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

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Abstract

Background

Many patients with HIV are being diagnosed late in the course of their disease. There are many missed opportunities for early diagnosis of these patients. The aim of this study is to characterize missed opportunities for earlier HIV diagnosis in patients diagnosed with advanced AIDS.

Methods

A retrospective observational cohort of patients with advanced HIV disease. Documented past medical history was assessed for HIV clinical indicator conditions prior to HIV diagnosis.

Results

Between 2010-2015, 356 patients were diagnosed with HIV, 57 (16 %) with advanced HIV disease. Old age (OR=1.45 [95% CI 1.16-1.74]) and being heterosexual (OR=2.65 [95% CI 1.21-5.78]) were significant risk factors for being diagnosed late. All patients with advanced disease had at least one clinical indicative disease (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 month (IQR 10-30). 60% of CIDs were missed by a general practitioner and 40% by a specialist.

Conclusions

Missed opportunities to diagnose HIV occur both in primary and secondary care in Israel. In order to prevent ongoing very late presentation additional support and training are required to increase timely HIV-testing.

'Strengths and limitations of this study'

- *This study shows for the first time 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 to diagnose HIV earlier*
- *Ignoring HIV clinically indicator diseases is a major reason for missed diagnosis of HIV*
- *This study was carried out in one center and may not reflect the picture in the all country*

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Introduction

Late detection of HIV decreases life expectancy (1,2), impairs life quality (3), increases treatment complexity while decreasing drug adherence (1,2), increases total costs (4) and increases the rates of HIV transmission in the community (5). Unfortunately, about half of the HIV patients worldwide are late presenters (LP): subjects presenting for care with a CD4+ T-cell count below 350 cells/mm³ or very late Presenters (VLP): those presenting with a CD4+ T-cell count below 200 cells/mm³ or with an AIDS-defining event, regardless of CD4+ T-cell count (6).

Successful implementation of the World Health Organization (WHO) guidelines (7), European AIDS clinical society (EACS) (8) and the NIH guidelines (9) which recommend anti-retroviral therapy (ART) initiation in all adults living with HIV regardless of 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 to HIV diagnosis and testing. For example, a quarter to half of patients with advanced HIV had a former visit to a physician or health care facility with an HIV related disease and yet an HIV test was not done (10,11).

In Israel, the annual incidence of newly diagnosed HIV patients ranges between 58.5-61 cases per million population (12). 44% of the 8,000 diagnosed HIV patients living in Israel are immigrants from Sub-Saharan Africa, most of them are Jewish immigrants from Ethiopia; a third are men who have sex with men (MSM), 20% are 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 done 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 centers which are located in the main hospitals (referred to HIV centers). In these centers

the test is confidential but not anonymous. Tests can also be done anonymously in 2 governmental funded sexually transmitted infections (STI) centers and the Israeli AIDS task force which is a non-governmental organization (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, intravenous drug users (IVDU) etc). Incarcerated subjects were routinely offered an HIV test until recently but this practice has been stopped. 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 AIDS (12).

In this study we have examined rate and risk factors for late presenters and for presentation with advanced HIV disease and characterized missed opportunities for earlier diagnosis of HIV among patients who presented with advanced HIV disease in a tertiary teaching center.

Methods

The Sheba Medical Center is a 1,400 bed tertiary medical center 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 that were diagnosed with HIV between 1 January 2010 and 31 December 2015 in Sheba Medical Center. Every newly diagnosed HIV or AIDS patient is referred to the Infectious Disease Unit from several hospitals in the area and from primary care physicians, as well as those diagnosed during hospitalization. We excluded from the study patients that 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.

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Definitions

Late presenters were defined as patients with a CD4 cell count between 201 and 350 cells/mm³ with no AIDS defining disease at the time of diagnosis while patients with advanced HIV disease (AHD) were defined as patients with a CD4 T cell count of less than 200 cells/mm³ or patients that had an AIDS defining event during presentation. 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 health care system due to a medical complaint 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 as defined in a consensus paper (14,17) although not an AIDS defining event (e.g. thrombocytopenia, lymphadenopathy, etc).
2. The patient belonged to a risk group for contracting HIV.
3. The recommendations for HIV testing according to the CDC (15) or the UK national guidelines for HIV testing (16) were not followed.

