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Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis

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Short title: Missed Opportunities for HIV testing from 2010-2015

Key words: missed opportunities, HIV diagnosis, HIV testing, HIV indicator conditions, late presenters

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Abstract

Objectives: To determine the frequency of missed opportunities (MOs) among patients newly-diagnosed with HIV, risk factors for presenting MOs, and the association between MOs and late presentation to care.

Design: Retrospective analysis

Setting: HIV outpatient clinic at a Swiss tertiary hospital

Participants: Patients aged ≥18 years old newly presenting for HIV care between 2010 and 2015

Measures: Number of medical visits, up to five years preceding HIV diagnosis, at which HIV testing had been indicated, according to Swiss HIV testing recommendations. A visit at which testing was indicated but not performed was considered a MO for HIV testing.

Results

Complete records were available for all 201 new patients of whom 51% were male and 33% from sub-Saharan Africa (SSA). Thirty patients (15%) presented with acute HIV infection while 119 patients (59%) were late presenters (LPs) (CD4 counts <350 cells/mm^3 at diagnosis). Ninety-four patients (47%) had presented at least one MO, of whom 44 (47%) had multiple MOs. MOs were more frequent among individuals from SSA, men who have sex with men, and patients under follow-up for chronic disease. MOs were less frequent in LPs than non-LPs (42.5% versus 57.5%, P = 0.03).

Conclusions

At our centre, 47% of patients presented at least one MO. Whilst our late presentation rate is higher than the national figure of 49.8%, LPs were less likely to experience MOs, suggesting that these patients were diagnosed late through presenting late, rather than through being failed by our hospital. We conclude that, in addition to optimising physician-initiated testing, access to testing must be improved among patients unaware they are at HIV risk and who do not seek health care.

Article summary

Strengths and limitations of this study

- We defined the term, 'missed opportunities', currently lacking a consensus definition, based on the Swiss HIV testing recommendations applicable to our institution.
- A centralized database enabled us to examine all patient episodes at our centre, to determine the number and type of missed opportunities.
- We used multivariate logistic regression to show a robust association between patient characteristics and the risk of missed opportunities for HIV testing.
- As with any monocentric study, our findings may not be applicable to all centres in Switzerland, due to differences in hospital structure and local patient population.

Introduction

Late presentation to care among people living with HIV prolongs the period between seroconversion and treatment, and leads to an avoidable increase in morbidity, mortality, health care costs and risk of onward transmission (1). In Europe, even in countries with adequate health care provision and HIV testing recommendations, late presenters (LPs) make up to half of all new HIV diagnoses (2). In Switzerland, while 81% of adults living with HIV in 2012 were estimated to be diagnosed (3), 49.8% of patients diagnosed and enrolled in the Swiss HIV Cohort Study (SHCS) between 2009 and 2012 were LPs, with CD4 counts below 350 cells/mm^3 and/or an AIDS-defining illness (ADI) at presentation (4).

To maximise early HIV diagnosis, HIV testing recommendations have been published by the Swiss Federal Office of Public Health (FOPH) since 2007 and updated three times (5-8). In 2007, the recommendations introduced *physician-initiated counselling and testing* (PICT), proposing targeted and diagnostic testing and describing HIV testing indications in the text (5). In 2010, testing indications were mentioned in the text and presented as tables (6). Although the term *HIV-associated indicator conditions* (HIV ICs) was not in general use at this time, HIV ICs were included in the 2010 recommendations. In 2013, the recommendations highlighted ICs and introduced HIV screening of patients commencing immunosuppressive therapy (7). In 2015, the content of the recommendations remained similar but the table of symptoms and signs of acute HIV infection was presented first to emphasise acute infection as an indication for testing (8). In summary, apart from the addition of screening of patients commencing immunosuppressive therapy in 2013, the recommendation updates between 2010 and 2015 involved changes in format but not overall content.

When an individual presents to a health care provider with indications for HIV testing but is not offered a test, this constitutes a missed opportunity (MO) for HIV testing (1). In 2016, several studies were published on MOs in Europe (9-12) and Israel (13) (Supplementary table S1). These studies covered four to seven-year periods between 2007 and 2015 and reported MO rates of 14.5% (12) to 34% (10). Many highlighted the importance of physician

awareness of testing indications in reducing MOs (9, 12, 13). Whilst the Swiss PICT recommendations, by definition, emphasise the responsibility of the physician, we have observed that, for example, only 18% of Emergency Department (ED) doctors in French-speaking Switzerland were aware of the 2010 FOPH recommendations and that, even if aware, they did not adhere to them (14). In the ED and other services at our centre, these recommendations made no difference to HIV testing rates (15).

The aims of this study were therefore to determine the frequency of MOs among newly-diagnosed patients presenting for care at our outpatient HIV service, and patient risk factors for presenting MOs, and to determine the association between MOs and late presentation to care.

Methods

Ethics Statement

This study was approved by the Ethical Committee on Human Research of the Canton of Vaud, Switzerland (protocol number 2016-00333). Due to the retrospective design, the requirement of patient informed consent was waived.

Study setting

The study was conducted at Lausanne University Hospital (LUH), a 1500-bed teaching hospital which serves as a primary-level community hospital for Lausanne (catchment population 300,000) and as a secondary and tertiary referral hospital for Western Switzerland (catchment population 1-1.5 million). HIV seroprevalence in the region is estimated to be 0.2-0.5% (3, 16). At LUH, medical records are electronic and include all hospital visits, discharge summaries (inpatients), clinical letters (outpatients) and laboratory reports.

In Switzerland, health insurance is mandatory. Whilst most patients have a primary care physician (general practitioner, GP), individuals may visit a specialist without referral. Outpatient HIV care at LUH is provided by the Infectious Diseases Service. All patients are

invited to be enrolled in the Swiss HIV Cohort Study (SHCS), a national prospective cohort study with ongoing enrolment since 1988 (17).

Definitions

Late presentation was defined as presenting for care with a CD4 count <350 cells/mm^3 in accordance with the European consensus working group definition (18).

The term MO for HIV testing has no consensus definition. For this study, a MO was defined as a visit to LUH at which HIV testing was indicated but not performed. Testing was considered as indicated according to five broad indications, based on the FOPH 2015 recommendations (8) but present in the FOPH recommendations from 2010 onward: signs and symptoms of acute HIV infection; AIDS-defining illness (ADIs); HIV ICs in which HIV prevalence is considered to be >0.5%; situations in which HIV infection should be excluded (for example, planned immunosuppressive treatment and pregnancy) and epidemiological risk (belonging to or having a sexual partner from a high-risk group: men who have sex with men [MSM], injecting drug users [IDUs] and individuals originating from a high-prevalence region, notably, sub-Saharan Africa).

Study design

The study retrospectively analysed all patients with newly-diagnosed HIV presenting to the LUH infectious diseases outpatient clinic from 1st January 2010 to 31st December 2015.

For each patient, the following data were collected: sociodemographic data (age, sex, geographical origin, marital status, parental status, risk factor(s) for HIV acquisition); HIV infection data (CD4 count, ADIs, mode of infection); visits to LUH during the five years preceding HIV diagnosis (chronic disease with regular follow-up, inpatient and outpatient consultations); and HIV testing data (date of previous HIV tests, reason for performing diagnostic test, site of diagnostic test). The limit of five years for LUH visits was selected based on the LP figure of 49.8% of patients newly-enrolled in the SHCS (4), in whom infection was likely to have occurred within five years preceding diagnosis (19), and the

observation that, elsewhere in Europe, 59% of new HIV patients exhibited HIV ICs during a similar pre-diagnosis period (20). MOs were identified using medical records and analysed by absolute MO number and by MO category (based on the five groups of HIV testing indications: acute HIV, ADI, HIV ICs, test of exclusion and epidemiological risk).

Given the low HIV testing rates observed in the ED at our centre and elsewhere in French-speaking Switzerland (1% of all patients seen) (14, 15), we additionally conducted a search of all pre-diagnosis visits to the ED, using the central hospital database. We focused on ED visits estimated to have occurred after HIV seroconversion based on CD4 cell count at diagnosis, accounting for variations related to age and sex (19). All pre-diagnosis visits were matched with laboratory reports to determine whether HIV testing had been performed. A single pre-diagnosis ED visit after which testing was performed within 72 hours was not considered a MO, to allow for patients admitted prior to the weekend or referred for testing by a designated hospital team, where testing may be delayed in the interest of continuity of care. At the time of this study, rapid HIV testing was not available in the ED and so all HIV tests requested and performed were documented in the laboratory database.

Data and Statistical Analysis

Patient details, stripped of all identifiers, were entered in to a coded database by the study investigators (LL, EM) for each of the six 12-month periods. Categorical data were presented as absolute frequencies and percentages and compared using the Chi squared test; continuous data were presented as means (standard deviation, SD) or medians (interquartile range, IQR) and analysed using the Mann-Whitney U test. Multivariate logistic regression was applied to calculate the adjusted odds ratio for various risk factors for presenting MOs. Data were stratified according to patient demographic characteristics in order to reduce confounding. All analysis was performed using Stata 14.1 (StataCorp LP, Texas, USA).

Results

Patient characteristics

We identified 201 patients newly-presenting for HIV care during the study period, all of whom had complete electronic medical records. Mean age at diagnosis was 38 years ± SD (range 18 to 75 years). Mode of HIV transmission was listed as heterosexual in 57% of patients, MSM in 34%, IDU in 4% and unknown in 5% (Table 1). The majority of patients (59%) had never been HIV tested prior to their diagnostic test.

Missed opportunities (MOs)

In total, 359 separate MOs were presented by 94 patients (47%) during the five years preceding their diagnosis (Figure 1A). Considering patients presenting MOs, 74 patients (78%) had presented on more than one visit (range 2 to 17) with a MO of any category. Considering MO categories, 58 patients (62%) had presented a single category of MO, 30 patients had presented two categories (32%) and six patients (6%) had presented three categories. Figure 1B shows the distribution of MO categories by testing indication.

Risk factors for MOs

In multivariate analysis, older patients (aged >50 years) had less risk of presenting MOs than patients aged <30 years (P=0.01), while patients of sub-Saharan African origin (P=0.01), those under regular follow up for chronic illness (P=0.01) and MSM (P=0.02) had increased risk (Table 1). In patients from sub-Saharan Africa and those under regular follow-up for chronic illness, all MO categories were distributed equally compared to the rest of the population. In contrast, MOs in MSM patients were more frequently related to the fact they were MSM (epidemiological risk; 46% versus 33%, P<0.01).

Clinical presentation at diagnosis, site of testing and reason for testing

Most patients (85%) were diagnosed in the chronic phase of infection (Table 2). The median CD4 count at diagnosis was 293 (IQR 147-452). In total, 119 (59%) were LPs of whom 74% were enrolled in the SHCS.

A greater proportion of new HIV diagnoses were made in the primary care and outpatient settings than during hospital admission (Table 2). The top three reasons for testing, regardless of testing site, were presence of HIV ICs, epidemiological risk and symptoms and signs of acute HIV infection (Table 2).

MOs and late presentation

Multivariate analysis demonstrated a lower risk of late presentation in patients presenting MOs (OR 0.5, 95% 0.2-0.9, *P*<0.01). Indeed, the median CD4 count at diagnosis among MO patients was significantly higher than for non-MO patients (351 cells/mm^3 versus 244 cells/mm^3, *P*<0.01). MOs were less frequent in LPs compared to patients presenting with CD4 > 350 cells/mm^3 (42.5% versus 57.5%, *P*<0.01). Among subgroups, the LP rate among MSM was lower compared to the rest of the study population (22% versus 78%, *P*<0.001).

MOs in the ED

Of 201 patients, 58 (29%) were identified as having presented to the ED prior to diagnosis, 27 of whom (47%) had presented more than once (range 2-7 visits). All 58 patients had presented within three years preceding their HIV diagnosis and 53 patients (91%) within the preceding 12 months. Although 15 patients (26%) were diagnosed within 72 hours of their most recent ED visit, seven of these had presented to the ED on at least one previous occasion. In total, 50/58 patients (86%) presented to the ED during the interval between seroconversion and diagnosis, none of whom were tested.

Discussion

In this single-centre study, we observed that 47% of 201 patients newly-presenting for HIV care had presented at least one MO for earlier testing. Although thirty patients (15%) were diagnosed during acute infection, nine patients (5%) who presented with symptoms or signs of acute HIV were not tested. Of patients who had visited the ED pre-diagnosis, 86% had

presented at least one MO for testing. Finally, MOs occurred significantly less frequently in LPs than in non-LPs.

Our patient population differed from that of Switzerland as a whole (FOPH HIV notifications) in terms of HIV acquisition risk profile: 57% heterosexual transmission and 34% MSM, compared to 42% heterosexual and 57% MSM (21). As heterosexual transmission was a risk factor for late presentation in the SHCS study by Hachfeld *et al*, this might explain our higher rate of LPs (59%) compared to the SHCS figure of 49.8% (4). A lower SHCS figure through underrepresentation of our patients in the Hachfeld *et al* study is unlikely as the majority were enrolled in the SHCS.

Our analysis showed that patients under regular follow-up for chronic illness, patients from sub-Saharan Africa and MSM were at increased risk for MOs. In patients under regular follow-up, there may be the assumption by the hospital physician that the patient's GP has performed an HIV test and *vice versa* (1). In our institution, we have previously reported suboptimal testing rates among oncology patients, particularly those of non-European origin (22). Among patients with risk factors for HIV acquisition, MOs will occur if there is non-disclosure of at-risk behaviour by the patient and incomplete history taking by the doctor. This was described in a French cross-sectional study of 1,008 patients newly-diagnosed with HIV of whom 48% were MSM (23). Fewer than half the MSM who consulted disclosed being MSM and only 21% of all MSM were offered testing by their health care provider (23). In Switzerland, physicians frequently do not discuss sexual behaviour with their male patients, potentially missing those with risk factors (24).

Our non-association between LPs and MOs suggests a distinction between 'missed' opportunity and 'no' opportunity. Whilst it is logical that late presentation may result from repeated MOs in positive individuals, LPs do not necessarily present opportunities for earlier testing. If individuals feel well, are unaware of HIV risk factors and/or have poor access to health care, they may have sporadic if any contact with health care systems (4): their late presentation may be their only presentation. Optimal HIV testing practice is the cornerstone towards attaining the first 90 of the 90-90-90 goal set by the WHO (25). However, even

perfect PICT practice cannot eliminate late presentation when physicians can initiate testing only if individuals present to them. It is necessary to reach out to individuals who are at risk of infection but who do not present for health care. HIV testing can be expanded by introducing community-level testing innovations tailored to each community, depending on whether non-presentation is related to lack of awareness of HIV risk factors or symptoms of infection or to lack or awareness of services available. Innovations include walk-in access to free testing, testing by non-traditional providers, improving risk perception and tackling stigma (26).

Regarding risk perception, the MO umbrella can be extended from MOs for HIV testing to those for HIV prevention. Whether or not the patients in this sample had HIV at their first few visits to LUH, they were, by definition, at risk of HIV acquisition. Delivering a prevention message at the time of testing could avert future infection and may also be a means of reaching individuals outside the hospital by dissemination of information. In the ED at our centre, offering non-targeted screening, as recommended in the United States (27) and the United Kingdom (28), would have enabled diagnosis of 86% of the patients of our sample who had presented to this service. Delivering a preventing message at this time could have prevented infections among contacts in the community.

The MO rates at our centre were higher than those reported in other studies of similarly-sized samples of newly-diagnosed patients presenting for HIV care in European hospital outpatient settings. Tominski *et al* observed a rate of 21% among 270 patients, based on HIV ICs (9); Noble *et al* observed a rate of 16.3% among 124 patients, based on ICs or ADIs up to five years pre-diagnosis (11); Gullón *et al* observed a rate of 14.5% among 354 patients, based on ICs up to one year pre-diagnosis (12). As there is no consensus definition of MOs, it is important to examine the criteria for MOs and the time prior to diagnosis examined. In our study, the MO definition was wide, based not only on HIV ICs and ADIs but also on epidemiological risk, symptoms and signs of acute HIV infection and situations in which HIV should be excluded, and over a period of five years pre-diagnosis. Considering MOs based on HIV ICs and ADIs alone, our MO rate was 16%. However, applying the most recent HIV

testing recommendations, we consider the MO rate obtained according to our study criteria as being a baseline on which to improve.

This study has limitations. As in any retrospective study, identifying and classifying MOs relied on available clinical documentation. As we reviewed medical notes only from our institution, the number or categories of MO may be prone to bias. This study examined only MOs occurring in our hospital; using the LUH database it was not possible to quantify potential MOs occurring in the primary care setting or in other hospitals. We could therefore have underestimated the number of MOs. Equally, although we could determine that most diagnostic tests were made in the primary care setting, this study did not examine the untested patient denominator. Finally, as our study was monocentric, our risk-factor associations with MOs reflect our local patient population. Against these limitations, the non-association between late presentation and MOs observed in our study has important implications for a national testing strategy based on PICT, as many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis.

In conclusion, by defining MOs according to the most recent national HIV testing recommendations, we observe that 47% of the patients newly-presenting for HIV care at our centre could have been tested and diagnosed at an earlier stage. The lower rate of LPs among patients presenting MOs suggests that the PICT approach must now be expanded to reach at-risk communities rather than waiting for these individuals to become sufficiently symptomatic to access care themselves.

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Contributorship statement

Loïc Lhopitallier contributed to study design, data collection, data analysis, manuscript preparation and critical review, Estelle Moulin contributed to study design, data collection and manuscript preparation, Olivier Hugli contributed to manuscript preparation and critical review, Matthias Cavassini contributed to study design and critical review, Katharine Darling contributed to study desgin, data analysis, manuscript preparation and critical review.

Data sharing statement

The database used for the analyses performed in the study is available on request

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Figure legend

Figure 1. Panel A: Histogram showing the percentage of MOs occurring during the five years preceding diagnosis in our patient population. As 94 patients presented MOs, the percentage values shown are similar to patient numbers; **Panel B:** Pie chart showing the distribution of the categories of missed opportunities (MOs) experienced during this time.

Table S1. Recent studies examining missed opportunities (MOs) in persons newly-diagnosed with HIV, listed in alphabetical order of the country of study.

Country	Study focus	Setting	Study period	Subjects analysed	Subject number	Data source	MO definition (time period examined)	% MOs of subjects analysed	MO risk factors
Germany (9)	Characteristics of LPs & % of MOs	Hospital ID service	2009-2013	Newly-diagnosed adults presenting late (CD4 count < 350 cells/mm^3)	270	Medical records	Presentation with documented HIV IC but no testing offered (not stated)	21	Women, 'non-MSM'
Israel (13)	MOs for earlier diagnosis in patients presenting with advanced HIV disease (AHD, CD4 count < 200 cells/mm^3)	Hospital	2010-2015	Patients with AHD	57 of 356 new HIV diagnoses	Medical insurer electronic data files and patient interviews	Patient presenting with 2 out of: -IC -belonging to risk group -US(27) or UK(29) indications for testing (up to 5 years pre-HIV diagnosis)	65 MO episodes among 47 patients with AHD (5 yrs)	Only LP risk factors given
Netherlands (10)	HIV testing offered to high risk groups during STI-related GP consultations	Sentinel general practices	2008-2013	STI-related consults with high-risk groups	3209	GP report database & national HIV cohort data	HIV testing indicated in high-risk groups but not offered (study period)	34	Only LP risk factors given
Scotland (11)	Factors	Hospital	2009-	Newly-	124	National	Failure to	16.3	Only LP

	associated with late diagnosis	ID & GUM service	2014	diagnosed adults		surveillance data & case notes	diagnose HIV within 3 months of IC or ADI presentation (up to 5 years pre-HIV diagnosis)		risk factors given
Spain (12)	Frequency of late diagnosis and associated risk factors	Hospital ID service	2007-2014	Newly-diagnosed adults	354	Medical records	Presentation with IC but no testing offered or testing performed >6 months after symptom onset (up to 1 year pre-HIV diagnosis)	14.5	Only LP risk factors given

Abbreviations: LP, late presenter; ID, infectious diseases; IC, indicator condition; STI, sexually transmitted infection; GP, general practitioner; GUM, genitourinary medicine; ADI, AIDS defining illness; AHD, advanced HIV disease; US, United States; UK, United Kingdom.

Table 1. Demographic characteristics of patients who had not presented any missed opportunity and who had presented at least one missed opportunity.

Demographic characteristic	All patients (n = 201)	Patients with no MO (n = 107)	Patients with ≥1 MO (n = 94)	Univariate analysis (OR ±95% CI)	Multivariate analysis (adjusted OR ±95% CI; *P-value*)
Age (years), n (%)					
18-29	56 (28%)	23 (41%)	33 (59%)	*Ref value*	
30-49	112 (56%)	59 (53%)	53 (47%)	0.6 (0.3 – 1.2)	0.6 (0.3 – 1.2; 0.17)
>50	33 (16%)	25 (76%)	8 (24%)	0.2 (0.1 – 0.6)	0.2 (0.1 – 0.7; 0.01)
Sex, n (%)					
Male	126 (63%)	66 (52%)	60 (48%)	*Ref value*	
Female	75 (27%)	41 (55%)	34 (45%)	1.09 (0.6 - 1.9)	0.7 (0.3 – 1.6; 0.41)
Geographical Origin, n (%)					
Europe, North America, Australasia	106 (53%)	58 (55%)	48 (45%)	*Ref value*	
Sub-Saharan Africa	66 (33%)	32 (49%)	34 (51%)	1.2 (0.7 – 2.4)	3.5 (1.4 – 8.6; 0.01)
Other[1]	29 (24%)	17 (59%)	12 (41%)	0.9 (0.4 – 2.0)	1.0 (0.3 – 2.7; 0.96)
Parental Status, n (%)					
No children	125 (62%)	60 (48%)	65 (52%)	*Ref value*	
Children	76 (38%)	47 (62%)	29 (38%)	0.6 (0.3 – 1.0)	0.7 (0.3 -1.5; 0.34)

Marital Status, n (%)					
Single	117 (58%)	56 (48%)	61 (52%)	*Ref value*	
Married / with stable partner	84 (42%)	51 (61%)	33 (39%)	0.6 (0.3 – 1.0)	0.9 (0.5 – 1.7; 0.71)
Chronic Illness, n (%)					
No	161 (80%)	92 (57%)	69 (43%)	*Ref value*	
Yes	40 (20%)	15 (37%)	25 (63%)	2.2 (1.1-4.5)	4.5 (1.8 – 11.1, 0.01)
Mode of transmission, n (%)					
Heterosexual	114 (57%)	67 (59%)	47 (41%)	*Ref value*	
MSM	68 (34%)	29 (43%)	39 (57%)	1.91 (1.0 – 3.5)*	3.3 (1.2 – 9.4; 0.02)
IDU	9 (4%)	3 (33%)	6 (67%)	2.8 (0.7 – 12)	2.7 (0.5 – 14.4;0.24)
Unknown	10 (5%)	8 (80%)	2 (20%)	0.3 (0.7 – 1.8)	0.3 (0.1 – 1.6;0.14)
Time since previous HIV test, n (%)					
No previous test	119 (59%)	72 (61%)	47 (39%)	*Ref value*	
≤1 year	28 (14%)	12 (43%)	16 (57%)	2.0 (0.9 – 4.7)	1.6 (0.6 -4.4; 0.36)
>1 year ago	54 (27%)	23 (43%)	31 (57%)	2.0 (1.0 – 4.0)*	1.4 (0.7 – 3.1; 0.30)

Abbreviations: MO, missed opportunity; MSM, men who have sex with men; IDU, injecting drug use. [1]Asia, South America, North Africa, Middle East

Table 2. Clinical presentation, site of testing and reason for testing at time of diagnostic HIV test among all patients and those presenting at least one missed opportunity (MO)

	Number of patients, n (%)
Clinical presentation	
Acute HIV infection	30 (15%)
Chronic HIV infection:	
CD4 count > 350 cells/mm^3	65 (32%)
Late Presenters (< 350 cells/mm^3)	44 (22%)
Advanced Disease (< 200 cells/mm^3)	62 (31%)
Site of diagnostic HIV test	
Primary care	
Primary care physician	64 (32%)
Anonymous consultation	26 (13%)
Lausanne University Hospital	
Outpatient care	41 (20%)
Inpatient care	17 (8%)
Emergency Department	4 (2%)
Gynaecology/Obstetrics	16 (8%)
Infectious diseases service	5 (3%)
Other	28 (14%)
Reason for testing	
HIV indicator condition	59 (29%)
Epidemiological risk	42 (21%)
Symptoms / signs of acute HIV infection	36 (18%)
AIDS-defining illness	21 (10%)
Pregnancy	14 (7%)
Prior to immunosuppressive treatment	1 (1%)

Patient-initiated	28 (14%)

Table S2. Categories of prior missed opportunities (MOs) and site of eventual diagnostic test among the 94 patients who had presented at least one MO prior to diagnosis.

Site of diagnostic test / **MO type**	All sites	Primary care physician	Anonymous testing	LUH OP	LUH IP	ED	Gynaecology / Obstetrics	Infectious diseases service	Other
HIV indicator condition	32	5	5	9	4	0	2	1	6
Epidemiological risk	84	22	10	27	6	0	4	1	14
Acute HIV	11	2	2	2	1	0	0	1	3
AIDS-defining event	1	0	0	0	0	0	0	0	1
Pregnancy	7	2	0	2	1	0	2	0	0
Pre-immunosuppressive treatment	1	1	0	0	0	0	0	0	0
Total	136	32	17	40	12	0	8	3	24

Abbreviations: MO, missed opportunity; LUH, Lausanne University Hospital; OP, outpatient; IP, inpatient

References

1. Darling KE, Hachfeld A, Cavassini M, Kirk O, Furrer H, Wandeler G. Late presentation to HIV care despite good access to health services: current epidemiological trends and how to do better. Swiss Med Wkly. 2016;146:w14348.

2. Mocroft A, Lundgren JD, Sabin ML, Monforte A, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS medicine. 2013;10(9):e1001510.

3. Kohler P, Schmidt AJ, Cavassini M, Furrer H, Calmy A, Battegay M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. Aids. 2015;29(18):2509-15.

4. Hachfeld A, Ledergerber B, Darling K, Weber R, Calmy A, Battegay M, et al. Reasons for late presentation to HIV care in Switzerland. Journal of the International AIDS Society. 2015;18(1):20317.

5. FOPH. Office fédéral de la santé publique. Dépistage du VIH et conseil initiés par les médecins. http://www.bag.admin.ch. Bulletin de l'OFSP. 2007;21:371-3.

6. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins: recommandations pour les patients adultes. http://www.bag.admin.ch. Bulletin de l'OFSP. 2010;11/10:364-6.

7. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins en présence de certaines pathologies (maladies évocatrices d'une infection à VIH) www.bag.admin.ch. Bulletin de l'OFSP 2013:1-5.

8. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins http://www.bag.admin.ch. Bulletin de l'OFSP. 2015;21:237-41.

9. Tominski D, Katchanov J, Driesch D, Daley MB, Liedtke A, Schneider A, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. HIV Med. 2016.

10. Joore IK, Reukers DF, Donker GA, van Sighem AI, Op de Coul EL, Prins JM, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. BMJ open. 2016;6(1):e009194.

11. Noble G, Okpo E, Tonna I, Fielding S. Factors associated with late HIV diagnosis in North-East Scotland: a six-year retrospective study. Public Health. 2016;139:36-43.

12. Gullon A, Verdejo J, de Miguel R, Gomez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. AIDS care. 2016;28(10):1296-300.

13. Levy I, Maor Y, Mahroum N, Olmer L, Wieder A, Litchevski V, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. BMJ open. 2016;6(11):e012721.

14. Darling KE, de Allegri N, Fishman D, Kehtari R, Rutschmann OT, Cavassini M, et al. Awareness of HIV testing guidelines is low among Swiss emergency doctors: a survey of five teaching hospitals in French-speaking Switzerland. PloS one. 2013;8(9):e72812.

15. Darling KE, Hugli O, Mamin R, Cellerai C, Martenet S, Berney A, et al. HIV Testing Practices by Clinical Service before and after Revised Testing Guidelines in a Swiss University Hospital. PloS one. 2012;7(6):e39299.

16. UNAIDS epidemiology figures 2013: Switzerland [Available from: http://www.unaids.org/en/regionscountries/countries/switzerland/.

17. Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, Furrer H, Yerly S, Francioli P. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. 2010;39(5):1179-89.

18. Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: a consensus definition. HIV medicine. 2011;12(1):61-4.

19. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011;53(8):817-25.

20. Joore IK, Arts DL, Kruijer MJ, Moll van Charante EP, Geerlings SE, Prins JM, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. Sexually transmitted infections. 2015;91(7):467-72.

21. FOPH. Office fédéral de la santé publique. Nombre de cas de VIH et d'IST en 2013: rapport, analyses et tendances. http://www.bag.admin.ch. Bulletin de l'OFSP. 2014;20:351-80.

22. Merz L, Zimmermann S, Peters S, Cavassini M, Darling KE. Investigating Barriers in HIV-Testing Oncology Patients: The IBITOP Study, Phase I. Oncologist. 2016;21(10):1176-82.

