The European Journal of General Practice

ISSN: 1381-4788 (Print) 1751-1402 (Online) Journal homepage: informahealthcare.com/journals/igen20

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To cite this article: Meaghan M. Kall, Ruth D. Smith & Valerie C. Delpech (2012) Late HIV diagnosis in Europe: A call for increased testing and awareness among general practitioners, The European Journal of General Practice, 18:3, 181-186, DOI: 10.3109/13814788.2012.685069

To link to this article: https://doi.org/10.3109/13814788.2012.685069

Published online: 08 May 2012.

European Journal of General Practice, 2012; 18: 181–186

informa
healthcare

Background Paper

Late HIV diagnosis in Europe: A call for increased testing and awareness among general practitioners

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KEY MESSAGE(S):

- In Europe, half of people diagnosed with HIV are diagnosed late, or after treatment should have begun
- Barriers to testing exist at the patient and healthcare provider level
- Routine, universal HIV testing in general practice in high prevalence areas is a feasible strategy to prevent late diagnosis of HIV infection

ABSTRACT

Major advancements in the treatment of HIV infection mean near normal life expectancy of persons diagnosed at an early stage of infection. Nevertheless, a significant proportion of HIV infected persons remain undiagnosed and are diagnosed at a late stage of infection, putting them at higher risk for preventable HIV-related morbidity and mortality and risking onward transmission to others. In Europe, half of people diagnosed with HIV in 2010 were diagnosed late with a CD4 $<$ 350 cells/ul, at a point after which treatment should have begun. The causes of late diagnosis are manifold, and comprise barriers to testing at the patient, healthcare provider, and institutional level. Strategies to address barriers to HIV testing are essential to ensure prompt diagnosis. Routine universal HIV testing in general practice consisting of informed consent and a pre-test discussion is feasible and acceptable and should be considered in high prevalence areas to normalize HIV testing, reduce stigma, and reduce the number of infected individuals who are diagnosed late.

Key words: HIV, STD and HDS, public health, preventions, HIV

INTRODUCTION

Since the advent of effective antiretroviral therapy (ART) in the mid-1990s, HIV has become a chronic, manageable condition and rates of HIV-related morbidity and mortality have drastically declined (1). The survival of HIV infected individuals now approaches that of the HIV uninfected population where antiretroviral therapy is available (2,3). While this should serve as an incentive for people to have an HIV test and know their status, around a third of HIV-infected people living in Europe remain undiagnosed (4). Rates of HIV-related morbidity and mortality have plateaued since the late 1990s with an estimated 8000 HIV-related deaths (5) and 5000 AIDS diagnoses reported in western and central Europe in 2010 (6). Most AIDS diagnoses and deaths are preventable, and the main predictor of HIV related morbidity and mortality is late diagnosis of HIV infection. We review the impact of high rates of late diagnosis and ongoing transmission in Europe and highlight the role of general practitioners (GPs) in HIV testing and early diagnosis.

METHODS

In September 2011, a computerized literature search of Medline was undertaken using the NHS Evidence Health Information Resources website (http://www.library.nhs.uk). Key terms, including 'late diagnosis' or 'late presentation' AND 'Human Immunodeficiency Virus' AND 'General Practitioner' or 'Primary Care' were used to search article titles and abstracts and MESH terms. The computerized search was limited to publications from EU and EEA/EFTA countries and the United States, Canada, and

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(Received 12 January 2012; accepted 14 March 2012)

ISSN 1381-4788 print/ISSN 1751-1402 online
DOI: 10.3109/13814788.2012.685069

Australia. Quality control checks using PubMed were undertaken to ensure a high sensitivity in identifying the appropriate bibliography. Manual searches of the bibliography of publications identified through the computerized literature search were completed. The search was focussed on key papers published since 2005; however, no date limitations were used. A manual internet key word search using Google Scholar was conducted to identify grey literature including country-specific and international HIV testing and treatment programme documents and guidelines.