Clinical and laboratory data regarding clinical events in the 5 years prior to HIV diagnosis including HIV related clinical indicator diseases were extracted from electronic data files. Where possible interviews with primary care physician was performed.

Where possible we contacted by telephone the primary care physician or the specialist who missed an opportunity to diagnose HIV and asked three 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 clinical indicator diseases? 4. Why didn't you send an HIV test regarding the specific event (e.g. a clinical indicator disease diagnosed)? We told the physicians that in any case their identity will not be revealed but still they were not "blinded" to the researcher that 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 t-test, the Pearson chi-square 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 AHD was considered as 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 (Table 1)

Between 2010-2015, 356 patients were diagnosed with HIV in our center, of whom 61 (17.4%) were late presenters and 57 (16%) presented with advanced HIV disease.

The highest proportion of patients that presented with advanced HIV disease was among heterosexuals (32.2% compared to 11% among MSM and 9.6% among IVDU ($p<0.001$)) and among people older than 50 years old (21% versus 8% in patients that did not presented late) ($p<0.001$).

Of those with advanced HIV disease 41 (72%) were males, median age was 40 years. 24 (42%) were MSM, 28 (49%) heterosexuals and 5 (9%) were 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).

49% of the patients that were diagnosed with an advanced disease were married; 9/24 (37.5%) of the MSM that were diagnosed late were married to women (as opposed to 7/153 (4.6% of MSM that were not late presenters); $p<0.001$) and 8 of them did not reveal their homosexuality to their spouse neither to their primary care physician.

Risk factors for being diagnosed with advanced HIV disease (Table 2 and 3)

In 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 multivariate logistic regression model (Table 3) only age and being heterosexual were significantly and independently associated with $CD4<200$. The odds of age on diagnosis adjusted for gender, risk group and Israeli born, increased 45% for each 10-year increase in age (adjusted OR = 1.45; 95%CL=1.16-1.74). Gender and Israeli born were associated with $CD4<200$ only in the unadjusted analysis. The adjusted odds of heterosexual *risk group* were 2.65 times higher for 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

53% of patients with advanced HIV disease were diagnosed during hospitalization due to an AIDS defining event, 25% were detected due to a medical problem that did not bring to a hospitalization, 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 a birth of a child with AIDS (PCP).

The AIDS defining events that led to hospitalization were severe wasting (8 patients), cryptococcal meningitis (7 patients), *Pneumocystis jirovecii* pneumonia (PCP) (3 patients), central nervous system (CNS) toxoplasmosis (2 patients), progressive multifocal leukoencephalopathy (PML) (2 patients), systemic Cytomegalovirus infection (2 patients), lymphoma (2 patients), AIDS dementia complex and disseminated Kaposi sarcoma were diagnosed each in one patient. Three patients died soon after diagnosis (one due to

overwhelming sepsis, one due to lymphoma and one due to PML) compared to no death reported among patients that were late presenters but no advanced HIV disease and patients that were not presented late.

Median CD4 cell count at diagnosis was 40 (range 1-186) cells/mm³ and median viral load was 185,000 (range 3,900-3,600,000) copies/ml.

Missed opportunities

Complete data was 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 five years prior to AIDS diagnosis. The median time between the missed opportunity and AIDS diagnosis was 24 month (IQR 10-30), the range was between one and 60 month.

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

Clinical indicator diseases that were missed (Table 4)

From the 65 episodes of missed opportunities, 52 were associated with clinical indicator diseases that were missed. The most common missed clinical indicator diseases were dermatological problems (23%) including herpes zoster in young patients (15%), new onset psoriasis and new onset severe seborrheic dermatitis (12%). Other CIDs included newly diagnosed HBV, HCV or STD (15%), unexplained hematological problems (13%), 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 an Ethiopian immigrant with many physical complaints including tuberculosis who was seen more than 90 different times by health authorities in the last decade and finally diagnosed with HIV after he developed brain toxoplasmosis. Another patient

had more than 50 visits in the last 5 years by the GP including two CIDs (oral warts and severe condyloma).