23. Champenois K, Cousien A, Cuzin L, Le Vu S, Deuffic-Burban S, Lanoy E, et al. Missed opportunities for HIV testing in newly-HIV-diagnosed patients, a cross sectional study. BMC infectious diseases. 2013;13:200.

24. Dubois-Arber F, Meystre-Agustoni G, André J, De Heller K, Alain P, Bodenmann P. Sexual behaviour of men that consulted in medical outpatient clinics in Western Switzerland from 2005-2006: risk levels unknown to doctors? BMC Public Health. 2010;10:528.

25. Fauci AS, Marston HD. Ending the HIV-AIDS Pandemic--Follow the Science. N Engl J Med. 2015;373(23):2197-9.

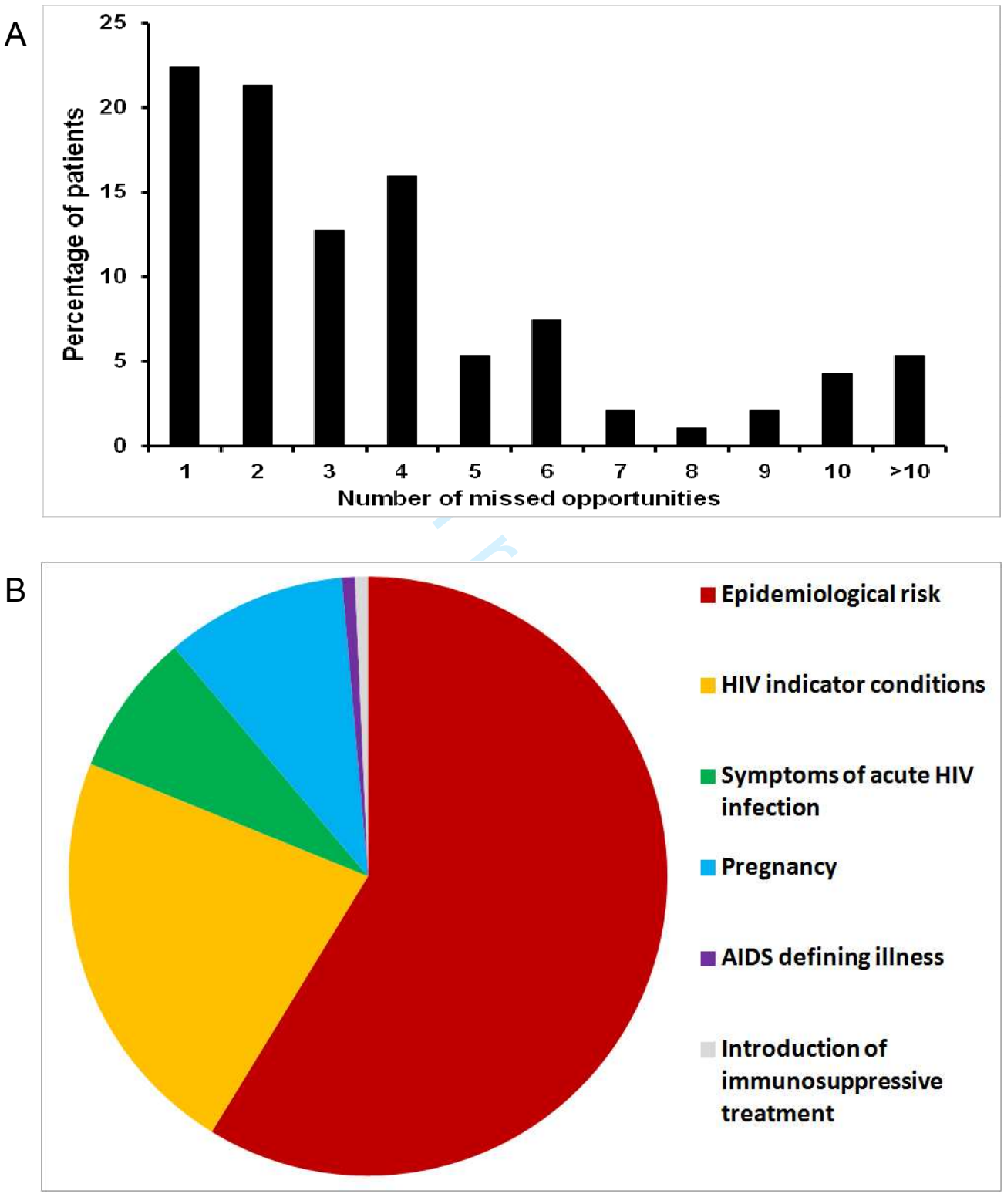
26. Bath R, O'Connell R, Lascar M, Ferrand R, Strachan S, Matin N, et al. TestMeEast: a campaign to increase HIV testing in hospitals and to reduce late diagnosis. AIDS care. 2015:1-4.

27. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. Morbidity & Mortality Weekly Report Recommendations & Reports. 2006;55(RR-14):1-17; quiz CE1-4.

28. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. UK National Guidelines for HIV Testing 2008. http://www.bhiva.org/documents/Guidelines/Testing/GlinesHIVTest08.pdf2008.

29. Palfreeman A, Fisher M, Ong E, Wardrope J, Stewart E, Castro-Sanchez E, et al. Testing for HIV: concise guidance. Clin Med. 2009;9(5):471-6.

Figure 1.


A
Percentage of patients
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
>10
Number of missed opportunities
B
Epidemiological risk
HIV indicator conditions
Symptoms of acute HIV infection
Pregnancy
AIDS defining illness
Introduction of immunosuppressive treatment

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Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis

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Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis

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Short title: Missed Opportunities for HIV testing from 2010-2015

Key words: missed opportunities, HIV diagnosis, HIV testing, HIV indicator conditions, late presenters

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Abstract

Objectives: To determine the frequency of missed opportunities (MOs) among patients newly-diagnosed with HIV, risk factors for presenting MOs, and the association between MOs and late presentation to care.

Design: Retrospective analysis

Setting: HIV outpatient clinic at a Swiss tertiary hospital

Participants: Patients aged ≥18 years old newly presenting for HIV care between 2010 and 2015

Measures: Number of medical visits, up to five years preceding HIV diagnosis, at which HIV testing had been indicated, according to Swiss HIV testing recommendations. A visit at which testing was indicated but not performed was considered a MO for HIV testing.

Results

Complete records were available for all 201 new patients of whom 51% were male and 33% from sub-Saharan Africa. Thirty patients (15%) presented with acute HIV infection while 119 patients (59%) were late presenters (LPs) (CD4 counts <350 cells/mm^3 at diagnosis). Ninety-four patients (47%) had presented at least one MO, of whom 44 (47%) had multiple MOs. MOs were more frequent among individuals from sub-Saharan Africa, men who have sex with men, and patients under follow-up for chronic disease. MOs were less frequent in LPs than non-LPs (42.5% versus 57.5%, P = 0.03).

Conclusions

At our centre, 47% of patients presented at least one MO. Whilst our late presentation rate is higher than the national figure of 49.8%, LPs were less likely to experience MOs, suggesting that these patients were diagnosed late through presenting late, rather than through being failed by our hospital. We conclude that, in addition to optimising physician-initiated testing, access to testing must be improved among patients unaware they are at HIV risk and who do not seek health care.

Article summary

Strengths and limitations of this study

- We defined the term, 'missed opportunities', currently lacking a consensus definition, based on the Swiss HIV testing recommendations applicable to our institution.
- A centralized database enabled us to examine all patient episodes at our centre, to determine the number and type of missed opportunities.
- We used multivariate logistic regression to show a robust association between patient characteristics and the risk of missed opportunities for HIV testing.
- As with any monocentric study, our findings may not be applicable to all centres in Switzerland, due to differences in hospital structure and local patient population.

Introduction

Late presentation to care among people living with HIV prolongs the period between seroconversion and treatment, and leads to an avoidable increase in morbidity, mortality, health care costs and risk of onward transmission (1). In Europe, even in countries with adequate health care provision and HIV testing recommendations, late presenters (LPs) make up to half of all new HIV diagnoses (2). In Switzerland, while 81% of adults living with HIV in 2012 were estimated to be diagnosed (3), 49.8% of patients diagnosed and enrolled in the Swiss HIV Cohort Study between 2009 and 2012 were LPs, with CD4 counts below 350 cells/mm^3 and/or an AIDS-defining illness at presentation (4).

To maximise early HIV diagnosis, HIV testing recommendations have been published by the Swiss Federal Office of Public Health since 2007 and updated three times (5-8). In 2007, the recommendations introduced *physician-initiated counselling and testing* (PICT), proposing targeted testing and describing HIV testing indications in the text (5). In 2010, testing indications were mentioned in the text and presented as tables (6). Although the term *HIV-associated indicator conditions* (HIV ICs) was not in general use at this time, HIV ICs were included in the 2010 recommendations. In 2013, the recommendations highlighted HIV ICs and introduced HIV screening of patients commencing immunosuppressive therapy (7). In 2015, the content of the recommendations remained similar but the table of symptoms and signs of acute HIV infection was presented first to emphasise this clinical presentation as an indication for HIV testing (8). In summary, apart from the addition of screening of patients commencing immunosuppressive therapy in 2013, the recommendation updates between 2010 and 2015 involved changes in format but not overall content.

The Swiss health care system relies on mandatory private health insurance coverage regulated at a federal level. It is estimated that >98% of the population has coverage and access to care is excellent(9). However, we have observed that certain vulnerable populations, for example sex workers, use the ED as a primary health care facility(10) and that the percentage of patients presenting to the ED who have a primary care physician is

below 98%(11). Further, out-of pocket costs are amongst the highest in the OECD (Organisation for Economic Co-operation and Development)(9).

When an individual presents to a health care provider with indications for HIV testing but is not offered a test, this constitutes a missed opportunity (MO) for HIV testing, regardless of his/her serostatus (1). In 2016, several studies were published on MOs in Europe (12-15) and Israel (16) (Supplementary table S1). These studies covered four to seven-year periods between 2007 and 2015 and reported MO rates of 14.5% (15) to 34% (13). Many highlighted the importance of physician awareness of testing indications in reducing MOs (12, 15, 16). Whilst the Swiss PICT recommendations, by definition, emphasise the responsibility of the physician in ordering HIV testing (stating that appropriately recommending testing corresponds to due diligence), we have observed that, for example, only 18% of Emergency Department (ED) doctors in French-speaking Switzerland were aware of the 2010 Swiss Federal Office of Public Health recommendations and that, even if aware, they did not adhere to them (17). In the ED and other services at our centre, these recommendations made no difference to HIV testing rates (18).

The aims of this study were therefore to determine the frequency of MOs among newly-diagnosed patients presenting for care at our outpatient HIV service, and patient risk factors for presenting MOs, and to determine the association between MOs and late presentation to care.

Methods

Ethics Statement

This study was approved by the Ethical Committee on Human Research of the Canton of Vaud, Switzerland (protocol number 2016-00333). Due to the retrospective design, the requirement of patient informed consent was waived.

Study setting

The study was conducted at Lausanne University Hospital, a 1,500-bed teaching hospital which serves as a primary-level community hospital for Lausanne (catchment population 300,000) and as a secondary and tertiary referral hospital for Western Switzerland (catchment population 1-1.5 million). HIV seroprevalence in the region is estimated to be 0.2-0.5% (3, 19). At Lausanne University Hospital, medical records are electronic and include all hospital visits, discharge summaries (inpatients), clinical letters (outpatients) and laboratory reports.

In Switzerland, health insurance is mandatory. Whilst most patients have a primary care physician, individuals may visit a specialist without referral. Outpatient HIV care at Lausanne University Hospital is provided by the Infectious Diseases Service. All patients are invited to be enrolled in the Swiss HIV Cohort Study, a national prospective cohort study with ongoing enrolment since 1988 (20).

Definitions

Late presentation was defined as presenting for care with chronic HIV infection with a CD4 count <350 cells/mm^3, in accordance with the European consensus working group definition (21).

Acute HIV infection was defined as a positive blood HIV-RNA assay or a positive p24 antigen assay with an incomplete Western Blot(22)

The term MO for HIV testing has no consensus definition. For this study, a MO was defined as a visit to LUH at which HIV testing was indicated but not performed, regardless of the serostatus of the patient. Testing was considered as indicated according to five broad indications, based on the Swiss Federal Office of Public Health 2015 recommendations (8) but present in the recommendations from 2010 onwards: signs and symptoms of acute HIV infection; AIDS-defining illness; HIV ICs in which HIV prevalence is considered to be >0.5% (8) (such as herpes zoster, ongoing mononucleosis-like illness or unexplained thrombocytopenia) (23, 24) ; situations in which HIV infection should be excluded (for example, planned immunosuppressive treatment and pregnancy) and epidemiological risk

(belonging to or having a sexual partner from a high-risk group: men who have sex with men [MSM], injecting drug users [IDUs] and individuals originating from a high-prevalence region, notably, sub-Saharan Africa).

Study design

The study retrospectively analysed all consecutive patients with newly-diagnosed HIV presenting to the Lausanne University Hospital infectious diseases outpatient clinic from 1st January 2010 to 31st December 2015.

For each patient, the following data were collected: sociodemographic data (age, sex, geographical origin, marital status, parental status, risk factor(s) for HIV acquisition); HIV infection data (CD4 count, AIDS defining illness, mode of infection); visits to Lausanne University Hospital during the five years preceding HIV diagnosis (chronic disease with regular follow-up, inpatient and outpatient consultations); and HIV testing data (date of previous negative HIV test, reason for performing diagnostic test, site of diagnostic test). The limit of five years for LUH visits was selected based on the LP figure of 49.8% of patients newly-enrolled in the Swiss HIV Cohort Study (4), in whom infection was likely to have occurred within five years preceding diagnosis (25), and the observation that, elsewhere in Europe, 59% of new HIV patients exhibited HIV ICs during a similar pre-diagnosis period (26). MOs were identified using medical records and analysed by absolute MO number and by MO category (based on the five groups of HIV testing indications: acute HIV, AIDS defining illness, HIV ICs, test of exclusion and epidemiological risk).

Given the low HIV testing rates observed in the ED at our centre and elsewhere in French-speaking Switzerland (1% of all patients seen) (17, 18), we additionally conducted a search of all pre-diagnosis visits to the ED, using the central hospital database. We focused on ED visits estimated to have occurred after HIV seroconversion based on CD4 cell count at diagnosis, accounting for variations related to age and sex (25). All pre-diagnosis visits were matched with laboratory reports to determine whether HIV testing had been performed. A single pre-diagnosis ED visit after which testing was performed within 72 hours was not

considered a MO, to allow for patients admitted prior to the weekend or referred for testing by a designated hospital team, where testing may be delayed in the interest of continuity of care. At the time of this study, rapid HIV testing was not available in the ED and so all HIV tests requested and performed were documented in the laboratory database.

