Recency staging of HIV Infections Through Routine Diagnostic Testing

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INTRODUCTION

• HIV recency results on individual patients, obtained at the time of diagnosis (as practiced in some national programmes and being contemplated in other large-scale systems) helps guide psychosocial support strategies, contact tracing, and inclusion in clinical trials.

• However, as recency testing is currently a specialist service used custom recency assays, this implies additional expense and a delay between HIV diagnosis and the delivery of the recency result.

• Previously, the microtitre-based HIV screening and confirmatory assays were only able to give qualitative results which could not be used to stage infection based on the levels of reactivity – at least not without altering either the specimen input or incubation conditions, or disrupting the chemical interactions measured in the test.

• The introduction of high dynamic range (such as chemiluminescent) platforms has opened up the possibility of adding staging interpretations to diagnostic test results, for both clinical and epidemiological applications.

• We explore whether this under-utilized quantitative information (e.g., signal-to-cutoff ratio, S/CO) can immediately stage new diagnoses as recent, or at least support prioritisation, by identifying specimens that should, or need not, be referred for specialised recency testing.

• 2500 specimens with good clinical characterisation were tested diagnostically using an Abbott ARCHITECT HIV Ag/Ab Combo Assay (ARCHITECT) and by Sedia™ HIV-1 Limiting Antigen for HIV recency determination (LAg).

• ART-naive specimens with a well-defined duration of infection were used to represent specimens from new diagnoses.

• We compared the recency classifications based on the two platforms through a number of regressions and correlations.

• To provide a systematic basis for utility in a surveillance application, a hypothetical epidemiological scenario was constructed where:

  • HIV Prevalence is 30% (HIV being detected with individual-level nucleic acid amplification testing)
  • HIV Incidence is 1.5 cases per 100 person-years
  • Treatment Coverage is 80% of infected individuals (with no false recent results among treated individuals, as long as a supplementary viral load threshold is applied)
  • Mean Duration of Recent Infection (MDRI), estimated for a range of recency discrimination thresholds, is adjusted for sensitivity of the HIV screening algorithm in the hypothetical survey
  • Context-specific False-Recent Rate (FRR) is calculated by estimating the probability of testing recent as a function of time since infection in the hypothetical population.

METHODS

• 2500 specimens with good clinical characterisation were tested diagnostically using an Abbott ARCHITECT HIV Ag/Ab Combo Assay (ARCHITECT) and by Sedia™ HIV-1 Limiting Antigen for HIV recency determination (LAg).

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RESULTS

Figure 1. The probability of a specimen being classified as LAg recent (ODn>1.5), as a function of the ARCHITECT platform result (signal-to-cutoff ratio, or S/CO). The probability curve is generated by means of a logistic regression model. Note that at S/CO values below 200 the majority of specimens will yield a LAg normalised optical density (ODn) below 1.5, and at S/CO above 500, almost no specimens will produce a LAg recent classification.

Figure 2. Mean Duration of Recent Infection, as a function of primary assay result (ODn for LAg and S/CO for ARCHITECT) recency discrimination threshold. This indicates that the notion of recent infection can be robustly defined, over comparable time scales, by tuning a threshold on the two platforms.

Figure 3. Context-specific relative standard error of incidence estimate based on 1) the unmodified ARCHITECT platform, 2) the minimally diluted (‘untreated well’) of the previously described avidity modification of the ARCHITECT platform, and 3) the LAg assay.

CAVEAT: On all three curves, for increasing values of MDRI there is increasing exposure to difficult-to-quantify artifacts affecting the estimation of the FRR. These have been handled pragmatically in the present analysis, as it would be difficult to justify and harmonise the many assumptions required to fully specify the contextual challenges experimenters will face. Sensitivity analysis to uncertainty in FRR is recommended in all cases. The present figure probably provides a somewhat flattering picture of all three assays in the regime MDRI > 250 days, where more detailed accounting for FRR estimation is expected to lead to a degradation of performance.

Table 1. Properties of ARCHITECT-defined recency test (recent infection means S/CO below a threshold, and viral load above a threshold). The proportions in the last two columns are as in the specimen panel, which reflects a diverse mix of recent and longstanding infections.

DISCUSSION

• The quantitative measurements produced by the ARCHITECT platform strongly predicts Sedia™ HIV-1 Limiting Antigen recency classifications, especially at high and low S/CO values.

• Positive but low ARCHITECT S/CO values are strongly indicative of infection having occurred less than one year prior to diagnosis. (Note: HIV false positives, which generally give a low S/CO, should be excluded through normal confirmatory testing).

• The natural ‘growth’ of ARCHITECT S/CO values, like the evolution of LAg ODn and other recency markers is suggestive of an additional interpretation of recency assays at the individual level:

  • Surveillance-applied recency screening is usually summarised as a categorical recent/non-recent discrimination, the frequency of which is the central component of an incidence estimate.

  • Clinical use of such a broad category fails to leverage subject-specific reactivity values.

  • Interpreting subject-specific reactivity values, according to the MDRI curves of figure 2, offers a formal estimation of an individually-specific post-infection time scale to be incorporated into post-test counselling and clinical decision-making, the utility of which warrants further investigation.

CONCLUSIONS

• High dynamic range diagnostic assays provide substantial staged information, which is routinely available immediately at the time of diagnosis.

• This reduces (through prioritisation), or may have the potential to eliminate, the need for additional post-diagnosis recency testing, reducing unnecessary costs and delays in providing guidance for counselling, contact tracing and expedited treatment initiation.

• Given that epidemiological assessments are seldom based entirely on a single recency marker survey, new generations of routine diagnostic assays may have the potential to be used as the primary recent infection assays in surveillance.

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Computing innumate. None.

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