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The reasons for providing HIV testing in patients with newly-diagnosed HIV infection in Lodz region, Poland in the years 2009-2017

Analiza wskazań do wykonania testu w kierunku HIV u pacjentów z nowo zdiagnozowanym zakażeniem HIV w regionie łódzkim, Polska w latach 2009-2017

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Summary

Early diagnosis increases life expectancy in HIV-infected patients.

Aim: The aim of this study was to determine the reasons for HIV testing in newly-diagnosed patients with HIV registered in Lodz, Poland in years 2009-2017. The study examines also whether HIV testing was performed following the recommendation of physicians or at the request of patients.

Results: The study group consisted of 401 (83.72%) males and 78 (16.28%) females. The median age at the moment of diagnosis was 33 years (LQ 27-UQ 40). In total, 285 (62.91%) patients were late presenters. Clinical indications constituted the main reason for undergoing HIV testing and were reported in 228 out of 479 patients (47.59%) including AIDS-defining diseases were a reason for HIV testing in 105 patients. Thirty-four patients underwent HIV testing following diagnosis of sexually-transmitted diseases (STDs); in 91.18% of these cases the STDs was syphilis. However, high-risk sexual contact was the main reason for HIV testing in asymptomatic patients (160 of 257 cases; 62.27%). Patients in the non-AIDS group were significantly more likely to take the initiative to order an HIV test than patients in the AIDS group ($p < 0.0001$).

Conclusions: In conclusion, in the Lodz region, patients with HIV infection are most commonly diagnosed at an advanced stage of infection. This may be associated with the low number of HIV tests performed following the doctors recommendation.

Keywords: HIV testing • high-risk groups • reasons

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INTRODUCTION

A total of 23153 HIV cases, 3612 AIDS cases and 1398 deaths of AIDS patients were reported from the implementation of epidemiological surveillance of HIV/AIDS in Poland from 1985 to the 31 May 2018 [13].

In Europe, the proportion of people living with HIV who are aware of the infection ranges from 38% to 98% depending on the country. Poland is characterised by considerably lower numbers of HIV screening tests than other European countries as well as a high proportion of late presenters of HIV [16]. Fifty percent of HIV-infected patients in Poland are diagnosed late, with a CD4 cell count below 350 cells/ μ L and/or an AIDS-defining event at the moment of HIV diagnosis [1].

The expansion of HIV counselling and testing remains a priority for reducing the undiagnosed population and the number of late presenters.

Routine HIV testing should be incorporated into clinical practice and not be limited to groups with a higher risk of HIV infection. The CDC recommends that health care providers should test every patient aged 13-64 years old at least once as part of routine health care, regardless of their perceived risk. The general recommendation for patients with risk factors is to get tested annually; sexually-active gay and bisexual men may benefit from more frequent testing, even every three to six months [3]. According to European Guidelines, HIV testing should be offered to individuals who display conditions associated with immune deficiency or share a common route of transmission [8]. Similarly, the WHO recommends routinely offering HIV testing to clients who present with symptoms or medical conditions that could indicate HIV infection, including those with presumed and confirmed tuberculosis cases, viral hepatitis and malnutrition, or pregnant women, and to all individuals whose partners have HIV [5]. However, the HIDES study on auditing HIV testing demonstrates poor implementation of these guidelines in people presenting with indicator conditions [20].

AIMS

The aim of this study was to determine the reasons for providing HIV testing in patients with newly-diagnosed HIV infections registered in a Lodz HIV centre, Poland from January 2009 to December 2017. The study also examines whether HIV testing was performed in response to a recommendation by a physician, or at the initiative of the person wishing to be tested.

METHODS

The Lodz HIV center is the only antiretroviral treatment clinic in the Lodzkie province which performs both HIV Western blot and HIV viral load tests.

HIV test data collected in the period January 2009 to December 2017 and stored in the medical database of the center were analyzed. Patient characteristics such as age, gender, route of HIV transmission and CD4 cell count at HIV diagnosis were assessed based on the medical records of the patient. Routes of HIV transmission were declared by the patients.

