Recent infection testing algorithm technical update
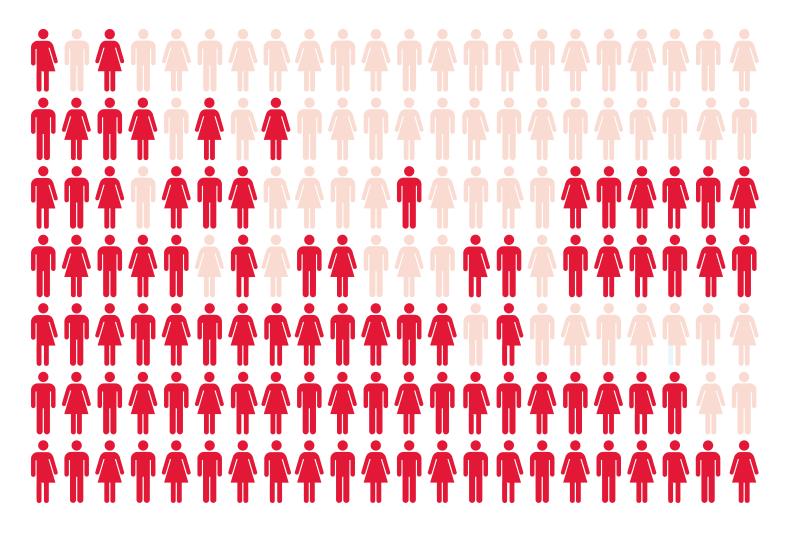
Applications for HIV surveillance and programme monitoring

Contents

Introduction

This technical update provides public health officials with guidance on applying HIV incidence assays and testing algorithms for recent HIV infection in order to monitor the HIV epidemic and assess the impact of interventions. A major theme of this update is the importance of calibrating two of the key performance characteristics of recent testing infections algorithms—mean duration of recent infection and false recent ratio—to account for the context in which the testing is being done. This technical update also describes several emerging use cases in the application of recent infection testing algorithms and tests, including those for individual-level use. A final section on further research directions is provided to highlight areas that still require investigation.

The contents of this document and the recommendations that it presents are primarily based on newly published literature and the deliberations that took place at meetings of the World Health Organization (WHO) Technical Working Group on HIV Incidence Assays in Geneva (June 2015), Boston (February 2016) and Seattle (February 2017). This document supersedes the previous technical update published in 2015 *(1)*, and it supplements the 2011 guidelines When and how to use assays for recent infection to estimate HIV incidence at a population level *(2)*. For countries that need additional guidance on the implementation of recent infection testing algorithms in population-based surveys, please see the 2015 Guidelines on monitoring the impact of the HIV epidemic using population-based surveys *(3)*.

Readers who are not technical experts in this field may prefer to read the 2011 Guidelines on when and how to use assays for recent infection to estimate HIV incidence at a population level for a basic introduction.

Key recommendations and new tools

Since 2015, WHO and UNAIDS have recommended the use of an HIV incidence assay alongside of a viral load threshold in order to estimate incidence *(1)*. A critical issue when estimating incidence using assay-based algorithms is accurately quantifying the algorithm's performance characteristics, specifically the mean duration of recent infection and the false recent ratio *(2)*. Both variables are used to calculate HIV incidence in recent infection testing algorithms *(2)*.

The primary recommendations in this technical update stem from mounting evidence that suggest that appropriate contextual calibration of mean duration of recent infection and the false recent ratio can help to improve the accuracy of incidence estimates *(4, 5)*. When calculating incidence based on a recent infection testing algorithm, it is recommended that country teams should do the following:

- Estimate, as much as possible, a context-specific, locally appropriate mean duration of recent infection, taking into account the sensitivity of the HIV screening algorithm and HIV subtype distribution.

- Estimate a context-specific false recent ratio by considering the composition of the population where the recent infection testing algorithm is being applied, including incidence, prevalence, treatment coverage and the distribution of time since infection.

- Evaluate the robustness of incidence estimates with respect to uncertainty in the mean duration of recent infection and the false recent ratio.

The next section in this document will provide more detailed considerations that are specific to these recommendations.

In addition to the new recommendations, this update describes new tools that combine standard survey analysis methods with the recommended formula for estimating incidence. Additional information about the tools are described in the section "Accounting for survey design when estimating incidence."

Contextual adaptation of recent infection testing algorithms for surveillance applications

Both the mean duration of recent infection and the false recent ratio are known to be highly context-dependent, including for algorithms based on the widely-used Sedia Limiting Antigen (LAg) Avidity EIA *(6)*, and they vary according to the following:

- The subtype or subtypes of virus circulating in the population.

- Antiretroviral therapy coverage and the average time between infection and initiation of treatment.

- Other epidemiological factors, such as the incidence and prevalence of HIV, the age distribution of the population living with HIV, and the distribution of time since infection in the untreated population.

These variations have implications for the accuracy and precision of incidence estimates across settings *(4)*.

