Reviewer’s report

Title: Diagnostic performance of line-immunoassay based algorithms for incident HIV-1 infection

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Reviewer: Maurizio Zazzi

Reviewer’s report:

Major Compulsory Revisions
None

Minor Essential Revisions

1. This study extends and in some respect complements two previous studies by the same group. The first (Schüpbach et al., PLoS Med 2007) reported the use of the INNO-LIA assay as a system to discriminate recent (<12 months) vs. chronic infection. The second (Schüpbach et al., BMC Infect Dis 2011) showed that the specificity of the system was generally unaffected by HIV-1 subtype, viral load, CD4 counts and disease stage yet specificity decreased when testing patients under successful HAART and with increasing patient age. The novelty of the present study appears to be the selection of a validation dataset which I understand has no overlap with the one used for training the system in the first study (Schüpbach et al., PloS Med 2007). This dataset is characterized by having more defined information about the estimated date of infection. However, both this and the previous study indicate that the INNO-LIA system is particularly suitable to detect a ‘recent’ infection when the infection occurred in the early phase of recent infection. It would be advisable to highlight the new knowledge conveyed by this paper in the discussion section.

2. Page 7. The authors say that they conducted two studies to address whether any virus or patient related factors can impact the accuracy of the system. Then, they refer to only one of these two studies. The reader may miss what the second study showed in this context.

3. Page 9. The inclusion of “Documented signs of ARS no more than 90 days before diagnosis”, in the absence of documented seroconversion (definition #3), as a proof of recent infection among the HIV notification subset appears to be much less accurate than the other criteria. As cited by the authors themselves, the paper by Hecht et al. (AIDS 2002) indicated that fever and rash are the most significant predictors of primary HIV infection. Did the authors consider the combination of these two signs to classify recent infection by definition #3 in their dataset? In general, the algorithms were more specific than sensitive. Also, a large proportion of reference recent infection cases were contributed by the notification registry. How does sensitivity change if definition #3 is removed from the criteria to classify recent infections? It is unclear to me whether adjusted sensitivity according to model 3 of table 3 addresses this issue.
4. Page 12. The inclusion of the “94 samples with a less precise EDI” in the sub-analysis of the performance of the algorithms after stratification by quarter seems incorrect. These samples have indeed uncertainty right in the parameter used for stratification. I suggest to do the analysis without these cases or confirm that they do not bias the results.

5. Discussion. The authors make it clear that the different algorithms provide (slightly) different results and are confident that using multiple algorithm has the advantage to minimize the impact of the inadequacy of any individual algorithm. However, it remains elusive to me how one should use all the algorithms to analyse a dataset in practice. Is there a preferential summary measurement derived from the individual measurements provided by the different algorithms?

Discretionary Revisions

6. Discussion. Although not uniformly supported by international and national guidelines, the use of molecular diagnostics has been replacing second-line serology as a confirmatory test for HIV diagnosis. It should be emphasized that a confirmatory antibody assay such as INNO-LIA has the added value of detecting recent infection, an information not provided by HIV DNA/RNA assays. Cost differences between the two approaches should probably also be mentioned.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests