SACEMA Policy Brief August 2014

Status update in the search for laboratory tests for 'Recent HIV infection' to support HIV surveillance

Summary

*Robust tests for **recent HIV infection** (as opposed to just HIV infection) would substantially reduce the enormous challenges of estimating **HIV incidence** (the rate of occurrence of new infections). This Policy Brief provides background information and an up to date assessment of the latest developments in the search for such tests – in particular by placing in context the first consistent evaluation of the primary candidate tests which have been developed and deployed for some years. **Researchers in the Global South are playing a critical role** in supporting international efforts, by leading the development and application of formal **analytical concepts and tools**.*

Background

It is a persistent challenge in epidemiology that incidence (the rate of occurrence of new cases) is much more informative than prevalence (the proportion of a population affected by a condition of interest at a certain point in time) but incidence is much more difficult to measure. Traditionally, the 'gold standard' for incidence estimation has been considered to be the explicit recruitment and follow up of a cohort of individuals 'at risk' but initially 'not infected' (or not yet 'affected', in the case of non-communicable conditions). This is technically/theoretically straightforward, but has substantial limitations in terms of time, effort, cost and complexity of execution, not to mention potential bias arising from non-representative recruitment or retention in study protocols.

Since 1995 (ref 1) it has been repeatedly pointed out that it would be tremendously useful if some biomarkers could be identified, and measured in a robust reproducible fashion, which would not just classify study subjects as infected or uninfected, but also distinguish recent from non-recent infections. The heuristic is that a larger number of 'recent infections' is indicative of a higher 'recent incidence', and hence that incidence could be estimated without follow up, from a single cross sectional survey. This is approximately valid, but requires considerable nuance and sophistication to be expressed rigorously in terms of conventional formal statistical indicators which quantify *incidence* and *incidence trend* estimates (ref 2). Also, many qualitatively sensible markers of 'recent infection' can be found, but for this approach to be very informative, quite stringent performance criteria need to be met (ref 3).

Since 2008, SACEMA has played a leading role in formulating the concepts and analytical techniques required to define and quantitatively characterise recent infection tests, and generate cross sectional incidence estimates. UNAIDS has published a formal guidance document for field use of 'incidence assays' (ref 4), as recent infection tests are also known.

For normal diagnostic tests, there is a more or less consistent process of validation and characterisation, based on the concepts of test *sensitivity* (ability to detect cases), *specificity* (ability to avoid false positive) and predictive

value (the likelihood that someone returning a particular test result is in fact infected, or not, as indicated). Even if we assume that the *sensitivity* and *specificity* are well defined and have the same values in all scenarios, the predictive value of positive and negative results depends additionally on the frequency of cases in a test-use setting. In reality, even sensitivity and specificity vary by context, making test performance evaluation challenging.

With tests for 'recent infection' the situation is considerably more complex than for conditions not defined by an explicit reference to time (ref 2). The usual notions of sensitivity and specificity are problematic at best, and at worst are overtly misleading for these purposes. Some consensus has emerged that, for surveillance applications, it is most informative to characterise a recent infection test by two critical performance parameters:

- A *mean duration of recent infection* (MDRI) which is largely an innate biological attribute. For effective surveillance, the MDRI needs to be a substantial fraction of a year, so that surveys are able to detect a sufficiently large number of new cases on which to base robust estimates.
- A *false recent rate* (FRR) which is the proportion of long-infected individuals that nevertheless are classified, by the putative recent infection test, as recently infected. It appears inevitable that such cases will arise, and that the FRR will never be perfectly known, and will vary by context. For a good test the FRR will be about 1 percent, and a context-appropriate estimate of it can be systematically used in the analysis of data.

Recent Developments

To build consensus on methodological approaches and the utility of existing assays, and to support the development of new emerging products, the Bill & Melinda Gates Foundation has for three years funded the Consortium for the Evaluation and Performance of HIV Incidence Assays (a.k.a. CEPHIA: http://www.incidence-estimation.org/page/cephia). The CEPHIA core is comprised of scientists at the Virology reference laboratory at Public Health England, the University of California – San Francisco, Blood Systems Research Institute – San Francisco, and SACEMA – Stellenbosch. The San Francisco based collaborators have assembled and characterised a unique repository of specimens which facilitate the lab work that give concrete quantitative meaning to 'recent infection' as defined by biomarkers; the PHE collaborators have led the standardisation of laboratory procedures, a critical step in moving these tests from research platforms towards tradable technology; and the SACEMA team is leading the data analysis.

