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Late presentation to HIV care despite good access to health services: current epidemiological trends and how to do better

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Summary

In 2014, there were 36.9 million people worldwide living with human immunodeficiency virus (PLWH), of whom 17.1 million did not know they were infected. Whilst the number of new human immunodeficiency virus (HIV) infections has declined globally since 2000, there are still regions where new infection rates are rising, and diagnosing HIV early in the course of infection remains a challenge.

Late presentation to care in HIV refers to individuals newly presenting for HIV care with a CD4 count below 350 cells/µl or with an acquired immune deficiency syndrome (AIDS)-defining event. Late presentation is associated with increased patient morbidity and mortality, healthcare costs and risk of onward transmission by individuals unaware of their status. Further, late presentation limits the effectiveness of all subsequent steps in the cascade of HIV care. Recent figures from 34 countries in Europe show that late presentation occurs in 38.3% to 49.8% of patients newly presenting for care, depending on region. In Switzerland, data from patients enrolled in the Swiss HIV Cohort Study put the rate of late presentation at 49.8% and show that patients outside established HIV risk groups are most likely to be late presenters. Provider-initiated testing needs to be improved to reach these groups, which include heterosexual men and women and older patients. The aim of this review is to describe the scale and implications of late presentation using cohort data from Switzerland and elsewhere in Europe, and to highlight initiatives to improve early HIV diagnosis. The importance of recognising indicator conditions and the potential for missed opportunities for HIV testing is illustrated in three clinical case studies.

Key words: *HIV testing; late presentation; missed opportunities*

Introduction

One of the United Nations Sustainable Development Goals for health is to end the HIV epidemic by 2030 [1]. To achieve this, the Joint United Nations Programme on HIV/AIDS (UNAIDS) set out the target that 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy (ART) and 90% of all people receiving ART will have HIV viral suppression by 2020 [1]: in other words, 90% diagnosed, 90% treated and 90% suppressed. So far, Switzerland is close to reaching this target: of 15 200 people estimated to be living with HIV in Switzerland in 2012, 12 300 (81%) were diagnosed, 10 800 (88% of those diagnosed) were receiving ART and 10 400 (96% of those receiving ART) were reported to have suppressed HIV RNA [2, 3]. Although diagnosing HIV infection is important as the first step in the 90-90-90 target, diagnosis *per se* is no longer enough. We now have evidence that early diagnosis optimises patient outcome, and that patients benefit from ART even at higher CD4 counts (>350 cells/µl) [4, 5]. Conversely, failure to diagnose HIV early is associated, on a patient level, with increased morbidity and mortality [6] and, on a public level, with increased healthcare costs [7, 8] and risk of onward transmission [9]. Of new HIV diagnoses made in the past decade in Switzerland, 49.8% were in individuals already at the stage of late presentation [10].

Over the last three decades, the epidemiology of HIV infection in industrialised countries has changed. In the pre-ART era, new HIV infections were most frequently in three classical risk groups: men who have sex with men (MSM), people who inject drugs (PWID) and individuals with sexual partners from regions of high HIV prevalence, notably sub-Saharan Africa. The current epidemic is driven by MSM and heterosexual transmission. Among 519 new HIV infections reported in 2014 in Switzerland, these groups accounted for 57% and 42% of cases, respectively, while PWID accounted for 2% (rounded figures) [11]. Individuals not from classical risk groups account for fewer new HIV infections overall but may be at greater risk of presenting late because they are not offered HIV testing by healthcare providers or because they do not consider themselves

at risk. In order to facilitate early HIV diagnosis, a number of indicator diseases have been identified. These are conditions either caused by infections which share routes of transmission with HIV or favoured by immune deficiency, in which HIV prevalence is sufficiently high to make testing cost-effective [12, 13]. In addition, certain serious non-AIDS (SNA) conditions, such as cardiovascular, renal and liver disease, and non-AIDS-defining malignancy, have been observed to occur more frequently in PLWH than in HIV-negative individuals [14]. As individuals with HIV and an SNA event have a risk of death more than six times greater than that among individuals without an SNA event, the association between SNA events and HIV is important to recognise.

