Late Diagnosis of HIV Infection: Epidemiological Features, Consequences and Strategies to Encourage Earlier Testing

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Summary: A substantial proportion of HIV-infected individuals do not present for HIV testing until late in infection; these individuals are often ill, have a high mortality risk, and are less likely to respond to treatment when initiated. Furthermore, late presentation means that opportunities to reduce onward transmission, either by reducing high-risk behaviours or by reducing an individual's infectivity, are missed. The proportion of HIV-infected individuals who present late has remained relatively stable over the past decade, despite several attempts to encourage earlier diagnosis. Late presenters tend to be those at lower perceived risk of infection, those who are not routinely offered HIV testing, and are often from marginalized groups. Strategies that encourage earlier testing, including routine HIV testing in healthcare settings where high-risk individuals attend frequently, the availability of HIV testing services in non-medical settings, and partner notification schemes or peer-led projects to encourage high-risk individuals to attend for testing, may all increase the proportion of HIV-infected individuals who are aware of their HIV status, thus helping to control the spread of the epidemic. This review summarizes recent evidence on the epidemiology of late presentation and its impact on clinical progression, and describes several key strategies that may encourage earlier diagnosis.

Key Words: earlier diagnosis, epidemiology, late presenters, public health

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INTRODUCTION

Two decades have passed since HIV testing first became available. Despite this, it is estimated that at least a quarter of individuals living with HIV in industrialized countries, and the vast majority of individuals with HIV in resource-limited, high-prevalence countries are unaware of their infection.[1–3] Many of these individuals are diagnosed very late, often after developing a serious AIDS-defining condition. Even after diagnosis, these individuals may not immediately seek, or be provided access to, medical care.[4,5] Late diagnosis of HIV infection has negative consequences, not only for the individual but also for the wider population. Individuals who present at an advanced stage of immunosuppression are at high risk of clinical events and death[6] as well as being more likely to have a poorer response when they do start highly active antiretroviral therapy (HAART).[7] The costs of treating these cases, which tend to be complex, are high. Furthermore, those who remain undiagnosed are unable to reduce their risk of onward transmission, either by adopting risk reduction behaviours,[8] or by initiating HAART to lower their plasma HIV-RNA level.[9] In this paper we will focus on the epidemiological aspects of late presentation and its clinical consequences, and will describe strategies that may be used to encourage earlier presentation.

HOW COMMON IS LATE PRESENTATION?

A number of studies from industrialized countries have described the frequency of late presentation among individuals with newly diagnosed HIV infection (Table 1), with estimates ranging from 15 to 43% depending on the definition of late presentation used. In the United Kingdom, a survey conducted among 977 newly diagnosed individuals in 2003[17] revealed that a third of patients had presented with a CD4 cell count of less than 200 cells/μl. In Italy, of the 968 patients enrolled in the multicentre Italian Cohort Naive from Antiretrovirals (ICoNA) study between 1997 and 2000, 29% were first tested for HIV either after an AIDS-defining illness or with a CD4 cell count of less than 200 cells/μl.[15] It is noteworthy that presentation at even more advanced stages of immunosuppression is not uncommon, as shown, for example, in a study from the Royal Free Hospital in London, where 15% of individuals first seen between 1996 and 2002 had a CD4 cell count below 50 cells/μl at the time of presentation.[12] While available evidence would suggest that the proportion of those diagnosed with a low CD4 cell count has not increased greatly over time,[16,18,19] studies that have considered the proportion of individuals who are diagnosed with HIV at the time of, or shortly before, an AIDS diagnosis have generally shown that this proportion has increased from approximately 20% in the early 1990s to

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TABLE 1. Prevalence of late presenters among individuals diagnosed with HIV infection in industrialized countries.