Having previously presented a number of preliminary results at conferences and workshops, CEPHIA has just published (ref 5) the first ever comprehensive head-to-head evaluation of leading candidate test for recent HIV infection. Comparison with a 'Target Product Profile' circulating within the research community since 2010 suggests that existing assays are not yet ready, if used in stand-alone form, for widespread use as a generally informative surveillance tool. CEPHIA's work to date lays the foundation for:

- a more nuanced and in-depth exploration of the potential of existing assays, used in combination with each other, or with supplementary biomarkers not traditionally regarded as individually indicative of recent infection (such as viral load);
- supporting discovery of new biomarkers being investigated in independently funded projects.

Uses of Recent Infection Tests

- Estimation of incidence from a single cross sectional survey (for epidemiological surveillance, or for baseline assessments to support major study design).
- Estimation of incidence trends from two or more cross sectional surveys (such as for intervention impact assessment).
- Staging of newly diagnosed patients for clinical purposes such as contact tracing, study referral, and priority early intervention (this clinical application is de-emphasized in the current brief, but is an important, related and rapidly moving, area of research).

Biological Basis of Known Biomarkers/Tests for recent infection

- Antibody quantity (formally *titre*) which grows over the early phases of infection.
- HIV specific *proportion* of major antibody classes, which also grows over the early phases of infection.
- Strength of antibody binding (to viral material) - technically known as '*avidity*' which improves over time as antibodies progressively adapt to virus 'antigen'.
- Viral genetic diversity, which increases rapidly over time. A usually very small number of viral genetic variations (known as 'founder strains') transmitted to a new human host accumulate mutations in the famously error-prone replication cycle of HIV.

Primary Approaches to Estimating HIV incidence

- Directly counting new infection occurring in study cohorts of initially uninfected individuals. This is also known as 'prospective' follow up. See body of policy brief for limitations
- Cross sectional use of recent infection biomarker prevalence – the main subject of this brief.
- 'Fitting models' to complex time structured data sets, thus searching for (inferring) values of HIV incidence which make the models fit well. This approach is widely used, but it too is not a mature paradigm, and it remains a substantial separate area of research.

Is there a Market for Recent Infection Tests?

Currently, perceptions are that from surveillance applications alone, there is too little demand to stimulate substantial corporate investment in recent infection tests. However, it is increasingly apparent that individual level clinical staging (see also **Uses of Recent Infection Tests)** offers a potential dual use for a suitable product which could then have routine clinical and well as surveillance application.

A 'Target Product Profile' for a Surveillance-Worthy Recent Infection Test.

It is not unusual to summarise requirements for as yet immature classes of medical devices into 'Target Product Profiles' which support development, funding and peer evaluation of emerging candidates. In the case of HIV incidence assays, a TPP, which emerged from an engagement with industry insiders by the Clinton Health Access Initiative and the Bill & Melinda Gates Foundation, has been in circulation since 2010. This TPP is generic and does not account explicitly for the many differences between 1) epidemiological contexts and 2) intended uses, and is therefore currently being revisited.

How to Define / Evaluate the Performance of a Recent Infection Test.

Translating the core recent infection test characteristics (MDRI and FRR, defined above) into an evaluation of test utility, or 'optimising' test algorithm details, involves some concepts not usually deployed in the evaluation of laboratory tests. Of importance, when discussing surveillance, is to understand that:

- Favourable MDRI and FRR values tend to be traded off against each other, and together they conspire to imply a performance level which can be summarised into the precision (statistical confidence) of an incidence estimate which is attainable with a particular study, protocol in a particular context.
- There is no significant bias inherent in cross sectional biomarker based incidence estimates, no matter how poor the performance of the test –poor tests just lead to low, barely meaningful statistical confidence. Bias can arise, but not so much from the performance of the recent infection test, as from incorrect estimates of the test properties.

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References:

1. Brookmeyer R, Quinn TC. Estimation of current human immunodeficiency virus incidence rates from a cross-sectional survey using early diagnostic tests. American Journal of Epidemiology 1995; 141:166–172. http://www.ncbi.nlm.nih.gov/pubmed/7817972
2. Kassanjee R, McWalter TA, Barnighausen T, Welte A. A new general biomarker-based incidence estimator. Epidemiology, 2012; 23:721–728. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3500970/
3. Kassanjee R, McWalter TA, Welte A. Defining optimality of a test for recent infection for HIV incidence surveillance. AIDS Research and Human Retroviruses 2014; 30:45–49. http://online.liebertpub.com/doi/abs/10.1089/aid.2013.0113
4. UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. When and how to use assays for recent infection to estimate HIV incidence at a population level. Geneva: WHO; 2011. www.who.int/diagnostics_laboratory/hiv_incidence_may13_final.pdf
5. Kassanjee R, Pilcher CD, Keating SM, et al.; Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA). Independent assessment of candidate HIV incidence assays on specimens in the CEPHIA repository. AIDS. 2014 Oct 23;28(16):2439-49. http://journals.lww.com/aidsonline/Fulltext/2014/10230/Independent_assessment_of_candidate_HIV_incidence.12.aspx (Note: open access – no subscription needed)