This review will focus on late presentation in individuals who have adequate access to healthcare but who miss being diagnosed with HIV early in the infection. In this way, the late presentation epidemiology and risk factors presented come from Swiss and European cohort data rather than from those of resource-poor settings. Indicator conditions and SNA events now included in the Swiss HIV testing recommendations are presented, together with three case studies to highlight how linking these to possible HIV infection can avoid missed opportunities for early HIV testing.

Case study 1

A 32-year-old man, previously well, presents to his general practitioner (GP) complaining of persistent diarrhoea associated with weight loss, fatigue and low-grade fever. He is married with children and has no travel history of note. He is referred for investigations and seen in two separate hospital gastroenterology departments and a private gastroenterology clinic. During the subsequent two years, multiple diagnostic procedures are performed: two gastroscopies, three colonoscopies, one capsule endoscopy of the small bowel, one magnetic resonance imaging (MRI) scan, one abdominal computed tomography (CT) scan, two abdominal ultrasounds and multiple stool cultures, serology tests and autoantibody screens. These demonstrate intra-abdominal lymphadenopathy, histiocytic colitis, gastritis and reflux oesophagitis; worm-like structures are found on capsule endoscopy but no pathogens are identified on stool microscopy or culture. In the absence of a conclusive diagnosis, he receives several courses of steroids, mesalazine, antibiotics and anti-helminth treatments without resolution of the diarrhoea. Two years after the start of his symptoms, he self-presents to request anonymous HIV-testing and the test is positive. On direct questioning, he reports long-standing regular unprotected sex with men. The CD4 count is 34 (4%) and HIV RNA viral load is 300 000 copies/ml at diagnosis. By this time, the patient reports a weight loss of 25 kg and has cervical lymphadenopathy. Gastrointestinal and biliary tract cryptosporidiosis is subsequently identified.

Methods

We conducted a literature search using PubMed, entering the following key words separately or in combination: “late”, “late presenter”, “late presentation”, “missed opportunities”, “HIV”, “HIV testing”, “Switzerland”, “Europe”. The case studies presented were selected from those encountered at our two centres within the last five years.

Late presentation: definition and context

According to the European Late Presenter Consensus Working Group definition published in 2011, late presentation for HIV care refers to individuals presenting for care with a CD4 count below 350 cells/µl, or with an AIDS-defining event regardless of the CD4 cell count [15]. Having this definition allows comparison of surveillance data and standardises the way that late presentation risk factors are identified across different settings. Late presentation figures in turn are indicators of the success of HIV testing strategies. Although the updated European AIDS Clinical Society HIV treatment guidelines now state that ART should be considered in all patients regardless of CD4 count [4, 5], the limit of 350 cells/µl to define late presentation remains unchanged at present. Despite some criticisms of the consensus definition [16], it is the definition used in this review.

Late presentation can be separated into: late HIV diagnosis, which reflects the disease stage at the initial positive HIV test; and delayed presentation for HIV care, which reflects the time elapsed between initial HIV diagnosis and initial presentation for HIV medical care [17]. In Europe, less than 10% of late presentation is believed to result from delayed presentation for HIV care post-diagnosis [6, 10].

The term “missed opportunities” in the context of late presentation refers to the situation where an individual has risk factors for HIV acquisition or presents to a healthcare provider with symptoms or signs suggestive of HIV infection, but is not offered a test [18].