Physician reasons for not sending an HIV test (table 5)

In 29 of the 57 (50.8%) of the patients with HAD we could interview the physician that missed the opportunity for early HIV diagnosis. 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 communicating 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). Two of the PCP and none of the specialist knew the CDC guidelines for HIV testing, the same two PCP knew also the clinical indicator diseases that guide an HIV test. Not perceiving the patient as being in risk for acquiring an HIV infection was a more common answer among primary care physicians (64% versus 24% among specialists ($p < 0.05$) and "not thinking on HIV" was more common among specialists (60% versus 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 that did not think that the patient was in 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 that reported communication issues were mainly afraid that they may insult the patient by suggesting an HIV test.

Discussion

Our study shows that 33% of HIV patients diagnosed in our center during 2010-2015 were late presenters, half of them were diagnosed with advanced

disease. Being older and heterosexual were significant risk factors for delayed diagnosis. All the patients that were diagnosed with advanced disease had multiple encounters with health care givers prior to HIV diagnosis. All of them were diagnosed with HIV clinical indicator diseases in the year prior to HIV diagnosis, and more than half during the five years preceding the diagnosis of HIV. All patients could have been detected much earlier if their treating physicians were aware to HIV diagnosis or would have comply with guidelines for HIV testing according to HIV indicator diseases (14,17).

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 (6, 18, 19,20). In a recent Dutch paper it was found that more than half of their patients were diagnosed with late HIV disease and 35% of their cohort were diagnosed with advanced AIDS (18). Similar rates of late diagnosis are present all over Europe (19). In Metropolitan USA the rate maybe somewhat lower but still ranges between 23.3% to 47.7% (20). In our center 33.1% of the patients were diagnosed late, 16% with advanced disease.

Many of the late diagnosed patients had missed opportunities for earlier HIV diagnosis. In Europe 61.8% - 89% (10, 18, 19, 21, 22) of HIV patients consulted their GP in the year prior to HIV diagnosis. In the United Kingdom a high proportion of patients that were diagnosed with advanced HIV disease had encounters in the prior year to diagnosis with their general practitioner (76.4%) or with a specialist in an outpatient setting (38.3%) or inpatient setting (15.2%). This study included African patients and yet the fact that the patients came from countries with high prevalence of HIV this did not led to an HIV test in the patients encounter with the medical health care 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 advanced AIDS consulted their GP at least once and 40% of the patients visited physicians from other disciplines in the year prior to their HIV diagnosis. In a recently published case control study that examined the number of patient consultations in six general practices in Amsterdam and the

incidence of clinical indicator diseases, 61.8% of HIV patients visited their GP at least once in the year prior to diagnosis, twice as often as their HIV negative controls. Furthermore, two thirds of HIV patients had at least one clinical indicator disease in the 5 years prior to diagnosis (11). Missed opportunities for diagnosing HIV occurred both among specialists and non-specialists services in the United Kingdom (10) and Scotland (23).

As early treatment is recommended now in all national and international guidelines to prevent AIDS and HIV associated diseases and to prevent ongoing infections (TaP – treatment as prevention) early diagnosis is more crucial than ever. Primary care physicians as well as internists, neurologists, oncologists, gynecologists and proctologists may have a pivotal role in early diagnosis of HIV. The CDC guidelines that recommends that a non-targeted opt-out HIV screening test in all individuals aging 13-64 years presenting in any health care setting (15), could have contributed to earlier diagnosis.

However, unfortunately these guidelines were not universally adopted. For example, only 33% of community health care 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 less than 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 health care settings still exist. One of those barriers may be connected to the insecurity that health care 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 that cooperated with our telephonic questionnaire was small these findings are being supported by similar findings from other studies (26,27).

Other HIV testing guidelines recommend to test 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 that are considered to be at risk for HIV (28). This approach has several limitations mainly lack of awareness and lack of comfort communicating HIV issues with patients. This approach may miss many patients since it may reflect 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, risk group targeted testing may miss a great number of patients because many of the patients that 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 eight never told their wife nor their primary care 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 clinical indicator diseases 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 clinical indicator disease decreases the probability of late HIV diagnosis by 50% (30). In a USA 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 advanced AIDS patients had a previous HIV associated Clinical Indicator Disease which should have prompted an HIV test. The fact that all patients had numerous encounters with the health care system prior to diagnosis practically rules out lack of access to routine health care services as a cause for late HIV presentation. The fact that many classical HIV clinical indicator diseases like thrombocytopenia, bacterial pneumonia, diarrhea 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.