Country	Author, year	Definition	Prevalence
Australia	Hocking et al., 2000[10]	< 8 Weeks from diagnosis to AIDS event	249/1021 (24%)
Spain	Castilla et al., 2002[11]	HIV-positive test in the same/preceding month as AIDS event	8499/30778 (28%)
United States	Klein et al., 2003[12]	CD4 < 200 cells/μl	167/388 (43%)
Scotland	Manavi et al., 2004[13]	CD4 < 200 cells/μl	249/1021 (24%)
Canada	Krentz et al., 2004[14]	CD4 < 200 cells/μl	93/241 (39%)
Italy	Girardi et al., 2004[15]	CD4 < 200 cells/μl or AIDS in preceding month	379/968 (39%)
UK	Sabin et al., 2004[16]	CD4 < 50 cells/μl	110/719 (15%)
UK and Ireland	Sullivan et al., 2005[17]	CD4 < 200 cells/μl	301/977 (33%)

35–60% in more recent years.[11,20–25] Such individuals now make up an increasing proportion of AIDS diagnoses in these countries. These findings do not necessarily imply that there has been an increase in the proportion of HIV-infected individuals who are unaware of their serostatus, nor a tendency for HIV to be diagnosed later in the course of HIV infection. Instead, as more diagnosed patients are able to benefit from the use of HAART, AIDS rates among those already diagnosed with HIV have dropped dramatically.[26] It is thus not surprising that those who present late for care now contribute disproportionately to these AIDS cases.

Interestingly, even in countries where HIV care is provided free of charge, delay in seeking care may be common among individuals diagnosed with HIV. For example, in Italy a quarter of all patients enrolled in the ICoNA Study from 1997 to 2000 did not receive HIV-related care until at least 6 months after their first positive HIV test.[15] In England and Wales, in 1996 and 1997, only 57% of newly reported cases of HIV infection had a CD4 cell count reported to the national surveillance system within 6 months of their HIV diagnosis, suggesting a possible delay of entry into care for a substantial proportion of patients.[27]

FACTORS ASSOCIATED WITH LATE PRESENTATION

Although the factors associated with late HIV presentation may differ in different populations, late diagnosis is generally more common among those who are not perceived, or who do not perceive themselves, to be at high risk of infection, among those who are not actively offered HIV testing, and among marginalized groups (e.g. immigrants). In line with this, late presentation tends to be less common among men who have sex with men and among individuals who inject drugs compared with heterosexuals and individuals with an unknown mode of transmission,[11,15–17,21] reflecting both a higher perceived risk and the availability of routine HIV testing in genitourinary medicine clinics and drug addiction treatment centres. In the United Kingdom, only 20% of women diagnosed with HIV as a result of active screening in antenatal clinics had a CD4 cell count of less than 200 cells/μl at diagnosis compared with 42% of women diagnosed in other settings.[28] Other factors associated with late diagnosis include older age[15,25,29] and being born in a country other than the one of current residence;[11,15,16,30] these findings may reflect a lack of knowledge about AIDS or reduced access to medical services in these groups. In France,[30] however, the association between country of birth and late diagnosis did not remain significant after adjusting for socioeconomic status, suggesting that geographical origin may not, itself, be the major determinant of late diagnosis.

The factors associated with late diagnosis may be different to those associated with delayed presentation to care after testing positive. In the ICoNA study, although injecting drug users were less likely to be diagnosed late, they were more likely to experience a delay in presenting for clinical care once diagnosed;[15] this finding has also been reported elsewhere.[31]

CLINICAL IMPLICATIONS OF LATE PRESENTATION

As expected, patients who present to care for the first time when they are already severely immunosuppressed are more likely to have an AIDS-defining condition at the time, or to develop one shortly after.[16] In addition, among those presenting with AIDS, opportunistic infections such as *Pneumocystis jirovecii* pneumonia or toxoplasmosis may be more common in late presenters,[10,16,21] who may also be more likely to present with multiple illnesses within a short time period and to be hospitalized as a result of their first AIDS event.[10,16,21] The greater clinical severity of HIV infection among late presenters is also illustrated by the significant short-term mortality in this group, which is much higher that that recorded among those with an earlier diagnosis.[10,11,16,19]