Approaches to HIV testing

HIV testing is key in diagnosing HIV early and reducing late presentation. Three broad approaches to HIV testing exist: diagnostic testing, performed when a patient presents with symptoms or signs suggestive of HIV infection; targeted testing, offered to patients with HIV risk factors; and non-targeted testing, which is a screening approach in patients who are symptom free. In 2006, the Centers for Control and Prevention of Diseases recommended non-targeted HIV testing of all individuals aged 13 to 64 attending a healthcare system in areas where local HIV seroprevalence is ≥0.1% [19]. In 2008, the British HIV Association published HIV testing guidelines recommending routine (non-targeted) testing for all individuals at GP registration or hospital admission in areas where local HIV seroprevalence is ≥0.2% [20]. In 2011, this recommendation was incorporated into the National Institute for Health and Care Excellence (NICE) guidelines to increase HIV testing among individuals at higher risk of exposure (in MSM and sub-Saharan African communities) [21, 22].

In Switzerland, where seroprevalence is 0.2 to 0.4% [2, 23], the Federal Office of Public Health (FOPH) published HIV testing recommendations in 2007 [24], 2010 [25], 2013 [26] and 2015 [27]. These propose Physician-Initiated

Counselling and Testing (PICT), which is diagnostic, targeted and requires oral patient consent [27]. At Lausanne University Hospital, no difference in HIV testing rates was observed in inpatient or outpatient clinical services following publication of the 2010 FOPH recommendations [28]. One explanation might have been low awareness of these recommendations among clinicians. Only 18% of emergency department doctors working in hospitals in French-speaking Switzerland were aware of the recommendations [29].

Following the 2010 recommendations, the results of the HIV Indicator Diseases in Europe Study I (HIDES I), a European multicentre study of 3588 individuals in 14 countries across Europe (excluding Switzerland) were published [13]. HIDES I examined eight indicator diseases to identify those with HIV prevalence over 0.1%, a threshold shown to be cost-effective for HIV testing [30, 31]. All eight indicator diseases (shown with an asterisk in table 1) fulfilled the >0.1% criterion for cost-effectiveness. Importantly, HIV prevalence exceeded the 0.1% target even among individuals presenting with an indicator disease who were not from high-risk groups. The indicator diseases were added to the testing indications listed in the updated FOPH testing recommendations of 2013 and 2015 [26, 27]. Other conditions, in which not diagnosing HIV would adversely affect patient management, were also added to these recommendations and are shown in table 2.

Although indicator conditions enable targeted testing before individuals present with an AIDS-defining event, they do not facilitate testing among PLWH who are asymptomatic, who consult healthcare providers for reasons unrelated to HIV and who do not disclose risk factors. Taking a focused sexual history to elicit risk factors depends on the individual volunteering accurate details. The non-targeted approach is the only way to test asymptomatic individuals without discussing risk factors. However, several barriers to HIV testing exist and relate to policy structure, healthcare providers and patients [32, 33]. Knowledge of the testing barriers specific to each setting enables optimisation of testing strategies prior to their implementation (De Rossi et al., unpublished data). Community HIV testing campaigns, such as offering HIV testing on World AIDS Day [34], can explore new testing models. By promoting the normalisation of testing and reducing stigma, they can also circumvent some policy- and physician-related testing barriers whilst expanding testing uptake [34].

Late presentation: epidemiology and risk factors

The most recent late presentation figures for Switzerland come from 1366 patients enrolled in the Swiss HIV Cohort Study (SHCS) between 2009 and 2012. In this study by Hachfeld et al., late presentation occurred in 49.8% of patients presenting for HIV care with variation between SHCS centres, from 44.4% in Zurich to 58.6% in Basel [10]. Late presentation was more frequent among women and individuals from sub-Saharan Africa and less frequent among highly-educated individuals and MSM. The main patient-related reasons for late testing were: not feeling at risk (72%), not feeling ill (65%) and not knowing the symptoms of HIV (51%). In a single-centre study of 281 patients presenting for HIV care between 2009 and 2011 in Zurich, the late presentation rate was 45% [35]. Risk factors for late presentation in this study included older age (odds ratio 3.16 for age ≥50 years vs <30 years), Asian versus Caucasian ethnicity and being a heterosexual man in a stable partnership [35].