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 center is located in central Israel where there is more awareness for HIV testing and where most MSM population is situated along with the Israeli AIDS task force and many other HIV testing centers. 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 center study which may not reflect the picture in medical centers which are located in the periphery of the country where the percentage of immigrants is much higher and openly MSM is much lower compared to the central part.

In order to prevent true missed opportunities for earlier diagnosis and treatment, HIV testing according to clinical indicator diseases should be emphasized to physicians from all disciplines; alternatively, non-targeted HIV testing should be implemented even in low prevalence countries like Israel. The use of a pop-up message in the computerized medical file of the patients that reminds the physician about sending an HIV test each time a clinical indicator disease 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 HIV specialist are some suggestions that were shown already in some settings to reduce the number of missed opportunities (33). The efficacy of these measures should be studied in general practice and subspecialties settings in Israel and elsewhere.

In conclusion, missed opportunities for earlier HIV diagnosis occurs in most of our patients with advanced AIDS. Both GPs and physicians from different disciplines do not comply with the clinical indicator diseases policy and thus contribute to late diagnosis. Additional training, as well as reminding alerts should lead physicians to perform HIV testing for any patients with clinical

indicator diseases in order to prevent ongoing late presentation with both individual and public health implications.

Table 1: Characteristics of patients diagnosed with advanced HIV disease (CD4 < 200 cells/mm³ and/or ADE), late presenters (CD4 > 200 cells/mm³ and < 350 cells/mm³, and not late presenters (CD4 > 350 cells/mm³) diagnosed in Sheba Medical Center between 2010-2015 (total no=356)

Variable	Category	Total (%)	Advanced disease, no=57 (16%)	Late presenters (LP), no=61 (17%)	Non late presenters (NLP), no=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						
	MSM	217 (61)	24 (11%)	39 (18)	154 (71)	<0.0001
	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 old			12 (21%)	11 (18%)	19 (8%)	0.0002

Table 2: risk factors for very late detection, univariate analysis

Variable Name		Odds Ratio	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 old	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	0.1484
Israeli born		0.50	0.28	0.90	0.0202
risk group	HETERO	3.80	2.05	7.05	<.0001
risk group	IVDU	0.85	0.31	2.35	0.0950

Table 3: risk factors for very late detection, multivariate analysis

Variable Name		Odds Ratio	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	0.6430
HETERO		2.65	1.21	5.78	0.0145
Israeli born		0.85	0.42	1.69	0.6385

Table 4: Clinical indicator diseases (CIDs) that were missed among patients who presented with advanced AIDS

CID	Number (%)
Thrombocytopenia, lymphopenia, unexplained lymphadenopathy or other non-explainable hematological disease	9 (17)
Herpes zoster in a young patient that belongs to a risk group	8 (15)
Severe unexplained dermatological problems (e.g. severe verrucae, new psoriasis, seborrheic dermatitis)	6 (12)
New diagnosed HBV or HCV infection	6 (11)
anal condyloma	6(11)
unexplained weight loss with or without diarrhea	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	one each (6)

Table 5: Characteristics of physicians that did not send nor offered an HIV test

Variable	Category	Total (%)	The patient not in risk	Did not think about "HIV"	Other	P-value
Specialty						0.05
	PCP	25 (71.4)	16 (64)	6 (24)	3 (12)	
	Specialist	10 (28.6)	2 (20)	6 (60)	2 (20)	
Country of medical studies						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)	

Contributorship statement

IL (corresponding author), YM, NM and GR conceived and initiated the study design, helped with the implementation, with data collection, data analysis and interpretation and drafting the article; YM and LO helped with study design and statistical analysis, AW, VL and OM contributed with data collection; All authors contributed to refinement of the study protocol and approved the final manuscript

