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Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study

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ABSTRACT

Objective: To quantify and characterise missed opportunities for earlier HIV diagnosis in patients diagnosed with advanced HIV.

Design: A retrospective observational cohort study.

Setting: A central tertiary medical centre in Israel.

Measures: The proportion of patients with advanced HIV, the proportion of missed opportunities to diagnose them earlier, and the rate of clinical indicator diseases (CIDs) in those patients.

Results: Between 2010 and 2015, 356 patients were diagnosed with HIV, 118 (33.4%) were diagnosed late, 57 (16%) with advanced HIV disease. Old age (OR=1.45 (95% CI 1.16 to 1.74)) and being heterosexual (OR=2.65 (95% CI 1.21 to 5.78)) were significant risk factors for being diagnosed late. All patients with advanced disease had at least one CID that did not lead to an HIV test in the 5 years prior to AIDS diagnosis. The median time between CID and AIDS diagnosis was 24 months (IQR 10–30). 60% of CIDs were missed by a general practitioner and 40% by a specialist.

Conclusions: Missed opportunities to early diagnosis of HIV occur in primary and secondary care. Lack of national guidelines, lack of knowledge regarding CIDs and communication barriers with patients may contribute to a late diagnosis of HIV.

Strengths and limitations of this study

- This study shows for the first time the rate and reasons for missed opportunities to diagnose HIV in a low-prevalence country like Israel.
- This study may shed light on the reasons why primary care physicians or specialists are missing opportunities to diagnose HIV earlier.
- Non-existence of clear national guidelines for HIV testing and ignoring HIV 'clinical indicator diseases' (CIDs) are major reasons for a missed diagnosis of HIV.
- This study was carried out in one centre and may not reflect the picture in other parts of the country. Also, the total number of patients is low and this may limit the generability of the study.

Successful implementation of the WHO guidelines,[7] European AIDS Clinical Society (EACS) guidelines[8] and the National Institutes of Health (NIH) guidelines,[9] which recommend antiretroviral therapy (ART) initiation in all adults living with HIV regardless of the WHO clinical stage and at any CD4 cell count, will require a meticulous approach to diagnose and initiate ART early in the course of infection.

Yet many physicians are unaware of HIV diagnosis and testing. For example, a quarter to half of the patients with advanced HIV had a former visit to a physician or healthcare facility with an HIV-related disease and yet an HIV test was not conducted.[10] Furthermore, in a recently published case–control study that examined the number of patient consultations in six general practices in Amsterdam, it was found that 61.8% of patients with HIV visited their general practitioner (GP) at least once in the year prior to diagnosis, twice as often as their HIV-negative controls.[11]

In Israel, the annual incidence of newly diagnosed patients with HIV ranges between

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INTRODUCTION

Late detection of HIV decreases life expectancy, increases treatment complexity while decreasing drug adherence,[1][2] impairs life quality,[3] increases total costs[4] and increases the rates of HIV transmission in the community.[5] Unfortunately, about half of the patients with HIV worldwide are late presenters (LP): participants presenting for care with a CD4+ T-cell count below 350 cells/mm^3 or with an AIDS-defining event regardless of the CD4+ T-cell count or with an advanced HIV disease (AHD) with a CD4+ T-cell count below 200 cells/mm^3.[6]

