Delay in Diagnosis of HIV Infection

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ABSTRACT

Late presentation of HIV is common. It has been associated with greater risk of AIDS, death, lower immunological response, greater toxicity and a higher probability of transmission. In this study we review the impact of different definitions in terms of mortality and morbidity, associated factors, economic implications, as well as strategies for increasing diagnosis.

Key words: HIV; Sexually transmitted infections; Prisons; Economics, medical; Public health; Early diagnosis; Disease prevention; Epidemiology.

Text received: 15/11/11

Text accepted: 21/01/12

INTRODUCTION

The introduction of high activity antiretroviral therapy (HAART) has changed the natural history of infection by the human immunodeficiency virus (HIV), reducing morbidity and mortality amongst HIV infected patients[1]. Delay in diagnosis (DD) of HIV infection currently represents a major public health problem and a lost opportunity to limit the progress of the infection and reduce transmission in a country like Spain which has universal, free access to health services and HAART.

The number of CD4 T lymphocytes is the principal marker of clinical progression of an HIV infection, as a good correlation has been demonstrated between the level of CD4, restoration of cellular immunity, delay in progression and increase of survival[2].

In Europe, the CD4 count is the most frequently used indicator of delay in diagnosis, either alone, in combination with clinical practice or the time of presentation of AIDS after diagnosis of HIV.

There are over twenty definitions of DD in the scientific literature[3]. This variation in definition means there is an important variation in estimating incidence[4]. Thus, in a study published in the UK in 2003, the delay in diagnosis was situated at 15% or 33% if this was defined as the presence of less than 50 CD4/µl or 200 CD4/µl[5]. In the case of Spain in 2009, the delay was set at 30% when infection was diagnosed with a CD4 figure lower than 200 cel/µl, while it increased to 50% if the CD4 level was less than 350 cel/µl[6].

Another factor to be borne in mind when calculating incidence is the denominator, in other words, when the delay is presented as the proportion of individuals amongst people infected with HIV or as the proportion amongst people with AIDS. In the first case, this will always be lower than when this proportion is restricted to those diagnosed with AIDS. Thus, in Sweden between 1996 and 2002, an increase was observed in delays in diagnosis throughout the studied period, increasing from 20% in the first years to 60% in the final period. However, this increase was due to the drop in the number of individuals with AIDS rather than in a real increase in the number of individuals with DD[7].

This wide variation in definition has been highlighted as a severe limitation to estimating prevalence and determining trends in DD in Europe.

In 2009, the objective was established to identify people with increased risk of progression of the infection, to improve surveillance and to facilitate compar-

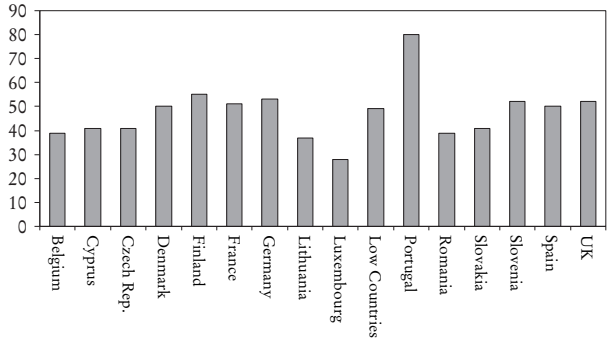
isons between countries and regions within a country throughout this period. To this end consensus was reached on the following definitions[8]:

- Late presentation: people starting therapy with a CD4 count of less than 350 cell/µl or with a diagnosis of AIDS, independently of their CD4 count.
- Presentation with advanced HIV illness: people with a CD4 count lower than 200 cell/µl or with a diagnosis of AIDS independently of the CD4 level.

Despite formulating the previous definitions, the defining criteria for delays in diagnosis have yet to be unified and the debate persists with similar proposals being made[9].

MAGNITUDE OF THE PROBLEM

An important problem when estimating DD is the lack of information about the CD4 level at the time of diagnosis in many EU countries. In at least 50% of the countries that have this information, the percentage of delay is between 24% and 80% (Figure)[10]. This estimate varies wildly between one country and another because of the percentage of cases without information about the lymphocyte sub-populations and the use of different definitions. Thus the delay varies between 10-15% if very low CD4 levels are taken into account, while if the delay in DD is defined with higher values, delay in diagnosis reaches 30-35%[3].



Source: Europen Centre for Disease Prevention and Control, 2010.

Figure 1. Percentage of new diagnoses with a CD4 count of less than 350 cell/µl in some countries of the European Union, 2009.