Over the past decade, the use of inpatient hospital resources by patients with HIV has dramatically decreased, in parallel with a decrease in morbidity associated with the use of HAART.[32] Those diagnosed late now account for a high proportion of resource use, particularly in the first few months after presentation.[16,33] In Canada,[14] the mean annual cost for healthcare in the year after HIV diagnosis has been estimated to be Can$18 488 (US$14 790) for late presenters compared with only Can$8455 (US$6764) for non-late presenters (an increase by a factor of approximately 2.2) (costs converted to 2004 US dollars using OECD Purchasing Power Parity rates).[34] After adjusting for patient characteristics, the estimated excess annual cost attributable to late diagnosis was calculated as Can$9723 (US$7778); this appears to be largely a result of hospital care costs, which are 15 times higher for those diagnosed late. In addition to

increasing costs of care, late diagnosis may be also associated with a decreased cost-effectiveness of combination antiretroviral therapy. Although it has been estimated that the cost-effectiveness ratio for three-drug therapy when started at a CD4 cell count of 200 cells/μl is US$17 000 per quality-adjusted year of life gained, this increases to US$26 000 when therapy is started at a CD4 cell count of less than 50 cells/μl.[35] Interestingly, in a cost-effectiveness analysis performed within the context of a resource-limited setting, the same association between late therapy initiation and a decreased cost-effectiveness was reported.[36]

Antiretroviral drug resistance in patients with undiagnosed long-term HIV infections may be rather common.[37] In a study conducted in 2004 in San Francisco among 3789 individuals undergoing HIV testing, a total of 136 infections were newly detected; of these, 81 were long-term infections and 55 recent or acute infections. A total of 17 drug-resistant cases detected. Of these 12 were long-term HIV infections and five were recent HIV infections. Mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) were the most common resistance pattern detected, present in 11 of 17 cases.[37]

WHAT ARE THE BENEFITS OF EARLIER PRESENTATION?

In addition to the obvious benefits to the individual, the main advantage of earlier diagnosis of HIV is the opportunity that it provides to reduce onward transmission, either by encouraging safer sexual behaviour, or by reducing an individual's infectiveness through the use of HAART. Although a positive HIV diagnosis is usually followed by a reduction in high-risk sexual behaviour,[8] a substantial proportion of individuals diagnosed with HIV continue to engage in these high-risk behaviours, suggesting that this intervention alone is unlikely to have a major impact on the spread of HIV over the longer term. The fact that an individual's infectivity can be reduced by the use of HAART is best illustrated by the dramatic reduction in mother-to-child transmission seen since the mid-1990s. After initial reports from the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group,[38] showing that treatment of the mother and newborn child with zidovudine was associated with a reduction in the risk of mother-to-child transmission, the subsequent increase in the uptake of antenatal HIV testing and the use of antiretroviral treatment (including HAART) during pregnancy, has meant that vertical transmission rates have dropped dramatically.[39] In Europe, the transmission rate declined from 15.5% in 1994 to 2.6% after 1998,[40] whereas in New York City, rates decreased from 11% in 1997 to 3.7% in 2000.[41] Nevertheless, approximately 7% of HIV-infected pregnant women remained undiagnosed at the time of delivery, and these births account for a substantial proportion of the vertically acquired HIV infections that still occur.[39]