Competing interests

None

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None

Data sharing statement

Extra data is available by emailing itsik.levi@sheba.health.gov.il

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract – p 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found p 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p 5
Objectives	3	State specific objectives, including any prespecified hypotheses p 6
Methods		
Study design	4	Present key elements of study design early in the paper p 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p 6
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p 7
Bias	9	Describe any efforts to address potential sources of bias p 8
Study size	10	Explain how the study size was arrived at NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding p 8
		(b) Describe any methods used to examine subgroups and interactions p 8
		(c) Explain how missing data were addressed p 8
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed NA
		(e) Describe any sensitivity analyses NA

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed P 8 (b) Give reasons for non-participation at each stage done where applicable (c) Consider use of a flow diagram did not use
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders P 8, Table 1 (b) Indicate number of participants with missing data for each variable of interest NA (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) not relevant
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time P 8, P 10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included P 9, Table 2, Table 3 (b) Report category boundaries when continuous variables were categorized P 9, Table 2, Table 3 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p 10, Table 4, P 11, Table 5

Discussion

Key results	18	Summarise key results with reference to study objectives p 11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p 15
Generalisability	21	Discuss the generalisability (external validity) of the study results p 15

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p 20
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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Abstract

OBJECTIVE

To quantify and characterize missed opportunities for earlier HIV diagnosis in patients diagnosed with advanced HIV.

DESIGN

A retrospective observational cohort study.

SETTING

A central tertiary medical center 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 2010-2015, 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 1.16-1.74]) and being heterosexual (OR=2.65 [95% CI 1.21-5.78]) 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 month (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 both in primary and secondary care. Lack of national guidelines, lack of knowledge regarding CIDs and communication barriers with patients may contribute to HIV late diagnosis.

'Strengths and limitations of this study'

- *This study shows for the first time 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 to diagnose HIV earlier*
- *Nonexistence of clear national guidelines for HIV testing and ignoring HIV clinically indicator diseases are major reasons for missed diagnosis of HIV*
- *This study was carried out in one center and may not reflect the picture in the all country; Also, the total number of patients is low and this may limit generability of the study*

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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 HIV patients worldwide are late presenters (LP): subjects presenting for care with a CD4+ T-cell count below 350 cells/mm³ or with an AIDS defining event regardless of CD4+ T-cell count or even worse, with an advanced HIV disease (AHD) with a CD4+ T-cell count below 200 cells/mm³ (6).

Successful implementation of the World Health Organization (WHO) guidelines (7), European AIDS clinical society (EACS) (8) and the NIH guidelines (9) which recommend anti-retroviral therapy (ART) initiation in all adults living with HIV regardless of 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 to HIV diagnosis and testing. For example, a quarter to half of patients with advanced HIV had a former visit to a physician or health care facility with an HIV related disease and yet an HIV test was not done (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 HIV patients visited their 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 HIV patients ranges between 58.5-61 cases per million population (12). 44% of the 8,000 diagnosed HIV patients living in Israel are immigrants from Sub-Saharan Africa, most of them are Jewish immigrants from Ethiopia; a third are men who have sex with men (MSM), 20% are 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 done 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 centers which are located in the main hospitals (referred to HIV centers). In these centers the test is confidential but not anonymous. Tests can also be done anonymously in 2 governmental funded sexually transmitted infections (STI) centers and the Israeli AIDS task force which is a non-governmental organization (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, intravenous drug users (IVDU) etc.). Incarcerated subjects 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 last 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 advanced HIV disease (12).

In this study we have examined rate and risk factors for presentation with advanced HIV disease and characterized missed opportunities for earlier diagnosis of HIV among patients who presented with advanced HIV disease in a tertiary teaching center.

Methods

The Sheba Medical Center is a 1,400 bed tertiary medical center 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 that were diagnosed with HIV between 1 January 2010 and 31 December 2015 in Sheba Medical Center. Every newly diagnosed HIV or AIDS patient is referred to the Infectious Disease Unit from several hospitals in the area and from primary care physicians, as well as those diagnosed during hospitalization. We excluded from the study patients that

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/mm³ or presenting with an AIDS defining event, regardless of CD4+ T-cell count (13).

