous drug use, migration from an area with high prevalence, others), whether and when they had had a negative HIV test before, and contained six questions on knowledge and attitudes towards HIV testing (Table 1). In addition, patients were asked, in case of high-risk sexual behavior or intravenous drug use, whether their general practitioner had been informed about this risk prior to the diagnosis. Patients were asked to fill in the questionnaire in a separate room during routine visits.

Both questionnaires were pseudonymized with the same identification code for common analysis.

Statistical analysis

Bivariate relations between patient characteristics and outcome data (number of CD4 cells) were determined by Spearman's Rho correlations. Reported p values (correlations) correspond to 2-tailed tests and were considered significant at the 0.05 level. For a more accurate analysis, a linear regression model with the number of CD4 cells as the dependent variable and patient characteristics as independent variables (predictors) was used. We entered variables blockwise. Model 1 describes the predictive value of socio-demographic variables (age, sex), models 2 additional inclusion of hypothesized mode of infection (intravenous drug use, region, heterosexual contacts, homosexual contacts, else), model 3 additional inclusion of previous test in HIV, model 4 additional inclusion of subjective theories on HIV. For all analyses, the variance inflation factor (VIF) was inspected to quantify multicollinearity. We used put in criterion $p < 0.05$, put out criterion $p > 0.10$ for the regressions. Reported p values (regressions) correspond to 2-tailed tests and were considered significant at the 0.05 level. Statistical analyses were computed using IBM SPSS Statistics 20 (IBM, Chicago, IL).

This study was approved by the Ethics committee of Rhineland-Palatinate, Mainz, No. 837.129.11(7671), and agreed by the Ethics committees of Hesse, Frankfurt/Main, (No. MC 188/2011), and Saarland, Saarbrücken (No. 134/11).

Results

Overall, 161 patients were included. The number of patients who refused to participate was low but was not documented. Recruitment was done in private practice Saarbrücken: 39 patients, Kemperhof Koblenz 33 patients, University Medical Centre Mainz 30 patients, St. Joseph´s Hospital Wiesbaden: 20 patients, University Medical Centre Giessen and Marburg: 19 patients, Westpfalz-Clinic Kaiserslautern: 6 patients, Clinic Ludwigshafen: 6 patients, University Medical Centre Homburg/Saar: 5 patients, private practice Giessen: 2 patients, private practice Mainz: 1 patient. Thus, 96 patients were recruited from cities with more than 150,000 inhabitants (Wiesbaden, Mainz, Saarbrücken, Ludwigshafen), whereas 65 patients were recruited from smaller towns.

CD4 T-cells at the time point of diagnosis accounted for 311/µl ± 251 [standard deviation (SD)]/µl (range 2–1,088 cells/µl). In 101 from 151 patients (63.5 %) with the respective data available, the initial CD4-count was below 350 CD4 T cells/µl. The distribution of CD4 T cell numbers is depicted in Fig. 1. Baseline viral load accounted for 356,790 ± 1,123,805 copies/ml. At the time point

Table 1 Items on patients' questionnaire, to be answered on a 1–4 point scale

Statement/question	To be answered on 1–4 point scales
1 "Do you think that prior the diagnosis you did know enough about ways of transmission of HIV? I knew…"	"…almost nothing"—"…almost everything"
2 "You know the most common risks for the acquisition of HIV: unprotected sex with changing partners and intravenous drug use. I think, my risk was…"	"…very low"—"…very high"
3 "Do you think you had sufficient information on where and when HIV tests could have been performed? on locations and times where an HIV test could be performed, I was…"	"…not at all informed"—"… very well informed"
4 "Did you know *prior to your diagnosis*, that HIV is a well-containable chronic disease?"	"Not at all"—"Yes"
5 "An early diagnosis helps to avoid further complications as well as transmission to others. Do you think that there are sufficient opportunities to get tested?"	"No"—"Yes"
6 "Some things you want to disavow, you may "repress" them. I knew that I *could* be infected with HIV…"	"…but I completely repressed it"—"it was quite clear to me"

of inclusion, the patient was aware of the diagnosis for 259.24 ± 207.0 (range 2–719) days.

90 of 161 patients (55.9 %) reported of having had at least one negative HIV test result in the past. In the 80 patients who provided the date, the previous test had been done 5.6 ± 6.6 years ago.

48 of 160 patients (29.8 %) stated to have had a "high" or "very high" risk to acquire HIV. However, only 10 of these had done a test in the 12 months preceding the diagnosis (20.7 %), 2 patients had done a test within the previous 2 years (4.2 %). In 13 patients this was more than 2 years ago (27.1 %), and in 3 patients the time point was not reported. Finally, 20 patients of those perceiving a high risk for HIV never had performed an HIV test in the past (41.7 %).

