HIV in hiding: Methods and data requirements for the estimation of the number of people living with undiagnosed HIV

Working Group on Estimation of HIV Prevalence in Europe*

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Abstract

Many people who are HIV positive are unaware of their infection status. Estimation of the number of people with undiagnosed HIV within a country or region is vital for understanding future need for treatment and for motivating testing programs. We review the available estimation approaches which are in current use. They can be broadly classified into those based on prevalence surveys and those based on reported HIV and AIDS cases. Estimation based on prevalence data requires data from regular prevalence surveys in different population groups together with estimates of the size of these groups. The recommended minimal case reporting data needed to estimate the number of patients with undiagnosed HIV are HIV diagnoses, including CD4 count at diagnosis and whether there has been an AIDS diagnosis in the three months before or after HIV diagnosis, and data on deaths in people with HIV. We would encourage all countries to implement several methods which will help develop our understanding of strengths and weaknesses of the various methods.

Introduction

HIV remains a major public health problem for Europe. It has been estimated that there are approximately 2.2 million people living with the virus in the WHO European Region, and approaching 1 million in the European Union and 1.4 million in eastern Europe and central Asia[1;2]. As HIV does not generally produce symptoms which lead to diagnosis around the time of infection, there are many people infected with HIV who are not diagnosed. Consequently, estimates of the total number of people with HIV, both undiagnosed and diagnosed, are imprecise. It is reported that as many as one-third of those infected in the European Union countries are unaware of their HIV status[3] and in some eastern European countries up to 60% of persons living with HIV/AIDS are undiagnosed[2]. One key step towards Europe fully responding to the threat of HIV is for all countries within the Region to produce updated estimates of the number of people living with HIV. This is important for understanding the true burden of HIV infection, the corresponding need for treatment and for intensifying HIV testing; i.e. increasing both the number of people who are tested and the frequency with which individuals get tested. It is important that testing is sufficiently frequent and widespread to ensure that people with HIV are diagnosed as rapidly as possible to reduce the risk of transmission[4] through unprotected sex or sharing of injecting equipment and to ensure that individuals receive appropriate and timely treatment and care[5-10]. Estimates of the number of people with HIV are also important for countries to use as a basis for projecting healthcare and drug treatment needs.

Currently, there is no consensus approach in European countries to estimating numbers of people with HIV. Different estimation approaches exist, using different sources of data, and many countries do not appear to produce any estimates. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health

Organization (WHO), as part of their global approach to tracking and predicting HIV trends in all countries of the world, have produced estimates of numbers of people living with HIV, annual numbers of new infections, and of AIDS mortality for every country for many years (using an approach based on prevalence surveys described below). In spite of methodological improvements and greater within-country involvement in use of surveillance data-based approaches, better estimation techniques and even greater country involvement would be of benefit. Since many methods using different data sources have been proposed, there is a widespread perceived need for some guidance on the various methods to set out in relatively simple terms the methods that have been developed, the data required to be collected, and how to go about the practical steps of actually implementing the methods.

Here we review the available approaches in the hope that this will further stimulate countries to produce estimates as a step towards a more integrated and comprehensive approach across Europe. It is recognised that the scope of this review is limited, and does not encompass methods for assessing trends in HIV incidence or modelling HIV transmission, but we believe it will help all European countries with obtaining the initial most basic piece of information about their HIV epidemic.

Description of data sources and data collection methods

Various sources of data may be used as a basis for estimating the number of people living with HIV. These can be broadly divided into: cross-sectional studies which provide estimates of HIV prevalence in specific risk categories such as men who have sex with men (MSM) or people who inject drugs (PWID); studies to estimate the sizes of these population groups; case reporting of HIV diagnoses, AIDS, and HIV-related deaths; and cross-sectional studies of patients in care.

Prevalence surveys

Prevalence surveys are performed on a sample of people from a specific risk category to obtain an estimate of the proportion of people with HIV infection. Estimates are subject to sampling error, which is dependent on the number of people in the sample and is quantifiable. The sample may not be fully representative of the risk category, so estimates are subject to bias which cannot always be accounted for, although some methods which use multiple prevalence surveys do account for possible bias[11].

Case reporting

HIV diagnoses

Many countries have surveillance systems so that information on people that have been diagnosed with HIV is reported. Besides basic demographic data, the information reported can include: date of diagnosis; the mode of HIV transmission; the first CD4 count after diagnosis; whether an AIDS condition or other symptoms

were present at the time of HIV diagnosis; or whether the person was recently infected, on the basis of data from antibody assays or a recent negative test.

