Impact of HIV-1 Subtype and Sex on Sedia Limiting Antigen Avidity Assay Performance

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Background

- The Sedia™ Limiting Antigen Avidity EIA (LAg-Avidity Assay) is the **most widely-used immunoassay** used in recent infection testing algorithms (**RITAs**) for population-level HIV incidence surveillance.
- We combined data from two groups (JHU/NIAID and CEPHIA) to assemble the **largest single dataset of Sedia LAg-Avidity results** from seroconverter cohorts, consisting of 2,297 subjects and 10,322 specimens.
- We evaluated a wide range of RITAs **combining** LAg-Avidity normalized optical density **(ODn) thresholds with viral load thresholds** for incidence surveillance performance.
  - Performance is defined as the **precision of incidence estimates** achievable in surveillance scenarios.
- We investigated the impact of HIV-1 subtype and sex on critical performance characteristics of the assay/RITA.

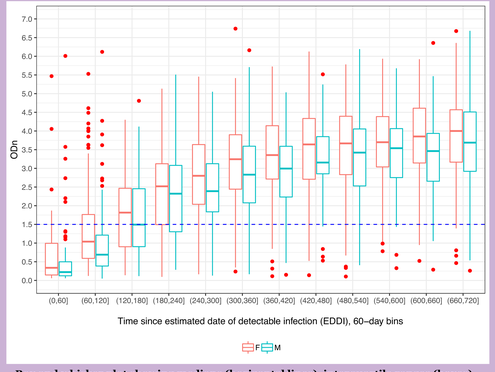
Methods

- **Harmonized estimated dates of detectable infection (EDDIs)** were produced for all subjects with full diagnostic testing histories (see Grebe et al. doi:10.1101/323808).
- Two key performance characteristics of a test for recent infection were estimated for each threshold combination:
  - The **mean duration of recent infection (MDRI)**: the average time post-EDDI that a subject exhibits the recent marker.
  - The **false-recent rate (FRR)**: the proportion of subjects infected for longer than a specified cut-off time (2 years) that nevertheless test recent.
- We tested for differences in MDRI by subtype and sex using two-sampled Z-tests.
- To evaluate surveillance performance, we defined epidemiological scenarios (subtype distribution, incidence, prevalence, treatment coverage) and estimated context-adapted MDRI (weighted average of subtype-specific MDRIs, adjusted for screening test) and context-specic FRR (weighted according to density of the times-since-infection and treatment coverage in the population).

Results

Sex differences

Figure 1: ODn values by sex andduration of infection



Box and whisker plot showing medians (horizontal lines), interquartile ranges (boxes), ranges (vertical lines) and outliers (red dots) for ODn measurments by sex and duration of infection.

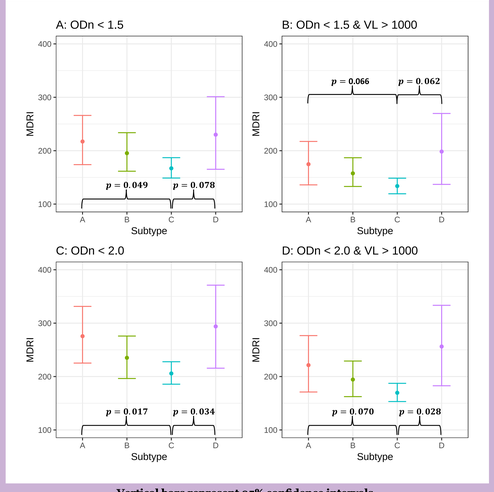
Table 1: Mean duration of recent infection (MDRI) by sex and pregnancy status

Group	Odn <	VL >	MDRI (95% CI)	SE	Specimens	Subjects	Difference	p-value
Male	1.5	N/A	210 (186,235)	13	1100	423		
Female	1.5	N/A	168 (150,188)	10	2287	745	**41.6**	**0.009****
Male	1.5	1000	175 (156,195)	10	1076	418		
Female	1.5	1000	132 (117,149)	8	1908	738	**42.7**	**0.001****
Female Not pregnant	1.5	N/A	171 (145,199)	14	1138	171		
Female Pregnant	1.5	N/A	159 (104,212)	27	305	43	12.8	0.675
Female Not pregnant	1.5	1000	141 (117,167)	13	858	167		
Female Pregnant	1.5	1000	126 (89,169)	20	224	42	14.5	0.542

- Females show **consistently higher ODn measurements** on the LAg-Avidity assay than males with similar durations of infection (Figure 1) and **significantly shorter MDRI** than males (Table 1).
- No statistically significant difference in MDRI by pregnancy status (Table 1).
- MDRI point estimates differed substantially between subtypes, and the **differences between subtypes A and C as well as C and D were statistically significant** (Figure 2).

Subtype differences

Figure 2: MDRI by HIV-1 Subtype



Vertical bars represent 95% confidence intervals

Performance in surveillance contexts

- **Scenario I (South Africa-like):** 100% clade C; Incidence: 0.99%, SE (σ)=0.04%; Prevalence: 18.9%, σ=1.12%; Treatment coverage: 56%, σ=5.6%.
- **Scenario II (Kenya-like):** 70% clade A, 25% clade D, 5% clade C; Incidence: 0.15%, σ=0.04%; Prevalence: 5.4%, σ=0.36%; Treatment coverage: 64%, σ=6.4%.
- **Scenario III (Concentrated MSM epidemic):** 100% clade B; Incidence: 0.5%, σ=0.05%; Prevalence: 15%, σ=1%; Treatment coverage: 90%, σ=9%.

Figure 3: Context-specific FRR against ODn threshold

Vertical bars represent 95% confidence intervals

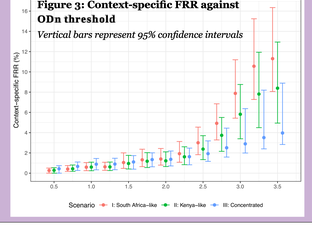
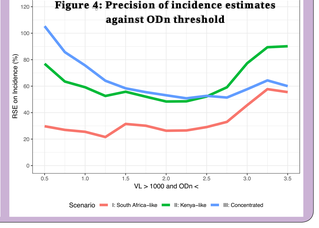


Figure 4: Precision of incidence estimates against ODn threshold



Conclusions

- **MDRI and FRR vary substantially by sex and HIV-1 subtype** (FRR data not shown).
  - **Sex-specific MDRIs differed** on the order of 40 days at the standard ODn threshold and differences were **statistically significant**. Our results **do not show a significant pregnancy effect**, although data were limited.
  - We observed **statistically significant MDRI differences** between **clades A and C**, and between **clades C and D**.
- **Optimal precision** in surveillance scenarios was achieved using ODn thresholds of approximately 1.0 to 2.5.
  - Context-adapted MDRI and FRR estimates are required to obtain accurate incidence estimates

A table with **MDRI and FRR estimates by threshold and HIV-1 subtype** available at: *tools.incidence-estimation.org/jhu-cephia-lag/*

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HPTN HIV Prevention Trials Network

NIH National Institute of Allergy and Infectious Diseases

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Consortium for the Evaluation and Performance of HIV Incidence Assays

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