The largest European analyses come from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE), which includes Swiss data. Among 84 524 HIV-positive individuals from 23 countries in Europe presenting for HIV care between 2000 and 2011, late presentation occurred in 53.8% of patients but decreased over the study period from 57.3% in 2000 to 51.7% in 2010/11 [6]. In this study, late presentation was highest in heterosexual men (66.1%), individuals treated in southern European countries (57.0%) and individuals from Africa (65.1%). Factors associated with late presentation included older age and being of non-European origin [6]. Two other national cohorts reported late presentation associations similar to those reported in Switzerland [10, 35]. In the national observational HIV cohort of the Netherlands (ATHENA), late presentation was examined in 20 965 HIV-infected patients under care at 27 HIV treatment

Table 1: Diseases in which the prevalence of undiagnosed human immunodeficiency virus (HIV) infection is probably greater than 0.5%: HIV testing should be recommended. (This is Table 2b of the FOPH 2015 HIV testing recommendations [27].)

Oral hairy leucoplakia	Dermatitis / seborrhoeic rash*
Sexually transmitted infections*	Invasive pneumococcal disease
Hepatitis B or C (acute or chronic)*	Candidaemia
Unexplained lymphadenopathy	Visceral leishmaniasis
Unexplained leukocytopenia/ thrombocytopenia persisting for >4 weeks*	Peripheral neuropathy of unknown origin
Severe or atypical psoriasis	Guillain-Barré syndrome
Lymphoma*	Mononeuritis
Lung carcinoma	Sub-cortical dementia
Anal carcinoma/dysplasia*	Multiple sclerosis-like disease
Cervical dysplasia*	Unexplained weight loss
Herpes zoster in an individual <50 years old*	Unexplained oral candidiasis
Unexplained chronic renal impairment	Unexplained chronic diarrhoea
* The eight indicator diseases from HIDES I	

Table 2: Conditions in which not identifying the presence of human immunodeficiency virus (HIV) infection may have significant adverse implications for the individual's clinical management. (This is Table 2c of the FOPH 2015 HIV testing recommendations together with indicator conditions listed in the Guidance for Implementing HIV Testing in Adults in Health Care Settings published by HIV in Europe, http://newsite.hiveurope.eu/Portals/0/Guidance.pdf.)

Conditions requiring aggressive immunosuppressive therapy:
Cancer
Transplantation
Autoimmune disease treated with immunosuppressive therapy
Primary space occupying lesion of the brain
Idiopathic/thombotic thombocytopenic purpura
Other conditions:
Tuberculosis Recurrent pneumonia Pregnancy

centres between 1996 and 2014 [36]. Although the rate of late presentation decreased over time from 62% (1996) to 42% (2013), it did not decline significantly among heterosexual men and women. In Sweden, Brannstrom et al. reported late presentation in 58% of 575 newly HIV-diagnosed patients and late presentation was higher in heterosexuals (67%) than in PWID (43%) or MSM (40%). Late presentation risk factors included being older than 30 years, originating from sub-Saharan Africa, Eastern Europe, Asia and the Pacific region, and acquiring HIV in sub-Saharan Africa [37].

In summary, the late presentation rates in Switzerland and the rest of Europe vary with region and risk population, from around 40 to 67%, and risk factors are similar, involving older individuals, heterosexual men and women, and those of non-European origin.

A foot note on late presentation epidemiology

Although individuals from regions of high HIV prevalence are not the focus of this review, this group can be highly vulnerable and often without access to health care, particularly when arriving in a new country and without documentation [38, 39]. Whilst many regions worldwide, including sub-Saharan Africa, have experienced a reduction in the number of new HIV infections since 2000 [1], four regions report a rise in HIV acquisition between 2000 and 2014: North Africa, the Middle East, Central Asia and Eastern Europe [1]. In the latter part of this period, there has been large-scale human displacement with people travelling from, or via, these regions to reach Europe [40]. Increasing data suggest that migrants from regions of high HIV prevalence do not necessarily arrive in Europe with HIV but can acquire the infection through assortative sexual mixing some months or years after arrival [41]. A description of late presentation epidemiology in Europe would therefore be incomplete without considering the combined effect that these three processes – increasing new HIV infections, human migration and post-migration HIV acquisition – may have on HIV epidemiology in Switzerland and the rest of Europe in the future.