DEFINITION OF LATE DIAGNOSIS

Late HIV diagnosis is best defined as presenting for diagnosis and treatment at a stage after which treatment should have begun. The current European definition of late diagnosis in an individual is a CD4 T-cell lymphocyte count of less than 350 cells/μl (with CD4 cell count acting as an indicator of immune function) and/or an AIDS defining illness at diagnosis (6), conforming with current World Health Organization (WHO) and European treatment guidelines (8,9). The definition of late diagnosis has evolved over time, and earlier reports frequently defined late diagnosis as a CD4 count below 200 cells/μl (10–12) or an AIDS-defining illness at the time of diagnosis (13,14) in accordance with treatment recommendations at that time.

LATE DIAGNOSIS IN EUROPE

An estimated 5.7 new HIV diagnoses per 100 000 population were reported across European Union countries in 2010 (8.6 per 100 000 men and 2.9 per 100 000 women) (6). The predominant modes of transmission are sex between men, injecting drug use, and heterosexual contact, particularly among individuals originating from high HIV prevalence countries, primarily sub-Saharan Africa.

The European Centres for Disease Prevention and Control (ECDC) reported that, in 2010, 49% of persons newly diagnosed with HIV were diagnosed late (with a CD4 count less than 350 cells/μl) (15). This translates into approximately 13 000 Europeans diagnosed late with HIV infection in 2010.

Across Europe, rates of late diagnosis are particularly high among persons infected through heterosexual contact and those who inject drugs (16–19). In comparison, late diagnosis amongst men who have sex with men (MSM) is less common (15). Individuals of black African, South American, or Asian ethnicity are significantly more likely to be diagnosed late, with many likely infected abroad in a high HIV prevalence country (20,21). A further factor strongly association with late diagnosis is age, with late diagnosis consistently more common in older adults (22).

High rates of late diagnoses are also reflected in the proportion of people with HIV who remain undiagnosed, estimated at 30% in Europe (4). Mathematical modelling from the UK and the Netherlands estimate that 24% (95% CI: 19–30%) and 40% of people living with HIV in those countries are unaware of their infection, respectively (23,24) The proportion of undiagnosed individuals has remained relatively stable over the past decade, with no evidence of decline (25).

IMPACT ON THE INDIVIDUAL AND PUBLIC HEALTH

Late diagnosed individuals are at high risk of developing an AIDS-defining illness or other HIV-related illnesses associated with advanced disease (26). For example, incidence of tuberculosis in untreated HIV infected individuals is between 10 and 30 times higher in those with a CD4 count of <50 cells/μl, compared to those with a normal CD4 count of ≥ 500 cells/μl (27). Low CD4 count has also been associated with increased risk of non-AIDS related illnesses including cardiovascular, renal, hepatic disease and some malignancies (28,29).

In the ART era, late diagnosis is the most important cause of HIV-related mortality, particularly short-term mortality (death within a year of diagnosis) (30). Short-term mortality rates are over ten times higher among UK residents diagnosed late (CD4 <350 cells/μl) compared to those diagnosed promptly (4.1% versus 0.3%), with 91% of all deaths within 12 months of diagnosis occurring in late diagnosed individuals (31).

Even after diagnosis, late diagnosed individuals experience sub-optimal benefit from ART compared to those who start early. Cohort studies report that those who start treatment at lower CD4 counts experience poorer CD4 recovery (32,33) and lower rates of virological suppression (34) compared to patients who initiate treatment at higher CD4 counts, due to longer exposure to HIV-associated inflammation and immune activation. Furthermore, life expectancy of HIV-diagnosis patients is significantly reduced if treatment is started later than guidelines suggest, with patients who start treatment with a CD4 <200 cells/μl estimated to lose an additional 10 years of life compared to those who started ART with a CD4 <350 cells/μl (3).