Advanced HIV disease: Persons presenting for care with a CD4+ T-cell count below 200 cells/mm³ or presenting with an AIDS-defining event, regardless of 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 health care system due to a medical complaint 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 as defined in a consensus paper (14, 15) although not an AIDS defining event (e.g. thrombocytopenia, lymphadenopathy, etc.).
2. The patient belonged to a risk group for contracting HIV.
3. The recommendations for HIV testing according to the 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 clinical indicator diseases 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 was 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 three 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 clinical indicator diseases? 4. Why didn't you send an HIV test regarding the specific event (e.g. a clinical indicator disease diagnosed)? We told the physicians that in any case their identity will not be revealed but still they were not "blinded" to the researcher that 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 t-test, the Pearson chi-square 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 AHD was considered as 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.

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Results

Patient's characteristics (Table 1)

Between 2010-2015, 356 patients were diagnosed with HIV in our center, of whom 118 (33) were late presenters, 57 (48.3%) of them presented with advanced HIV disease.

The highest proportion of patients that presented with advanced HIV disease was among heterosexuals (32.2% compared to 11% among MSM and 9.6% among IVDU ($p<0.001$)) and among people older than 50 years old (21% versus 8% in patients that did not presented late) ($p<0.001$).

Of those with advanced HIV disease 41 (72%) were males, median age was 40 years. 24 (42%) were MSM, 28 (49%) heterosexuals and 5 (9%) were 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).

49% of the patients that were diagnosed with an advanced disease were married; 9/24 (37.5%) of the MSM that were diagnosed late were married to women (as opposed to 7/153 (4.6% of MSM that were not late presenters); $p<0.001$) and 8 of them did not reveal their homosexuality to their spouse neither to their primary care physician.

Risk factors for being diagnosed with advanced HIV disease (Table 2 and 3)

In 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 multivariate logistic regression model (Table 3) only age and being heterosexual were

significantly and independently associated with $CD4 < 200$ cells/mm³ on diagnosis. The odds of age on diagnosis adjusted for gender, risk group and Israeli born, increased 45% for each 10-year increase in age (adjusted OR = 1.45; 95%CL=1.16-1.74). Gender and Israeli born were associated with $CD4 < 200$ cells/mm³ on diagnosis only in the unadjusted analysis. The adjusted odds of heterosexual *risk group* were 2.65 times higher for 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

53% of patients with advanced HIV disease were diagnosed during hospitalization due to an AIDS defining event, 25% were detected due to a medical problem that did not bring to a hospitalization, 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 a birth of a child with AIDS (PCP).

The AIDS defining events that led to hospitalization were severe wasting (8 patients), cryptococcal meningitis (7 patients), *Pneumocystis jirovecii* pneumonia (PCP) (3 patients), central nervous system (CNS) toxoplasmosis (2 patients), progressive multifocal leukoencephalopathy (PML) (2 patients), systemic Cytomegalovirus infection (2 patients), lymphoma (2 patients), AIDS dementia complex and disseminated Kaposi sarcoma were diagnosed each in one patient. Three patients died soon after diagnosis (one due to overwhelming sepsis, one due to lymphoma and one due to PML) compared to no death reported among patients that were late presenters but no advanced HIV disease and patients that were not presented late.

Median CD4 cell count at diagnosis was 40 (range 1-186) cells/mm³ and median viral load was 185,000 (rang 3,900-3,600,000) copies/ml.

Missed opportunities

Complete data was 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 five years prior to AIDS diagnosis. The median time between the missed opportunity and AIDS diagnosis was 24 month (IQR 10-30), the range was between one and 60 month.

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

Clinical indicator diseases that were missed (Table 4)

From the 65 episodes of missed opportunities, 52 were associated with clinical indicator diseases that were missed. The most common missed clinical indicator diseases were dermatological problems (23%) including herpes zoster in young patients (15%), new onset psoriasis and new onset severe seborrheic dermatitis (12%). Other CIDs included newly diagnosed HBV, HCV or STD (15%), unexplained hematological problems (13%), 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 an Ethiopian immigrant with many physical complaints including tuberculosis who was seen more than 90 different times by health authorities in the last decade and finally diagnosed with HIV after he developed brain toxoplasmosis. Another patient had more than 50 visits in the last 5 years by the GP including two CIDs (oral warts and severe condyloma).