Data and Statistical Analysis

Patient details, stripped of all identifiers, were entered in to a coded database by the study investigators (LL, EM) for each of the six 12-month periods. Categorical data were presented as absolute frequencies and percentages and compared using the Chi squared test; continuous data were presented as means (standard deviation, SD) or medians (interquartile range, IQR) and analysed using the Mann-Whitney U test. Multivariate logistic regression was applied to calculate the adjusted odds ratio for various risk factors for presenting MOs. Data were stratified according to patient demographic, clinical and epidemiological characteristics in order to reduce confounding. Patients with acute HIV infections were excluded from all analyses concerning late presentation.

All analysis was performed using Stata 14.1 (StataCorp LP, Texas, USA).

Results

Patient characteristics

We identified 201 patients newly-presenting for HIV care during the study period, all of whom had complete electronic medical records (100% participation). Mean age at diagnosis was 38 years ± SD (range 18 to 75 years). Mode of HIV transmission was listed as heterosexual in 57% of patients, MSM in 34%, IDU in 4% and unknown in 5% (Table 1). The majority of patients (59%) had never been HIV tested prior to their diagnostic test.

Missed opportunities (MOs)

In total, 359 separate MOs were presented by 94 patients (47%) during the five years preceding their diagnosis (Figure 1). Considering patients presenting MOs, 74 patients (78%)

had presented on more than one visit (range 2 to 17) with a MO of any category. Considering MO categories, 58 patients (62%) had presented a single category of MO, 30 patients had presented two categories (32%) and six patients (6%) had presented three categories. Figure 2 shows the distribution of MO categories by testing indication.

Risk factors for MOs

In multivariate analysis, older patients (aged >50 years) had less risk of presenting MOs than patients aged <30 years (*P*=0.01), while patients of sub-Saharan African origin (*P*=0.01), those under regular follow up for chronic illness (*P*=0.01) and MSM (*P*=0.02) had increased risk (Table 1). In patients from sub-Saharan Africa and those under regular follow-up for chronic illness, all MO categories were distributed equally compared to the rest of the population. In contrast, MOs in MSM patients were more frequently related to epidemiological risk (46%) than to other MO categories (33%) (*P*<0.01).

Clinical presentation at diagnosis, site of testing and reason for testing

Most patients (85%) were diagnosed in the chronic phase of infection (Table 2). The median CD4 count at diagnosis was 293 (IQR 147-452). In total, 119 (59%) were LPs. LPs consulted less often to Lausanne University Hospital than non-LPs (mean number of consults 1.4 for LPs versus 2.5 for non-LPs, *P* < 0.01).

A greater proportion of new HIV diagnoses were made in the primary care and outpatient settings than during hospital admission (Table 2). The top three reasons for testing, regardless of testing site, were presence of HIV ICs, epidemiological risk and symptoms and signs of acute HIV infection (Table 2). Acute HIV infection was confirmed in 24 of the 36 patients presenting with symptoms and signs of acute HIV infection, reasons for testing in this subset of patients are detailed in table S2.

We did not identify any situations in which HIV testing was recommended and not accepted by the patient.

MOs and late presentation

Multivariate analysis demonstrated a lower risk of late presentation in patients presenting MOs (OR 0.5, 95% 0.2-0.9, *P*<0.01). Indeed, the median CD4 count at diagnosis among MO patients was significantly higher than for non-MO patients (351 cells/mm^3 versus 244 cells/mm^3, *P*<0.01). MOs were less frequent in LPs compared to patients presenting with CD4 > 350 cells/mm^3 (42.5% versus 57.5%, *P*<0.01). Among subgroups, the LP rate among MSM was lower compared to the rest of the study population (22% versus 78%, *P*<0.001).

MOs in the ED

Of 201 patients, 58 (29%) were identified as having presented to the ED prior to diagnosis, 27 of whom (47%) had presented more than once (range 2-7 visits). All 58 patients had presented within three years preceding their HIV diagnosis and 53 patients (91%) within the preceding 12 months. Although 15 patients (26%) were diagnosed within 72 hours of their most recent ED visit, seven of these had presented to the ED on at least one previous occasion. In total, 50/58 patients (86%) presented to the ED during the interval between seroconversion and diagnosis, none of whom were tested. As with the patient sample as a whole, the two main MO categories for these 58 patients were epidemiological risk and HIV ICs.

Discussion

In this single-centre study, we observed that 47% of 201 patients newly-presenting for HIV care had presented at least one MO for earlier testing. Although thirty patients (15%) were diagnosed during acute infection, nine patients (5%) who presented with symptoms or signs of acute HIV were not tested. Of patients who had visited the ED pre-diagnosis, 86% had presented at least one MO for testing. Finally, MOs occurred significantly less frequently in LPs than in non-LPs.

Our patient population differed from that of Switzerland as a whole (Swiss Federal Office of Public Health HIV notifications) in terms of HIV acquisition risk profile: 57% heterosexual

transmission and 34% MSM, compared to 42% heterosexual and 57% MSM (27). As heterosexual transmission was a risk factor for late presentation in the Swiss HIV Cohort Study by Hachfeld *et al*, this might explain our higher rate of LPs (59%) compared to the Swiss HIV Cohort Study figure of 49.8% (4). A lower Swiss HIV Cohort Study figure through underrepresentation of our patients in the Hachfeld *et al* study is unlikely as the majority were enrolled in the Swiss HIV Cohort Study.

Our analysis showed that patients under regular follow-up for chronic illness, patients from sub-Saharan Africa and MSM were at increased risk for MOs. In patients under regular follow-up, there may be the assumption by the hospital physician that the patient's general practitioner has performed an HIV test and *vice versa* (1). In our institution, we have previously reported suboptimal testing rates among oncology patients, particularly those of non-European origin (28). Among patients with risk factors for HIV acquisition, MOs will occur if there is non-disclosure of at-risk behaviour by the patient and incomplete history taking by the doctor. This was described in a French cross-sectional study of 1,008 patients newly-diagnosed with HIV of whom 48% were MSM (29). Fewer than half the MSM who consulted disclosed being MSM and only 21% of all MSM were offered testing by their health care provider (29). In Switzerland, physicians frequently do not discuss sexual behaviour with their male patients, potentially missing those with risk factors (30).

Our non-association between LPs and MOs suggests a distinction between 'missed' opportunity and 'no' opportunity. Whilst it is logical that late presentation may result from repeated MOs in positive individuals, LPs do not necessarily present opportunities for earlier testing. If individuals feel well, are unaware of HIV risk factors and/or have poor access to health care, they may have sporadic if any contact with health care systems (4): their late presentation may be their only presentation. We have shown in our study that late presenters consult less often to our hospital. Optimal HIV testing practice is the cornerstone towards attaining the first 90 of the 90-90-90 goal set by the WHO (31). However, even perfect PICT practice cannot eliminate late presentation when physicians can initiate testing only if individuals present to them. It is necessary to reach out to individuals who are at risk of

infection but who do not present for health care. HIV testing can be expanded by introducing community-level testing innovations tailored to each community, depending on whether non-presentation is related to lack of awareness of HIV risk factors or symptoms of infection or to lack or awareness of services available. HIV testing also implies expenditure by the patient which could act as another barrier to access. Innovations include walk-in access to free testing, testing by non-traditional providers, improving risk perception and tackling stigma (32).

Regarding risk perception, the MO umbrella can be extended from MOs for HIV testing to those for HIV prevention. Whether or not the patients in this sample had HIV at their first few visits to Lausanne University Hospital, they were, by definition, at risk of HIV acquisition. Delivering a prevention message at the time of testing could avert future infection and may also be a means of reaching individuals outside the hospital by dissemination of information. In the ED at our centre, offering non-targeted screening, as recommended in the United States (33) and the United Kingdom (34), would have enabled diagnosis of 86% of the patients of our sample who had presented to this service. Delivering a preventing message at this time could have prevented infections among contacts in the community.

The MO rates at our centre were higher than those reported in other studies of similarly-sized samples of newly-diagnosed patients presenting for HIV care in European hospital outpatient settings. Tominski *et al* observed a rate of 21% among 270 patients, based on HIV ICs (12); Noble *et al* observed a rate of 16.3% among 124 patients, based on ICs or AIDS defining illness up to five years pre-diagnosis (14); Gullón *et al* observed a rate of 14.5% among 354 patients, based on ICs up to one year pre-diagnosis (15). As there is no consensus definition of MOs, it is important to examine the criteria for MOs and the time prior to diagnosis examined. In our study, the MO definition was wide, based not only on HIV ICs and AIDS defining illness but also on epidemiological risk, symptoms and signs of acute HIV infection and situations in which HIV should be excluded, and over a period of five years pre-diagnosis. Considering MOs based on HIV ICs and AIDS defining illness alone, our MO rate was 16%. However, applying the most recent HIV testing recommendations, we consider the

MO rate obtained according to our study criteria as being a baseline on which to improve. Considering future directions, we plan to apply the findings from this study in several ways. We have piloted rapid testing in the ED by screening patients for HIV risk factors using anonymous electronic tablet-based questionnaires in the waiting area to improve HIV testing in this service (manuscript submitted). The lack of testing among pregnant women who are consulting to terminate their pregnancy is illogical and merits review of obstetric guidelines. Finally, ICs should be mentioned in the practice guidelines of the relevant (non-HIV) specialty(23)

This study has limitations. As in any retrospective study, identifying and classifying MOs relied on available clinical documentation. As we reviewed medical notes only from our institution, the number or categories of MO may be prone to bias. Whilst the number of included patients was small, complete medical records for each patient ensured data quality. This study examined only MOs occurring in our hospital; using the Lausanne University Hospital database it was not possible to quantify potential MOs occurring in the primary care setting or in other hospitals. We could therefore have underestimated the number of MOs. Equally, although we could determine that most diagnostic tests were made in the primary care setting, this study did not examine the untested patient denominator and the number of tests performed in primary care which could lead to an overestimation of the number of MOs for our population. Finally, as our study was monocentric, our risk-factor associations with MOs reflect our local patient population. Against these limitations, the non-association between late presentation and MOs observed in our study has important implications for a national testing strategy based on PICT, as many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis.

In conclusion, by defining MOs according to the most recent national HIV testing recommendations, we observe that 47% of the patients newly-presenting for HIV care at our centre could have been tested at an earlier stage. The lower rate of LPs among patients presenting MOs suggests that the PICT approach must now be expanded to reach at-risk

communities rather than waiting for these individuals to become sufficiently symptomatic to access care themselves.

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Contributors' statement

Loïc Lhopitallier contributed to study design, data collection, data analysis, manuscript preparation and critical review, Estelle Moulin contributed to study design, data collection and manuscript preparation, Olivier Hugli contributed to manuscript preparation and critical review, Matthias Cavassini contributed to study design and critical review, Katharine Darling contributed to study design, data analysis, manuscript preparation and critical review.

Data sharing statement

The database used for the analyses performed in the study is available on request

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Figure legend

Figure 1: Histogram showing the percentage of MOs occurring during the five years preceding diagnosis in our patient population. As 94 patients presented MOs, the percentage values shown are similar to patient numbers;

Figure 2: Pie chart showing the distribution of the categories of missed opportunities (MOs) experienced during this time, with percentages in each case.

Table 1. Demographic characteristics of patients who had not presented any missed opportunity and who had presented at least one missed opportunity.

Demographic characteristic	All patients (n = 201)	Patients with no MO (n = 107)	Patients with ≥1 MO (n = 94)	Univariate analysis (OR ±95% CI)	Multivariate analysis (adjusted OR ±95% CI; *P-value*)
Age (years), n (%)					
18-29	56	23 (41%)	33 (59%)	*Ref value*	
30-49	112	59 (53%)	53 (47%)	0.6 (0.3 – 1.2)	0.5 (0.3 – 1.1; 0.08)
>50	33 (	25 (76%)	8 (24%)	0.2 (0.1 – 0.6)	0.2 (0.1 – 0.6; <0.01)
Sex, n (%)					
Male	126	66 (52%)	60 (48%)	*Ref value*	
Female	75	41 (55%)	34 (45%)	1.09 (0.6 - 1.9)	0.7 (0.3 – 1.5; 0.36)
Geographical Origin, n (%)					
Europe, North America, Australasia	106	58 (55%)	48 (45%)	*Ref value*	
Sub-Saharan Africa	66	32 (49%)	34 (51%)	1.2 (0.7 – 2.4)	3.5 (1.3 – 7.7; 0.01)
Other[1]	29	17 (59%)	12 (41%)	0.9 (0.4 – 2.0)	1.0 (0.4 – 2.5; 0.96)
Chronic Illness, n (%)					
No	161)	92 (57%)	69 (43%)	*Ref value*	
Yes	40	15 (37%)	25 (63%)	2.2 (1.1-4.5)	4.4 (1.7 – 10.9, <0.01)

Mode of transmission, n (%)					
Heterosexual	114	67 (59%)	47 (41%)	*Ref value*	
MSM	68	29 (43%)	39 (57%)	1.91 (1.0 – 3.5)[2]	4 (1.5 – 10.7; 0.01)
IDU	9	3 (33%)	6 (67%)	2.8 (0.7 – 12)	2.9 (0.6 – 15.3;0.20)
Unknown	10	8 (80%)	2 (20%)	0.3 (0.7 – 1.8)	0.3 (0.1 – 1.8;0.2)
Time since previous HIV test, n (%)					
No previous test	119)	72 (61%)	47 (39%)	*Ref value*	
≤1 year	28	12 (43%)	16 (57%)	2.0 (0.9 – 4.7)	1.6 (0.6 -4.3; 0.38)
>1 year ago	54	23 (43%)	31 (57%)	2.0 (1.0 – 4.0)[2]	1.4 (0.7 – 3.0; 0.31)

Abbreviations: MO, missed opportunity; MSM, men who have sex with men; IDU, injecting drug use.

[1]Asia, South America, North Africa, Middle East.

[2]*P*-value < 0.05.