Reports of HIV diagnoses originate from laboratories or clinicians. Often, people are tested in more than one laboratory and seen in more than one clinic during the course of their infection. As cross-linking can be problematic unless patient identifiers are accurately recorded, there is a risk of double counting, and in some countries privacy laws may prohibit such linkage. Reporting delays are another well-known problem. European comparisons are further complicated by the variable quality and coverage of national surveillance systems and because national HIV data are not reported by all countries in the WHO European Region[12].

AIDS cases

Reporting of AIDS cases has traditionally provided the basis for much of the surveillance of the epidemic, but has been perceived as less useful since the advent of effective therapy[13]. However, as cases of AIDS in people who have not previously been diagnosed with HIV can provide information on the size of the undiagnosed population, this remains an important source of data that should continue to be prioritized.

Deaths in people with HIV

Several methods for estimating the number of people with HIV involve estimating the number of people who have ever been infected with HIV. As calculation of the number of people living with HIV requires subtraction of the number who have died, reporting of deaths in people with HIV is important for generating estimates. Death is reported by clinicians but also, in several countries, linkage is made to national death

registers so that deaths in people with diagnosed HIV can be identified. This relies on accurate identifier information for cross-linking data. The number of deaths is subject to bias as some people living with HIV may never be diagnosed as HIV-positive, even at death.

Cross-sectional assessment of people seen for HIV care

In some European countries, such as the United Kingdom, clinicians are regularly asked to report on all people seen for care. The data include information such as the latest CD4 count and whether the patient is on therapy. In the ideal situation, such as in the Netherlands, all people diagnosed with HIV are followed longitudinally so that all information collected as part of routine clinical care is available for public health purposes.

Approaches to estimating the number of people with undiagnosed HIV

Methods based on prevalence surveys

The estimation of overall HIV prevalence by combining estimates of HIV prevalence within risk categories with estimates of the size of each risk category is known as the direct method[14-16]. The population is divided up according to HIV risk category: the risk categories used may vary by setting. Within each category, HIV prevalence and the number of people are estimated, then multiplied together to produce an estimated number with HIV: this is summed across all risk categories to estimate the total number with HIV. The total number with undiagnosed HIV can be obtained by subtracting the number with diagnosed HIV, if this is available, either overall, or within each category prior to summing across categories. In a variation on this approach, if the information is available then the prevalence of undiagnosed HIV in each risk category may be estimated directly from the prevalence survey.

This approach provides the basis for UNAIDS/WHO estimates via the Workbook and Estimation and Projection Package (EPP) approaches[17-19], the latter using a Bayesian approach to estimate uncertainty. Workbook and EPP are closely linked with the Spectrum programme[18;20].

Prevalence survey sampling issues

It is unlikely that HIV prevalence will be uniform across a transmission risk category. For example, for MSM and PWID there is a range of risk activity, and it is probable that HIV prevalence will increase with increasing risk activity. If a prevalence survey

uses a sampling approach targeting those with the highest levels of risk, then applying this prevalence to the total estimated population of MSM or PWID will overestimate HIV prevalence. A potential solution to this, adopted in some applications of this method, is to treat high and low risk MSM as separate risk groups. This reduces the possibility of bias, but requires estimation of the respective sizes and HIV prevalence of the separate risk groups.

Estimation of the size of population groups with high risk behaviour

A discussion of various methods for estimating the size of risk categories used in prevalence surveys is contained in UNAIDS/WHO guidelines[11], and some developments and applications are discussed in a recent report of the UNAIDS Reference Group on Estimates, Modelling and Projections[21]. The most appropriate method varies according to risk category. Capture-recapture, multiplier, census and nomination methods have all been used. Other indirect estimation methods - such as benchmark calculations which make use of police arrests, drug dependence treatment and drug related deaths and other existing data sources - are increasingly used to estimate the size of PWID populations. The size of some populations (such as MSM and PWID) may also be estimated directly from household surveys, however they generally underestimate the prevalence of stigmatized behaviours. The network scale-up method has recently been developed and field testing is ongoing: this method uses data on a survey respondent's network of acquaintances rather than data on the respondent themselves. All of these methods suffer from potential biases.

The Multi-parameter Evidence Synthesis (MPES) method

The MPES method[22-24] is based on the principles of prevalence surveys and estimation of the size of transmission risk populations but, unlike other approaches, is designed to include the often multiple sources of data providing information on both prevalence and risk size. The MPES method synthesises the multiple diverse types of evidence, performing a formal statistical 'triangulation' of these data, in a framework that also allows the detection of possible conflicts between evidence informing the same quantity or parameter. Conflicts may arise due to the bias that must exist in some sources of information and the MPES method allows explicit modelling of these biases to resolve inconsistency. Estimation is performed using a Bayesian approach, ensuring the correct and coherent propagation of uncertainty in the data and estimation process through to final estimates of the numbers with HIV.