In the European context, information about the size of the undiagnosed fraction of infection is scarce. In a study published in 2008, it was estimated that 30% of infected people did not know their serological status, in proportions that range from 12-20% in Sweden to over 50% in Poland[11]. In Spain at least 50% of the new diagnoses of HIV infection in 2009 had not undergone therapy (CD4<350 cell/µl) and that 30% presented severe immunosuppression (CD4<200 cell/µl)[6].

INDIVIDUAL EFFECTS OF DELAY IN DIAGNOSIS

The time between infection and initiating HAART is a determining factor in avoiding progression of the infection and facilitating immunological recovery[12]. Overall, it is estimated that one third of HIV deaths are related to a delay in starting HAART[13].

The consequences linked to DD are a reduction in life expectancy, an increase in the incidence of mortality and the progression to AIDS, increases in death rates from AIDS-defining events, neoplasms associated or not with AIDS, kidney failure and liver disease[14].

The benefits of HAART when therapy commences with a CD4 level above 200 cell/µl are well documented. In Denmark in 2004, it was observed that mortality diminished amongst 95% of patients starting HAART with CD4 levels of over 200 cell/µl when compared to others starting HAART with CD4 levels under 50 cell/µl[15]. In another study in the UK in 2005, it was observed that patients with a delayed diagnosis were 10 times more likely to die than those who had not been given a DD[16]. In France in 2007, mortality was 13 times greater amongst patients with DD in comparison to diagnoses with no delay, with 65% of the deaths being attributed to DD[17]. A strong link between DD and reductions in survival has also been observed in Spain[18].

Data from a large number of prospective cohort studies and clinical tests show greater morbidity and mortality when HAART is started below 350 cell/µl or when the patient presents symptoms[19]. Although no clear benefits to starting therapy above 500 cell/µl have been found due to lack of conclusive studies on the subject[20], for some years now there has been a growing body of evidence showing reductions in mortality when HAART is started above 500 cell/µl in asymptomatic patients[21,22].

Besides the increase in mortality, DD is associated with an increase in the incidence of opportunistic diseases, both those associated with AIDS and those that are not, such as cardiovascular, kidney and liver diseases and non-AIDS-defined malignant tumours[23,24,25].

RISK FACTORS ASSOCIATED WITH DELAY IN DIAGNOSIS

There is sufficient scientific evidence on the factors associated with DD in most regions worldwide. Although the comparability between studies may be partially limited due to different defining criteria for a delayed diagnosis, most of them show a strong association between age and DD. Although DD affects all ages, distribution is not homogeneous[26]. Thus older patients are more affected by delays[5,7,18,16,17,27,28]. This is explained by the low perception of risk and by the natural history of the infection[29]. Another added factor is that the test tends to be offered less to people of a more advanced age. In general, heterosexuals of more than 50 years of age are not usually the target population for prevention campaigns [30].

As regards gender, there are different results. Most studies indicate that men are more often associated with DD [5,16,17,27,28,31]. This may be influenced by the higher perception of risk amongst women [32] and the probability that they are offered the test during pregnancy or birth and so are more likely to receive an early diagnosis. However some studies indicate that there is a greater association of women with higher risks of DD[33]. In any case, it should be borne in mind that that socio-demographic factors do not necessarily act independently in delayed diagnoses.

Another factor frequently associated with DD is immigration. National[27,28] and international [34,35,36] studies have associated immigration with an increase in DD. Amongst the causes explaining the delay in these groups are cultural, linguistic and socio-economic barriers, low perception of the risk of acquiring the infection and fear of stigmatisation.

The route of transmission has also been described as a factor that is strongly linked to DD[37,38]. In the UK it is estimated that men with heterosexual relationships (HTS) and HTS women present 42% and 36% of DD in comparison to 19% amongst HSH[5,16]. HTS transmission is described in different countries as an important risk factor in diagnostic delay[16,17,27,28]. It has even been observed that while in some population sub-groups the delay tends to decrease, going from 38% to 25% in 9 years, in others a constant increase can be seen[16,34]. In Barcelona, a study carried out from 2001-2009 showed a decrease in DD only in the first years of the study which then remained stable in the following years[28]. In Spain[27] and some other European countries[36], intravenous drug use (IDU) is also identified as a risk factor associated with DD, almost in the same proportions as those in HTS. In Italy this same proportion of DD amongst substance abusers has also been observed, but only amongst those abusers that remained distant from social and health care resources[38]. In this group, scientific evidence would suggest that DD is more a consequence of a delay in starting treatment than a delay in diagnosis[39,40].

As regards diagnostic delay in subjects with a prison background, an inverse association can be seen, in other words a reduction in the risk of delayed diagnosis[41]. This can be explained by the inclusion of an HIV diagnosis in the clinical examination protocol when entering prison and the availability of HAART in some countries[42].