The test that revealed the infection was initiated by the patient in 60 cases (37.5 %), by the physician in 89 (55.6 %) cases, and in 11 cases (6.9 %) it was performed in a routine situation. 119 patients reported information whether the general practitioner was informed about high-risk sexual behavior or i.v. drug use prior to the diagnosis, of whom 29 (24.4 %) had informed their general practitioner, whereas 71 (59.7 %) had not, and 19 patients (16.0 %) were not completely sure.

Table 2 shows baseline characteristics of all included patients, self-reported risk factors for infection, and results of the patient questionnaire. In addition, it depicts bivariate correlation coefficients of these parameters with the initial CD4 T cell count. When applying the more appropriate linear regression model, age was found to be negatively related with the CD4 T cell count at the time point of the diagnosis (regression coefficient −4.745 ± 1.661, $p = 0.005$), whereas having performed a test in the past was positively correlated with a higher CD4 T cell count (regression coefficient 93.890 ± 39.429, $p = 0.018$). These two variables explained 6.6 % of the CD4 T cell count at the time point of the diagnosis.

Symptoms and diseases preceding the diagnosis

At the time point of diagnosis, 83 patients were diagnosed as CDC stadium A (52.5 %), 28 as stadium B (17.4 %), and 50 as stadium C (31.1 %). All patients in CDC stadium C had less than 350 CD4 T cells/µl. Overall, 209 disease episodes that had occurred prior to the diagnosis were reported. From 161 patients, 48 (29.8 %) did not have any disease episode before. The remaining patients currently or in the past on average had 1.30 ± 1.20 disease episodes (range 1–5). 175 episodes were reported to have led to the diagnosis of HIV infection (83.7 %) (Table 3, supplementary data).

Discussion

Late presentation with HIV is of major individual and epidemiological concern. In our region, the rate of late presentation with 63.5 % was higher compared to recent surveys in Germany as well as in Europe [9, 10]. The increased rate of late presentation may be associated with the fact that in the area of investigation is not a hotspot of overt living MSM, and a comparable low prevalence of HIV, presumably leading to a decreased awareness. This goes along with the observation that the epidemic among MSM spreads from the larger cities into the rural areas due to an increased use of internet dating and an increased mobility [23]. Like in previous studies, late presentation was found to be associated with higher age [24, 25], however, we could not corroborate migration and heterosexual infection as risk factors for late presentation, most likely due to insufficient patient numbers in these subgroups [10].

It is a strength of our study to closely characterize patients who present for primary diagnosis. We found that patients having performed a previous HIV test were more likely to be diagnosed early, suggesting that a general

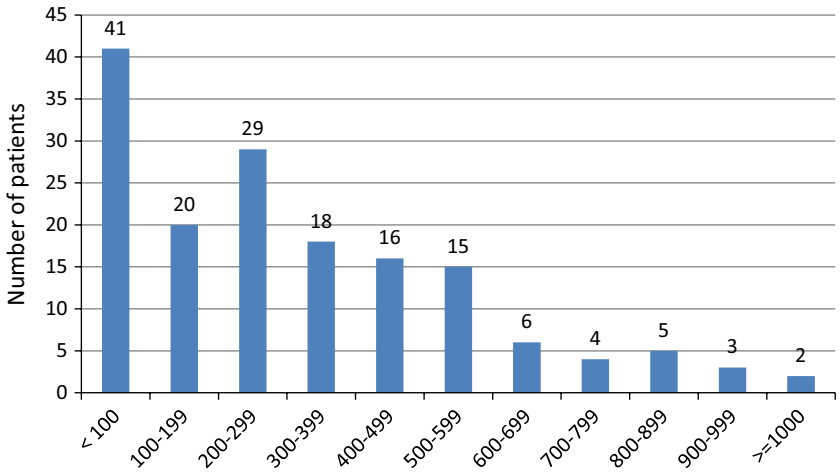

Fig. 1 $CD4^+$ T cell distribution at the time point of presentation ($n = 159$)

Table 2 Baseline characteristics, results of patients' questionnaires, and correlation with $CD4^+$ T cell nadir in a bivariate analysis