Methods based on reporting of HIV/AIDS diagnoses involving calculation of cumulative incidence of HIV

The methods described in this section are all primarily for estimating the historical incidence of HIV infection as well as the current incidence, although the latter is estimated with considerable uncertainty. The cumulative number of deaths in people with HIV is required to estimate current prevalence: this is subtracted from the cumulative HIV incidence during the epidemic.

The back-calculation method was initially described and used early in the HIV epidemic[25;26]. At the time, effective treatment was not available so HIV-positive individuals progressed to AIDS according to the natural, variable course of infection. Using the number of reported AIDS cases in each year, and the assumed known distribution of time from infection to AIDS, it was possible to estimate the number of people infected in each previous year. If data on cumulative HIV-related deaths were

available and accurate, it was possible to estimate the number of people living with HIV and hence, using the number diagnosed with HIV, the number of people living with undiagnosed HIV.

With the use of effective antiretroviral therapy (ART), most people with HIV do not progress to AIDS. Therefore back-calculation models based exclusively on incident AIDS cases are no longer viable because the distribution of time from infection to AIDS is difficult to estimate. Furthermore, even if it were possible to estimate the distribution of time from infection to AIDS, this method could not provide reliable information on recent trends in HIV incidence because individuals currently diagnosed with AIDS are likely to have been infected with HIV for some time. Consequently, this method is generally considered to be no longer relevant. The back-calculation method has been modified to consider the number of HIV diagnoses instead of the number of AIDS cases[27;28]. Some variants of this method are described below[29-33]. Each of the methods described here makes use of techniques for smoothing the incidence curve. They also all make some correction for reporting delay of AIDS and HIV cases. We refer to each of these approaches as a method, although they are in some ways variants of the same method. These methods are mainly applied to the adult population only.

Cambridge method[29]

Sweeting et al. (MRC Biostatistics Unit, Cambridge, United Kingdom) describe Bayesian back-calculation using a multi-state model, and apply it to United Kingdom Health Protection Agency (HPA) data on HIV in MSM[29]. The method is re-considered by Birrell and applied to an updated dataset[34]. The data required are number of new HIV diagnoses per calendar quarter, with data on AIDS diagnosis occurring in the same calendar quarter (late diagnosis). CD4 counts around diagnosis for a subset of

the diagnoses are strongly recommended but not essential, and data should be stratified by risk group.

Atlanta method[30]

Hall et al. (Center for Disease Control and Prevention, Atlanta, United States) describe their extended back-calculation method and use it to generate estimates of HIV incidence in the United States, and compare with estimates obtained using assays that differentiate between recent and longstanding infection[30]. The extended back-calculation method was subsequently used to obtain estimates of HIV prevalence in the United States, including estimates of undiagnosed HIV prevalence[35;36]. In addition to demographic information, the data required are the number of new HIV diagnoses per calendar year with information on whether AIDS was diagnosed within the same calendar year as HIV (disease severity).

Ottawa / Sydney method [31]

Wand et al. (National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia) describe and adopt a methodology developed by colleagues in the Public Health Agency of Canada. Their extended back-calculation method is used to reconstruct the HIV epidemic in Australia in the MSM, PWID, and heterosexual exposure categories[31]. The same method was also used in different provinces in Canada, to determine the national HIV incidence and prevalence[37]. The data required are HIV diagnoses, with additional data on whether the HIV infection is recent or not using either enhanced surveillance (evidence of a prior negative test, or a diagnosis of seroconversion illness, or an indeterminate western blot within one year of HIV diagnosis), or using laboratory techniques. This methodology does not

require a test for a biomarker such as CD4 count. The method also uses data on AIDS diagnoses in years before effective treatment was available.

Paris method [32]

Ndawinz et al. (INSERM U943, Paris, France) describe an extended back-calculation method, which is used to estimate both the incidence of HIV infection in France and the time-dependent intervals of time from infection to diagnosis in different transmission categories[32]. If HIV and AIDS case surveillance has been in place for some time, the method can also be used to estimate the HIV prevalence and the number of undiagnosed people with HIV. The data required are times of HIV diagnosis, risk category and clinical status at diagnosis divided into three categories: primary infection, AIDS and other clinical statuses.

