Independent Evaluation of Predicate Incidence Assays for HIV Surveillance

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Consortium for the Evaluation and Performance of HIV Incidence Assays

www.incidence-estimation.com/page/cephia

Background

Accurate estimates of HIV incidence are needed to assess epidemics, calibrate models, and design and evaluate interventions. The cross-sectional use of biomarker-based **Tests for Recent HIV Infection (TRIs)** in principle offers affordable, low-bias options for incidence estimation. To date, there has been no independent, directly comparative benchmarking of candidate TRIs.

The **Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA)**[1], tasked with advancing the understanding of biomarkers distinguishing 'recent' from 'non-recent' infection for incidence surveillance, has assembled a large repository of samples and begun assessing candidate TRIs.

Methodology

The CEPHIA repository currently consists of replicate plasma samples from 5641 specimens; representing 2007 subjects from studies in Africa, Brazil and the United States; with suitably characterized longitudinal subject information (demographic information, testing history for estimation of 'infection' dates, treatment history, viral load and CD4 cell counts).

Five TRIs, namely **BED, Limiting Antigen (LAg), Detuned Vitros, Vitros Avidity and Biorad Avidity**, which were previously assessed on a 250-sample 'Qualification Panel'[2] were evaluated using a clade-diverse 2500-member 'Evaluation Panel', using developers' previously published recent/non-recent discrimination criteria.

Regression and frequency estimation yielded estimates of the two TRI properties of relevance for incidence estimation[3]:

- The **Mean Duration of Recent Infection (MDRI)** is the average time spent alive and 'recently' infected, while infected for less than some time cut-off *T*.
- The **False-Recent Rate (FRR)** is the context-dependent proportion of those individuals infected for longer than *T* who nevertheless return a 'recent' result.

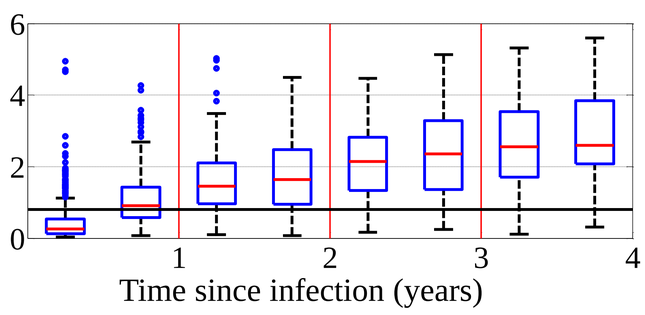
The FRR was calculated by time since infection for untreated patients, and separately for subjects virally suppressed by antiretroviral treatment (ART).

Results

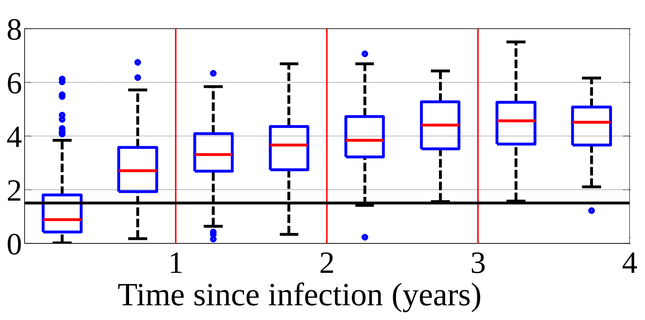
Evolution of Biomarkers with Time After Infection

Biomarker readings by time since estimated 'infection' (defined here as detectability by Western Blot) for each of the TRIs **[A]**:

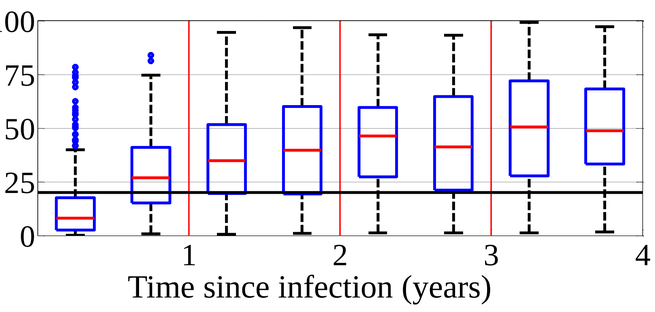
BED



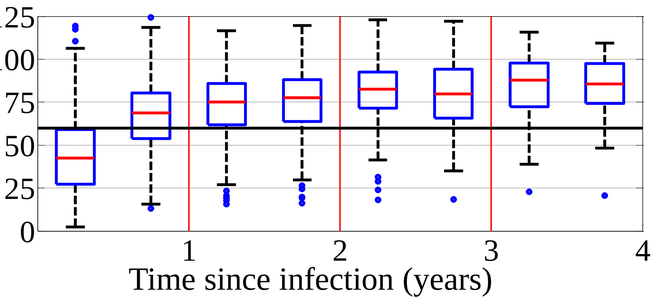
LAg



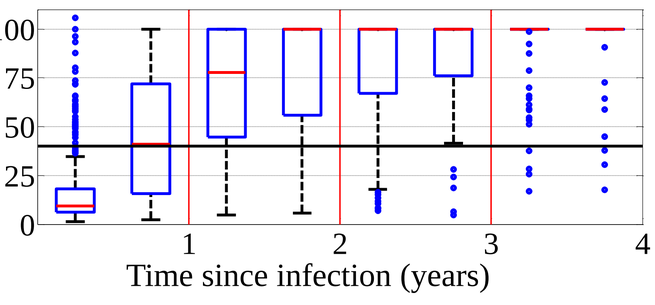
Detuned Vitros



Vitros Avidity



BioRad Avidity



[A]: The central 50% and median of measurements are captured by the box and its dividing line respectively. Whiskers and circles capture remaining measurements and outliers respectively. There are 35-450 observations in each group. Subjects on treatment are excluded, as well as subjects from studies that specifically recruited 'elite controllers' (ART-naïve, yet virally suppressed, subjects). Conventional thresholds, used to discriminate 'recent' and 'non-recent' infections, are shown (black, solid lines).

Mean Duration of Recent Infection and False-Recent Rates

- Subjects enter the operational HIV-positive state when they test Western Blot positive; $T = 1$ year (see Methodology).
- FRR is reported a) by treatment status, and b) in an illustrative population (30% of HIV-positive subjects are treated).
- Treated and untreated subject FRR differences are significant ($p<0.001$).

Assay	Mean Duration of Recent Infection, in days (95% CI) [B]	False-Recent Rate, as % [C]		
		ART-naïve [D]	ART virally-suppressed [E]	30% treated population [F]
BED	232 (214-249)	8.9	40.5	18.4
LAg	161 (144-178)	1.0	27.0	8.8
Detuned Vitros	211 (193-230)	8.6	54.1	22.3
Vitros Avidity	206 (187-226)	6.6	51.4	20.0
BioRad Avidity	253 (236-271)	5.3	33.8	13.8

[B]: Mean time under the recent/non-recent threshold, in a treatment naïve population, is estimated using 679 observations from 287 subjects. Regression is used to model the probability of testing 'recent' by time since infection (fitting a Weibull functional form). The 95% confidence interval (CI) is obtained by subject-level bootstrap resampling.

[C]: Proportions of 'recent' results were measured in subsets of subjects (created by stratifying by time since infection and treatment status) and are crudely weighted, according to the hypothetical population considered, to produce FRR estimates.

[D]: 'ART-naïve' FRR is estimated by measuring the proportion of 'recent' results among 378 subjects, in one year bins after estimated infection. Post-infection survival of the hypothetical population is Weibull-distributed with a mean of 10 years and standard deviation of 2.5 years.

[E]: 'ART virally-suppressed' FRR is estimated by measuring the proportion of 'recent' results among 37 subjects on treatment (initiated more than 6 months after estimated infection) and with a viral load (HIV-1 RNA) below 75 copies/ml.

[F]: '30% treated population' FRR is a weighted average of the FRRs in the preceding two columns, assuming 30% of the long-infected HIV-positive population is virally suppressed by treatment.

Conclusion

This is the first independent evaluation of predicate incidence assays. Used strictly according to developers' published protocols, none appears suitable, in stand-alone form, as a widely applicable incidence surveillance tool.

Since viral suppression is the main driver of false-recent results, optimal use of these serological markers is likely to involve explicit viral load criteria.

Further optimisation considerations include variation of recent/non-recent thresholds, and the use of multiple incidence assays in algorithms. Assessment of context-specific performance of TRIs requires formal estimation of the context-dependent FRR, using realistic population-representative distributions of clinical stages.

References

1. CEPHIA project website: www.incidence-estimation.com/page/cephia.
2. Kassanjee R, Murphy G, Busch M, Pilcher C, McKinney E, Keating SM, Facente S, MacArthur J, Welte A. The Performance of Candidate Assays to Detect Recent HIV Infection for Cross-sectional Incidence Estimation: An Independent, Comparative Evaluation. Poster 1056 at the *20th Conference on Retroviruses and Opportunistic Infections*, 3-6 March 2013, Atlanta, GA, USA.
3. Kassanjee R, McWalter TA, Bärnighausen T, Welte A. A new general biomarker-based incidence estimator. *Epidemiology* 2012; 23(5): 721–28.

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