Mean duration of recent infection

Mean duration of recent infection is defined as the average length of time over a fixed period (typically two years) that persons with newly acquired infection are classified by the assay as having recently acquired infection. Published estimates of mean duration of recent infection should be calibrated to account for *(1)* the sensitivity of the HIV screening algorithm used, and *(2)* the predominant HIV subtypes circulating in the infected population.

- **Sensitivity of the HIV screening algorithm.** Estimates of mean duration of recent infection reported in the literature are derived using panels of samples against which consistent criteria for determining HIV positivity are applied. Typically, the definition of HIV positivity is based on a reference diagnostic test, such as the western blot or a nucleic acid test with a detection threshold of 1 copy/mL *(4, 7)*. When a screening assay or algorithm is used that differs from the one used to produce a previously-published estimate of mean duration of recent infection, the relative diagnostic delay (i.e., the window period of the screening test) must be taken into account. The literature on diagnostic delays is extensive *(8)*, and a database of test properties is now available online.[1]

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[1] The database of test properties is available on-line at https://tools.incidence-estimation.org/idt/. Registration is required.

- HIV subtypes. If the distribution of the HIV subtypes in the setting is known, a weighted average of the mean durations of recent infection should be calculated rather than using only the value for the predominant subtype. Subtype-specific estimates of mean duration of recent infection for LAg-based recent infection testing algorithms (with and without viral load thresholds) have been published by the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA) and presented at Technical Working Group meetings *(5, 9)*.[2] Efforts are ongoing to pool assay calibration data generated by CEPHIA, Johns Hopkins University and the United States Centers for Disease Control and Prevention (CDC) to produce more precise subtype-specific estimates for use with LAg-based algorithms. Subtype-specific CEPHIA calibration data are available for 10 assays for recent infection *(9)*. Anonymized and curated CEPHIA evaluation datasets that can support additional and customized analyses are scheduled for public release within the next 12 months.

False recent ratio

The false recent ratio of a recent infection testing algorithm, which is defined as the proportion of long-term HIV infections misclassified as recent, is highly influenced by the distribution of time since infection in the population and by treatment coverage. In general, immunoassay-based testing algorithms are likely to misclassify people living with HIV who are on treatment as being recently infected. There is strong evidence that this misclassification can be reduced—and the false recent ratio lowered—by incorporating a viral load threshold in the testing algorithm, since treated subjects who are virally suppressed would be classified as not recently infected *(5)*. However, some treated but virally unsuppressed people are still likely to be misclassified.

Since the cohort participants who contribute specimens to the panels from which estimates of the false recent ratio are drawn are not typically representative of the population of interest, an overall context-specific false recent ratio should be constructed from a weighted average of the ratios in the untreated and treated subpopulations. The statistical procedures for calibrating a weighted false recent ratio that accounts for these factors are complex, and the relevant formulae are described elsewhere *(7)*. Briefly, the procedure relies on either estimating or assuming the following in the population of interest:

- The distribution of HIV subtypes.

- The distribution of time since infection in the untreated subpopulation.

- The viral suppression rate among the treated subpopulation.

- Antiretroviral therapy coverage.

In addition, where data are available, known long-term HIV-positive individuals may be classified as nonrecent based on diagnostic and treatment history data.

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[2] For more information on subtype-specific estimates of the mean duration of recent infection, please see http://www.incidence-estimation.org/page/cephia-assay-evaluations.

The recommended estimation procedure for the false recent ratio is sensitive to assumptions (such as the distribution of time since infection). For this reason, the WHO Technical Working Group on HIV Incidence Assays recommends that planners and analysts conduct sensitivity analyses to investigate the possible impact on incidence estimates of (a) variation in the false recent ratio and (b) mean duration of recent infection.

Tools for estimating test basic performance characteristics have been made available by the South African Centre for Epidemiological Modelling Analysis (SACEMA).[3] Web-based tools that are more user-friendly are under development. While no specific tools are yet available to assist survey planners in the contextual adaptation of recent infection testing algorithms, the WHO Technical Working Group on HIV Incidence Assays is identifying possible tools to help support this work. It will disseminate them as they become available.

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[3] Information, tools and source code are available at https://github.com/SACEMA/inctools.

Accounting for survey design when estimating incidence

For logistical and cost reasons, most large-scale surveys do not make use of simple random sampling, and the nonequal weighting and clustering of survey design is accounted for when analysing survey results (for example "PROC SURVEY" in SAS, "SVY" in Stata, or the "survey" package in R). These analysis tools furnish estimates of the variance for inputs to the incidence calculation formula, which are then propagated through the incidence estimate using the Taylor series linearization method. Incidence point estimates will be the same, but in most cases, properly accounting for survey design will lead to wider confidence intervals around the point estimate.

A calculator to estimate incidence from HIV prevalence and incidence assay results has been developed for the UNAIDS Reference Group on Estimates, Modelling and Projections.[4] Incidence estimation methods also are newly available using a bootstrapping approach in the "inctools" R package.

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[4] The incidence and prevalence calculator is available at https://incidence.shinyapps.io/incidence_calculator/.