Bordeaux method [33]

The method described by Sommen et. al. (INSERM U897, Bordeaux, France) is based on a Markov model which, unlike the other methods in this section, models treatment uptake. The method is illustrated using HIV/AIDS surveillance data on MSM in France. The data required are HIV and AIDS diagnosis data. The method is described in a context where HIV diagnosis data is only available for the most recent years, but can be adapted for situations where HIV diagnosis monitoring has been in place for longer.

Methods based on CD4 count and simultaneous HIV/AIDS

Each year, a proportion of the undiagnosed population will present with AIDS and be diagnosed with HIV at the same time (referred to as simultaneous HIV/AIDS diagnosis). As the incidence of AIDS at a given CD4 count can be estimated from cohort studies, we can directly use data on the number of simultaneous HIV/AIDS diagnoses during a given year to estimate the size of the undiagnosed population for a given risk group[38;39]. Two variations of this method are described, both of which require the number of simultaneous HIV/AIDS diagnoses in a year, and assume that the underascertainment rate of simultaneous HIV/AIDS diagnoses can be estimated. The uncertainty associated with each estimate is evaluated by assuming the AIDS incidence varies according to a Normal distribution, and that the number of simultaneous HIV/AIDS diagnoses varies according to a Poisson distribution. Both methods could be refined by assuming that a continuous function describes the relationship between CD4 count and AIDS rate.

London method 1

This requires the CD4 count at HIV/AIDS diagnosis. For each CD4 count stratum, the number of people with undiagnosed HIV can be estimated by dividing the number of simultaneous HIV/AIDS diagnoses in that stratum by the CD4-specific AIDS rate. Summing across all strata gives the total number with undiagnosed HIV. For high CD4 count strata in which the AIDS rate is low the estimates will be associated with considerable uncertainty.

London method 2

This method assumes that CD4 count in the undiagnosed population can be approximated by the CD4 count at diagnosis in patients presenting for care with asymptomatic HIV. Consequently data may also be required on whether patients are

asymptomatic at HIV diagnosis, if this information is not available from appropriate cohort studies.

Transmission model approach

For some countries, models which reconstruct the processes of transmission of HIV, diagnosis, treatment and occurrence of AIDS and death have been developed and fitted to multiple data sources[40;41]. The purpose of such models is not restricted to estimation of the current number with HIV but this nevertheless can be obtained from them. These methods are not suitable for use by countries which are initially focussed only on obtaining an estimate of the number of people with HIV. However, their use is possible when there are multiple sources of data and it may be possible for countries to set up ad hoc collaborations to implement such models, which are useful for analysing trends and the reasons behind them, and for predicting incidence.

Discussion

We have reviewed the various methods for estimating the number of people with undiagnosed HIV. Each approach has its strengths but also each has limitations. All methods involve significant assumptions which generally cannot be checked. The main limitation of the approach based on prevalence surveys is the need to match up risk categories for which prevalence estimates have been obtained with estimates of the size of those categories. If, for example, prevalence surveys tend to be carried out in MSM with relatively high numbers of unprotected sex partners it is important that this estimate is applied to a population of similar risk activity, and not to the entire population of men who have reported a male partner in the past few years.

The methods based on estimation of cumulative incidence of HIV infections aim to reconstruct the epidemic and have the key limitation that it is difficult to distinguish changes in diagnosis rates from changes in incidence. This distinction may be helped by additional data at diagnosis on whether AIDS is present, the CD4 count, or whether infection was recent. These methods also rely on the assumption that all people infected with HIV will be diagnosed as such, either during their life or at death, which may be true to a varying extent in different countries depending on the countries' health infrastructure and HIV testing practices. They also require data on the cumulative total number of deaths in people with HIV, which may be underestimated by the registered number of deaths.

The methods based on data on surveillance of simultaneous HIV/AIDS cases are limited by the assumption that the CD4 count at diagnosis in asymptomatic people reflects the distribution in the undiagnosed population. The estimates of numbers of undiagnosed people with high CD4 count may be unstable due to a very large

multiplication factor being applied to those presenting with simultaneous HIV/AIDS at higher CD4 counts. The methods also rely heavily on high levels of ascertainment of simultaneous HIV/AIDS cases.

It is desirable that as many of the approaches as possible be implemented to build up the most reliable overall picture of the number of people living with HIV and the bounds of uncertainty around this. In the short-term, the methods that a country can apply will be dictated by the data sources available, but this review is intended to also provide guidance to countries on which data they wish to start to collect. The data required to apply the available methods are summarised in Figure 1.

