Performance of commercial Herpes Simplex Virus type-2 (HSV-2) tests on samples from sub-Saharan Africa: A systematic review and meta-analysis

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Background: Several commercial type-specific serologic tests are available for Herpes Simplex Virus type 2 (HSV-2). Poor specificity of some tests has been reported on samples from sub-Saharan Africa. To summarise the performance of the tests, we performed a systematic review of publications reporting performance of commercially available HSV-2 tests against a gold standard (Western Blot or monoclonal antibody EIA) on samples from sub-Saharan Africa.
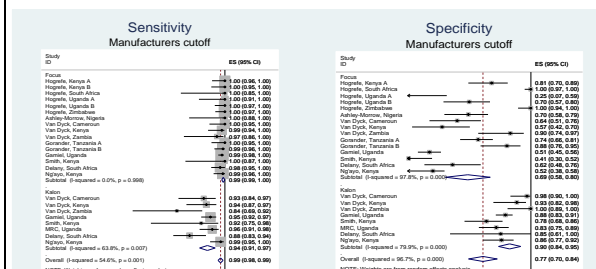
Methods: We used random-effects meta-analyses to summarise sensitivity and specificity of the two most commonly evaluated tests: Kalon gG2 ELISA and Focus HerpeSelect HSV-2 ELISA. Possible heterogeneity due to HIV infection was explored using meta-regression.

Results: We identified **11** eligible papers which included **19** studies of the performance of Focus, **11** of Kalon, **4** of the Monoclonal Antibody EIA (MAb EIA) and **4** of the Biokit test (see **Table I**).

### Table I: Performance of HSV-2 serological tests in Africa

Figure 1: Sensitivity and specificity of Focus and Kalon HSV-2 assays in Sub-Saharan Africa

Focus had high sensitivity (random effects summary estimate 99%, [95% CI, 99% - 100%]) but lower specificity (69%, [58% - 80%]). Kalon had **sensitivity** of 94% [91% - 97%] and **specificity** of 90% [84% - 95%].

Figure 2: Sensitivity and Specificity of Focus and Kalon HSV-2 assays at higher cut-off than recommended by manufacturer
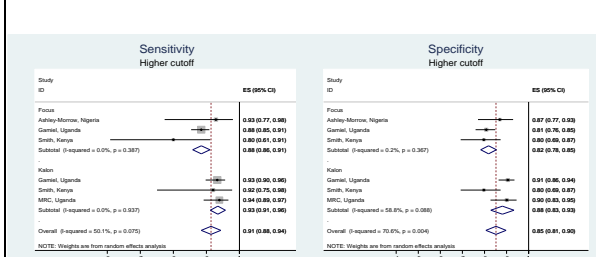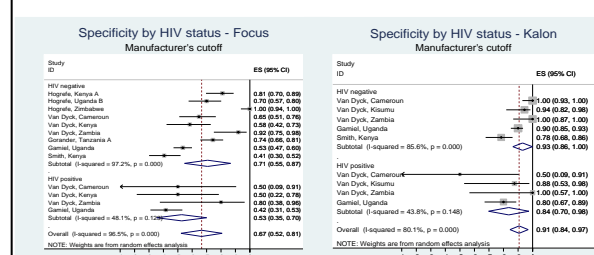

Three studies evaluated a higher cut-off of 3.5 for Focus, which improved specificity to **82%** [78% – 85%].

Figure 3: Specificity of Focus and Kalon HSV-2 assays by HIV status in Sub-Saharan Africa

Specificity of Focus was lower among HIV-positive (**53%** [35% -70%]) vs. HIV-negative individuals (**71%** [55% - 87%]), although this was not statistically significant (p=0.2). There was substantial between-study heterogeneity amongst HIV-negatives. There was a similar trend for Kalon, although the difference by HIV status was less marked (specificity in HIV positives 84% [70% - 98%] vs. **93%** [86% - 100%] in HIV negatives.

Conclusions: The **specificity** of commercially available HSV-2 serological tests **using African samples** appears **generally inferior** to that reported from industrialised countries.

There is a **large variation in performance depending on geographical location, characteristics of the study populations and HIV serostatus**. Therefore, studies using HSV-2 testing would benefit from an evaluation of test performance in the proposed study population, bearing in mind the aims of the testing e.g. estimation of prevalence, establishing aetiology of genital ulcer, estimating the effect of HSV-2 on risk of HIV acquisition or infectivity. Different assays could be used for different purposes.

Focus tended to have low specificity (summary estimate **69%**) compared with the gold standard when using the manufacturer's recommended cut-off (OD=1.1). Kalon tends to perform better when compared with Focus in the same study populations, although performance also varied across studies.

Improved specificity was obtained when the **cut-off was increased** above that recommended by the manufacturer (OD>1.5 for Kalon; OD>3.4 for Focus).