It was also examined whether HIV testing was performed following referral to the HIV clinic by a physician, or whether the test was performed at the request of the patient.

The following persons were excluded from the analysis: those who tested HIV-positive but failed to return to the center for a confirmatory Western-blot test, those who did not collect the confirmatory test, or those who collected the Western blot test but failed to attend after diagnosis. Prisoners and patients younger than 18 years were not also enrolled in this study. Patients with a prior HIV diagnosis, either reported or presumed, were also excluded from the analysis. In patients displaying concomitance of several diseases, the main three causes of HIV testing were chosen for this analysis. According to the Center for Disease Control and Prevention (CDC), an AIDS-defining illness is classified as one that is directly associated with advanced HIV infection (stage C), other clinical conditions were considered as non AIDS-defining diseases. Late presentation is understood as diagnosis of HIV with a CD4 count < 350 cells/ μ L or with an AIDS-defining event, regardless of the CD4 cell count.

STATISTICAL ANALYSIS

In order to evaluate the frequency of categorical variables, the chi-square test or Fisher's exact test were used. The Mann-Whitney U-test was used to compare continuous variables. P-values < 0.05 were considered significant.

RESULTS

The study group consisted of 401 (83.72%) males and 78 (16.28%) females. The median age at the moment of diagnosis was 33 years (LQ 27-UQ 40). The highest incidence of HIV infection was observed in the group of patients aged 30 to 39 (41.21%). Among patients with newly-diagnosed HIV infection, 32.06% were over the age of 50. The characteristics of the study group are presented in Table 1.

Table 1. Characteristics of the study population

	Number of patients n (%)
Male	401 (83.72)
Female	78 (16.28)
Route of HIV transmission	
Homo/bisexual contact	247 (51.57)
Heterosexual contact	119 (24.84)
Intravenous drug usage	60 (12.53)
Sexual risk behaviours in drug users	8 (1.67)
Unknown or missing data	45 (9.39)
Decision for HIV testing	
Patient' s decision	215 (44.88)
Doctor' s suggestion	206 (43.00)
Unknown or no data available	58 (12.12)
Total	479 (100)

The median CD4 count was 255 cells/ μ L (LQ 80-UQ 487). Two hundred and eighty-five (62.91%) patients were late presenters, including AIDS defining diseases were diagnosed in 105 patients. However, CD4 counts within three months of diagnosis were provided in 453 patients. Some of the HIV-positive tested patients failed to attend the next visit after diagnosis or were transferred to another clinic. Information about clini-

cal stage of HIV infection according to CDC was not available for 28 patients.

Reasons for HIV Testing

Nearly half of the patients with newly-diagnosed HIV infections (44.88%) were tested for HIV at their own request, and 43.00% were tested following a recommen-

Table 2. Clinical stages of HIV infection at the moment of HIV diagnosis

n=451	Stage A n (%)	Stage B (%)	n Stage C n (%)	p
Patient' s decision	168 (65.37)	37 (41.57)	4 (3.81)	p < 0.0001 In patients classified as stage A or B, HIV test was performed more frequently at the request of the patient.
Doctor' s suggestion	66 (25.68)	44 (49.44)	90 (85.71)	
Unknown reason	23 (8.95)	8 (8.99)	11 (10.48)	
Total (n=451)	257 (100)	89 (100)	105 (100)	

dation by their physician. The decision to order HIV testing was not provided by 12.12% of the patients.

Among the 257 asymptomatic patients (stage A according to CDC), 168 (65.37%) received an HIV test at the request of the patient and 66 (25.68%) received one at the recommendation of the physician.

Of the 194 symptomatic patients with clinical conditions related to immune deficiency (stages B and C according to CDC), 41 received HIV tests (21.13%) on their own initiative while 134 (69.07%) did so following the recommendation of a physician (Table 2).

Patients in the non-AIDS group (stages A and B according to the CDC) were significantly more likely to take initiative and get tested for HIV than those in the AIDS group ($p < 0.0001$) (Table 2).