While methods involving prevalence surveys have the potential to provide a comprehensive assessment of the state of the epidemic, the collection of case reporting data also has an important role in allowing the estimation of the number of people with undiagnosed HIV. We recommend that in order to produce estimates of the number of patients with undiagnosed HIV, the minimal case reporting data that a country should collect are HIV diagnoses, including CD4 count at diagnosis and whether there has been an AIDS diagnoses in the three months before or after HIV diagnosis, and data on deaths in people with HIV. However, to allow a greater range of methods to be used, we suggest that more extensive surveillance data be collected, including data on whether infection is recent.

As more European countries employ multiple methods[42], it may become clear whether there are systematic differences in results from the various estimation approaches, with perhaps one method producing higher or lower estimates than others. Efforts to try to understand the reasons behind such discrepancies will help to move us forward with improving data collection methods.

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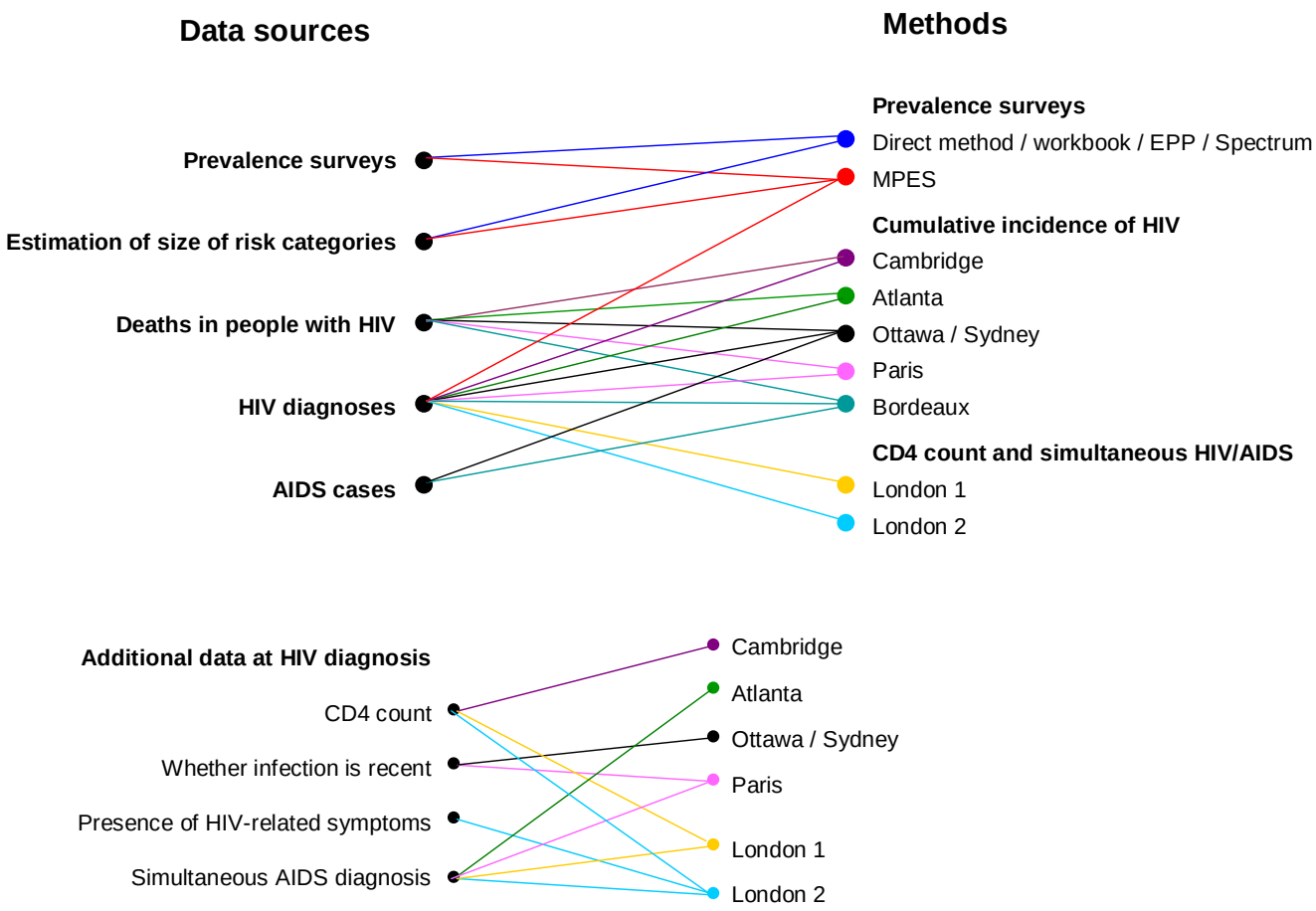
Figure 1. Summary of available methods and the data required



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