

# EPI ALERT



UNAIDS quarterly update on HIV epidemiology / 1Q 2010

---

## Methods for estimating HIV incidence

### Introduction

*The prevalence of HIV has been used for many years to assess epidemic patterns and trends. However, it is increasingly difficult to interpret prevalence data because of changes in the survival period from infection to death as a result of the increased provision of antiretroviral therapy. The incidence of HIV infection, the rate at which new infections are acquired over a defined time period, is much more sensitive to the changing dynamics of disease transmission and provides a more sensitive measure of the current state of the epidemic and of the impact of programmes. However, while estimates of HIV prevalence are widely available from sentinel surveillance or cross-sectional studies, estimates of HIV incidence are more difficult and more costly to obtain.*

*This article provides a summary of current issues and recommended methods for estimating HIV incidence, including cohort studies for direct measures of incidence, mathematical models that can be used to estimate incidence indirectly from HIV prevalence data and biological assays based on HIV antigen or antibody measurements to distinguish recent from established HIV infections.*



Accurate estimates of incidence are essential for monitoring the HIV epidemic and for evaluating the impact of interventions.

## EPI ALERT

### Prospective cohort studies

Following uninfected people over time until HIV seroconversion in large population cohorts is generally the gold standard for measuring the incidence of infection. However, such studies are very costly and are logistically and ethically difficult to carry out, and estimates are generally only available after a long period of follow-up. Furthermore, intrinsic biases may occur because of increased exposure to prevention programmes, counselling, treatment and care practices within the study setting, or through loss to follow up of some participants. To date, few cohort studies have been conducted to estimate HIV incidence and those that have been conducted were limited to small geographic areas.

### Mathematical models

Mathematical and statistical models can be used to estimate HIV incidence with reasonable

levels of confidence. Several models have been developed over time that generally depend on reliable HIV prevalence data and on assumptions about survival after infection. These methods include, for example, dynamical models, demographic models, back-calculation techniques and birth cohort methods.<sup>1-4</sup>

Among the most commonly used methods to derive HIV incidence is the UNAIDS/WHO recommended Estimation and Projection Package (EPP) and Spectrum AIDS Impact Model. EPP fits an epidemiological model to observed HIV prevalence data collected over time using maximum likelihood procedures, while Bayesian techniques are employed to estimate the level of uncertainty around the epidemic curve.<sup>5</sup> EPP version 2009 calculates incidence from HIV prevalence by taking account of the number of people receiving antiretroviral therapy. Together with the epidemic curve

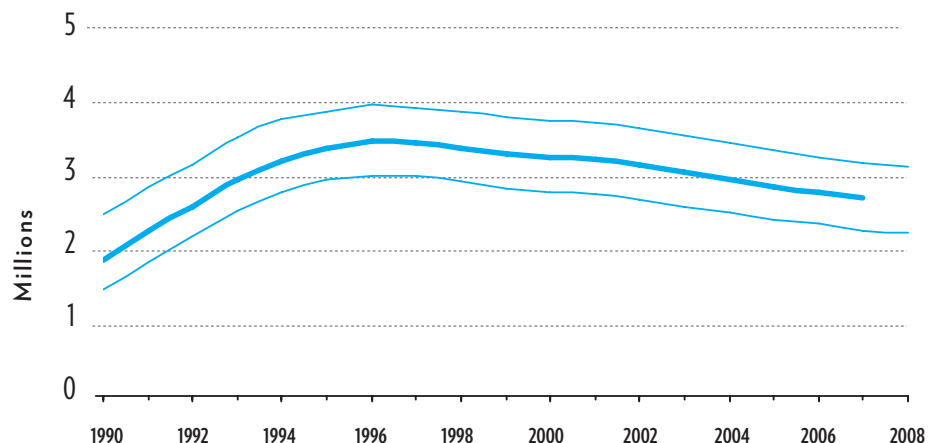


Figure 1. Number of people estimated to be newly infected globally between 1990 and 2008. Source: 2009 UNAIDS epidemic update.<sup>7</sup>

produced in EPP, the Spectrum software uses demographic data, information on adult and child treatment coverage and assumptions about the epidemiology of HIV to generate estimates of national (adult and child) HIV prevalence, incidence, mortality and treatment needs.<sup>6</sup> These methods, which have been developed with the guidance of and using recommendations from the UNAIDS Reference Group on Estimates, Modelling and Projections, have been used in more than 120 countries worldwide to provide national, regional and global estimates of the impact of HIV. Using these methods, UNAIDS estimated that there were 2.7 million [2.4–3.0 million] new HIV infections in 2008 (Figure 1).<sup>7</sup>

A model developed by the South African Actuarial Society (ASSA)<sup>8</sup> has been used by some countries in southern Africa (South Africa and Botswana) to project the demographic impact of HIV, with results consistent with those obtained from Spectrum.

Hallett et al., on behalf of the ALPHA Network,<sup>9</sup> have recently developed methods to estimate HIV incidence by age in the general population using successive rounds of cross-sectional prevalence data. The methods examine the change in HIV prevalence in a cohort observed at two time points,



allowing for changes due to new infections and mortality among infected and uninfected persons, using either cohort mortality rates or using the distribution of survival after HIV infection. The modelled estimates of Incidence showed good agreement with those obtained directly from three community-based cohorts in Africa.<sup>9</sup> The model, which has been extended to take account of the effect of antiretroviral therapy on prevalence, has already been applied to data from several countries<sup>10</sup> and is highly recommended for use in other countries that have done (or are planning to do) more than one national HIV survey.

Another method that has recently been used widely is the UNAIDS model to estimate the distribution of new HIV infections by modes of transmission for a one-year period.<sup>11</sup> The modes

of transmission model was developed to guide prevention activities in countries by identifying those groups at highest risk of HIV infection and to make countries aware of changing patterns of HIV risk. The model requires data on risk behaviour, population sizes, prevalence of HIV and sexually transmitted infections by risk group, and application is therefore limited to those countries that have the required data. In the absence of reliable data, uncertainty ranges are likely to be very wide. The Asian Epidemic Model (AEM) was developed to assess infection patterns in risk groups over time.<sup>12</sup> The AEM model replicates the key processes driving HIV transmission in Asia and offers opportunities to explore the effectiveness of different intervention and care programmes. The model requires



**The use of mathematical models currently remains the most common method for estimating HIV incidence.**

extensive behavioural input data over time and the application has been limited to only a few countries for which such data are available.

Back-calculation techniques have been used mainly in developed countries with reliable data on the number of AIDS diagnoses over time and with information on the distribution of the incubation period. More recently, extended back-calculation methods have been developed to overcome some of the shortcomings of the original methods, such as the modification of parameters by the use of antiretroviral therapy, by utilizing more information about AIDS cases than before.<sup>13,14</sup>

Trends in HIV prevalence among young people aged 15 to 24 years have been suggested as a surrogate measure for trends in incidence.<sup>15</sup> As the onset of sexual activity in this age group is expected to be recent, the prevalence should reflect recent infections. It has been shown that HIV prevalence among young pregnant women (aged 15 to 24 years) attending antenatal clinics can provide reasonable estimates of incidence under stable conditions.<sup>16</sup>

### Biological assays for estimating HIV incidence

Several antibody assays and testing strategies based on HIV antigens, RNA or HIV antibodies have been developed over the past 20 years to distinguish recent from established HIV infections. While some of these methods have been used in several settings around the world, work still needs to be done to validate and calibrate assays and algorithms for

estimating incidence from cross-sectional collection of blood specimens.<sup>17</sup>

The advantage of these assays is that they can be carried out retrospectively on stored blood samples from cross-sectional studies, and they are cheaper and simpler to perform than following cohort studies. However, there are several limitations of the assays that currently limit their widespread applicability, the most important of which relate to the estimation of the window period, which varies substantially by HIV subtype and host population, low reproducibility and the high level of misclassification of the tests.

