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Moving Towards a reliable HIV Incidence test: How far have we come and how far do we have to go?

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In 1998, on the banks of Lake Geneva, a buzz went around the conference centre as the United States Centres for Disease Control and Prevention (CDC) proudly announced the publication of a simple laboratory technique that would allow the differentiation of 'recent' from 'longstanding' HIV infections (1). Estimating HIV incidence is hard because it is an infection that people survive with for an extended period, which means that prevalence data reflects incidence accumulated over a long period of time. Detection of recent infections with a laboratory test recovers some of the simplicity of transient conditions by measuring the prevalence of a condition ('recent HIV infection') acquired on a shorter time scale, which allows one to estimate HIV incidence from a cross-sectional survey.

But in order to measure incidence using surveys with feasible sample sizes, the 'recent' state must persist for a sufficient period — in the order of months — to ensure that more than a handful of participants are detected as recently infected. This property of the test is known as the Mean Duration of Recent Infection or MDRI. Although the CDC test was not the first laboratory method to provide information on when an HIV infection was acquired, it was the first that had a sufficiently long MDRI to make incidence surveys feasible. We believed the quest to be able to measure HIV incidence and monitor the epidemic in real time was over. How wrong we were!

Difficulties remain in applying HIV incidence assays

Eighteen years later we published a paper titled "Moving towards a reliable HIV incidence test – current status, resources available, future directions and challenges ahead" (2). This paper, written in collaboration with the WHO Technical Working Group on HIV Incidence Assays (WHOTWG), highlights the incredible progress that has been made, but also outlines the many difficulties that remain.

The application of HIV incidence assays (laboratory tests for recent infection) has been fraught with difficulties. The original so-called 'detuned assay' that was the cornerstone of the 1998 paper was withdrawn by the manufacturer because the technology required to run the assay was old and no longer supported. A microtitre-based assay that was developed to replace it soon lost favour because it was technically demanding to perform, and its performance was hindered by frequent failures, 'uncontrolled' assay variability and an inability to perform robustly with different HIV subtypes. A new assay was developed to deal with the issue of different HIV subtypes and was aptly named the BED assay (it used consensus peptides from HIV subtypes B, E and D). But issues with the misclassification of longstanding infections as recent (the False-Recent Rate or FRR) and the over-estimation of HIV incidence led to UNAIDS advising against its use (3).

Establishment of the Consortium for the Evaluation and Performance of HIV Incidence Assays

These difficulties made it seem like the use of laboratory assays for determining HIV incidence was all but dead. But a hardy group of individuals, who had met regularly at International AIDS Society meetings, was called to action in 2006. The WHOTWG was formed, and steady progress was made on laboratory approaches for detecting recent HIV infections, and methods for 'calibrating' tests for recent infection (i.e. estimating performance characteristics) and for estimating incidence using these tests. Within a few years many assays had been developed for use in HIV incidence estimation. However, there was limited independent evaluation of these assays, and many of the evaluations used only a small number of well-characterised specimens. In 2012, with funding from the Bill and Melinda Gates Foundation, the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA) was formed to address these problems. SACEMA, Public Health England in London, the University of

California in San Francisco, and the Blood Systems Research Institute in San Francisco were the main partners in CEPHIA.

CEPHIA developed an extensive repository of well-characterised specimens and conducted comprehensive independent evaluations of candidate HIV incidence assays. A critical component of these evaluations was to estimate test properties such as the MDRI and FRR. In this collaboration SACEMA led the methods development and data analysis, while the other partners focused on obtaining the specimens and developing robust laboratory procedures.

Moving towards a reliable HIV incidence test

Over recent years, CEPHIA completed numerous evaluations of HIV incidence assays and supported a number of research projects into new biomarkers by providing specimens, specimen background data, tools for data analysis, and by setting standards for the development of new assays. However, many challenges remain – both in the performance of the tests themselves and in their application. Our recent publication details the most important factors that need to be considered when employing HIV incidence assays and explains the key concepts of the field, including performance characteristics of tests for recent infection, a standardised infection dating method (necessary for estimating performance characteristics), and the CEPHIA specimen panels used for test development and evaluation (2).

With vast sums of money being spent on interventions aimed at reducing the burden of HIV infection, it is critical to measure the impact of these interventions by monitoring incidence. In our paper we outline how the performance characteristics of currently available assays may limit the usefulness of these assays in many situations.

Despite its notable successes, the CEPHIA collaboration is only one part of a major programme of work to support the development of new incidence assays. Our paper discusses the development of Target Product Profiles to support researchers and industry in developing new assays and the regulatory hurdles that any new test must overcome. These have become especially relevant as we look to broaden the application of these assays beyond cross-sectional incidence estimation. New applications include individual clinical infection staging and case-based surveillance and to inform prioritised contact tracing. We also highlight the technical issues in ensuring robust assay performance, including an external quality assurance scheme designed to ensure that both the assays and laboratory procedures are of the highest quality.

Finally, our paper highlights the need for continued global coordination and investment in this important tool for HIV surveillance and prevention impact assessment. The introduction of the first incidence assay in 1998 seems like a lifetime ago, but in many ways we have only just begun.

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