Table 2. Clinical presentation, site of testing and reason for testing at time of diagnostic HIV test among all patients and those presenting at least one missed opportunity (MO)

	Number of patients, n (%)
Clinical presentation	
Acute HIV infection	30 (15%)
Chronic HIV infection:	
CD4 count > 350 cells/mm^3	65 (32%)
Late Presenters (< 350 cells/mm^3)	44 (22%)
Advanced Disease (< 200 cells/mm^3)	62 (31%)
Site of diagnostic HIV test	
Primary care	
Primary care physician	64 (32%)
Anonymous consultation	26 (13%)
Lausanne University Hospital	
Outpatient care	41 (20%)
Inpatient care	17 (8%)
Emergency Department	4 (2%)
Gynaecology/Obstetrics	16 (8%)
Infectious diseases service	5 (3%)
Other	28 (14%)
Reason for testing	
HIV indicator condition	59 (29%)
Epidemiological risk	42 (21%)
Symptoms / signs of acute HIV infection	36 (18%)
AIDS-defining illness	21 (10%)
Pregnancy	14 (7%)
Prior to immunosuppressive treatment	1 (1%)

Patient-initiated	28 (14%)

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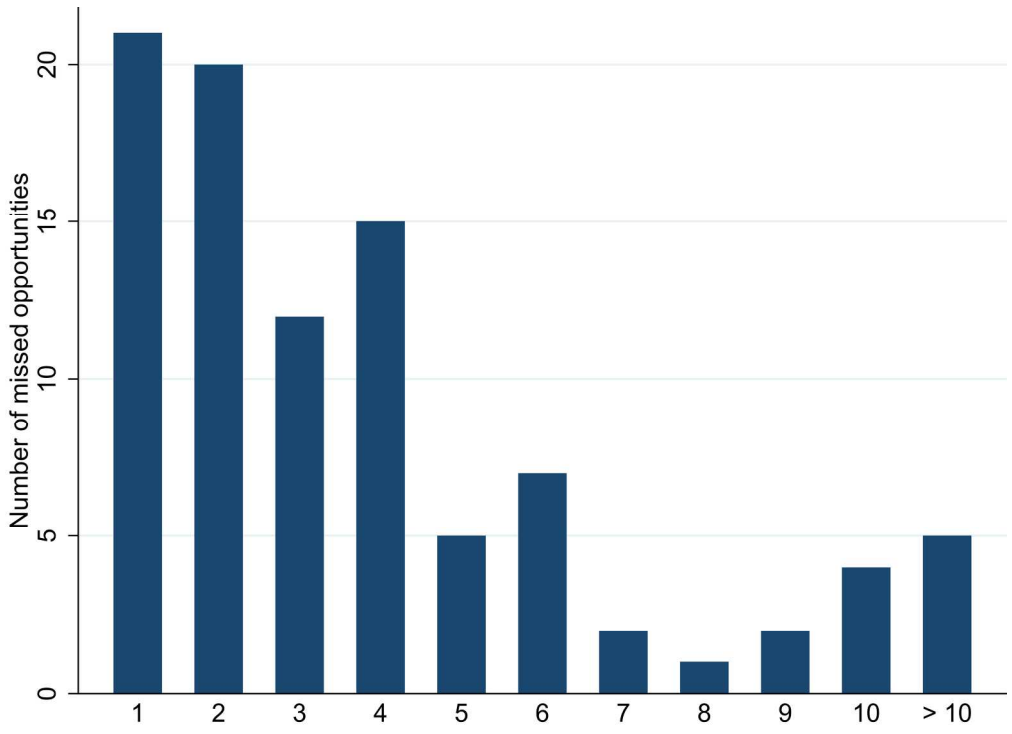
References

1. Darling KE, Hachfeld A, Cavassini M, Kirk O, Furrer H, Wandeler G. Late presentation to HIV care despite good access to health services: current epidemiological trends and how to do better. Swiss Med Wkly. 2016;146:w14348.
2. Mocroft A, Lundgren JD, Sabin ML, Monforte A, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med. 2013;10(9):e1001510.
3. Kohler P, Schmidt AJ, Cavassini M, Furrer H, Calmy A, Battegay M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS. 2015;29(18):2509-15.
4. Hachfeld A, Ledergerber B, Darling K, Weber R, Calmy A, Battegay M, et al. Reasons for late presentation to HIV care in Switzerland. Journal of the International AIDS Society. 2015;18(1):20317.
5. FOPH. Office fédéral de la santé publique. Dépistage du VIH et conseil initiés par les médecins. http://www.bag.admin.ch. Bulletin de l'OFSP. 2007;21:371-3.
6. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins: recommandations pour les patients adultes. http://www.bag.admin.ch. Bulletin de l'OFSP. 2010;11/10:364-6.
7. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins en présence de certaines pathologies (maladies évocatrices d'une infection à VIH) www.bag.admin.ch. Bulletin de l'OFSP 2013:1-5.
8. FOPH. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins http://www.bag.admin.ch. Bulletin de l'OFSP. 2015;21:237-41.
9. Biller-Andorno N, Zeltner T. Individual Responsibility and Community Solidarity--The Swiss Health Care System. N Engl J Med. 2015;373(23):2193-7.
10. Darling KE, Gloor E, Ansermet-Pagot A, Vaucher P, Durieux-Paillard S, Bodenmann P, et al. Suboptimal access to primary healthcare among street-based sex workers in southwest Switzerland. Postgrad Med J. 2013;89(1053):371-5.
11. De Rossi N, Dattner N, Cavassini M, Peters S, Hugli O, Darling KEA. Patient and doctor perspectives on HIV screening in the emergency department: A prospective cross-sectional study. PLoS One. 2017;12(7):e0180389.
12. Tominski D, Katchanov J, Driesch D, Daley MB, Liedtke A, Schneider A, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. HIV Med. 2016.
13. Joore IK, Reukers DF, Donker GA, van Sighem AI, Op de Coul EL, Prins JM, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. BMJ open. 2016;6(1):e009194.
14. Noble G, Okpo E, Tonna I, Fielding S. Factors associated with late HIV diagnosis in North-East Scotland: a six-year retrospective study. Public Health. 2016;139:36-43.
15. Gullon A, Verdejo J, de Miguel R, Gomez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. AIDS care. 2016;28(10):1296-300.
16. Levy I, Maor Y, Mahroum N, Olmer L, Wieder A, Litchevski V, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. BMJ open. 2016;6(11):e012721.

17. Darling KE, de Allegri N, Fishman D, Kehtari R, Rutschmann OT, Cavassini M, et al. Awareness of HIV testing guidelines is low among Swiss emergency doctors: a survey of five teaching hospitals in French-speaking Switzerland. PloS one. 2013;8(9):e72812.
18. Darling KE, Hugli O, Mamin R, Cellerai C, Martenet S, Berney A, et al. HIV Testing Practices by Clinical Service before and after Revised Testing Guidelines in a Swiss University Hospital. PloS one. 2012;7(6):e39299.
19. UNAIDS epidemiology figures 2013: Switzerland [Available from: http://www.unaids.org/en/regionscountries/countries/switzerland/.
20. Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, Furrer H, Yerly S, Francioli P. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. 2010;39(5):1179-89.
21. Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: a consensus definition. HIV Med. 2011;12(1):61-4.
22. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS. 2003;17(13):1871-9.
23. Lord E, Stockdale AJ, Malek R, Rae C, Sperle I, Raben D, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. HIV Med. 2017;18(4):300-4.
24. Sullivan AK, Raben D, Reekie J, Rayment M, Mocroft A, Esser S, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). PLoS One. 2013;8(1):e52845.
25. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011;53(8):817-25.
26. Joore IK, Arts DL, Kruijer MJ, Moll van Charante EP, Geerlings SE, Prins JM, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. Sex Transm Infect. 2015;91(7):467-72.
27. FOPH. Office fédéral de la santé publique. Nombre de cas de VIH et d'IST en 2013: rapport, analyses et tendances. http://www.bag.admin.ch. Bulletin de l'OFSP. 2014;20:351-80.
28. Merz L, Zimmermann S, Peters S, Cavassini M, Darling KE. Investigating Barriers in HIV-Testing Oncology Patients: The IBITOP Study, Phase I. Oncologist. 2016;21(10):1176-82.
29. Champenois K, Cousien A, Cuzin L, Le Vu S, Deuffic-Burban S, Lanoy E, et al. Missed opportunities for HIV testing in newly-HIV-diagnosed patients, a cross sectional study. BMC infectious diseases. 2013;13:200.
30. Dubois-Arber F, Meystre-Agustoni G, André J, De Heller K, Alain P, Bodenmann P. Sexual behaviour of men that consulted in medical outpatient clinics in Western Switzerland from 2005-2006: risk levels unknown to doctors? BMC Public Health. 2010;10:528.
31. Fauci AS, Marston HD. Ending the HIV-AIDS Pandemic--Follow the Science. N Engl J Med. 2015;373(23):2197-9.
32. Bath R, O'Connell R, Lascar M, Ferrand R, Strachan S, Matin N, et al. TestMeEast: a campaign to increase HIV testing in hospitals and to reduce late diagnosis. AIDS care. 2015:1-4.

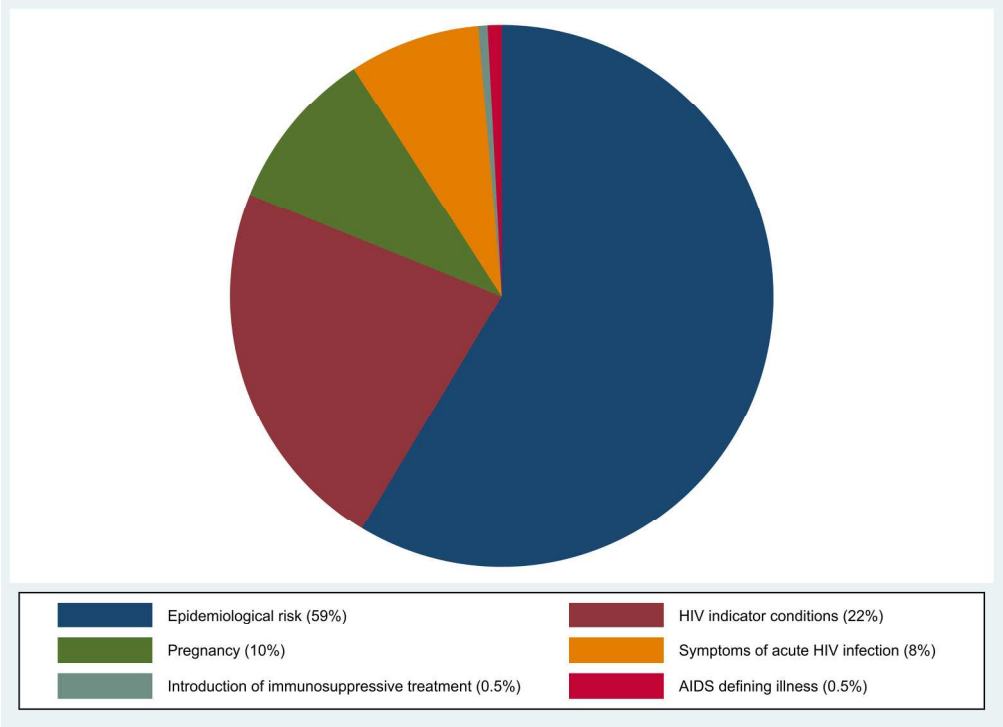
33. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. Morbidity & Mortality Weekly Report Recommendations & Reports. 2006;55(RR-14):1-17; quiz CE1-4.

34. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. UK National Guidelines for HIV Testing 2008. http://www.bhiva.org/documents/Guidelines/Testing/GlinesHIVTest08.pdf2008.



Histogram showing the percentage of MOs occurring during the five years preceding diagnosis in our patient population. As 94 patients presented MOs, the percentage values shown are similar to patient numbers.

101x73mm (600 x 600 DPI)



Pie chart showing the distribution of the categories of missed opportunities (MOs) experienced during this time, with percentages in each case.

101x73mm (600 x 600 DPI)

Table S1. Recent studies examining missed opportunities (MOs) in persons newly-diagnosed with HIV, listed in alphabetical order of the country of study.

Country	Study focus	Setting	Study period	Subjects analysed	Subject number	Data source	MO definition (time period examined)	% MOs of subjects analysed	MO risk factors
Germany (12)	Characteristics of LPs & % of MOs	Hospital ID service	2009-2013	Newly-diagnosed adults presenting late (CD4 count < 350 cells/mm^3)	270	Medical records	Presentation with documented HIV IC but no testing offered (not stated)	21	Women, 'non-MSM'
Israel (16)	MOs for earlier diagnosis in patients presenting with advanced HIV disease (AHD, CD4 count < 200 cells/mm^3)	Hospital	2010-2015	Patients with AHD	57 of 356 new HIV diagnoses	Medical insurer electronic data files and patient interviews	Patient presenting with 2 out of: -IC -belonging to risk group -US or UK indications for testing (up to 5 years pre-HIV diagnosis)	65 MO episodes among 47 patients with AHD (5 yrs)	Only LP risk factors given
Netherlands (13)	HIV testing offered to high risk groups during STI-related GP consultations	Sentinel general practices	2008-2013	STI-related consults with high-risk groups	3209	GP report database & national HIV cohort data	HIV testing indicated in high-risk groups but not offered (study period)	34	Only LP risk factors given
Scotland (14)	Factors	Hospital	2009-	Newly-	124	National	Failure to	16.3	Only LP

	associated with late diagnosis	ID & GUM service	2014	diagnosed adults		surveillance data & case notes	diagnose HIV within 3 months of IC or ADI presentation (up to 5 years pre-HIV diagnosis)		risk factors given
Spain (15)	Frequency of late diagnosis and associated risk factors	Hospital ID service	2007-2014	Newly-diagnosed adults	354	Medical records	Presentation with IC but no testing offered or testing performed >6 months after symptom onset (up to 1 year pre-HIV diagnosis)	14.5	Only LP risk factors given

Abbreviations: LP, late presenter; ID, infectious diseases; IC, indicator condition; STI, sexually transmitted infection; GP, general practitioner; GUM, genitourinary medicine; ADI, AIDS defining illness; AHD, advanced HIV disease; US, United States; UK, United Kingdom.

Table S2. Reasons for HIV testing in patients diagnosed during acute infection:

Reasons for doing HIV test	**Number of patients with acute infection (%)**
Patient initiated	1 (3.33 %)
Suspicion of acute infection	24 (80%)
AIDS defining illness	1 (3,33 %)
HIV indicator condition	3 (10%)
Epidemiological risk	1 (3,33%)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional 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 **DONE (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **DONE (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **DONE (page 4-5)**
Objectives	3	State specific objectives, including any prespecified hypotheses **DONE (page 5, stated as aims)**
Methods		
Study design	4	Present key elements of study design early in the paper **DONE, (page 7 and 8, stated after definitions to enhance clarity of the paper)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **DONE (page 6)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **DONE (page 7, first paragraph under study design)**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **DONE (outcomes on page 7 second paragraph under study design, definitions for missed opportunities, late presentation and acute HIV on page 6)**
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 **DONE (page 5 under study setting and page 7 under study design)**
Bias	9	Describe any efforts to address potential sources of bias **DONE (page 7 first paragraph under study design, inclusion of all consecutive patients to diminish selection bias)**
Study size	10	Explain how the study size was arrived at **DONE (page 7 first paragraph under study design, second paragraph five year limit also diminishes recall bias due to the absence of a centralized database prior to that date)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **DONE (page 8)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **DONE (page 8)**
		(*b*) Describe any methods used to examine subgroups and interactions NOT APPLICABLE
		(*c*) Explain how missing data were addressed NOT APPLICABLE
		(*d*) If applicable, describe analytical methods taking account of sampling strategy

		NOT APPLICABLE
		(*e*) Describe any sensitivity analyses NOT APPLICABLE
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 **DONE (page 8, results)**
		(b) Give reasons for non-participation at each stage **DONE (page 8 results)**
		(c) Consider use of a flow diagram NOT DONE
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **DONE (page 8, patient characteristics)**
		(b) Indicate number of participants with missing data for each variable of interest NOT APPLICABLE
Outcome data	15*	Report numbers of outcome events or summary measures **DONE (ages 8-10)**
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 **DONE (page 9 and table 1) for Missed Opportunities** **DONE (page 10) for late presentation**
		(*b*) Report category boundaries when continuous variables were categorized **DONE (table 1)**
		(*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 NOT APPLICABLE
Discussion		
Key results	18	Summarise key results with reference to study objectives **DONE (page 10 under discussion)**
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 **DONE (page 13)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **DONE (page 12, page 14)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **DONE (page 12)**
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 (page 14) **DONE**

*Give information separately for exposed and unexposed groups.