The serological testing algorithm for recent HIV seroconversion (STARHS) generally measures the immunological response against the virus based on specific HIV antibody concentration, proportion, isotype or avidity. The duration of the period from seroconversion (when antibodies are detectable) to the cut-off value that defines the established infection status of the test for recent infection, or the window period, must be well defined and is essential to the STARHS assays' ability to provide a population incidence rate.<sup>18</sup>

A number of different assays can be used within STARHS, including the 'detuned' ELISA and the BED capture enzyme immunoassay (BED). The sensitive/less-sensitive testing strategy (or 'detuned' assay) was developed to provide a simple laboratory tool to detect recent seroconversion in a cross-sectional population.<sup>19</sup> Generally,



blood samples testing positive on a standard sensitive ELISA but negative on a less sensitive assay are classified as recent infections.

To overcome some of the limitations of the sensitive/less-sensitive assays, which include variability in the window period and subtype-dependent performance, the BED assay was developed to detect HIV infection by measuring the HIV-specific proportion of IgG.<sup>20,21</sup> However, differences in window periods between subtypes still occur<sup>22</sup> and an additional limitation of the BED assay is that a significant proportion of people who have been infected for longer than the window period never develop a significant BED response and appear to have been infected recently—known as false-recents.<sup>23</sup> This misclassification leads to overestimation of incidence using BED assays.

Misclassification of non-recent infections as recent generally occurs among individuals who mount a weak serological response to HIV and who remain below the target threshold of the assay. Furthermore, studies have shown that the false-recent rate of BED is typically higher among people with low CD4 cell counts (<50/ $\mu$ l) and among people receiving antiretroviral therapy. A study in South Africa showed that the proportion of people testing false-recent increases with the time since antiretroviral therapy initiation.<sup>24</sup>

While the BED assay has been successfully used in the United States of America, where essential clinical and



epidemiological information is generally available for people newly infected with HIV,<sup>14</sup> data from several countries in Africa and Asia as well as from validation studies have shown that BED methods applied in surveys consistently overestimate HIV incidence.<sup>23</sup>

If the BED method is to be used in countries to obtain reliable estimates of incidence, it is essential to adequately adjust for the level of misclassification in the study population. This may be achieved either by applying a mathematical adjustment, as suggested by Hargrove et al.<sup>26</sup> or McDougal et al.,<sup>25</sup> or in clinical settings to remove from the analysis those people who test recent but are known to have true long-term infections, including those with low CD4 cell counts and those known to be receiving antiretroviral therapy. It is essential to accurately establish the use of antiretroviral therapy among study participants (e.g. through testing blood samples) to correct

for false-recency among HIV-infected people on antiretroviral therapy.

Variation in the level of misclassification between settings has emphasized the importance of determining the value of an adjustment factor that is locally relevant.<sup>27</sup> One way of estimating the proportion of false-recent cases is to apply BED to a large number of samples from people known to have been infected with HIV for more than one year and to calculate the proportion who test as recent.<sup>26</sup> Research is currently being conducted to calibrate the proportion of false-recents in general settings.<sup>28,29</sup>

Further research is also under way to investigate other and new assays, including the use of avidity assays, where the avidity index of antibodies is used as a marker for recent infections.<sup>30</sup> Using algorithms that involve two assays based on different principles has been suggested as a way to improve the accuracy of incidence estimates.<sup>30</sup>



The use of mathematical models currently remains the most common method for estimating HIV incidence.

The UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance currently recommends that estimates of HIV incidence based on results of BED and other assays should only be derived in settings that allow validation against measures of incidence derived by other methods.<sup>31</sup>

A global initiative coordinated by WHO and the Centers for Disease Control and Prevention has been created to combine the experience and resources of laboratory scientists, epidemiologists and statisticians to work on the complexities of the laboratory methods and on calibrating their performance, with the expectation that an improved STARHS method will be developed in the next few years.<sup>22</sup> More information on the work of this group can be obtained from the WHO web site at:

[www.who.int/diagnostics\\_laboratory/links/hiv\\_incidence\\_assay/en/index.html](http://www.who.int/diagnostics_laboratory/links/hiv_incidence_assay/en/index.html).

## Summary

Accurate estimates of incidence are essential for monitoring the HIV epidemic and for evaluating the impact of interventions. Obtaining direct estimates of incidence from cohort studies is costly and logistically difficult and could in itself be subject to a number of biases.

Several biological assays have been developed over the past few years that distinguish recent HIV infections from long-standing infections, but the level of misclassification and variation in the duration of the window period assigned by different assays remain serious challenges. Because of the high level of misclassification, countries that are currently using BED and similar assays to estimate HIV incidence should apply locally relevant correction factors to adjust for the long-term specificity of the assay and for misclassification of people on antiretroviral therapy and with low CD4 cell counts.

The use of mathematical models currently remains the most common method for estimating HIV incidence. Given good prevalence data and reliable model assumptions, it has been shown that models can provide estimates of incidence with reasonable levels of confidence.

Since early 2009, analysts in countries around the world have been trained on and are using the revised versions of EPP and Spectrum, as recommended by UNAIDS, to derive estimates of the impact of HIV and for measuring HIV incidence. It is anticipated that trends in incidence will be published for the first time in 2010, emphasizing the importance of incidence estimation for future monitoring of the HIV epidemic.