In the entire study group, the main reasons for undergoing HIV testing were clinical conditions, as reported in 228 out of 479 patients (47.59%) (Table 3). Primary HIV infection was reported in 17 out of 479 patients (3.54%). This number includes 105 patients who presented an AIDS-defining illness.

The most common AIDS-defining diseases included recurrent bacterial pneumonia (in 27 out of 105 patients, 25.71%), *Pneumocystis jirovecii* pneumonia (22 patients, 20.95%), tuberculosis or non-tuberculosis mycobacterial infection (19 patients, 16.09%), and cerebral toxoplasmosis (11 patients, 10.48%) (Table 4).

Thirty-four patients underwent HIV testing following diagnosis of sexually-transmitted diseases (STDs);

in 91.18% of these cases the STDs was syphilis. Two patients underwent HIV testing due to HPV infection and one patient due to *gonorrhoea*. A positive test result for STDs was a stronger motivation to perform HIV testing among male patients than female patients ($p = 0.01$). In our study, lymphadenopathy, either isolated or in combination with fever or weight loss, was reported in 17 patients. Thirteen subjects (14.60%) requested a test due to abnormal complete blood count test result. The other frequent clinical indicators for HIV testing were fever and weight loss (seven patients), and coinfection with HBV or HCV and HAV (seven patients) (Table 5).

Among asymptomatic patients, the main reason for HIV testing was the presence of high-risk sexual contacts (160 of 257 cases; 62.27%). In this group, 42 (8.76%) patients had a stable sexual partner infected with HIV.

The reasons for HIV testing in patients with AIDS-defining diseases and those with non-AIDS-defining conditions are listed in Tables 4 and 5.

DISCUSSION

According to the Sialon II Network, one third of the subjects living with HIV in Europe are unaware of their infection [12]. In the Lodz HIV centre, HIV infection is often diagnosed in patients exhibiting clinical symptoms. Our findings indicate that in the Lodz region, 194 out of 451 patients (43.02%) were diagnosed with symptoms related to immune deficiency (B and C according to CDC). Interestingly, in almost half of the symptomatic patients (stage B), HIV testing was performed at the request of the patients. The current guidelines for HIV testing in Poland recommend the routine offer of an

Table 3. Summary of reasons for HIV testing

	Men n (%)	Women n (%)	p
AIDS-defining diseases	90 (22.44)	15 (19.23)	NS
Varied symptoms and diseases (non-AIDS defining)	105 (26.18)	18 (23.07)	NS
Sexual risk behaviours or partner HIV(+)	141 (35.16)	19 (24.36)	NS
Intravenous drug use	16 (3.99)	3 (3.85)	NS
Pregnancy	0 (0)	9 (11.55)	
HIV-infected child	0 (0)	1 (1.28)	
The source patient in post-exposure prophylaxis	2 (0.50)	0 (0)	NS
Testing of blood donors	3 (0.75)	2 (2.56)	NS
Unknown reasons or missing data	44 (10.98)	11 (14.10)	NS
Total (n=479)	401 (100)	78 (100)	

NS - differences not statistically significant

HIV test in patients with a number of AIDS-defining diseases or those with non-AIDS defining conditions believed to be associated with HIV, or to members of groups at highest risk of HIV infection [17]. However, this recommendation is rather poorly implemented in clinical practice.

It is interesting to note that while 44.88% of the newly-diagnosed HIV patients requested their test following the advice of a physician, this was the case for only 25.68% of asymptomatic patients. This is in contrast to the Swiss HIV Cohort Study, where the majority of patients with newly-diagnosed HIV infection (60%) were referred for HIV testing by a physician [2]. It is likely

that physicians in Poland rarely offer HIV screening, even to patients from high-risk groups. The low number of HIV tests offered by doctors, particularly to asymptomatic patients, suggests a lack of interest in the sexual activity of the patient and an insufficient perception of the risk of HIV. These findings highlight the urgent need for improved testing strategies, such as increasing the use of HIV testing among asymptomatic patients with high-risk behaviours.