58.5 and 61 cases per million population.[12] Forty-four per cent of the 8000 diagnosed patients with HIV living in Israel are immigrants from sub-Saharan Africa, most of whom are Jewish immigrants from Ethiopia; one-third are men who have sex with men (MSM), 20% are intravenous drug users (IVDU), mainly immigrants from Eastern European countries, and the rest are heterosexuals or belong to an unknown risk group. According to the ministry of health, there are at least 2000 undiagnosed patients. All Israeli citizens have a national health insurance that covers HIV testing and treatment. Thus, HIV testing can be performed free of charge in all primary care settings by the initiative of the treating physician depending on the clinical presentation or the request of the patient. In emergency departments, an HIV test is usually not offered. In addition, any person can request an HIV test in one of seven dedicated HIV centres which are located in the main hospitals (referred to as HIV centres). In these centres, the test is confidential but not anonymised. Tests can also be carried out anonymously in two governmental-funded sexually transmitted infections (STI) centres and the Israeli AIDS Task Force, which is a non-governmental organisation (NGO). Routine HIV screening in pregnant women is not mandatory and is offered mainly to women who belong to a risk group (immigrants from endemic countries, IVDU, etc). Incarcerated individuals were routinely offered an HIV test until recently, but this practice has been stopped. Immigrants from Africa (mainly Ethiopia) were universally screened in the past but not in the past decade, and immigrants from other geographical areas (like Eastern Europe) were never offered an HIV test on a routine base upon immigration. All blood donations are screened for HIV using Combo ELISA test and pooled PCR.

Still, at least 33% are discovered late and about 10% are discovered with AHD.[12]

In this study, we have examined rate and risk factors for presentation with AHD and characterised missed opportunities for earlier diagnosis of HIV among patients who presented with AHD in a tertiary teaching centre.

METHODS

The Sheba Medical Center is a 1400 bed tertiary medical centre affiliated to the Sackler Medical School of Tel Aviv University that serves a diverse population in central Israel. The HIV clinic treats 1500 patients. The study included all patients who were diagnosed with HIV between 1 January 2010 and 31 December 2015 and were referred to the Sheba Medical Center. We excluded from the study patients who immigrated illegally to the country and did not have medical insurance, although many of them were detected late, because accurate data regarding their medical history could not be gathered.

Sociodemographic data (gender, age at HIV diagnosis, country of birth, marital status, location of HIV diagnosis, HIV transmission route) and clinical and laboratory data (CD4 cell counts at diagnosis, HIV viral load, AIDS-defining events at diagnosis) were included in the analyses.

DEFINITIONS

Late presentation: Persons presenting for care with a CD4+ T-cell count below 350 cells/mm^3 or presenting with an AIDS-defining event, regardless of the CD4+ T-cell count.[13]

Advanced HIV disease (AHD): Persons presenting for care with a CD4+ T-cell count below 200 cells/mm^3 or presenting with an AIDS-defining event, regardless of the CD4+ T-cell count. This is in accordance with the European Late Presenter Consensus working group.[13]

A major missed opportunity was defined when the patient was in contact with the healthcare system due to a medical symptom consistent with HIV infection, and at least two of the following conditions were fulfilled.

1. The medical diagnosis in that contact was compatible with an HIV clinical indicator disease (CID) as defined in a consensus paper,[14 15] although not as an AIDS-defining event (eg, thrombocytopenia, lymphadenopathy, etc).
2. The patient belonged to a risk group for contracting HIV.
3. The recommendations for HIV testing according to the Centers for Disease Control and Prevention (CDC)[16] or the UK national guidelines for HIV testing[17] were not followed.

Clinical and laboratory data regarding clinical events in the 5 years prior to HIV diagnosis including HIV-related CIDs were extracted from the medical insurer electronic data files. For most of the patients, the electronic data file was accessible to the treating physician in the hospital and hence to the researchers. In the few cases where the electronic file was not accessible, the primary care physician was reached and helped the researcher accessing the data. All patients were asked about their former encounters with the medical system (primary care, specialists and hospital-based care) and the data were cross-matched and compared with the data in the electronic files.

Where possible, we contacted by telephone the primary care physician or the specialist who missed an opportunity to diagnose HIV and asked four questions: (1) what is your specialty? (2) Where did you study medicine? (3) Are you familiar with the CDC guidelines for HIV testing or with the HIV CIDs? (4) Why did you not send an HIV test regarding the specific event (eg, a CID diagnosed)? We told the physicians that in any case their identity will not be revealed but still they were not 'blinded' to the researcher who posed the questions.

Statistical methods

All information retrieved from patients' charts and laboratory results was abstracted in a tabular manner, using an Excel datasheet. Statistical analysis was performed using SPSS software. The Student's t-test, the Pearson χ^2 test and the Fisher exact test were used for

comparisons, as appropriate, with the level of significance set at a p value of <0.05.

Variables included in the univariate analysis were: age, gender, nationality and transmission mode. In order to identify factors associated with being AHD, we built a multivariate logistic regression model in which being diagnosed with advanced HIV disease (AHD) was considered as a dependent variable. Variables with a p value of <0.05 were entered in the model. The fitness of the final model was assessed with the likelihood ratio test.

The study was approved by the Institutional Review Board of Sheba Medical Center.

RESULTS
Patient's characteristics
Between 2010 and 2015, 356 patients were diagnosed with HIV in our centre, of whom 118 (33) were LP, and 57 (48.3%) of them presented with AHD (table 1).

The highest proportion of patients who presented with AHD was among heterosexuals (32.2% compared with 11% among MSM and 9.6% among IVDU (p<0.001)) and among people aged older than 50 years (21% vs 8% in patients who did not presented late) (p<0.001).

Of those with AHD, 41 (72%) were male, median age was 40 years. Twenty-four (42%) were MSM, 28 (49%) heterosexuals and 5 (9%) IVDU. Most of the MSM (23/24, 96%) were born in Israel, whereas 19 from 28 (68%) of the heterosexuals were immigrants (76% from Eastern Europe countries, 24% from sub-Saharan Africa, mainly Ethiopia).

Forty-nine per cent of the patients who were diagnosed with an advanced disease were married; 9/24 (37.5%) of the MSM who were diagnosed late were married to women (as opposed to 7/153 (4.6% of MSM

who were not LP; p<0.001) and 8 of them did not reveal their homosexuality neither to their spouse nor to their primary care physician.

Risk factors for being diagnosed with AHD
In a univariate logistic regression model (table 2), older age and being heterosexual increased the risk of being diagnosed with advanced disease, whereas being born in Israel decreased the risk. However, by the multivariate logistic regression model (table 3), only age and being heterosexual were significantly and independently associated with CD4 <200 cells/mm^3 on diagnosis. The odds of age on diagnosis adjusted for gender, risk group and being born in Israel increased by 45% for each 10-year increase in age (adjusted OR=1.45; 95% , confidence limits (CL) 1.16–1.74). Gender and being Israeli born were associated with CD4 <200 cells/mm^3 on diagnosis only in the unadjusted analysis. The adjusted odds of the heterosexual *risk group* were 2.65 times higher for the heterosexual *risk group* than for other *risk group* patients (OR=2.65, 95% CL 1.21–5.78).

Clinical and laboratory characteristics of patients with advanced AIDS
Fifty-three per cent of patients with AHD were diagnosed during hospitalisation due to an AIDS-defining event, 25% were detected due to a medical problem that did not result in a hospitalisation, 22% were diagnosed on screening (physician or patient induced), and one patient was detected after his newborn child and wife were detected with HIV due to the birth of a child with AIDS (*Pneumocystis jirovecii* pneumonia, PCP).

The AIDS-defining events that led to hospitalisation were severe wasting (8 patients), cryptococcal meningitis

Table 1 Characteristics of patients diagnosed with AHD, LP and NLP diagnosed in Sheba Medical Center between 2010 and 2015 (total number=356)

Variable	Category	Total (%)	AHD N=57 (16%)	LP N=61 (17%)	NLP N=238 (67%)	p Value (2 sided)
Gender						0.003
	Male	300 (84)	41 (13.6%)	51 (17%)	208 (69.3%)	
	Female	56 (16)	16 (28.6%)	10 (17.8%)	30 (53.6%)	
Transmission mode						<0.0001
	MSM	217 (61)	24 (11%)	39 (18)	154 (71)	
	Heterosexuals	87 (24.4)	28 (32.2)	17 (19.5%)	42 (48.3%)	
	IVDU	52 (14.6)	5 (9.6%)	5 (9.6%)	42 (80.8%)	
Place of birth						0.03
	Israel	246 (69.5)	32 (13%)	40 (16.3%)	174 (70.7%)	
	East Europe	92 (26)	19 (20.6%)	19 (20.6%)	54 (58.8%)	
	Ethiopia	16 (4.5)	6 (37.5%)	2 (12.5%)	8 (50%)	
	Other		0	0	2 (0.8%)	
Median age at diagnosis			40.2	36.8	34.4	0.0003
Age >50 years			12 (21%)	11 (18%)	19 (8%)	0.0002

AHD, advanced HIV disease; IVDU, intravenous drug user;
LP, late presenters; MSM, men who have sex with men;
NLP, not late presenters.

Table 2 Risk factors for advanced HIV disease, univariate analysis

Variable	OR	Lower 95% CL	Upper 95% CL	p Value
Age on diagnosis				
Per 10 years	1.64	1.37	1.91	0.0004
Age on diagnosis				
>50 years	2.38	1.14	4.99	0.0215
Female	2.52	1.29	4.90	0.0067
Born in East Europe		1.57	0.85	2.89
Israeli born	0.50	0.28	0.90	0.0202
Risk group				
Heterosexual	3.80	2.05	7.05	<0.0001
Risk group				
IVDU	0.85	0.31	2.35	0.0950

CL, confidence limits; IVDU, intravenous drug user.

Table 3 Risk factors for advanced HIV disease, multivariate analysis

Variable	OR	Lower 95% CL*	Upper 95% CL*	p Value
Age on diagnosis				
By 10 years*	1.45	1.16	1.74	0.0129
Female	1.22	0.52	2.88	0.643
Risk group				
Heterosexual	2.65	1.21	5.78	0.0145
Israeli born	0.85	0.42	1.69	0.6385

*CL, confidence limits.

(7 patients), PCP (3 patients), central nervous system toxoplasmosis (2 patients), progressive multifocal leukoencephalopathy (PML) (2 patients), systemic *Cytomegalovirus* infection (2 patients), lymphoma (2 patients), AIDS dementia complex (1 patient) and disseminated Kaposi sarcoma (1 patient). Three patients died soon after diagnosis (1 due to overwhelming sepsis, 1 due to lymphoma and 1 due to PML) compared with no death reported among patients who presented late (LP) but not with advanced HIV disease (AHD) and patients that were not presented late.

Median CD4 cell count at diagnosis was 40 (range 1–186) cells/mm^3 and median viral load was 185 000 (range 3900–3 600 000) copies/mL.

Missed opportunities

Complete data were available in 47 of 57 (82.45%) patients. Among the 47 patients, there were 65 episodes of missed opportunities to diagnose HIV in the preceding 5 years prior to AIDS diagnosis. The median time between the missed opportunity and AIDS diagnosis was 24 months (IQR 10–30), while the range was between 1 and 60 months.

Sixty per cent of opportunities were missed by primary care physicians and 40% were missed during hospitalisation: six in internal medicine departments, four in surgical departments, two in oncology departments, two in psychiatric wards and one each in neurology, obstetrics and gynaecology and dermatology departments.

CIDs that were missed

From the 65 episodes of missed opportunities, 52 were associated with CIDs that were missed (table 4). The most common missed CIDs were dermatological problems (23%) including herpes zoster in young patients (15%), new-onset psoriasis and new-onset severe seborrhoeic dermatitis (12%). Other CIDs included newly diagnosed hepatitis B virus, hepatitis C virus or sexually transmitted disease (15%), unexplained haematological problems (13%) and anal condyloma (13%), and tuberculosis was diagnosed in 4% of the patients.

The longest duration of missed opportunity lasted for 15 years (a frozen blood sample dating to 1999 was found to be HIV positive); it was of an Ethiopian immigrant with many physical symptoms including tuberculosis who was seen more than 90 different times by health authorities in the past decade and finally diagnosed with HIV after he developed brain toxoplasmosis. Another patient had more than 50 visits in the past 5 years by the GP including two CIDs (oral warts and severe condyloma).

Physician reasons for not sending an HIV test

In 29 of the 57 (50.8%) patients with AHD, we could interview the physician who missed the opportunity for early HIV diagnosis (table 5). In the rest of the cases, we did not succeed in reaching the physician (80%) or the physician did not want to answer our questions (20%). In the 29 patients that we did succeed in communicating

Table 4 CIDs that were missed among patients who presented with advanced HIV disease

CID	Number (%)
Thrombocytopenia, lymphopenia, unexplained lymphadenopathy or other non-explainable haematological disease	9 (17)
Herpes zoster in a young patient who belongs to a risk group	8 (15)
Severe unexplained dermatological problems (eg, severe verrucae, new psoriasis, seborrhoeic dermatitis)	6 (12)
New diagnosed HBV or HCV infection	6 (11)
Anal condyloma	6 (11)
Unexplained weight loss with or without diarrhoea	6 (11)
Infectious mononucleosis	3 (6)
Neurological (culture negative meningitis and rash, cryptococcal meningitis, peripheral neuropathy)	3 (6)
Tuberculosis	2 (4)
STD in MSM	2 (4)
Abortion, undiagnosed non-resolving pneumonia, HPV-related laryngeal carcinoma	3 (6)

CID, clinical indicator disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; MSM, men who have sex with men; STD, sexually transmitted disease.

with the physician, we were able to talk with 35 physicians due to the fact that in some cases more than one physician had missed an opportunity to diagnose HIV: 25 (67.5%) were primary care physicians and the rest specialists, 23 (62%) finished their medical school in Israel, the rest in East Europe (mainly Russia and Ukraine). Only two of the primary care physicians and none of the specialists knew the CDC guidelines for HIV testing, and the same two primary care physicians also knew the CIDs that guide an HIV test. Not perceiving the patient as being at risk for acquiring an HIV infection was a more common answer among primary care physicians (64% vs 24% among specialists, p<0.05) and 'not thinking on HIV' was more common among specialists (60% vs 24% among primary care physicians, p<0.05). There was not a significant difference in the country of medical study between physicians who did not think about HIV and those who did not think that

the patient was at risk for HIV. Among other reasons for not sending an HIV test were: difficulties in communicating the subject of HIV with the patient (3 physicians) and not knowing the legal issues of sending an HIV test (2 physicians). The physicians who reported communication issues were mainly afraid that they may insult the patient by suggesting an HIV test.

DISCUSSION

Our study shows that 33% of patients with HIV diagnosed in our centre during 2010–2015 were LP, half of whom were diagnosed with AHD. Being older and heterosexual were significant risk factors for delayed diagnosis. All the patients who were diagnosed with AHD had multiple encounters with health caregivers prior to HIV diagnosis. All of them were diagnosed with HIV associated CIDs in the year prior to HIV diagnosis, and more than half during the 5 years preceding the diagnosis of HIV. All patients could have been detected much earlier if their treating physicians had been aware of the possibility of HIV diagnosis or would have complied with international guidelines for HIV testing according to HIV indicator diseases or the recommendations for HIV testing according to the CDC or the UK national guidelines for HIV testing.

Unfortunately, more than three decades after the HIV epidemic started, many patients all over the world are still diagnosed very late in the course of their disease: in a recent Dutch paper, it was found that more than half of their patients were diagnosed late with HIV disease and 35% of their cohort were diagnosed with AHD.[18] Similar rates of late diagnosis are present all over Europe.[19] In Metropolitan USA, the rate may be somewhat lower but still ranges between 23.3% and 47.7%.[20] In our centre, 33% of the patients were diagnosed late, 16% with AHD.

Many of the patients who were diagnosed with AHD had missed opportunities for earlier HIV diagnosis. In Europe, 61.8–89% of patients with HIV consulted their GP in the year prior to HIV diagnosis. In the UK, a high proportion of patients who were diagnosed with AHD had encounters in the prior year to diagnosis with their GP (76.4%) or with a specialist in an outpatient (38.3%) or inpatient (15.2%) setting. This study included African patients and yet, in spite of the fact that the patients came from countries with a high

Table 5 Characteristics of physicians who did not send or offer an HIV test in patients with advanced HIV disease

Variable	Category	Total (%)	The patient is not at risk	Did not think about 'HIV'	Other	p Value
Specialty						
	Primary care	25 (71.4)	16 (64)	6 (24)	3 (12)	0.05
	Specialist	10 (28.6)	2 (20)	6 (60)	2 (20)	
Country of study						0.1
	Israel	23 (65.7)	9 (39.1)	10 (43.5)	2 (8.7)	
	East Europe	12 (34.3)	7 (58.4)	2 (16.6)	3 (25)	

prevalence of HIV, this did not led to an HIV test in the patients' encounter with the medical healthcare provider.[21] In France, about 80% of patients with newly diagnosed HIV sought care prior to diagnosis and were not offered an HIV test both in patients from formal risk groups and those without a risk group.[22] In our population, all patients with AHD consulted their GP at least once and 40% of the patients visited physicians from other disciplines in the year prior to their HIV diagnosis. Missed opportunities for diagnosing HIV occurred among specialist and non-specialist services in the UK and Scotland.[23]

Since early treatment is recommended now in all national and international guidelines to prevent AIDS-associated and HIV-associated diseases and to prevent ongoing infections (treatment as prevention, TaP), early diagnosis is more crucial than ever. Primary care physicians as well as internists, neurologists, oncologists, gynaecologists and proctologists may have a pivotal role in early diagnosis of HIV. The CDC guidelines that recommend that a non-targeted opt-out HIV screening test in all individuals aged 13–64 years presenting in any healthcare setting could have contributed to earlier diagnosis. However, unfortunately, these guidelines were not universally adopted. For example, only 33% of community healthcare personnel from Massachusetts incorporated HIV screening into their practices.[24] In another study, only one-quarter of eligible patients in an emergency department were offered HIV screening, and <5% of adults seen in an emergency or urgent care setting were tested for HIV.[25] These studies demonstrate that significant barriers to implementation of universal HIV testing in healthcare settings still exist. One of those barriers may be connected to the insecurity that healthcare professionals may feel while discussing the topic of HIV testing with their patients, particularly those from low-risk backgrounds, citing that discussing HIV testing would be uncomfortable for the patient and might damage the patient–physician relationship.[26] In our study, we found that the two most common barriers to send or offer an HIV test were under-recognition of the patients as belonging to a risk group mainly by primary care physicians and not thinking on HIV at all, which was more common among specialists. Although the number of physicians who cooperated with our telephonic questionnaire was small, these findings are supported by similar findings from other studies.[26 27]

Other HIV testing guidelines recommend testing patients according to their belonging to a definite 'risk group'. For example, the Israeli guidelines for HIV testing in pregnant women concentrate on testing only women who are considered to be at risk for HIV.[28] This approach has several limitations, mainly lack of awareness and lack of comfort in communicating HIV issues with patients. This approach may miss many patients since it may reflect the local clinician's stigma and false assumption of low risk in heterosexuals and the elderly.[29] Also, in our present cohort, age of 50 years or older and heterosexuality were found to be independent risk factors for late detection of HIV. This is in accordance with other studies that show that older age and being heterosexual are independent risk factors for late HIV diagnosis.[29 30] This supports the notion that testing should be encouraged based on the basis of clinical indications and not only on perception of risk. Moreover, the risk group targeted testing may miss a great number of patients because many of the patients who are detected late do not declare that they belong to a risk group. In our cohort of patients with advanced AIDS, 9 from 24 (37.5%) MSM were married to a woman and 8 never told their wife or their primary care physician or any physician about their sexuality.