Physician reasons for not sending an HIV test (table 5)

In 29 of the 57 (50.8%) of the patients with advanced HIV disease we could interview the physician that missed the opportunity for early HIV diagnosis. 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 communicating 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). Two of the primary care physicians and none of the specialist knew the CDC guidelines for HIV testing, the same two primary care physicians knew also the clinical indicator diseases that guide an HIV test. Not perceiving the patient as being in risk for acquiring an HIV infection was a more common answer among primary care physicians (64% versus 24% among specialists ($p < 0.05$) and "not thinking on HIV" was more common among specialists (60% versus 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 that did not think that the patient was in 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 that reported communication issues were mainly afraid that they may insult the patient by suggesting an HIV test.

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Discussion

Our study shows that 33% of HIV patients diagnosed in our center during 2010-2015 were late presenters, half of them were diagnosed with advanced HIV disease. Being older and heterosexual were significant risk factors for delayed diagnosis. All the patients that were diagnosed with advanced HIV disease had multiple encounters with health care givers prior to HIV diagnosis. All of them were diagnosed with HIV clinical indicator diseases in the year prior to HIV diagnosis, and more than half during the five years preceding the diagnosis of HIV. All patients could have been detected much earlier if their treating physicians were aware to the possibility of HIV diagnosis or would have comply 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 with late HIV disease and 35% of their cohort were diagnosed with advanced HIV disease (18). Similar rates of late diagnosis are present all over Europe (19). In Metropolitan USA the rate maybe somewhat lower but still ranges between 23.3% to 47.7% (20). In our center 33% of the patients were diagnosed late, 16% with advanced HIV disease.

Many of the patients that were diagnosed with advanced HIV disease had missed opportunities for earlier HIV diagnosis. In Europe 61.8% - 89% of HIV patients consulted their GP in the year prior to HIV diagnosis. In the United

Kingdom a high proportion of patients that were diagnosed with advanced HIV disease had encounters in the prior year to diagnosis with their general practitioner (76.4%) or with a specialist in an outpatient (38.3%) or inpatient setting (15.2%). This study included African patients and yet the fact that the patients came from countries with high prevalence of HIV this did not lead to an HIV test in the patients encounter with the medical health care 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 advanced HIV disease 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 both among specialists and non-specialists services in the United Kingdom and Scotland (23).

As early treatment is recommended now in all national and international guidelines to prevent AIDS and HIV associated diseases and to prevent ongoing infections (TaP – treatment as prevention) early diagnosis is more crucial than ever. Primary care physicians as well as internists, neurologists, oncologists, gynecologists and proctologists may have a pivotal role in early diagnosis of HIV. The CDC guidelines that recommends that a non-targeted opt-out HIV screening test in all individuals aging 13-64 years presenting in any health care setting could have contributed to earlier diagnosis. However, unfortunately these guidelines were not universally adopted. For example, only 33% of community health care 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 less than 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 health care settings still exist. One of those barriers may be connected to the insecurity that health care 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

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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 that cooperated with our telephonic questionnaire was small these findings are being supported by similar findings from other studies (26, 27).

Other HIV testing guidelines recommend to test 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 that are considered to be at risk for HIV (28). This approach has several limitations, mainly lack of awareness and lack of comfort communicating HIV issues with patients. This approach may miss many patients since it may reflect 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, risk group targeted testing may miss a great number of patients because many of the patients that 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 eight never told their wife nor their primary care 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 clinical indicator diseases 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 clinical indicator disease decreases the probability of late HIV diagnosis by 50% (30). In a USA 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 advanced HIV disease had a previous HIV associated Clinical Indicator Disease which should have prompted an HIV test. The fact that all patients had numerous encounters with the health care system prior to diagnosis practically rules out lack of access to routine health care services as a cause for late HIV presentation. The fact that many classical HIV clinical indicator diseases like thrombocytopenia, bacterial pneumonia, diarrhea 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 done (and actually until now) there are no local guidelines concerning HIV testing in Israel other than those concerning pregnant women.

In Israel a study that examined the economical evaluation of a non-targeted, universal, HIV testing was not done. 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 clinical indicator diseases should be emphasized to physicians from all disciplines; the use of a pop-up message in the computerized medical file of the patients that reminds the physician about sending an HIV test each time a clinical indicator disease 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 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 subspecialties settings in Israel and elsewhere.