Although routine testing for HIV in pregnant women has been recommended since 2012, one case of HIV vertical transmission was reported in our group in 2012. While accurate data concerning HIV screening during preg-

Table 4. Reasons for HIV testing in patients with AIDS-defining diseases according to gender

	n (%)
Pulmonary diseases	
Recurrent bacterial pneumonia	19 (18.09)
Tuberculosis or Mycobacterium avium complex infection	14 (13.34)
Pneumocystis jirovecii pneumonia	16 (15.26)
Neurologic diseases	
Brain toxoplasmosis	10 (9.53)
Fungal meningitis	3 (2.86)
HIV-related myelopathy	1 (0.95)
HIV-related encephalopathy	4 (3.80)
Progressive multifocal leukoencephalopathy	1 (0.95)
AIDS-associated cancers	
Non-Hodgkin Lymphoma	4 (3.80)
Kaposi sarcoma	4 (3.80)
Others AIDS-defining diseases	
Oesophageal candidiasis	5 (4.76)
Recurrent salmonella septicemia	1 (0.95)
Cytomegalovirus retinitis	1 (0.95)
Wasting syndrome	3 (2.86)
Concomitant different AIDS defining diseases	

nancy in Poland is not available, it appears that not all pregnant women are being offered HIV tests, as cases of vertical HIV transmissions are still being reported [14].

A diagnosis of HIV infection during the acute phase of the disease reduces the chance of HIV transmission and maximizes the potential benefits obtained from

early antiretroviral treatment (ART). In the present study, acute retroviral syndrome was diagnosed in only 17 of 479 studied patients (3.54%). This percentage was lower than rates observed in other European countries; for instance, primary or early HIV infection was diagnosed in 19.5% of patients in Slovenia and 6% in Turkey [4, 15].

In the present study, 228 out of 479 patients (47.59%) underwent HIV testing in response to various symptoms or illnesses. Our results are in accordance with those of Dokuzoguz et al., who report that less than half of patients (48.8%) underwent HIV testing as a result of suffering an illness [7].

In the present study, 160 out of 479 patients (33.40 %) gave their high-risk sexual behaviour as the reason

to perform HIV tests. Similar results were obtained in a study from Japan, where such high-risk behaviour was the reason for HIV testing in 38.6% of patients [10].

Similarly, data from 30 voluntary testing and counselling sites in Poland over the period 2008–2010 show that the higher HIV testing rate was independently associated with exposure category (MSM or intravenous drug using), number of sex partners or having a high-risk

Table 5. Reasons for HIV testing in symptomatic patients with non-AIDS defining diseases according to gender

	n (%)
Sexually-transmitted diseases	34 (27.66)
Acute retroviral syndrome	17 (13.84)
Hematologic disorders	12 (9.88)
Hodgkin lymphoma	2 (1.60)
Shingles	2 (1.60)
Molluscum contagiosus	1 (0.80)
Oral hairy leukoplakia	1 (0.80)
Oral candidiasis	1 (0.80)
Cervical intraepithelial neoplasia	2 (1.60)
HBV/HCV infection	4 (3.26)
Non-viral hepatitis	3 (2.44)
Atrioventricular conduction block	1 (0.80)
Chronic diarrhoea	2 (1.60)
Weight loss	4 (3.26)
Fever	2 (1.60)
Fever and weight loss	3 (2.44)
Lymphadenopathy	12 (9.88)
Aseptic meningitis	4 (3.26)
Cerebral infarction	1 (0.80)
HPV infection	2 (1.60)
Purulent meningitis	1 (0.80)

partner [19]. In 7.10% of study patients, the detection of STDs inspired HIV testing. Similarly, Horino et al. report that an STD diagnosis motivated HIV testing in 11.5% of newly-diagnosed HIV patients [10]. Although the present study does not evaluate the incidence of HIV infections in patients with diagnosed STDs, it is reasonable to assume that in Poland, HIV screening in this group of patients is insufficient. However, the results from the HIDES study found the HIV prevalence to be 4.06% in individuals presenting with an STI [18].

Our study shows that AIDS-defining clinical conditions were reported in 21.92% of all patients with newly-diagnosed HIV infection, this is a higher value than observed in Italian (15.89%) or Swiss (15.73%) patients [6, 9]. Furthermore, the percentage of late presenters in our study, is still high: 62.91%. These findings indicate that a significant proportion of AIDS cases could be prevented by improving testing rates among the general population.