Undiagnosed individuals also unknowingly risk transmitting HIV to uninfected individuals before their infection is diagnosed. The rate of HIV transmission is estimated to be 3.5 times higher for HIV infected individuals who are unaware of their infection compared to those who know their status (35). Diagnosed individuals are able to protect their partners from acquiring HIV infection in two ways.

First, through access to antiretroviral treatment. Adherence to antiretrovirals not only decelerate disease

progression but also reduces the risk of onward transmission to sexual partners and from mother to child, through low viral load response (36,37). A recent randomized clinical trial demonstrated a 96% reduction in the risk of sexual transmission of HIV among treated patients compared to those untreated (38). This means fewer lifetime sexual partners will become infected. A meta-analysis of cohort data found that individuals with low viral load on antiretroviral therapy infect on average less than one other person in their lifetime, whereas those not on treatment infect between five and six other people (39). At the population level, some speculate that universal annual HIV testing and immediate treatment after HIV diagnosis could result in virtual elimination of HIV transmission (40).

Second, behavioural changes by HIV-infected individuals after they are diagnosed can also reduce the risk of onward transmission. Evidence suggests that HIV diagnosed individuals reduce their risky sexual practices, by increased condom use with partners of unknown or negative HIV status, or by reducing their number of sexual partners (41–43). A meta-analysis comparing rates of unprotected intercourse of HIV-infected persons both aware and unaware of their status, found that rates of unprotected intercourse with partners of negative or unknown HIV status were 68% lower in those who were aware of their HIV status compared to those who were unaware (44).

ECONOMIC IMPACT

The full cost of late diagnosis is difficult to measure, particularly prior to diagnosis. However, late diagnosed individuals consume a great deal of medical resources, due to high costs associated with inpatient care, more frequent visits to outpatient specialist care, and additional pharmaceutical costs, resulting in considerable higher lifetime cost of treatment and care (45). In Canada, the direct medical costs of treating HIV patients who were diagnosed late (CD4 $<$ 350 cells/μl) are reported to be more than double that of patients diagnosed promptly, and remained high even in subsequent years after their CD4 count improves (46). This was largely due to the residual cost of morbidity from some AIDS conditions and the complex psychosocial needs of late diagnosed patients, such as denial, psychiatric illness, and substance use. Furthermore, for those diagnosed with very advanced disease or an AIDS defining illness, medical costs rise exponentially with inpatient hospitalization costs accounting for most of the difference. In France, the average monthly cost of management of an HIV-infected patient with a good CD4 count ($>$500 cells/μl) has been assessed at €670, compared with €1760 for a patient with a CD4 count less than 50 cells/μl, and €4530 for a patient with an AIDS defining illness, depending on the infection (47).

BARRIERS TO EARLIER TESTING

Awareness of the barriers to HIV testing from the perspective of the individual, the test provider, and at the institutional level is an essential part of designing effective HIV testing programmes and reducing rates of late diagnosis. The asymptomatic phase of HIV can last for many years, during which individuals may not perceive that they are at risk of HIV infection. Low risk perception has been cited as the main reason for not testing earlier among the highest-risk populations, such as black Africans and MSM (48,49). This belief can arise from a lack of knowledge about HIV transmission or failure to recognize risks in their own behaviours (50). Stigma associated with HIV may also deter high-risk individuals from an HIV test due to fear of a positive result (51). Cultural, linguistic or socio-economic barriers to the healthcare system may also contribute to the decision not to test (50).

There is evidence of greater opportunities for earlier diagnosis in the health setting. Several studies have looked retrospectively at healthcare visits made by late diagnosed individuals in the year or years prior to diagnosis, and found that many late diagnosed individuals attend primary and secondary healthcare services with HIV-related symptoms prior to diagnosis without being offered an HIV test (52,53). In the UK, examination of medical attendance histories of HIV-infected black Africans found that 82% of HIV-infected individuals attended their GP in the year prior to their diagnosis (54). While in some cases, this reflects patient's unwillingness to disclose risk the healthcare providers themselves may feel they lack appropriate training to provide pre-test counselling or perform the test itself, or healthcare provider's discomfort with approaching the topic of HIV (55,56).