The fact that some of the physicians that were asked about their reason for not sending an HIV test replied that they were afraid to insult the patient is interesting and may indicate stigma among health care workers regarding

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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 at the meantime with the help of such measures as pop ups and rapid testing are 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 center is located in central Israel where there is more awareness for HIV testing and where most MSM population is situated along with the Israeli AIDS task force and many other HIV testing centers. 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 center study which may not reflect the picture in medical centers which are located in the periphery of the country where the percentage of immigrants is much higher and openly MSM is much lower compared to the central part.

Another limitation is the fact that only about a half of the physicians that 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 advanced HIV disease. Both GPs and physicians from different disciplines do not test for HIV patients with clinical indicator diseases 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 clinical indicator diseases in order to prevent ongoing late presentation with both individual and public health implications.

Table 1: Characteristics of patients diagnosed with advanced HIV disease (AHD), late presenters (LP) and not late presenters (NLP) diagnosed in Sheba Medical Center between 2010-2015 (total no=356)

Variable	Category	Total (%)	HAD No=57 (16%)	LP No=61 (17%)	NLP No=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 old			12 (21%)	11 (18%)	19 (8%)	0.0002

*HAD – HIV advanced disease

**LP – late presenters

***NLP – non late presenters

Table 2: risk factors for advanced HIV disease, univariate analysis

Variable Name		Odds Ratio	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 old	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	HETERO	3.80	2.05	7.05	<.0001
risk group	IVDU	0.85	0.31	2.35	0.0950

Table 3: risk factors for advanced HIV disease, multivariate analysis

Variable Name		Odds Ratio	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	HETERO	2.65	1.21	5.78	0.0145
Israeli born		0.85	0.42	1.69	0.6385

Table 4: Clinical indicator diseases (CIDs) that were missed among patients who presented with advanced HIV disease

CID	Number (%)
Thrombocytopenia, lymphopenia, unexplained lymphadenopathy or other non-explainable hematological disease	9 (17)
Herpes zoster in a young patient that belongs to a risk group	8 (15)
Severe unexplained dermatological problems (e.g. severe verrucae, new psoriasis, seborrheic dermatitis)	6 (12)
New diagnosed HBV or HCV infection	6 (11)
anal condyloma	6 (11)
unexplained weight loss with or without diarrhea	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	one each (6)

Table 5: Characteristics of physicians that did not send nor offered an HIV test in patients with advanced HIV disease

Variable	Category	Total (%)	The patient is not in 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	Israel	23 (65.7)	9 (39.1)	10 (43.5)	2 (8.7)	0.1
	East Europe	12 (34.3)	7 (58.4)	2 (16.6)	3 (25)	

Contributorship statement

IL (corresponding author), YM, NM and GR conceived and initiated the study design, helped with the implementation, with data collection, data analysis and interpretation and drafting the article; YM and LO helped with study design and statistical analysis, AW, VL and OM contributed with data collection; All authors contributed to refinement of the study protocol and approved the final manuscript

Competing interests

None

Funding

None

Data sharing statement

Extra data is available by emailing itsik.levi@sheba.health.gov.il

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For peer review only

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract – p 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found p 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p 5
Objectives	3	State specific objectives, including any prespecified hypotheses p 6
Methods		
Study design	4	Present key elements of study design early in the paper p 6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p 6
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up p 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable p 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group p 7
Bias	9	Describe any efforts to address potential sources of bias p 8
Study size	10	Explain how the study size was arrived at NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding p 8
		(b) Describe any methods used to examine subgroups and interactions p 8
		(c) Explain how missing data were addressed p 8
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed NA
		(e) Describe any sensitivity analyses NA

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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed P 8 (b) Give reasons for non-participation at each stage done where applicable (c) Consider use of a flow diagram did not use
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders P 8, Table 1 (b) Indicate number of participants with missing data for each variable of interest NA (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) not relevant
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time P 8, P 10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included P 9, Table 2, Table 3 (b) Report category boundaries when continuous variables were categorized P 9, Table 2, Table 3 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p 10, Table 4, P 11, Table 5

Discussion

Key results	18	Summarise key results with reference to study objectives p 11,12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias p 15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p 15
Generalisability	21	Discuss the generalisability (external validity) of the study results p 15

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p 20
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.