*Eleanor Gouws, UNAIDS/EMA, estimates@unaids.org*

## References

1. Gregson S et al. (1996). Demographic approaches to the estimation of incidence of HIV-1 infection among adults from age-specific prevalence data in stable endemic conditions. *AIDS*, 10:1689–1697.
2. Williams B et al. (2001). Estimating HIV incidence rates from age prevalence data in epidemic situations. *Statistics in Medicine*, 20(13):2003–2016.
3. Dorrington RE, Bradshaw D, Budlender D (2002). *AIDS profile in the provinces of South Africa: indicators for 2002*. Cape Town, University of Cape Town, Medical Research Council, Actuarial Society of South Africa, 35.
4. Downs AM et al. (2000). Back-calculation by birth cohort, incorporating age-specific disease progression, pre-AIDS mortality and change in European AIDS case definition. *European Union Concerted Action on Multinational AIDS Scenarios. AIDS*, 14(14):2179–2189.
5. Brown T et al. (2008). Progress and challenges in modelling country-level HIV/AIDS epidemics: the UNAIDS Estimation and Projection Package 2007. *Sexually Transmitted Infections*, 84 (Supp. 1):i5–i10.
6. Stover J et al. (2008). The Spectrum projection package: improvements in estimating mortality, ART needs, PMTCT impact and uncertainty bounds. *Sexually Transmitted Infections*, 84 (Supp. 1):i24–i30.
7. UNAIDS (2009). *AIDS epidemic update*. Geneva, UNAIDS, WHO. Available at [www.unaids.org](http://www.unaids.org).
8. Dorrington R et al. (2002). The current state and future projections of the HIV/AIDS epidemic in South Africa. *Journal of the South African Dental Association*, 57(11):449–450.
9. Hallett T et al. (2008). Estimating incidence from prevalence in generalised HIV epidemics: methods and validation. *PLoS Medicine*, 5(4):e80.
10. Hallett TB et al. (2010). Estimates of HIV incidence from household-based prevalence surveys. *AIDS*, 24:147–152.
11. Gouws E et al. (2006). Short term estimates of adult HIV incidence by mode of transmission: Kenya and Thailand as examples. *Sexually Transmitted Infections*, 82 (Supp. 3):iii51–iii55.
12. Brown T, Peerapatnapokin W (2004). The Asian Epidemic Model: a process model for exploring HIV policy and programme alternatives in Asia. *Sexually Transmitted Infections*, 80(Supp. 1):i19–i24.
13. Campsmith ML et al. (2009). Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. *Journal of Acquired Immune Deficiency Syndromes*.
14. Hall HI et al. (2008). Estimation of HIV incidence in the United States. *Journal of the American Medical Association*, 300(5):520–529.
15. Ghys PD, Kufa E, George MV (2006). Measuring trends in prevalence and incidence of HIV infection in countries with generalised epidemics. *Sexually Transmitted Infections*, 82 (Supp. 1):i52–i56.
16. Zaba B, Boerma T, White R (2000). Monitoring the AIDS epidemic using HIV prevalence data among young women attending antenatal clinics: prospects and problems. *AIDS*, 14(11):1633–1645.
17. Barin F, Nardone A (2008). Monitoring HIV epidemiology using assays for recent infection: where are we? *Eurosurveillance*;13(3 6):pii=18967. Available at <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18967>.
18. Le Vu S et al. (2008). Principles and HIV incidence estimation from recent infection testing—a review. *Eurosurveillance*, 13(36):pii=18969. Available at <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18969>.
19. Janssens RS et al. (1998). New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *Journal of the American Medical Association*, 280:42–48.
20. Dobbs T et al. (2004). Performance characteristics of the immunoglobulin G-capture BED-enzyme immunoassay, an assay to detect recent human immunodeficiency virus type I seroconversion. *Journal of Clinical Microbiology*, 42:2623–2628.
21. Parekh BS, McDougal JS (2005). Application of laboratory methods for estimation of HIV-1 incidence. *Indian Journal for Medical Research*, 121:510–518.
22. Murphy G, Parry JV (2008). Assays for the detection of recent infections with human immunodeficiency virus type 1. *Eurosurveillance*, 13(36):pii=18966. Available at <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18966>.
23. UNAIDS. UNAIDS Reference Group on Estimates, Modelling and Projections statement on the use of the BED-assay for the estimates of HIV-1 incidence for surveillance or epidemic monitoring. Geneva, UNAIDS, 2005. Available at [http://data.unaids.org/pub/EPISlides/2006/Statement\\_BED\\_Policy\\_13Dec05\\_en.pdf](http://data.unaids.org/pub/EPISlides/2006/Statement_BED_Policy_13Dec05_en.pdf).
24. Marinda ET et al. (in press). Significantly diminished long-term specificity of the BED capture enzyme immunoassay among patients with HIV-1 with very low CD4 counts and those on antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*.
25. McDougal JS et al. (2006). Comparison of HIV type 1 incidence observed during longitudinal follow-up with incidence estimated by cross-sectional analysis using the BED capture enzyme immunoassay. *AIDS Research and Human Retroviruses*, 22(10):945–952.
26. Hargrove JW et al. (2008). Improved HIV-1 incidence estimates using the BED capture enzyme immunoassay. *AIDS*, 22(4):511–518.
27. Barnighausen T et al. (2008). HIV incidence in rural South Africa: comparison of estimates from longitudinal surveillance and cross-sectional cBED assay testing. *PLoS ONE*, 3(11):e3640.
28. Welte A, McWalter TA, Barnighausen T (2009). A simplified formula for inferring HIV incidence from cross-sectional surveys using a test for recent infection. *AIDS Research and Human Retroviruses*, 25(1):125–126.
29. McWalter T, Welte A. Relating recent infection prevalence to incidence with a sub-population of non-progressors.
30. Wei X et al. (2010). Development of two avidity-based assays to detect recent HIV type 1 seroconversion using a multisubtype gp41 recombinant protein. *AIDS Research and Human Retroviruses*.
31. UNAIDS (2009). *Memorandum to country and regional staff*. Geneva, UNAIDS.

Uniting the world against AIDS