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.

BMJ Open

Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis

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Keywords:	missed opportunities, HIV diagnosis, HIV testing, HIV indicator conditions, late presenters

Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis

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Abstract

Objectives: To determine the frequency of missed opportunities (MOs) among patients newly-diagnosed with HIV, risk factors for presenting MOs, and the association between MOs and late presentation to care.

Design: Retrospective analysis

Setting: HIV outpatient clinic at a Swiss tertiary hospital

Participants: Patients aged ≥18 years old newly presenting for HIV care between 2010 and 2015

Measures: Number of medical visits, up to five years preceding HIV diagnosis, at which HIV testing had been indicated, according to Swiss HIV testing recommendations. A visit at which testing was indicated but not performed was considered a MO for HIV testing.

Results

Complete records were available for all 201 new patients of whom 51% were male and 33% from sub-Saharan Africa. Thirty patients (15%) presented with acute HIV infection while 119 patients (59%) were late presenters (LPs) (CD4 counts <350 cells/mm^3 at diagnosis). Ninety-four patients (47%) had presented at least one MO, of whom 44 (47%) had multiple MOs. MOs were more frequent among individuals from sub-Saharan Africa, men who have sex with men, and patients under follow-up for chronic disease. MOs were less frequent in LPs than non-LPs (42.5% versus 57.5%, *P* = 0.03).

Conclusions

At our centre, 47% of patients presented at least one MO. Whilst our late presentation rate is higher than the national figure of 49.8%, LPs were less likely to experience MOs, suggesting that these patients were diagnosed late through presenting late, rather than through being failed by our hospital. We conclude that, in addition to optimising physician-initiated testing, access to testing must be improved among patients unaware they are at HIV risk and who do not seek health care.

Article summary

Strengths and limitations of this study

- We defined the term, 'missed opportunities', currently lacking a consensus definition, based on the Swiss HIV testing recommendations applicable to our institution.
- A centralized database enabled us to examine all patient episodes at our centre, to determine the number and type of missed opportunities.

- We used multivariate logistic regression to show a robust association between patient characteristics and the risk of missed opportunities for HIV testing.
- As with any monocentric study, our findings may not be applicable to all centres in Switzerland, due to differences in hospital structure and local patient population.

Introduction

Late presentation to care among people living with HIV prolongs the period between seroconversion and treatment, and leads to an avoidable increase in morbidity, mortality, health care costs and risk of onward transmission (1). In Europe, even in countries with adequate health care provision and HIV testing recommendations, late presenters (LPs) make up to half of all new HIV diagnoses (2). In Switzerland, while 81% of adults living with HIV in 2012 were estimated to be diagnosed (3), 49.8% of patients diagnosed and enrolled in the Swiss HIV Cohort Study between 2009 and 2012 were LPs, with CD4 counts below 350 cells/mm^3 and/or an AIDS-defining illness at presentation (4).

To maximise early HIV diagnosis, HIV testing recommendations have been published by the Swiss Federal Office of Public Health since 2007 and updated three times (5-8). In 2007, the recommendations introduced *physician-initiated counselling and testing* (PICT), proposing targeted testing and describing HIV testing indications in the text (5). In 2010, testing indications were mentioned in the text and presented as tables (6). Although the term *HIV-associated indicator conditions* (HIV ICs) was not in general use at this time, HIV ICs were included in the 2010 recommendations. In 2013, the recommendations highlighted HIV ICs and introduced HIV screening of patients commencing immunosuppressive therapy (7). It also became medically indefensible to not propose HIV testing to a patient presenting testing indications. In 2015, the content of the recommendations remained similar but the table of symptoms and signs of acute HIV infection was presented first to emphasise this clinical presentation as an indication for HIV testing (8). In summary, apart from the addition of screening of patients commencing immunosuppressive therapy in 2013, the recommendation updates between 2010 and 2015 involved changes in format but not overall content.

The Swiss health care system is based on compulsory individual health insurance coverage, which is regulated at a federal level. It is estimated that >98% of the population has coverage, and access to care is excellent (9). For vulnerable populations, including undocumented migrants, health care is provided through cantonal social services which cover health insurance charges, although not all individuals may be aware of this. We have observed that some vulnerable populations, for example sex workers, use the Emergency Department (ED) as a primary health care facility (10) and that fewer than 98% of patients presenting to the ED have a primary care physician is below 98 (11). Further, Switzerland has among the highest out-of-pocket costs in the Organisation for Economic Co-operation and Development (9). Whilst HIV testing is covered under basic health insurance, costs can be attributed directly to the patient according to their specific health insurance package, or if testing is performed on the demand of the patient, rather than on the recommendation of a physician.

When an individual presents to a health care provider with indications for HIV testing but is not offered a test, this constitutes a missed opportunity (MO) for HIV testing, regardless of his/her serostatus (1). In 2016, several studies were published on MOs in Europe (12-15) and Israel (16) (Supplementary table S1). These studies covered four to seven-year periods between 2007 and 2015 and reported MO rates of 14.5% (15) to 34% (13). Many highlighted the importance of physician awareness of testing indications in reducing MOs (12, 15, 16). Whilst the Swiss PICT recommendations, by definition, emphasise the responsibility of the physician in proposing HIV testing, we have observed that, for example, only 18% of ED doctors in French-speaking Switzerland were aware of the 2010 Swiss Federal Office of Public Health recommendations and that, even if aware, they did not adhere to them (17). In the ED and other services at our centre, these recommendations made no difference to HIV testing rates (18).

The aims of this study were therefore to determine the frequency of MOs among newly-diagnosed patients presenting for care at our outpatient HIV service, and patient risk factors for presenting MOs, and to determine the association between MOs and late presentation to care.

Methods

Ethics Statement

This study was approved by the Ethical Committee on Human Research of the Canton of Vaud, Switzerland (protocol number 2016-00333). Due to the retrospective design, the requirement of patient informed consent was waived.

Patient and Public Involvement Statement

The study being retrospective patients or the public were not involved in the design nor in the conduct of the study.

Study setting

The study was conducted at Lausanne University Hospital, a 1,500-bed teaching hospital which serves as a primary-level community hospital for Lausanne (catchment population 300,000) and as a secondary and tertiary referral hospital for Western Switzerland (catchment population 1-1.5 million). HIV seroprevalence in the region is estimated to be 0.2-0.5% (3, 19). At Lausanne University Hospital, medical records are electronic and include all hospital visits, discharge summaries (inpatients), clinical letters (outpatients) and laboratory reports.

In Switzerland, health insurance is mandatory. Whilst most patients have a primary care physician, individuals may visit a specialist without referral. Outpatient HIV care at Lausanne University Hospital is provided by the Infectious Diseases Service. All patients are invited to be enrolled in the Swiss HIV Cohort Study, a national prospective cohort study with ongoing enrolment since 1988 (20).

Definitions

Late presentation was defined as presenting for care with chronic HIV infection with a CD4 count <350 cells/mm^3, in accordance with the European consensus working group definition (21).

Acute HIV infection was defined as a positive blood HIV-RNA assay or a positive p24 antigen assay with an incomplete Western Blot (22).

The term MO for HIV testing has no consensus definition. For this study, a MO was defined as a visit to Lausanne University Hospital at which HIV testing was indicated but not performed, regardless of the serostatus of the patient. Testing was considered as indicated according to five broad indications, based on the Swiss Federal Office of Public Health 2015 recommendations (8) but present in the recommendations from 2010 onwards: signs and symptoms of acute HIV infection; AIDS-defining illness; HIV ICs (8)(such as herpes zoster, ongoing mononucleosis-like illness or unexplained thrombocytopenia) (23, 24) ; situations in which HIV infection should be excluded (for example, planned immunosuppressive treatment and pregnancy) and epidemiological risk (belonging to or having a sexual partner from a high-risk group: men who have sex with men [MSM], people who inject drugs [PWID] and individuals originating from a high-prevalence region, notably, sub-Saharan Africa) (8)

Since 2013, when it became a legal responsibility for the physician to propose HIV testing when indicated (7), any test offered but refused by the patient has been documented in the medical notes. The situation in which HIV testing was documented as indicated and proposed, but declined by the patient, was therefore not considered as a MO.

Study design

The study retrospectively analysed all patients with newly-diagnosed HIV presenting to the Lausanne University Hospital infectious diseases outpatient clinic from 1st January 2010 to 31st December 2015.

For each patient, the following data were collected: sociodemographic data (age, sex, geographical origin, marital status, risk factor(s) for HIV acquisition); HIV infection data (CD4 count, AIDS defining illness, mode of infection); visits to Lausanne University Hospital during the five years preceding HIV diagnosis (chronic disease with regular follow-up, inpatient and outpatient consultations); and HIV testing data (date of previous negative HIV test as referred to in clinic letters or obtained from the laboratory database, reason for performing diagnostic test, site of diagnostic test). The limit of five years for Lausanne University Hospital visits was selected based on the LP figure of 49.8% of patients newly-enrolled in the Swiss HIV Cohort Study (4), in whom infection was likely to have occurred within five years preceding diagnosis (25), and the observation that, elsewhere in Europe, 59% of new HIV patients exhibited HIV ICs during a similar pre-diagnosis period (26). MOs were identified using medical records and analysed by absolute MO number and by MO category (based on the five groups of HIV testing indications: acute HIV, AIDS defining illness, HIV ICs, test of exclusion and epidemiological risk).

Given the low HIV testing rates observed in the ED at our centre and elsewhere in French-speaking Switzerland (1% of all patients seen) (17, 18), we additionally conducted a search of all pre-diagnosis visits to the ED, using the central hospital database. We focused on ED visits estimated to have occurred after HIV seroconversion based on CD4 cell count at diagnosis, accounting for variations related to age and sex (25). All pre-diagnosis visits were matched with laboratory reports to determine whether HIV testing had been performed. A single pre-diagnosis ED visit after which testing was performed within 72 hours was not considered a MO, to allow for patients admitted prior to the weekend or referred for testing by a designated hospital team, where testing may be delayed in the interest of continuity of care. At the time of this study, rapid HIV testing was not available in the ED and so all HIV tests requested and performed were documented in the laboratory database.

Data and Statistical Analysis

Patient details, stripped of all identifiers, were entered in to a coded database by the study investigators (LL, EM) for each of the six 12-month periods. Categorical data were presented as absolute frequencies and percentages and compared using the Chi squared test; continuous data were presented as means (standard deviation, SD) or medians (interquartile range, IQR) and analysed using the Mann-Whitney U test. Multivariate logistic regression was applied to calculate the adjusted odds ratio for various risk factors for presenting MOs. Data were stratified according to patient demographic, clinical and epidemiological characteristics in order to reduce confounding. Patients with acute HIV infections were excluded from all analyses concerning late presentation.

All analysis was performed using Stata 14.1 (StataCorp LP, Texas, USA).

Results

Patient characteristics

We identified 201 patients newly-presenting for HIV care during the study period, all of whom had complete electronic medical records. Mean age at diagnosis was 38 years ± SD (range 18 to 75 years). Mode of HIV transmission was listed as heterosexual in 57% of patients, MSM in 34%, PWID in 4% and unknown in 5% (Table 1). The majority of patients (59%) had never been HIV tested prior to their diagnostic test.

Missed opportunities (MOs)

In total, 359 separate MOs were presented by 94 patients (47%) during the five years preceding their diagnosis (Figure 1). Considering patients presenting MOs, 74 patients (78%) had presented on more than one visit (range 2 to 17) with a MO of any category. Considering MO categories, 58 patients (62%) had presented a single category of MO, 30 patients had presented two categories (32%) and six patients (6%) had presented three categories. Figure 2 shows the distribution of MO categories by testing indication.

Risk factors for MOs

In multivariate analysis, older patients (aged >50 years) had less risk of presenting MOs than patients aged <30 years (P=0.01), while patients of sub-Saharan African origin (P=0.01), those under regular follow up for chronic illness (P=0.01) and MSM (P=0.02) had increased risk (Table 1). In patients from sub-Saharan Africa and those under regular follow-up for chronic illness, all MO

categories were distributed equally compared to the rest of the population. In contrast, MOs in MSM patients were more frequently related to epidemiological risk (46%) than to other MO categories (33%) (*P*<0.01).

Clinical presentation at diagnosis, site of testing and reason for testing

Most patients (85%) were diagnosed in the chronic phase of infection (Table 2). The median CD4 count at diagnosis was 293 (IQR 147-452). In total, 119 (59%) were LPs. LPs consulted less often to Lausanne University Hospital than non-LPs (mean number of consults 1.4 for LPs versus 2.5 for non-LPs, *P* < 0.01).

A greater proportion of new HIV diagnoses were made in the primary care and outpatient settings than during hospital admission (Table 2). The top three reasons for testing, regardless of testing site, were presence of HIV ICs, epidemiological risk and symptoms and signs of acute HIV infection (Table S2). Acute HIV infection was confirmed in 24 of the 36 patients presenting with symptoms and signs of acute HIV infection (Table S3).

We did not identify any situations in which HIV testing was proposed but declined by the patient.

MOs and late presentation

Multivariate analysis demonstrated a lower risk of late presentation in patients presenting MOs (OR 0.5, 95% 0.2-0.9, *P*<0.01). Indeed, the median CD4 count at diagnosis among MO patients was significantly higher than for non-MO patients (351 cells/mm^3 versus 244 cells/mm^3, *P*<0.01). MOs were less frequent in LPs compared to patients presenting with CD4 > 350 cells/mm^3 (42.5%

versus 57.5%, *P*<0.01). Among subgroups, the LP rate among MSM was lower compared to the rest of the study population (22% versus 78%, *P*<0.001).

