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SHORT COMMUNICATION

Late presentation of HIV infection: a consensus definition

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Objectives

Across Europe, almost a third of individuals infected with HIV do not enter health care until late in the course of their infection. Surveillance to identify the extent to which late presentation occurs remains inadequate across Europe and is further complicated by the lack of a common clinical definition of late presentation. The objective of this article is to present a consensus definition of late presentation of HIV infection.

Methods

Over the past year, two initiatives have moved towards a harmonized definition. In spring 2009, they joined efforts to identify a common definition of what is meant by a 'late-presenting' patient.

Results

Two definitions were agreed upon, as follows. Late presentation: persons presenting for care with a CD4 count below 350 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count. Presentation with advanced HIV disease: persons presenting for care with a CD4 count below 200 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count.

Conclusion

The European Late Presenter Consensus working group believe it would be beneficial if all national health agencies, institutions, and researchers were able to implement this definition (either on its own or alongside their own preferred definition) when reporting surveillance or research data relating to late presentation of HIV infection.

Keywords: definition, diagnosis, Europe, HIV, late presentation

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Background

Across Europe, almost one-third of individuals infected with HIV do not enter health care until late in the course of their infection [1,2]. Despite attempts to encourage earlier testing for HIV, this situation has remained stationary for several years without evidence of improvement. Late presentation for care is harmful to the infected person [3–5] is more costly [6] and is harmful to society [7]. Surveillance to identify the extent to which late presentation occurs is therefore crucial and remains inadequate across Europe, and is further complicated by the lack of a common clinical definition of late presentation.

In untreated HIV-infected persons, the risk of developing an AIDS-defining condition increases exponentially as the CD4 cell count drops, being particularly high in those with a CD4 count <200 cells/μL [8,9]. The longer therapy is delayed when clinically indicated, the poorer the patient outcome [10]. Recent guidelines [from the European AIDS

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Clinical Society (EACS), World Health Organization (WHO) Europe, International AIDS Society (IAS) and British HIV Association (BHIVA)] advocate antiretroviral therapy (ART) for all untreated persons with a CD4 count <350 cells/μL, and for some patient groups with a higher CD4 cell count [11–15]. Recently, it has been suggested that HIV may also accelerate the course of various end-organ diseases, such as cardiovascular disease, renal disease and liver disease, and may increase the risk of contracting non-AIDS-defining malignancies [16,17]. This suggestion was initially supported by data from the SMART trial, which found that those interrupting ART had higher rates of these diseases than those who remained on ART, but a strong link between the CD4 cell count and many non-AIDS diseases has also been seen in several observational studies [17]. These diseases are more common than AIDS diseases at CD4 counts higher than 350 cells/μl [18].

The process of reaching a consensus of the definition of a late presenter

In the literature, more than 20 different definitions have been cited for a late presenter [19]. A common definition would be helpful to more effectively manage late presentation of HIV disease across Europe and elsewhere. It would also facilitate cross-country or regional comparisons, and allow investigation of temporal trends after targeted interventions. Of note, health policy is a European Union (EU) member-state matter and not defined at the EU level; this in part explains why divergent definitions have emerged in various countries across Europe. Over the past year, two initiatives have moved towards a harmonized definition. In spring 2009, they joined efforts to identify a common definition of what is meant by a 'late-presenting' patient.

The 'Late presentation for HIV treatment in Europe' programme was initiated in November 2008 in Glasgow and culminated in March 2009 with a 2-day meeting on the challenges of late presentation for HIV treatment in Europe. The project focused on different aspects of late presentation [20]. The group highlighted the need for a common definition of late presentation.

The HIV in Europe initiative provides a European platform for exchange and activities to encourage early diagnosis and earlier care of HIV-infected patients across Europe (www.hiveurope.eu). The initiative has since 2007 gathered key European constituencies (civil society, health professionals and health policy makers) to discuss the prevailing obstacles to earlier diagnosis of HIV infection. As the HIV in Europe initiative focuses on attempts to ensure that HIV-infected patients enter care earlier in the course of their infection than is currently the case, the use of diverse definitions of late presentation was already identified as a major limitation in 2007 when attempting to obtain a precise estimate of the size of the problem, and when attempting to understand trends in this estimate over time.

The consensus definition was reached in October 2009 and presented at the HIV in Europe 2009 Conference in the Nobel Forum in Stockholm and at the EACS Conference in Cologne in November 2009, where the consensus definition appeared in several presentations [21,22].

The consensus definition of late presentation for HIV care

As a premise for the definition, it was agreed that, while the definition should be valid for identifying persons at particularly increased risk of clinical disease progression, it should also help to improve surveillance and satisfy public health needs.

Two definitions were agreed upon, as follows.