ROUTINE HIV TESTING IN GENERAL PRACTICE

Earlier diagnosis relies on availability of HIV testing. Traditionally, HIV testing has been performed in a limited number of settings, and was targeted to those deemed 'high-risk.' However, this strategy was later proven inadequate as a significant proportion of HIV-infected people have no discernible risk (57). Following the success of universal antenatal screening strategy adopted by many European countries, which both reduced the rate of mother to child transmission to less than 1% (58) and was effective at detecting HIV infection at an earlier stage (in the UK, for example, 20% of pregnant women are diagnosed with CD4 $<$350 cells/μl compared to 42% of non-pregnant women (31)), the call forward has been to 'normalize' and expand routine HIV testing outside the antenatal and STI clinic settings to identify more HIV infections at an earlier stage.

General practice represents an opportunity to diagnosed HIV at point-of-entry to the healthcare system for those individuals who attend their GP more frequently

or before other healthcare services (59). In countries such as the Netherlands where the healthcare system is mainly operated through GPs, half of late diagnosed individuals had consulted a GP three to 12 months prior to their HIV diagnosis without being offered an HIV test (60). However, access to HIV testing through general practice is variable across Europe. In a European policy survey, 17 of 24 (71%) responding countries indicated that HIV testing is available through GPs (50). A handful of European countries have a testing strategy that primarily operates through GPs (Denmark, Germany, the Netherlands, Norway, Spain, and Switzerland) and testing is also offered in other settings, while in most countries GPs remain marginally or not at all involved in HIV testing.

The European Centre for Disease Prevention and Control ECDC (61) and the WHO European Region framework on scaling up HIV testing and counselling advocate expanded HIV testing in general practice (62). A key principle in these guidelines is that HIV testing is conducted following informed consent (usually verbal) and a pre-test discussion explaining the benefits of testing and how results are given. Importantly, a detailed sexual or injecting history is not required before offering an HIV test. The UK has developed similar guidelines recommending expanded HIV testing of all new registrants in general practice aged 15–59 in areas of high diagnosed HIV prevalence (>2 per 1000 population) (63) and France has recommended rapid HIV testing in every primary care venue (64).

Results of pilot studies from the UK have shown that routine, universal offer of HIV testing in general practice is feasible and acceptable to patients, and results in high rates of case identification when conducted in high prevalence areas (65). Additionally, routine testing by GPs could result in earlier HIV diagnosis, as seen in one study where median CD4 count of HIV diagnoses rose from 280 cells/μl during targeted testing to 351 cells/μl with routine testing (66). Cost effectiveness analyses from France indicate that universal one-time screening of the population through general practitioners is cost-effective (67).

To maximize such a strategy, general practitioners must be trained to recognize the clinical presentation of HIV-infection and to confidently offer and perform HIV testing with a brief pre-test discussion. To that end, links to HIV-specialist services must be established for the availability of immediate psychosocial support and prompt assessment by an HIV-specialist for those testing positive.

Conclusions

Three decades of action for prevention, treatment, and care has led to major advances in the diagnosis of HIV infection and access to antiretroviral treatment, translating into longer survival with minimal risk of HIV-related illness or death. Despite these efforts, we have not yet seen a decrease in the number of new HIV infections in Europe, with continued high rates of late diagnosis, HIV-related morbidity and mortality and evidence of onward transmission of HIV.

Routine offer of an HIV test by non-HIV specialists, such as GPs is needed to reduce the high rates of late diagnosis, ensuring access to HIV specialist treatment and care. Innovative HIV testing strategies are encouraged to confront the challenge of late diagnosis and improve the prognosis for all HIV-infected individuals in Europe.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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