MOs in the ED

Of 201 patients, 58 (29%) were identified as having presented to the ED prior to diagnosis, 27 of whom (47%) had presented more than once (range 2-7 visits). All 58 patients had presented within three years preceding their HIV diagnosis and 53 patients (91%) within the preceding 12 months. Although 15 patients (26%) were diagnosed within 72 hours of their most recent ED visit, seven of these had presented to the ED on at least one previous occasion. In total, 50/58 patients (86%) presented to the ED during the interval between seroconversion and diagnosis, none of whom were tested. As with the patient sample as a whole, the two main MO categories for these 58 patients were epidemiological risk and HIV ICs.

Discussion

In this single-centre study, we observed that 47% of 201 patients newly-presenting for HIV care had presented at least one MO for earlier testing. Although thirty patients (15%) were diagnosed during acute infection, nine patients (5%) who presented with symptoms or signs of acute HIV were not tested. Of patients who had visited the ED pre-diagnosis, 86% had presented at least one MO for testing. Finally, MOs occurred significantly less frequently in LPs than in non-LPs.

Our patient population differed from that of Switzerland as a whole (Swiss Federal Office of Public Health HIV notifications) in terms of HIV acquisition risk profile: 57% heterosexual transmission and 34% MSM, compared to 42% heterosexual and 57% MSM (27).

As heterosexual transmission was a risk factor for late presentation in the Swiss HIV Cohort Study by Hachfeld *et al*, this might explain our higher rate of LPs (59%) compared to the Swiss HIV Cohort Study figure of 49.8% (4). A lower Swiss HIV Cohort Study figure through underrepresentation of our patients in the Hachfeld *et al* study is unlikely as the majority were enrolled in the Swiss HIV Cohort Study.

Our analysis showed that patients under regular follow-up for chronic illness, patients from sub-Saharan Africa and MSM were at increased risk for MOs. In patients under regular follow-up, there may be the assumption by the hospital physician that the patient's primary care physician has performed an HIV test and *vice versa* (1). In our institution, we have previously reported suboptimal testing rates among oncology patients, particularly those of non-European origin (28). Among patients with risk factors for HIV acquisition, MOs will occur if there is non-disclosure of at-risk behaviour by the patient and incomplete history taking by the doctor. This was described in a French cross-sectional study of 1,008 patients newly-diagnosed with HIV of whom 48% were MSM (29). Fewer than half the MSM who consulted disclosed being MSM and only 21% of all MSM were offered testing by their health care provider (29). In Switzerland, physicians frequently do not discuss sexual behaviour with their patients, potentially missing such risk factors (30, 31).

Our non-association between LPs and MOs suggests a distinction between 'missed' opportunity and 'no' opportunity. Whilst it is logical that late presentation may result from repeated MOs in positive individuals, LPs do not necessarily present opportunities for earlier testing. If individuals feel well, are unaware of HIV risk factors and/or have poor access to health care, they may have sporadic if any contact with health care systems (4): their late presentation may be their only presentation. However, this interpretation is limited by the fact that we were unable to quantify MOs potentially occurring in primary care.

We have observed in our study that LPs consult less frequently to our hospital. Optimal HIV testing practice is the cornerstone towards attaining the first 90 of the 90-90-90 goal set by the WHO (32). However, even perfect PICT practice cannot eliminate late presentation when physicians can initiate testing only if individuals present to them. It is necessary to reach out to individuals who are at risk of infection but who do not present for health care. HIV testing can be expanded by introducing community-level testing innovations tailored to each community, depending on whether non-presentation is related to lack of awareness of HIV risk factors or symptoms of infection or to lack of awareness of services available. An obstacle to HIV testing in Switzerland is that HIV testing may require expenditure by the patient, even if this is later reimbursed by health insurance. Innovations to improve access to testing include walk-in centres with free testing, testing by non-traditional providers, improving risk perception and tackling stigma (33).

Regarding risk perception, the MO umbrella can be extended from MOs for HIV testing to those for HIV prevention. Whether or not the patients in this sample had HIV at their first few visits to Lausanne University Hospital, they were, by definition, at risk of HIV acquisition. Delivering a prevention message at the time of testing could avert future infection and may also be a means of reaching individuals outside the hospital by dissemination of information. In the ED at our centre, offering non-targeted screening, as recommended in the United States (34) and the United Kingdom (35), would have enabled diagnosis of 86% of the patients of our sample who had presented to this service. Whilst data from our ED are lacking regarding the cost-effectiveness of non-targeted screening per new HIV diagnosis made, the prevention message that comes with screening could reduce onward transmission among contacts in the community.

The MO rates at our centre were higher than those reported in other studies of similarly-sized samples of newly-diagnosed patients presenting for HIV care in European hospital outpatient settings. Tominski *et al* observed a rate of 21% among 270 patients, based

on HIV ICs (12); Noble *et al* observed a rate of 16.3% among 124 patients, based on ICs or AIDS defining illness up to five years pre-diagnosis (14); Gullón *et al* observed a rate of 14.5% among 354 patients, based on ICs up to one year pre-diagnosis (15). As there is no consensus definition of MOs, it is important to examine the criteria for MOs and the time prior to diagnosis examined. In our study, the MO definition was wide, based not only on HIV ICs and AIDS defining illness but also on epidemiological risk, symptoms and signs of acute HIV infection and situations in which HIV should be excluded, and over a period of five years pre-diagnosis. Considering MOs based on HIV ICs and AIDS defining illness alone, our MO rate was 16%. However, applying the most recent HIV testing recommendations, we consider the MO rate obtained according to our study criteria as being a baseline on which to improve. Considering future directions, we plan to apply the findings from this study in several ways. We have piloted rapid testing in the ED by screening patients for HIV risk factors using anonymous electronic tablet-based questionnaires in the waiting area to improve HIV testing in this service (Gilet *et al*, manuscript accepted, PLoS One). The lack of testing among pregnant women who are consulting to terminate their pregnancy is illogical and merits review of obstetric guidelines. Finally, ICs should be mentioned in the practice guidelines of relevant (non-HIV) specialties (23).

This study has limitations. As in any retrospective study, identifying and classifying MOs relied on available clinical documentation. As we reviewed medical notes only from our institution, the number or categories of MO may be prone to bias. The date of the last performed HIV test may also be prone to recall bias. However, whilst the number of included patients was small, complete medical records for each patient ensured data quality. This study examined only MOs occurring in our hospital; using the Lausanne University Hospital database it was not possible to quantify potential MOs occurring in the primary care setting or in other hospitals. We could therefore have underestimated the number of MOs. On the other hand, although we could determine that most diagnostic tests were

made in the primary care setting, this study did not examine the untested patient denominator. As we have no means of quantifying HIV testing performed in the primary care setting, we cannot exclude an overestimation of the number of MOs for our population. Finally, as our study was monocentric, our risk-factor associations with MOs reflect our local patient population. Against these limitations, the non-association between late presentation and MOs observed in our study has important implications for a national testing strategy based on PICT, as many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis.

In conclusion, by defining MOs according to the most recent national HIV testing recommendations, we observe that 47% of the patients newly-presenting for HIV care at our centre could have been tested at an earlier stage. The lower rate of LPs among patients presenting MOs suggests that the PICT approach must now be expanded to reach at-risk communities rather than waiting for these individuals to become sufficiently symptomatic to access care themselves.

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Contributors' statement

Loïc Lhopitallier contributed to study design, data collection, data analysis, manuscript preparation and critical review, Estelle Moulin contributed to study design, data collection and manuscript preparation, Olivier Hugli contributed to manuscript preparation and critical review, Matthias Cavassini contributed to study design and critical review, Katharine Darling contributed to study design, data analysis, manuscript preparation and critical review.

Data sharing statement

Extra data can be accessed via the Dryad data repository at doi:10.5061/dryad.8jf67k4

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Figures legend

Figure 1. Histogram showing the percentage of MOs occurring during the five years preceding diagnosis in adult patients newly presenting for HIV care between 2010 and 2015 in Lausanne, Switzerland.

Figure 2. Pie chart showing the distribution of the categories of missed opportunities (MOs) experienced between 2010 in adult patients newly presenting for HIV care in Lausanne, Switzerland.

Table 1. Demographic characteristics of adult patients newly presenting to HIV care in Lausanne, Switzerland between 2010 and 2015 who had not presented any missed opportunity and who had presented at least one missed opportunity

Demographic characteristic	All patients (n = 201)	Patients with no MO (n = 107)	Patients with ≥1 MO (n = 94)	Univariate analysis (OR ±95% CI)	Multivariate analysis (adjusted OR ±95% CI; *P-value*)
Age (years), n (%)					
18-29	56	23 (41%)	33 (59%)	*Ref value*	
30-49	112	59 (53%)	53 (47%)	0.6 (0.3 – 1.2)	0.5 (0.3 – 1.1; 0.08)
>50	33 (	25 (76%)	8 (24%)	0.2 (0.1 – 0.6)	0.2 (0.1 – 0.6; <0.01)
Sex, n (%)[1]					
Male	126	66 (52%)	60 (48%)	*Ref value*	
Female	75	41 (55%)	34 (45%)	1.09 (0.6 - 1.9)	0.7 (0.3 – 1.5; 0.36)
Geographical Origin, n (%)					
Europe, North America, Australasia	106	58 (55%)	48 (45%)	*Ref value*	
Sub-Saharan Africa	66	32 (49%)	34 (51%)	1.2 (0.7 – 2.4)	3.5 (1.3 – 7.7; 0.01)
Other[2]	29	17 (59%)	12 (41%)	0.9 (0.4 – 2.0)	1.0 (0.4 – 2.5; 0.96)
Chronic Illness, n (%)					
No	161)	92 (57%)	69 (43%)	*Ref value*	
Yes	40	15 (37%)	25 (63%)	2.2 (1.1-4.5)	4.4 (1.7 – 10.9, <0.01)

Mode of transmission, n (%)					
Heterosexual	114	67 (59%)	47 (41%)	*Ref value*	
MSM	68	29 (43%)	39 (57%)	1.91 (1.0 – 3.5)[3]	4 (1.5 – 10.7; 0.01)
PWID	9	3 (33%)	6 (67%)	2.8 (0.7 – 12)	2.9 (0.6 – 15.3;0.20)
Unknown	10	8 (80%)	2 (20%)	0.3 (0.7 – 1.8)	0.3 (0.1 – 1.8;0.2)
Time since previous HIV test, n (%)					
No previous test	119)	72 (61%)	47 (39%)	*Ref value*	
≤1 year	28	12 (43%)	16 (57%)	2.0 (0.9 – 4.7)	1.6 (0.6 -4.3; 0.38)
>1 year ago	54	23 (43%)	31 (57%)	2.0 (1.0 – 4.0)[3]	1.4 (0.7 – 3.0; 0.31)

Abbreviations: MO, missed opportunity; MSM, men who have sex with men; PWID, people who inject drugs.

[1]There were no transgender patients in the group studied.

[2]Asia, South America, North Africa, Middle East.

[3]*P*-value < 0.05.

Table 2. Clinical presentation, site of testing and reason for testing at time of diagnostic HIV test among all patients presenting to care for a newly diagnosed HIV infection between 2010 and 2015 in Lausanne, Switzerland.

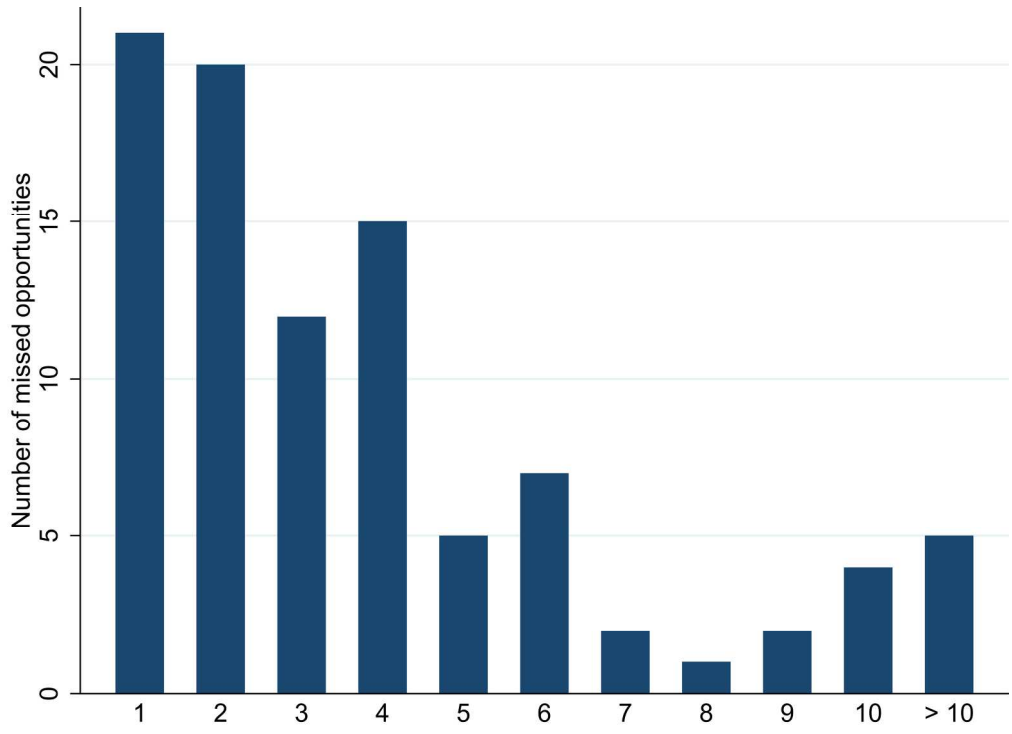
	Number of patients, n (%)
Clinical presentation	
Acute HIV infection	30 (15%)
Chronic HIV infection:	
CD4 count > 350 cells/mm^3	65 (32%)
Late Presenters (< 350 cells/mm^3)	44 (22%)
Advanced Disease (< 200 cells/mm^3)	62 (31%)
Site of diagnostic HIV test	
Primary care	
Primary care physician	64 (32%)
Anonymous consultation	26 (13%)
Lausanne University Hospital	
Outpatient care	41 (20%)
Inpatient care	17 (8%)
Emergency Department	4 (2%)
Gynaecology/Obstetrics	16 (8%)
Infectious diseases service	5 (3%)
Other	28 (14%)
Reason for testing	
HIV indicator condition	59 (29%)
Epidemiological risk	42 (21%)
Symptoms / signs of acute HIV infection	36 (18%)
AIDS-defining illness	21 (10%)
Pregnancy	14 (7%)
Prior to immunosuppressive treatment	1 (1%)
Patient-initiated	28 (14%)