- *Late presentation:* Persons presenting for care with a CD4 count below 350 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count.
- *Presentation with advanced HIV disease:* Persons presenting for care with a CD4 count below 200 cells/μL or presenting with an AIDS-defining event, regardless of the CD4 cell count.

The term 'late presentation' should be used to refer to all HIV-infected people who enter care at a stage of their disease where current guidelines suggest that they are unable to fully benefit from ART. In contrast, the term 'presentation with advanced HIV disease' should be reserved for the subgroup of these late presenters who are additionally at greater imminent risk of severe disease and death. As such, patients with a CD4 count <200 cells/μL will meet both criteria and will be both 'late presenters' and 'presenters with advanced HIV disease'. Furthermore, any person with an AIDS-defining condition will also meet both criteria, regardless of his/her CD4 cell count.

Of note, the term 'presentation for care' means attendance at a health care facility that is able to monitor progression of HIV infection and initiate appropriate medical care, including ART, as appropriate. Diagnosis of HIV infection alone does not signify presentation for care. It is recognized, and highly important to ensure, that earlier diagnosis of HIV infection is linked to appropriate access to care.

Although not necessary for the classification of late presenters, it is advisable to repeat the CD4 cell count because of laboratory variability in its measurement, and the fact that some individuals with certain conditions (e.g. acute HIV infection, other ongoing viral infections and pregnancy) or on certain treatments (e.g. anti-cancer and

other types of chemotherapy with bone marrow suppressive potential) may experience a temporary drop in CD4 cell count. If such a confirmatory CD4 cell count measurement is performed, both measurements should be below the threshold for the patient to fulfil the definition.

Discussion and conclusions

The consensus definitions of persons presenting late for HIV care and presenting with advanced HIV diseases given in this paper will hopefully end the long-standing debate and the subsequent confusion regarding what is actually meant by a 'late presenter'. Such a central concept in public health is best served when a common definition exists. A similar definition has recently been proposed by a group of UK investigators [23], and hence this report confirms that a consensus has been reached – in a parallel process – also on a European level. Europe-wide consensus on this issue is critical in formulating a continent-wide response to this public health crisis.

Current guidance on the use of ART is of utmost importance in our consensus definition of a late presenter. Until 2007, ART was recommended to be deferred in asymptomatic persons until their CD4 count reached 200 cells/μL [24], but the guidelines then changed when multiple studies demonstrated that persons living with HIV and with a current CD4 count in the range of 200–350 cells/μL remained at significant risk of contracting opportunistic diseases [25, 26]. The findings from the SMART trial strongly supported this policy of initiating therapy in people with CD4 count <350 cells/μL. Therefore, initiation of ART when the CD4 count nears 350 cells/μL would reduce the incidence of such events. Serious non-AIDS events are observed at a higher incidence than AIDS events in persons living with CD4 counts >350 cells/μL, particularly among those with an elevated underlying risk of such events [18, 27].

The December 2009 Department of Health and Human Services Antiretroviral (ARV) Guidelines for Adults and Adolescents recommend starting ARV therapy for patients with a CD4 count <500 cells/μL [28]. This controversial recommendation has not received general support across Europe at the present time. However, while our proposed threshold value of 350 cells/μL corresponds to the level at which ART is currently recommended in Europe, our proposed definition will not automatically change if future European guidelines change. Even if there is shown to be a relative benefit of starting ART at higher levels than at a CD4 count of 350 cells/μL (a point currently disputed), it is not evident that the definition of late presentation should change. This is because of the low risk of disease progression in people with CD4 counts >350 cells/μL and the fact that the time from infection to, for example, a CD4 count <500 cells/μL is relatively short, diluting the concept of 'late presentation' as a public health issue. The consensus group will reconvene to reconsider the issue at a time when (if ever) guidelines are consistently recommending starting ART earlier.

The definitions of 'late presentation' and 'presentation with advanced HIV disease' can be used in very diverse settings and for many purposes. It provides a unified way to define the problem, thereby targeting appropriate interventions. It will permit further studies to be conducted across the European continent to determine the size of the population at risk, and to identify vulnerable groups and risk factors for those patients with HIV infection presenting late for care. It will also facilitate studies of the social and medical barriers that may currently be limiting access to health care in different European countries, and studies on access to ART for late presenters across the continent. The definitions should also be viewed as an instrument that enables ongoing monitoring, and as such can be used to evaluate interventions aimed at reducing the number of late presenters.

We believe it would be beneficial if all national health agencies, institutions and researchers were able to implement this definition (either on its own or alongside their own preferred definition) when reporting surveillance or research data relating to late presentation of HIV infection. In order to achieve this, these agencies and institutions must ensure adequate capture of data on both the CD4 cell count and presence of AIDS at presentation. Such moves will facilitate comparisons between countries and assessment of trends over time.

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