EFFECTS AT COMMUNITY LEVEL

1 Transmission

Besides the effects on individual health, people with a delayed diagnosis increase the likelihood of transmitting the infection; the fact that they are unaware of their condition means that they do not adopt any changes in behaviour. It is estimated that more than 50% of new infections are produced by infected people and that they were unaware of their serostatus[43]. Patients with delayed diagnoses tend to carry high viral loads, which means that a delay in diagnosis can contribute towards an increase in the risk of transmission of HIV[44,45].

Several studies have clearly shown that after diagnosis of infection, most infected people continue to be sexually active but a large number of them will practice safer sex if they are aware of their serological status, thus limiting transmission of the infection. These changes include an increase in participation in syringe exchange programs, leaving sex work and a reduction in unprotected sex[46,47].

2. Economic impact

The economic impact is especially visible in the increase of morbidity associated with delayed diagnosis, which, as mentioned before, leads to a disproportional use of hospital resources on patients with low CD4 levels who have had AIDS-defining events[33]. It has been observed that the average annual cost of care of patients with DD was twice the amount spent on patients with timely diagnoses[48,49]. This difference is mainly due to the increase in hospitalisations and the use of HAART.

STRATEGIES FOR EARLY DIAGNOSIS

In Europe there are not as yet any plans to promote early diagnosis in all age groups as a short term strategy to reduce the incidence of new HIV infec-

tions, as recommended in the USA[50]. However, awareness-raising of health care personnel is necessary for establishing early diagnosis.

In this respect, general practitioners, as the patient's first point of contact with the health system, have a unique opportunity to reduce delays in diagnosis. In this case to establish the differential diagnosis of a clinical picture compatible with acute HIV infection, which is extremely vague, but which with knowledge of the patient's background can help to correctly guide the diagnosis[51]. In short, health care professionals should offer the HIV test to all pregnant women, to people who practice high-risk sex, to IDUs, to patients presenting symptoms of sexually transmitted diseases, tuberculosis or other HIV-related diseases, such as mononucleosis syndrome, herpes zoster, leukopenia/thrombocytopenia, as it is estimated that in these cases the prevalence of HIV infection may be over 1%[52] and obviously the test should be administered to all those who request it.

Another initiative to promote early detection of the infection is geared towards giving the HIV test the same status as other analytical tests[50]. Besides, the barriers that make it difficult to carry out, such as stigma, should be adequately managed, bearing in mind the personal and cultural needs of the people affected.

To reduce delays, some Autonomous Communities in Spain have specific pharmacies and programs (outreach programs) where community participation is essential for bringing the test closer to groups that are more vulnerable to infection, such as community centres[53]. Other programs are geared towards people at high risk of infection and which are practiced in places frequented by these groups[54].

Another proposal directed towards health care personnel and public health authorities is one involving the study of sexual partners[55,56]. This type of activity is routinely carried out in few European countries (England, Scotland, Switzerland and Sweden), where there is a heterogeneous approach to this type of activity[57]. The study of contacts in the health care environment brings early detection and treatment from which the patient, his/her contacts and the community can only benefit. The availability of effective treatment with free, universal access, the existence of preventive treatment recommendations for those who are examined during the early period of exposure, the right of people exposed to risk to know about their situation, and finally the possibility of taking preventive action to avoid infection or receive treatment, are activities that are well received by the users of these programs, which have been running for more than 20 years and whose experience is demonstrated in these studies[58].

If early diagnosis is essential for reducing DD, it is not enough to ensure reductions. Besides having access to the test, the patient is also expected to go to the health care system seeking the right medical management, which does not necessarily happen in all situations. Some studies have observed that up to 35% of patients that received a diagnosis of HIV infection were not seeking medical attention[59]. It is therefore recommended that the strategies geared towards reducing DD use different perspectives. An early diagnosis, especially in the group of IDUs, does not necessarily imply that the patient will be followed up or treated earlier[60,61]. For this reason strategies including referral and follow ups during treatment are essential if the intention is to reduce delays in diagnosis in this particular group. However, reinforcing the strategies that increase the offer to test should, as a priority, be directed towards people engaged in high-risk sexual activity and other vulnerable groups such as immigrants[36,52,62].

In the case of prison inmates, where there is evidence of greater prevalence of high-risk conducts and AIDS-defining diseases such as tuberculosis, sexually-transmitted diseases or hepatitis, the recommendation is for the test to be voluntary, confidential and with the guarantee of access to HAART and the health services[63].

By way of conclusion, to significantly reduce diagnostic delays in HIV infection, it is essential to promote initiatives that raise awareness amongst the population about the need to consult doctors so that they consider the possibility of infection in people that have been exposed and public health institutions so that they design innovatory strategies favouring early diagnosis. This will benefit the patient through early treatment and society as a whole by reducing transmission to uninfected people.

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