References

1. Darling KE, Hachfeld A, Cavassini M, Kirk O, Furrer H, Wandeler G. Late presentation to HIV care despite good access to health services: current epidemiological trends and how to do better. Swiss Med Wkly. 2016;146:w14348.
2. Mocroft A, Lundgren JD, Sabin ML, Monforte A, Brockmeyer N, Casabona J, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med. 2013;10(9):e1001510.
3. Kohler P, Schmidt AJ, Cavassini M, Furrer H, Calmy A, Battegay M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS. 2015;29(18):2509-15.
4. Hachfeld A, Ledergerber B, Darling K, Weber R, Calmy A, Battegay M, et al. Reasons for late presentation to HIV care in Switzerland. J Int AIDS Soc. 2015;18(1):20317.
5. Office fédéral de la santé publique. Dépistage du VIH et conseil initiés par les médecins. https://www.bag.admin.ch/bag/fr/home.html. Bulletin de l'OFSP. 2007;21:371-3.
6. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins: recommandations pour les patients adultes. https://www.bag.admin.ch/bag/fr/home.html Bulletin de l'OFSP. 2010(11/10):364-6.
7. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins en présence de certaines pathologies (maladies évocatrices d'une infection à VIH) https://www.bag.admin.ch/bag/fr/home.html. Bulletin de l'OFSP 2013:1-5.
8. Office fédéral de la santé publique. Dépistage du VIH effectué sur l'initiative des médecins https://www.bag.admin.ch/bag/fr/home.html Bulletin de l'OFSP. 2015;21:237-41.
9. Biller-Andorno N, Zeltner T. Individual Responsibility and Community Solidarity--The Swiss Health Care System. N Engl J Med. 2015;373(23):2193-7.
10. Darling KE, Gloor E, Ansermet-Pagot A, Vaucher P, Durieux-Paillard S, Bodenmann P, et al. Suboptimal access to primary healthcare among street-based sex workers in southwest Switzerland. Postgrad Med J. 2013;89(1053):371-5.
11. De Rossi N, Dattner N, Cavassini M, Peters S, Hugli O, Darling KEA. Patient and doctor perspectives on HIV screening in the emergency department: A prospective cross-sectional study. PLoS One. 2017;12(7):e0180389.
12. Tominski D, Katchanov J, Driesch D, Daley MB, Liedtke A, Schneider A, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. HIV Med. 2016.
13. Joore IK, Reukers DF, Donker GA, van Sighem AI, Op de Coul EL, Prins JM, et al. Missed opportunities to offer HIV tests to high-risk groups during general practitioners' STI-related consultations: an observational study. BMJ Open. 2016;6(1):e009194.
14. Noble G, Okpo E, Tonna I, Fielding S. Factors associated with late HIV diagnosis in North-East Scotland: a six-year retrospective study. Public Health. 2016;139:36-43.
15. Gullon A, Verdejo J, de Miguel R, Gomez A, Sanz J. Factors associated with late diagnosis of HIV infection and missed opportunities for earlier testing. AIDS care. 2016;28(10):1296-300.

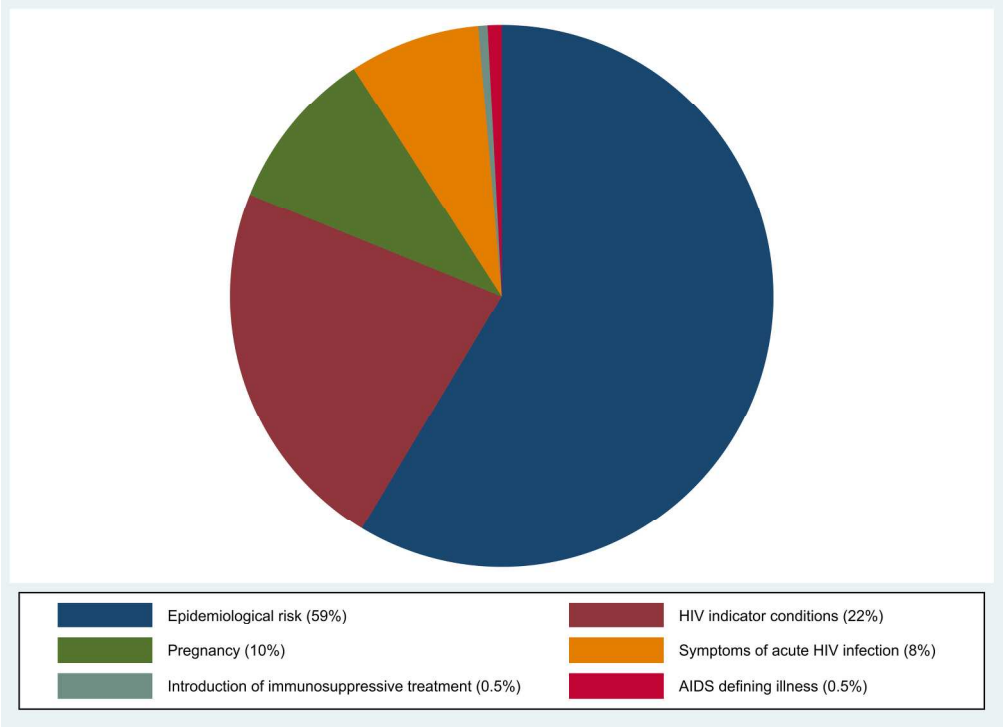
16. Levy I, Maor Y, Mahroum N, Olmer L, Wieder A, Litchevski V, et al. Missed opportunities for earlier diagnosis of HIV in patients who presented with advanced HIV disease: a retrospective cohort study. BMJ Open. 2016;6(11):e012721.
17. Darling KE, de Allegri N, Fishman D, Kehtari R, Rutschmann OT, Cavassini M, et al. Awareness of HIV testing guidelines is low among Swiss emergency doctors: a survey of five teaching hospitals in French-speaking Switzerland. PLoS One. 2013;8(9):e72812.
18. Darling KE, Hugli O, Mamin R, Cellerai C, Martenet S, Berney A, et al. HIV Testing Practices by Clinical Service before and after Revised Testing Guidelines in a Swiss University Hospital. PLoS One. 2012;7(6):e39299.
19. UNAIDS epidemiology figures 2013: Switzerland http://www.unaids.org/sites/default/files/epidocuments/CHE.pdf2013 [
20. Swiss HIV Cohort Study, Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, Furrer H, Yerly S, Francioli P. Cohort profile: the Swiss HIV Cohort study. Int J Epidemiol. 2010;39(5):1179-89.
21. Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al. Late presentation of HIV infection: a consensus definition. HIV Med. 2011;12(1):61-4.
22. Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS. 2003;17(13):1871-9.
23. Lord E, Stockdale AJ, Malek R, Rae C, Sperle I, Raben D, et al. Evaluation of HIV testing recommendations in specialty guidelines for the management of HIV indicator conditions. HIV Med. 2017;18(4):300-4.
24. Sullivan AK, Raben D, Reekie J, Rayment M, Mocroft A, Esser S, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). PLoS One. 2013;8(1):e52845.
25. Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 Cells/mm(3): assessment of need following changes in treatment guidelines. Clin Infect Dis. 2011;53(8):817-25.
26. Joore IK, Arts DL, Kruijer MJ, Moll van Charante EP, Geerlings SE, Prins JM, et al. HIV indicator condition-guided testing to reduce the number of undiagnosed patients and prevent late presentation in a high-prevalence area: a case-control study in primary care. Sex Transm Infect. 2015;91(7):467-72.
27. Office fédéral de la santé publique. Statistiques, analyses et tendances VIH/IST http://www.bag.admin.ch/hiv_aids/05464/12908/12909/12913/index.html?lang=fr2014 [
28. Merz L, Zimmermann S, Peters S, Cavassini M, Darling KE. Investigating Barriers in HIV-Testing Oncology Patients: The IBITOP Study, Phase I. Oncologist. 2016;21(10):1176-82.
29. Champenois K, Cousien A, Cuzin L, Le Vu S, Deuffic-Burban S, Lanoy E, et al. Missed opportunities for HIV testing in newly-HIV-diagnosed patients, a cross sectional study. BMC Infect Dis. 2013;13:200.
30. Dubois-Arber F, Meystre-Agustoni G, Andre J, De Heller K, Alain P, Bodenmann P. Sexual behaviour of men that consulted in medical outpatient clinics in Western Switzerland from 2005-2006: risk levels unknown to doctors? BMC Public Health. 2010;10:528.
31. Meystre-Agustoni G, Jeannin A, de Heller K, Pecoud A, Bodenmann P, Dubois-Arber F. Talking about sexuality with the physician: are patients receiving what they wish? Swiss Med Wkly. 2011;141:w13178.

32. Fauci AS, Marston HD. Ending the HIV-AIDS Pandemic--Follow the Science. N Engl J Med. 2015;373(23):2197-9.
33. Bath R, O'Connell R, Lascar M, Ferrand R, Strachan S, Matin N, et al. TestMeEast: a campaign to increase HIV testing in hospitals and to reduce late diagnosis. AIDS Care. 2015:1-4.
34. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. Morbidity & Mortality Weekly Report Recommendations & Reports. 2006;55(RR-14):1-17; quiz CE1-4.
35. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. UK National Guidelines for HIV Testing 2008. http://www.bhiva.org/documents/Guidelines/Testing/GlinesHIVTest08.pdf 2008.



Histogram showing the percentage of MOs occurring during the five years preceding diagnosis in our patient population. As 94 patients presented MOs, the percentage values shown are similar to patient numbers.

101x73mm (600 x 600 DPI)



Pie chart showing the distribution of the categories of missed opportunities (MOs) experienced during this time, with percentages in each case.

101x73mm (600 x 600 DPI)

Table S1. Recent studies examining missed opportunities (MOs) in persons newly-diagnosed with HIV, listed in alphabetical order of the country of study.

Country	Study focus	Setting	Study period	Subjects analysed	Subject number	Data source	MO definit (time perio examined)
Germany (12)	Characteristics of LPs & % of MOs	Hospital ID service	2009-2013	Newly-diagnosed adults presenting late (CD4 count < 350 cells/mm^3)	270	Medical records	Presentatio with documente HIV IC but testing offe (not stated)
Israel (16)	MOs for earlier diagnosis in patients presenting with advanced HIV disease (AHD, CD4 count < 200 cells/mm^3)	Hospital	2010-2015	Patients with AHD	57 of 356 new HIV diagnoses	Medical insurer electronic data files and patient interviews	Patient presenting 2 out of: -IC -belonging risk group -US(34) or UK(36) indications testing (up to 5 ye pre-HIV diagnosis)
Netherlands (13)	HIV testing offered to high risk groups during STI-related GP consultations	Sentinel general practices	2008-2013	STI-related consults with high-risk groups	3209	GP report database & national HIV cohort data	HIV testing indicated in high-risk groups but offered (study perio
Scotland (14)	Factors associated with late diagnosis	Hospital ID & GUM service	2009-2014	Newly-diagnosed adults	124	National surveillance data & case notes	Failure to diagnose H within 3 months of I or ADI presentatio (up to 5 ye pre-HIV diagnosis)
Spain (15)	Frequency of late diagnosis and associated risk factors	Hospital ID service	2007-2014	Newly-diagnosed adults	354	Medical records	Presentatio with IC but testing offe or testing performed months aft symptom onset (up t year pre-H diagnosis)

Abbreviations: LP, late presenter; ID, infectious diseases; IC, indicator condition; STI, sexually transmitted infection; GP, general practitioner; GUM, genitourinary medicine; ADI, AIDS defining illness; AHD, advanced HIV disease; US, United States; UK, United Kingdom.

Table S2. Categories of prior missed opportunities (MOs) and site of eventual diagnostic test among the 94 patients newly presenting to HIV care between 2010 and 2015 in Lausanne, Switzerland and who had presented at least one MO prior to diagnosis.

Site of diagnostic test / **MO type**	All sites	Primary care physician	Anonymous testing	LUH OP	LUH IP	ED	Gyn / Ob
HIV indicator condition	32	5	5	9	4	0	2
Epidemiological risk	84	22	10	27	6	0	4
Acute HIV	11	2	2	2	1	0	0
AIDS-defining event	1	0	0	0	0	0	0
Pregnancy	7	2	0	2	1	0	2
Pre-immunosuppressive treatment	1	1	0	0	0	0	0
Total	136	32	17	40	12	0	8

Abbreviations: MO, missed opportunity; LUH, Lausanne University Hospital; OP, outpatient; IP, inpatient

Table S3. Reasons for HIV testing in patients with acute infection newly presenting to HIV care between 2010 and 2015 in Lausanne, Switzerland:

Reasons for doing HIV test	**Number of patients with acute infection (%)**
Patient initiated	1 (3.33 %)
Suspicion of acute infection	24 (80%)
AIDS defining illness	1 (3,33 %)
HIV indicator condition	3 (10%)
Epidemiological risk	1 (3,33%)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional 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 **DONE (page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **DONE (page 2)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **DONE (page 4-5)**
Objectives	3	State specific objectives, including any prespecified hypotheses **DONE (page 5, stated as aims)**
Methods		
Study design	4	Present key elements of study design early in the paper **DONE, (page 7 and 8, stated after definitions to enhance clarity of the paper)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **DONE (page 6)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **DONE (page 7, first paragraph under study design)**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **DONE (outcomes on page 7 second paragraph under study design, definitions for missed opportunities, late presentation and acute HIV on page 6)**
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 **DONE (page 5 under study setting and page 7 under study design)**
Bias	9	Describe any efforts to address potential sources of bias **DONE (page 7 first paragraph under study design, inclusion of all consecutive patients to diminish selection bias)**
Study size	10	Explain how the study size was arrived at **DONE (page 7 first paragraph under study design, second paragraph five year limit also diminishes recall bias due to the absence of a centralized database prior to that date)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **DONE (page 8)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **DONE (page 8)**
		(*b*) Describe any methods used to examine subgroups and interactions NOT APPLICABLE
		(*c*) Explain how missing data were addressed NOT APPLICABLE
		(*d*) If applicable, describe analytical methods taking account of sampling strategy

		NOT APPLICABLE
		(*e*) Describe any sensitivity analyses NOT APPLICABLE
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 **DONE (page 8, results)**
		(b) Give reasons for non-participation at each stage **DONE (page 8 results)**
		(c) Consider use of a flow diagram NOT DONE
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **DONE (page 8, patient characteristics)**
		(b) Indicate number of participants with missing data for each variable of interest NOT APPLICABLE
Outcome data	15*	Report numbers of outcome events or summary measures **DONE (ages 8-10)**
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 **DONE (page 9 and table 1) for Missed Opportunities** **DONE (page 10) for late presentation**
		(*b*) Report category boundaries when continuous variables were categorized **DONE (table 1)**
		(*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 NOT APPLICABLE
Discussion		
Key results	18	Summarise key results with reference to study objectives **DONE (page 10 under discussion)**
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 **DONE (page 13)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **DONE (page 12, page 14)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **DONE (page 12)**
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 (page 14) **DONE**

*Give information separately for exposed and unexposed groups.

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.