FALSE POSITIVES IN RESOURCE LIMITED SETTINGS

Reaching the 90-90-90 Targets: The Implications of HIV Misdiagnosis

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Hints of a problem

- Reports from the field of false positives
  - Zambia
  - Democratic Republic of Congo (DRC)
  - Ethiopia
Bukavu, DRC: 2001-5

• 2001-2005 tested 13,678 people using 2 RDT algorithm

• Overall positivity rate of 13.7% (population prevalence 2-5%)

• 2004/5: Potential False Positives identified on basis of CD4 counts

• Eventually, 44 falsely diagnosed individuals identified
Immediate Actions

• Reviewed test kits/reagents and test procedures – detected supervision and testing problems and introduced improvements.

• Introduced repeat testing of all VCT positives and discordant tests by the laboratory to ensure the quality of testing.

• However the problems with false positivity continued.
Introduction of a confirmatory algorithm

- January – May 2006 all HIV-positive results on 2 RDTs (Determine/Unigold) were confirmed by Western blot

- A serological confirmation test suitable for a level 2 lab was evaluated for field use: the Orgenics Immunocomb Combfirm® (OIC)
Results

- 2864 samples tested
- 229 Determine/Unigold positive (D+U+) samples received Western blot (WB)
- 10.5% (CI 6.8% - 15.2%) were WB negative or indeterminate.
  - All 12 WB indeterminate samples had a single gp41 band
  - OIC showed good agreement (99.1% (CI 96.0-99.9))
Strength of test line

100% falsely reactive

3.3% double RDT +: FP
Cross Reactivity

Cross reactivity simultaneously targeting both RDTs can lead to misdiagnosis

- Direct reaction with another antigen
  OR
- Indirect reaction: polyclonal B lymphocyte activation
Policy Response

Introduce new standards in addition to routine QC

• Strengthen all aspects of testing service
• Repeat all VCT tests in the lab
• Introduce a confirmation test
• Consider re-testing cohort
Data from other sites

• Zambia
  • 19 cases of FP identified on re-testing

• Ethiopia
  • 7/149 (4.7%) re-tested cases
  • 29 of 407 (7.1%) FP tested prospectively

• Burundi
  • 2/78 (2.6%) re-tested cases
  • 0/43 (0%) FP tested prospectively

• India
  • 5/723 (0.7%) FP with 29 (3.9%) indeterminate results tested prospectively
Evaluation of HIV testing algorithms in Ethiopia: the role of the tie-breaker algorithm and weakly reacting test lines in contributing to a high rate of false positive HIV diagnoses

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Abstract

Background: In Ethiopia a tiebreaker algorithm using 3 rapid diagnostic tests (RDTs) in series is used to diagnose HIV. Discordant results between the first 2 RDTs are resolved by a third ‘tiebreaker’ RDT. Médecins Sans Frontières
Variability in test performance

Centre 1 - Discordance patterns between the two RDTs

Centre 2 - Discordance patterns between the two RDTs

Centre 3 - Discordancies patterns between the two RDTs

Centre 4 - Discordance patterns between the two RDTs
Modeling of discrepancy data

- Data from 51 MSF test centres using 2 RDTs in parallel with discrepant results (A1+;A2- or A1-;A2+)
- Bayesian modeling used to derive estimates of se/sp with various models

RESULTS:

1. Specificity varies by location, both within and between countries.
2. Specificity varies over time within a particular location
3. These variations are not confined to a single test.
Consequences of False Positives

Individual
- Abandonment, divorce, violence
- New relationship with HIV positive partner
- Exposure to medications
- Cessation of breastfeeding

Program
- Loss of faith in testing
- Loss of confidence of VCT staff
- Myths of cure
- Misuse of scarce resources
Conclusions

- Misdiagnosis linked to: test issues, user error, over-interpretation of weak + test lines, and cross-reactivity
- QA key in improving performance
- Re-testing is critical
- Tie-breaker algorithms to diagnose HIV to be avoided
- Cross reactivity remains a challenge and can be variable over time and place
Bottom Line

• It is possible to reduce the risk of misdiagnosis

• The costs to both patients and programs are too great to continue to ignore the problem…
References