Sexual transmission of HIV accounts for the vast majority of new HIV infections worldwide.[42] Not only is there a strong link between plasma HIV RNA and infectiousness by the sexual route,[43] but a positive correlation exists between the plasma viral load and virus shedding in genital secretions, and decreased viral levels in genital secretions after the initiation of HAART parallel decreases in plasma HIV RNA.[44,45] Therefore, although a certain level of infectiousness may remain, even in those with a good virological response to therapy,[46] the use of HAART should result in a significant decrease in HIV infectiousness at a population level. Results from a study of serodiscordant couples, in which an 80% reduction in sexual transmission was reported in the HAART era, support this hypothesis,[9] as do findings from Taiwan, where the HIV transmission rate has halved since HAART became available (although the incidence of other sexually transmitted diseases has remained stable).[47] In contrast, the incidence of HIV has remained stable, and even increased, in some industrialized countries over the past decade,[48–50] suggesting that HIV-infected individuals who remain undiagnosed may play a major role in the spread of the epidemics in these countries. For example, in the United States, the 25% of HIV-infected individuals who are currently unaware of their infection are thought to account for 54–70% of new infections.[51]

STRATEGIES TO ENCOURAGE EARLIER HIV DIAGNOSIS

Over the past decade, most HIV prevention programmes have focused on preventing infections in high-risk individuals, whereas relatively minor emphasis has been placed on earlier diagnosis of those already infected with HIV. Notable exceptions are programmes aimed at diagnosing HIV infection among pregnant women and those that promote easier access to voluntary counselling and testing.[52] Given the potential role of HAART in controlling the spread of the epidemic, however, greater emphasis has now been placed on promoting the earlier diagnosis of HIV infection.[53,54] In 2001, the United States Centers for Disease Control and Prevention (CDC) launched the Serostatus Approach to Fighting the HIV Epidemic (SAFE), an initiative that aims to increase the number of HIV-infected individuals who are aware of their serostatus, and to link these individuals into high-quality care and prevention services, which will help them adhere to HAART and adopt and sustain a reduction in high-risk behaviours.[55] A similar approach, which emphasizes the need for earlier diagnosis, has been proposed in many other countries.[2,56,57]

For any such initiatives to be successful, a number of complementary strategies are needed (Table 2). The first is to ensure that HIV testing is offered routinely in healthcare settings where high-risk individuals are seen frequently. There is consensus that individuals with diseases that share similar routes of transmission to HIV (e.g. sexually transmitted diseases, viral hepatitis), those with signs of immune suppression (e.g. tuberculosis), and those seen in places where individuals with a high prevalence of infection are expected to attend (e.g. drug addiction treatment

TABLE 2. Strategies to encourage earlier HIV diagnosis.

Routine (or opt-out) HIV screening for high-risk individuals:
Those with disease that share similar routes of transmission to HIV (e.g. sexually transmitted diseases, viral hepatitis)
Those with signs of immune suppression (e.g. tuberculosis)
Those attending healthcare settings where individuals with a high prevalence of infection are expected to attend (e.g. drug addiction treatment services)
Those living in areas with high incidence of HIV infection
Routine HIV testing for pregnant women
Targeting specific populations at risk of late testing for HIV (e.g. heterosexuals and members of racial/ethnic minority groups)
Use of rapid HIV tests
Partner notification to reduce transmission and prevent new infections
Social network strategies to identify individuals at high risk of HIV infection and encouraging them to be tested for HIV
Minimize barriers to the acceptability of HIV testing (e.g. reduce the stigma associated with HIV testing)

services) should be routinely offered HIV testing.[53,56] Given the effectiveness of interventions to prevent mother-to-child transmission, routine HIV testing is also recommended for pregnant women. In this latter group, policies that offer HIV testing based on individual risk assessment alone are likely to be ineffective; in one study from the United States, only between 8 and 57% of pregnant women who tested HIV positive had an identified risk factor for HIV infection.[52] Given the tremendous success of interventions in this group, universal antenatal screening for HIV infection appears to be cost-effective compared with a policy of only testing women who request a test or have an identified risk, even when the prevalence of HIV is as low as 0.005%.[58]

In 2001 the CDC recommended routine HIV counselling and testing in acute healthcare settings where the HIV prevalence was 1% or greater;[59] these guidelines have now been revised to recommend routine testing in all healthcare settings for patients aged 13–64 years, unless the local HIV prevalence is known to be less than 0.1%.[60]