In our study group, the most frequently reported AIDS-defining diseases included recurrent bacterial pneumonia and tuberculosis, or non-tuberculous mycobacterial infections. Interestingly, the most common AIDS-defining illness in Japanese patients was *Pneumocystis jirovecii* pneumonia (PCP) (59.5%) [10]; however, in our study, PCP was observed only in only 20.95% of newly-diagnosed patients in the present study. In con-

trast, Tominsky et al. report oesophageal candidiasis (51%), wasting syndrome (40%) and PCP (34%) to be the most prevalent AIDS-defining conditions in newly-diagnosed HIV patients in Germany; however, the median number of opportunistic diseases in the German study population was two [21].

Cytopenias are frequently reported to be associated with HIV infections, as their incidence has been found to correlate with the degree of HIV-induced immunosuppression [22]. Moreover, isolated cytopenias, particularly thrombocytopenia, can occur as initial signs of HIV infection [22]. HIV-infected patients are also at increased risk of developing not only hematologic disorders, but also AIDS-defining (Kaposi sarcoma, non-Hodgkin lymphoma, cervical cancer) and non-AIDS defining malignancies (e.g. lung cancer, anal cancer, Hodgkin's lymphoma) [11, 23]. Our results confirm also the need for HIV screening in patients with hematologic diseases and malignancies.

CONCLUSION

In conclusion, in the Lodz region, patients with HIV infection are diagnosed at an advanced stage of infection. This may be associated with the low number of HIV tests performed following the recommendation by a physician.

REFERENCES

- [1] Ankiersztejn-Bartczak M., Firląg-Burkacka E., Czeszko-Paprocka H., Kubicka J., Cybula A., Horban A., Kowalska J.D.: Factors responsible for incomplete linkage to care after HIV diagnosis: preliminary results from the Test and Keep in Care (TAK) project. *HIV Med.*, 2015; 16: 88-94
- [2] Buetikofer S., Wandeler G., Kouyos R., Weber R., Ledergerber B.: Prevalence and risk factors of late presentation for HIV diagnosis and care in a tertiary referral centre in Switzerland. *Swiss. Med. Wkly.*, 2014; 144: w13961
- [3] Centers for Disease Control and Prevention. <https://www.cdc.gov/hiv/testing/> (05.10.2018)
- [4] Cohen M.S., Chen Y.Q., McCauley M., Gamble T., Hosseinipour M.C., Kumarasamy N., Hakim J.G., Kumwenda J., Grinsztejn B., Pilotto J.H., Godbole S.V., Mehendale S., Chariyalertsak S., Santos B.R., Mayer K.H., et al.: Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.*, 2011; 365: 493-505
- [5] Consolidated guidelines on HIV testing services. World Health Organization 2015. http://apps.who.int/iris/bitstream/handle/10665/179870/9789241508926_eng.pdf;jsessionid=1B12B2170D992B4C79C910A1716078E2?sequence=1 (05.10.2018)
- [6] d'Arminio Monforte A., Cozzi-Lepri A., Girardi E., Castagna A., Mussini C., Di Giambenedetto S., Galli M., Cassola G., Vullo V., Quiros-Roldan E., Lo Caputo S., Antinori A., Icona Foundation Study Group: Late presenters in new HIV diagnoses from an Italian cohort of HIV-infected patients: prevalence and clinical outcome. *Antivir. Ther.*, 2011; 16: 1103-1112
- [7] Dokuzoguz B., Korten V., Gökengin D., Fincanci M., Yildirmak T., Kes U.N., Tasdelen Fisgin N., Inan D., Eraksoy H., Akalin H.: Transmission route and reasons for HIV testing among recently diagnosed HIV patients in HIV-TR cohort, 2011-2012. *J. Int. AIDS Soc.*, 2014; 17: 19595
- [8] Gökengin D., Geretti A.M., Begovac J., Palfreeman A., Stevanovic M., Tarasenko O., Radcliffe K.: 2014 European Guideline on HIV testing. *Int. J. STD AIDS*, 2014; 25: 695-704
- [9] Hachfeld A., Ledergerber B., Darling K., Weber R., Calmy A., Battegay M., Sugimoto K., Di Benedetto C., Fux C.A., Tarr P.E., Kouyos R., Furrer H., Wandeler G., Swiss HIV Cohort Study: Reasons for late presentation to HIV care in Switzerland. *J. Int. AIDS Soc.*, 2015; 18: 20317
- [10] Horino T., Sato F., Kato T., Hosaka Y., Shimizu A., Kawano S., Hoshina T., Nakaharai K., Nakazawa Y., Yoshikawa K., Yoshida M., Hori S.: Associations of HIV testing and late diagnosis at a Japanese university hospital. *Clinics*, 2016; 71: 73-77
- [11] Ji Y., Lu H.: Malignancies in HIV-infected and AIDS patients. *Adv. Exp. Med. Biol.*, 2017; 1018: 167-179
- [12] Marcus U., Nöstlinger C., Rosińska M., Sherriff N., Gios L., Dias S.F., Gama A.F., Toskin I., Alexiev I., Naseva E., Schink S.B., Mirandola M., Sialon II Network: Behavioural and demographic correlates of undiagnosed HIV infection in a MSM sample recruited in 13 European cities. *BMC Infect. Dis.*, 2018; 18: 368
- [13] National AIDS Centre. <https://www.aids.gov.pl/epidemiology/poland> (05.10.2018)
- [14] National Institute of Public Health. <http://www.pzh.gov.pl/> (05.10.2018)
- [15] Pirs M., Poljak M., Seme K., Babic D.Z., Tomazic J.: Clinical features and virologic characteristics of primary and early HIV-1 infection in Slovenian patients. *Coll. Antropol.*, 2006; 30: 47-52
- [16] Porter K., Gourlay A., Attawell K., Hales D., Supervie V., Touloumi G., Rosinska M., Vourli G., van Sighem A., Pharris A., Noori T., ECDC Dublin Declaration Monitoring Network: Substantial heterogeneity in progress toward reaching the 90-90-90 HIV target in the WHO European region. *J. Acquir. Immune Defic. Syndr.*, 2018; 79: 28-37