Missed opportunities for HIV testing

Case study 2

A 38-year-old woman is followed intermittently by her GP for hypertension. Two years after joining the practice, a routine blood test shows a mild normochromic normocytic anaemia with a slightly raised erythrocyte sedimentation rate. Two years later, she is admitted to hospital with a basal pneumonia complicated by a pleural effusion requiring drainage. CT reveals an ovarian cyst and she is referred to the gynaecology department. She is found to have high-grade superficial intraepithelial lesions of the cervix and cervical intraepithelial neoplasia, for which she receives treatment and outpatient follow-up over 6 months. At this point, the aetiology of the anaemia remaining unclear, she is referred for a colonoscopy (normal) and upper gastrointestinal endoscopy, which shows florid oesophageal candidiasis. The gastroenterologist performs an HIV test which is positive. CD4 count is 30 (3%) and HIV RNA viral load is 51 000 copies/ml at diagnosis.

Case study 3

A 67-year-old man lives in the Middle East and Switzerland, where he has been followed up for 3 years for peripheral vascular disease complicated by intermittent lower limb soft tissue infection. He has insulin-requiring type 2 diabetes, chronic renal insufficiency secondary to diabetes and hypertension, and is on thyroid replacement therapy. He now presents with lower limb cellulitis and confusion. Blood cultures grow *Staphylococcus aureus*. The patient develops signs of cauda equina syndrome. Spinal MRI reveals multifocal discitis and a compressive lumbar epidural abscess that requires surgical drainage. While conducting the preoperative work-up, the attending doctor suffers a needle-stick injury. An HIV test is performed with the patient's consent, in accordance with hospital protocol. The test is positive. CD4 count is 330 (18%) and HIV RNA viral load is 370 000 copies/ml at diagnosis.

Comment on the case studies

The three case studies describe missed opportunities for earlier HIV diagnosis in patients of European origin who had risk factors for late presentation according to the cohort studies presented here. In the study by Hachfeld et al., 71% of the 1366 participants were symptomatic during the year preceding their HIV diagnosis and the majority had presented to a healthcare provider. A study of 1008 adults living in France, newly diagnosed with HIV infection between 2009 and 2010, reported that 99% had presented to a health care setting and 89% had seen a GP at least once a year during the three years prior to HIV diagnosis [18]. Of 364 patients who sought medical care for possible HIV-related conditions, 82% had a missed opportunity for testing [18]. In the Swedish study of Brannstrom et al., 27% of all patients had presented with AIDS and/or HIV-associated conditions without being offered testing. In addition, a recent case-control study performed in six general practices in Amsterdam reported that at least one indicator condition was present in 59% of the cases but in only 7% of controls during the 5 years prior to HIV testing, leading the authors to conclude that HIV indicator conditions do not yet trigger early HIV testing in primary care [42].

We can apply the late presentation risk factor data and the HIV testing indications to the three case studies to identify missed opportunities for earlier HIV diagnosis: The patient in case study 1 underwent HIV testing at an anonymous testing facility to be diagnosed with HIV, despite having been followed for 2 years by several doctors in different hospitals for three symptoms of those listed in table 1: chronic diarrhoea, unexplained weight loss and lymphadenopathy. This case highlights the importance of keeping up to date with new trends in HIV epidemiology and subsequent testing recommendations. Regarding risk factors, the patient was assumed to be heterosexual because he was married with children and was probably not tested because he was not seen to belong to a classical risk group. The case demonstrates that, without taking a sexual history, it is difficult to fully assess HIV risk factors. The patient openly described his sexual contacts once asked directly but re-

marked that no one had previously asked him. However, not all patients disclose a full sexual history and this is where phrasing the question on HIV testing can be critical.