		Correlation with CD4 T-cells/µl at diagnosis	*p*
Age, sex, testing behavior			
Age (years) (± SD)	41.43 ± 11.83	**−0.21**[a]	**0.005**
Sex [male/female/transgender (%)]	80.1/19.9/0	−0.004	0.959
HIV test performed in the past	90 (55.9 %)	**0.183**	**0.021**
Risk factor for infection			
Homosexual contacts	59.5 %	**0.165**	**0.042**
Heterosexual contacts	26.8 %	−0.005	0.954
Intravenous drug use	2.0 %	−0.05	0.546
Migration from country with high prevalence	3.9 %	**−0.162**	**0.047**
Others/unknown	7.8 %	−0.151	0.065
Patient questionnaire scale results			
Knowledge about ways of transmission	3.07 ± 1.01	**0.172**	**0.030**
Knowledge about test facilities	2.95 ± 1.13	0.135	0.091
Testing opportunities satisfactory	3.19 ± 0.08	0.070	0.381
Informed about treatment options	2.43 ± 1.11	0.090	0.261
Subjective risk for infection	2.06 ± 1.01	0.094	0.242
Psychological repression of probably being infected	1.82 ± 0.86	0.120	0.138

Bold values indicate statistically significant ($p < 0.05$)

[a] Pearson's coefficient, all others Spearman's coefficient

willingness to be tested may lead to an early diagnosis. Patients stated that their knowledge about ways of transmission as well as on test facilities was high, and testing opportunities were felt to be satisfactory. Therefore, we can deny practical hindrances for testing in most cases. Does the possibility of modern HIV therapy mislead patients to carelessness, believing that treatment is successful in any case? When patients were asked on knowledge about treatment options prior to the diagnosis, many patients were not aware of these options. Therefore, we think that the reluctance of being tested is not due to an unrealistic belief in the potency of antiretroviral therapy.

It is remarkable that many patients stated that their personal risk was rather low, which, statistically, can be applicable only for single cases. Therefore, although we did not assess real behavior, the perception of a low risk has to be classified as a common misjudgment. Interestingly, even the perception of an increased risk did not result in increased testing, which is in substantial contrast to the recommendation to repeat testing at least once per year in this situation [26].

We hypothesize that a substantial part of patients repress the possibility of being infected. In general, repression is a common (but usually unsuccessful) mechanism of coping with a serious problem [27]. In our study, only one-fifth of patients answered to possibly have repressed the risk, but we cannot exclude that patients were unable to understand this psychological concept, and more elaborated research should be undertaken to reveal motivation of non-testing.

We describe disease episodes as noted by the attending physician prior to the diagnosis of HIV, and whether they have led to the diagnosis of HIV. As expected, not all reported diseases were followed by the diagnosis. For example, it was missed in four out of 30 patients with oral or esophageal candidiasis as well as in six out of 14 cases with a persistent lymphadenopathy, disease entities that are widely known to be closely associated with an HIV infection. Also other studies reported of frequent contacts with the health systems without being offered a test prior to the diagnosis [15, 28]. Diagnosis of a syphilis was found to be associated with early diagnosis [29]. Unfortunately, as also observed in our study, symptoms leading to a diagnosis can be quite nonspecific and of a broad spectrum. Therefore, in the clinical situation, it is often difficult to decide whether an HIV test is necessary or dispensable, and this decision could be facilitated by adequately reviewing the individual risk behavior with the patient. However, we and others found only a low rate of medical doctors being informed about their patients' risk profiles [30], and it was stated that the reluctance of primary care physicians to notice lifestyle-associated risks for HIV was the major barrier for adequate HIV screening across Europe [31].

In areas with a low overall prevalence < 1 % like in central Europe, general screening is not cost effective [32]. However, since the current strategy obviously is not sufficient, it may be useful to identify conditions which may be associated with higher rates of HIV, so-called indicator diseases [8, 17, 33]. In the European HIDES-I-Study,

all patients with one or more out of eight indicator diseases were tested, identifying a prevalence of HIV of 1.8 % in this sample [34]. However, this strategy has to be adapted to the region and, finally, the collaboration of primary care physicians as well as of several specialists is mandatory.

In a decentralized health care system, the accuracy of data on previous diseases is often compromised since they may be based only on the patients' reports. In addition, in our study, we cannot exclude that a disease, e.g., an episode of syphilis, occurred prior to HIV infection if no previous testing date was reported. Considering the use of a written questionnaire, we have to assume a bias towards recruitment of patients with better German literacy.

Conclusion

In the examined region, late presentation was even more common in comparison to other national or international surveys. The range of symptoms and diseases was large and in part quite nonspecific, but the diagnosis was missed also in typical complications. Our data show that in the majority of patients testing behavior is not rationally adapted to a personal risk behavior but rather erratic. It would be of interest to know whether persons at risk are aware of decreased life expectancy in case of late diagnosis. Willingness of physicians to consider patients' risk behavior may substantially increase the rate of early diagnosis.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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