Therefore, guidelines that are related to HIV indicator diseases were developed, but unfortunately are often not implemented. Testing for HIV using CIDs was suggested for the first time in Europe to overcome obstacles in earlier HIV diagnosis.[14] This approach was found useful in some countries. An Italian study demonstrated that HIV testing following diagnosis of a CID decreases the probability of late HIV diagnosis by 50%.[30] In a US study, it was also shown that increased recognition of clinical indicators for HIV testing prompted earlier HIV diagnosis in 22% of individuals.[31]

Our findings show that all of our patients with AHD had a previous HIV-associated CID which should have prompted an HIV test. The fact that all patients had numerous encounters with the healthcare system prior to diagnosis practically rules out lack of access to routine healthcare services as a cause for late HIV presentation. The fact that many classical HIV CIDs such as thrombocytopenia, bacterial pneumonia, diarrhoea and weight loss, lymphadenopathy and severe perianal condyloma did not lead to an HIV test shows lack of knowledge and awareness of physicians and supports the need for increasing awareness and training among physicians from different disciplines. This may also reflect the fact that during the time the study was conducted (and actually until now) there are no local guidelines concerning HIV testing in Israel other than those concerning pregnant women.

A study that examined the economical evaluation of a non-targeted, universal, HIV testing was not performed in Israel. However, an economic evaluation that compared universal prenatal HIV screening with targeted screening of 'at risk' pregnant women concluded that even in such a low prevalence country such as Israel, universal screening is cost saving.[32] Hence, non-targeted HIV testing should be implemented even in low-prevalence countries like Israel in order to prevent true missed opportunities for earlier diagnosis and treatment. Nevertheless, HIV testing according to CIDs should be emphasised to physicians from all disciplines; the use of a pop-up message in the computerised medical file of the patients that reminds the physician about sending an HIV test each time a CID is diagnosed may reduce the number of missed opportunities to diagnose HIV.[33]

Implementing a rapid test in the office, shortening the interval between the test and the result and between a positive answer and linkage to an HIV specialist are some suggestions that were shown already in some settings to reduce the number of missed opportunities.[34] The efficacy of these measures should be studied in general practice and subspecialty settings in Israel and elsewhere.

The fact that some of the physicians who were asked about their reason for not sending an HIV test and replied that they were afraid to insult the patient is interesting and may indicate stigma among healthcare workers regarding HIV. There is a need to keep on teaching in medical schools and encouraging medical students and physicians to speak openly about HIV with their patients. However, until this is achieved, overcoming those barriers in the meantime with the help of such measures as pop-ups and rapid testing is suggested.

Our study has several limitations that should be considered. Israel is a low endemic country for HIV. Our results may underestimate missed opportunities because our medical centre is located in central Israel where there is more awareness for HIV testing and where most of the MSM population is situated along with the Israeli AIDS Task Force and many other HIV testing centres. However, our study may possibly overestimate the number of missed opportunities because verbal discussion and refusal of an HIV test are not always documented in the patients' records. Another limitation is the fact that it is a one centre study which may not reflect the picture in medical centres which are located in the periphery of the country where the percentage of immigrants is much higher and openly MSM is much lower compared with the central part of the country.

Another limitation is the fact that only about half of the physicians who were interviewed regarding their reasons for not sending an HIV test cooperated in the study.

In conclusion, missed opportunities for earlier HIV diagnosis occurs in most of our patients with AHD. Both GPs and physicians from different disciplines do not test for patients with CIDs for HIV and thus contribute to late diagnosis. Writing local guidelines for HIV testing, as well as additional training and reminding alerts, should lead physicians to perform HIV testing for any patients with CIDs in order to prevent ongoing late presentation with both individual and public health implications.

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