Updates on expanded recent infection testing algorithms, assays and new use cases

Currently, efforts are underway to explore the use of expanded testing algorithms and new algorithm applications. A summary of recent, notable work in the field is described below.

- Many large population-based surveys—such as the South African National HIV Prevalence, Incidence and Behaviour Survey and the Population-based HIV Impact Assessments (PHIAs)—include testing for exposure to antiretroviral medications. Incorporating testing for antiretroviral medicine exposure into a recent infection testing algorithm can reduce potential treatment-related misclassification, thereby reducing the false recent ratio. A recent analysis using nationally representative data from South Africa and Kenya showed that including testing for treatment exposure further reduced the false recent ratio compared to viral load results alone *(10)*. However, the impact of including testing for exposure to treatment on the mean duration of a recent infection testing algorithm is not known, nor is the performance against directly observed incidence in the population of interest. This underscores the recommendation in this document about the importance of sensitivity analyses to account for uncertainty in algorithm performance characteristics.

- An emerging area of research and development is rapid point-of-care rapid HIV diagnostic tests that also detect recent infection. Because of the almost immediate availability of results, rapid tests for recent infection show promise for individual-level uses, like targeted prevention interventions and rapid treatment initiation *(11)*, as well as for population-level uses, such as providing real-time data on trends in recent infections among newly diagnosed individuals. These assays also may be suitable for population-based surveys, especially in resource-limited settings where access to laboratory services is poor. However, current recommendations would still require the inclusion of viral load testing, using point-of-care tests where they are available. A rapid test for HIV diagnosis and recent infection has been developed by Sedia Biosciences Corporation based on the same principle as the LAg assay, and it is currently undergoing validation by the manufacturer. Recommendations regarding the use of rapid point-of-care tests will be made once one or more products have been brought to market and data to support the manufacturer's claims are available.

- Several potential new biomarkers of recent HIV infection have been described in the recent literature *(9, 12–14)*. Many of these consist of modifications to the standard operating procedures of commercially available diagnostic assays to extend the dynamic range of the biomarker measurement, usually with a recency discrimination threshold applied to the quantitative measurement. A review of progress in developing a reliable test for recent infection, which includes an overview of available assays and assays in development, was published in 2017 *(9)*.

- In 2011, the Incidence Assay Critical Path Working Group, a sub-group of the WHO Technical Working Group on HIV Incidence Assays, published a preliminary target product profile for laboratory tests for recent HIV infection *(15)*. The profiles were confined to use cases involving estimating population-level incidence from representative cross-sectional surveys. To date, no single assay for recent infection has fully met the 2011 target product profile criteria *(9)*, although recent infection testing algorithms based on the LAg assay in conjunction with viral load have seen large scale adoption.

- After extensive consultation, the Foundation for Innovative Diagnostics published an updated set of target product profiles in 2017 that identified an expanded set of use cases for recent infection testing algorithms *(16)*. In conjunction with FHI 360, it also produced a market assessment for HIV incidence assays *(17)*. The new use cases include the potential application of recent testing algorithms in national population surveillance, programme planning, epidemic monitoring in key or sentinel populations, and intervention impact assessment. In addition, the use cases also describe nonincidence estimation applications, such as HIV case surveillance, research use, individual patient management and targeted prevention planning. The profiles and the market assessment serve to guide test developers on the needs and potential market for new and improved tests for recent infection. Quality assurance and laboratory procedures are critical for ensuring correct incidence estimates and appropriate patient feedback and interventions.

Additional research needs

While significant progress has been made in improving tests for recent infection and the consistent application of methods for estimating incidence using recent infection testing, several critical research gaps were identified at recent meetings of the Technical Working Group on HIV Incidence Assays. Areas in need of further investigation include the following:

- Further development of tools and methods for context adaptation and estimation of the performance characteristics of recent infection testing algorithms in mixed-subtype populations.

- Measurement of the impact of early treatment and treat-all strategies, discontinued antiretroviral therapy, treatment interruptions, incomplete viral suppression and pre-exposure prophylaxis on the performance of recent infection testing algorithms.

- Determination of the performance of tests for recent infection in populations infected with HIV subtypes that are insufficiently represented in current calibration data (e.g. CRF02_AG or CRF01_AE).

- Development of statistical methods for estimating incidence and the uncertainty of the estimate when test results from recent infection testing algorithms conducted as part of population-based surveys indicate low or zero case counts of recent infections.

- Validation and evaluation of new and proof of concept biomarkers/assays, including estimating performance characteristics and validation using larger specimen sets.

- Assessment of the performance of recent infection testing algorithms among pregnant women, who often are the source for routine measures of population-level HIV prevalence.

- Evaluation of the performance of recent infection testing algorithms among key populations.

Future meetings coordinated by WHO Technical Working Group on HIV Incidence Assays will serve as forums for reviewing efforts to address the gaps identified above. The WHO Technical Working Group on HIV Incidence Assays also will continue to serve as the primary developer of guidance on how countries should estimate HIV incidence using results from recent infection testing algorithms.

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