The benefits of wide-scale screening for HIV infection in the general population are still under debate.[61] Two studies have estimated that, compared with a policy of no screening, the cost-effectiveness of routine HIV screening in populations with an underlying prevalence of 1% ranges from US$38 000 to US$42 000 per quality-adjusted life-year.[62,63] With an underlying prevalence rate of 0.5%, the cost-effectiveness was still under US$50 000 per quality-adjusted life-year; when the benefits of a reduction in secondary transmission were incorporated into the model, cost-effectiveness remained at this level even if the prevalence dropped to 0.05%.[62] In contrast, when potential benefits for partners were not included in the analysis, the incremental cost-effectiveness of screening in a population with an underlying HIV prevalence of 0.1% was more than US$100 000 per quality-adjusted life year.[63] It should be noted that when planning a universal screening strategy, the operational difficulties of its implementation, the possibility of detracting resources away from other, more cost-effective, prevention interventions, and the risk that fear of stigmatization may represent a major barrier to access to medical care should be carefully considered.

It is also essential that within the context of a policy of routine HIV testing, the practice of obtaining informed consent for testing be maintained.[54] Currently, in most countries, individuals accessing an HIV test undergo pre-test counselling and are required to consent specifically to an HIV test (an 'opt-in' approach). More recently, many programmes have taken an 'opt-out' approach, in which individuals are informed that an HIV test will be included as one of a standard batch of laboratory tests and that they must specifically state if they do not want to be tested.[64] Such 'opt-out' approaches have been associated with greater rates of HIV testing than either opt-in approaches[64,65] or, more surprisingly, mandatory testing.[64]

The second important strategy to encourage earlier diagnosis, is to identify high-risk groups who would not normally seek testing, and to devise strategies that will take HIV testing to these groups. Partner notification, whereby partners of individuals diagnosed with HIV are notified of their risk by physicians or health department personnel and are then referred for counselling and testing, is one such example. In the United States, of 6394 sex or needle-sharing partners identified from individuals with newly diagnosed HIV infection, 10% subsequently tested positive (approximately 20% had already been diagnosed), suggesting that these programmes may have some success in identifying individuals with HIV.[66] Despite this, cases identified through partner notification still constitute a minority of new HIV diagnoses. More recently, the CDC funded a series of projects aimed at evaluating the effectiveness of using a social network strategy to identify individuals at risk of HIV infection. In these projects, HIV-infected and high-risk HIV-negative individuals identified people from their social, sexual, and drug-use networks believed to be at risk of infection and encouraged them to attend counselling and testing programmes.[67] Preliminary evidence suggests that these interventions may identify previously undiagnosed HIV-infected individuals as well as encouraging referral to care among those already diagnosed.

A third key strategy is to provide testing services that are appropriate to the personal and cultural needs of clients, and to minimize any barriers to the acceptability of testing.[59] In this context, interventions, including those based on rapid HIV testing, which could enable the provision of HIV testing in a variety of non-medical settings, need to be fully evaluated.[55] It is clear, however, that efforts to promote the early diagnosis of HIV infection will fail unless there are continued efforts to reduce the stigma associated with HIV infection, as this may be a major reason for not having an HIV test.[68]

Finally, it is worth remembering that early testing does not necessarily equate to early presentation for care, and interventions aimed at improving referral to care are needed, especially for those at risk of delayed access to care, such as drug users and marginalized population groups.[18,69] It also

goes without saying that to reap the full benefit of an early diagnosis of HIV infection, both at an individual and a population level, there must be provision of high-quality treatment and prevention services to all individuals in both industrialized and in resource-limited countries.[2,55]

In conclusion, late diagnosis is a major contributory factor to the continued incidence of AIDS and mortality among HIV-infected individuals, and is an important obstacle to the effective prevention of the further spread of infection. Attempts should thus continue to be made to diagnose individuals at an earlier stage of HIV infection.

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