[17] PTN AIDS. http://ww.ptnaids.pl/index.php?option=com_content&view=category&layout=blog&id=14&Itemid=24&lang=pl (05.10.2018)

[18] Raben D., Mocroft A., Rayment M., Mitsura V.M., Hadziosmanovic V., Sthoeger Z.M., Palfreeman A., Morris S., Kutsyna G., Vassilenko A., Minton J., Necsoi C., Estrada V.P., Grzeszczuk A., Johansson V.S., et al.: Auditing HIV Testing Rates across Europe: Results from the HIDES 2 Study. *PLoS One*, 2015; 10: e0140845

[19] Rosińska M., Simmons R., Marzec-Bogusławska A., Janiec J., Porter K.: Relating HIV testing patterns in Poland to risky and protective behaviour. *AIDS Care*, 2016; 28: 423-431

[20] Sullivan A.K., Raben D., Reekie J., Rayment M., Mocroft A., Esser S., Leon A., Begovac J., Brinkman K., Zangerle R., Grzeszczuk A., Vassilenko A., Hadziosmanovic V., Krasnov M., Sönnnerborg A., et al.: Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS One*, 2013; 8: e52845

[21] Tominski D., Katchanov J., Driesch D., Daley M.B., Liedtke A., Schneider A., Slevogt H., Arastéh K., Stocker H.: The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. *HIV Med.*, 2017; 18: 125-132

[22] Vannappagari V., Nkhoma E.T., Atashili J., Laurent S.S., Zhao H.: Prevalence, severity, and duration of thrombocytopenia among HIV patients in the era of highly active antiretroviral therapy. *Platelets*, 2011; 22: 611-618

[23] Vishnu P., Abouafia D.M.: Haematological manifestations of human immune deficiency virus infection. *Br. J. Haematol.*, 2015; 171: 695-709

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