The patient in case study 2 was not offered testing despite presenting for care repeatedly over a period of 4 years with unexplained anaemia, basal pneumonia and cervical intraepithelial neoplasia. Cervical dysplasia is an indication for HIV testing, following HIDES I [26, 27]; cervical carcinoma has been listed as an AIDS-defining condition since 1993 [43]. In spite of this, we recently reported HIV testing rates of 11% among women with invasive cervical carcinoma treated at Lausanne University Hospital between 2000 and 2012 [44].

The patient in case study 3 was HIV tested because of a needle-stick injury, having been followed-up over 3 years for chronic conditions. Vascular and renal disease constitute SNA events and chronic renal impairment is now an indication for testing [27]. The association between these conditions and the patient's long-standing diabetes and hypertension illustrates the age-old medical dilemma of Occam's razor (*lex parsimoniae*) – promoting a unifying diagnosis based on the rules of probability – versus Hickam's dictum – reminding us that patients can have many diseases concomitantly. The approach of looking for the fewest possible causes to account for all the symptoms is rational and appropriate, provided HIV is on the list. In this patient's case, vascular and renal disease being due to diabetes and hypertension can suffice as an explanation once HIV has been excluded.

How to address late presentation: the three Ps

The three Ps that contribute to HIV testing barriers and, therefore, to late presentation – policy, provider and patient – are the same as those that will address this problem. On the policy front, this would include means to facilitate testing by increasing the availability of rapid point-of-care testing and by targeting the groups at risk of late presentation as described above. Written consent prior to testing is not required in Switzerland and this circumvents an important logistical barrier [32, 33]. Among health care providers, improved risk assessment, including a detailed sexual history in patients with medical problems which remain unresolved over months or years, recognition of HIV-related conditions and understanding of the inextricable link between missed opportunities, late presentation and subsequent patient outcome, will help to reduce late presentation. In addition to missing the opportunity to test when faced with a testing indication, missed opportunities can arise among patients visiting more than one physician, where each doctor imagines one of the others will organise testing (de Rossi et al., unpublished data). Finally, among patients, awareness of symptoms related to acute [45] or advanced HIV infection, and of the benefits of early diagnosis and linkage to care, will improve patient-induced testing rates.

The following practical points relate to the patient-provider relationship and may facilitate HIV testing:

– Phrasing the question is important
  "Have you had unprotected sex since your last HIV test?" or "When was your last HIV test?" are two ways of de-dramatising HIV testing, because the implication is that testing should be a regular part of a health check in individuals who are or who have been sexually active. In contrast, asking the question "Do you consider yourself at risk for HIV infection?" will induce difficulties in manoeuvring the discussion into conducting a test if the patient's reply is no.
– Thinking wide – and beyond MSM, PWID and individuals from regions of high HIV prevalence
  Any patient with indications for HIV testing should be tested as soon as these indications become apparent. Any patient from a population at risk of late presentation should also be considered for testing: sexually-active heterosexual men and women, older individuals and individuals of non-European origin. SNA events and unexplained and unresolved medical problems are also indications for testing.
– Never assuming
  Patients not considered to be part of a high-risk group can engage in high-risk behaviour. The patient from case 1 was married with children but had male sexual partners. No doctor had asked him about his sexual history. And never assume with patients who have more than one doctor that one of the other doctors will offer testing.

Conclusion

In conclusion, one half of HIV-infected individuals who present for care are late presenters and this has consequences for both individual and public health. The main risk factors for late presentation in Switzerland are being female, heterosexual, older and of non-European origin. Missed opportunities for early HIV testing are frequent and relate to policy structure, healthcare providers and patients. Among healthcare providers, knowledge of the national HIV testing recommendations and awareness of current HIV epidemiology trends should serve to encourage testing in patients before they present late or with SNA events. Three principles – phrasing the question, thinking wide, never assuming – should assist in broaching the subject of HIV testing and performing a test. Above all, having an open discussion with patients is paramount.

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