HIV misdiagnosis: Assuring the quality of test kits

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World Health Organization
Likely drivers of misdiagnosis

- WHO systematic review showed misdiagnosis of HIV-positive status was common (range: 0.28-10.5%)

- WHO recommended testing strategy not used
  - use of Assay 3 as tiebreaker to rule in HIV infection

- National testing algorithm not validated

- Poor training and supportive supervision of testers

- Instructions for use issued by manufacturer not observed by end-users
  - Irregular reading of weakly reactive test lines
  - Reading results before minimum reading time
  - Incorrect storage of test kits
Misdiagnosis of HIV cont'd

Impact of ARVs on sensitivity

- Antibody production is affected by early initiation of ART
  - ↓ sensitivity for older generations of assays (1\textsuperscript{st}/2\textsuperscript{nd})
  - ↓ sensitivity for oral fluid RDTs
- Detection of nucleic acid is affected by ARV
  - Plasma RNA is suppressed
  - But cell-associated DNA is not likely be affected by ARV

Impact of x-reactivity on specificity

- Same antigen sources used
- ↑ re-branding arrangements, same assay is available under different brand names
- False reactive results due to interfering substances and concomitant infections
Importance of quality systems

- 12 aspects are critical to assure the quality of testing
  - Purchasing and inventory
    - Standards for test kits procured
  - Personnel
    - Training and supervision
  - Assessment
    - EQA (proficiency testing)
  - Post-market surveillance
    - Through records/documentation/occurrence management
WHO testing strategies

High prevalence (>5%)

- Perform A1
  - A1+: Report HIV-positive
    - Retest before ART
    - Perform A2
      - A1+ A2−: Report HIV-negative
      - A1+ A2+: Report HIV-positive
        - Retest before ART
        - A1+ A2−: Report HIV-negative
        - A1+ A2+: Report HIV-positive
          - Retest before ART
          - A1+ A2−: Report HIV-negative
          - A1+ A2+: Report HIV-positive
            - Retest before ART
            - A1+ A2−: Report HIV-negative
            - A1+ A2+: Report HIV-positive
              - Retest before ART
              - A1+ A2−: Report HIV-negative
              - A1+ A2+: Report HIV-positive

Low prevalence (<5%)

- Perform A1
  - A1+: Report HIV-negative
    - Perform A2
      - A1+ A2−: Report HIV-negative
        - A1+ A2+: Report HIV-positive
          - Report HIV-inconclusive, if A1 is 2nd or 3rd generation assay
        - A1+ A2+: Report HIV-positive
          - Retest before ART
          - A1+ A2−: Report HIV-negative
          - A1+ A2+: Report HIV-positive
            - Retest before ART
            - A1+ A2−: Report HIV-negative
            - A1+ A2+: Report HIV-positive
              - Retest before ART
              - A1+ A2−: Report HIV-negative
              - A1+ A2+: Report HIV-positive
                - Retest before ART
                - A1+ A2−: Report HIV-negative
                - A1+ A2+: Report HIV-positive
                  - Retest before ART
                  - A1+ A2−: Report HIV-negative
                  - A1+ A2+: Report HIV-positive

New HIV testing approaches

Test for triage

Perform HIV self-test

A0 +

Link to HIV testing for diagnosis, care & treatment

A0 –
Report HIV- Recommend repeat testing as needed & linkage to relevant HIV prevention

HIV self-testing

Perform HIV self-test

A0 +

Report reactive HIV test
Advised linkage to further HIV testing for diagnosis.
If confirmed HIV-positive, refer for treatment

A0 –
Report HIV-negative
Recommend retesting as needed
Advised linkage to relevant HIV prevention services
Re-testing recommendations

- **What is retesting?**
  - Same testing algorithm, different specimen different testing site

- **Objective?**
  - To rule out/rule in seroconversion
  - To rule out operator error, test device error, transcription errors

- **Who should be re-tested**
  - Individuals with **HIV-inconclusive** status after 14 days
  - Individuals with **newly diagnosed HIV-positive** status prior to care and treatment;
  - Individuals with **HIV-negative** status with ongoing risk
What is WHO prequalification?

- WHO PQ independently reviews safety, quality, performance of HIV diagnostics (and others)

- WHO PQ is similar to regulatory approval, it can be used in settings where regulation of diagnostics is poor

- WHO PQ is also used by UN agencies and governments to make procurement decisions
WHO prequalification process

Pre-submission form

Priority IVD

Yes

No

Dossier review

Site inspection

Laboratory evaluation

Prequalification decision. UN procurement eligibility.
Post-market surveillance

- An incident happens to the product
e.g. pouch of test kit is breeched, higher than expected rate of invalid tests

- An adverse event happens to a person
e.g. false negative or false positive result where it leads to a misdiagnosis

- The instructions for use for the test kit will state expected sensitivity and specificity and other claims such as storage conditions, specimen collection, incubation times, etc.

- End-users are expected to report when the assay does not work according to the claims and for incidents/adverse events
Quality of HIV testing has a continuum

Test kit quality

- Poorly designed
- Poorly manufactured
- Production defect

Testing quality

- Stored incorrectly during transportation or use
- Test procedure not followed correctly

Prequalification identifies test kits that don't meet WHO standards for quality, safety and performance

Quality systems and post-market surveillance are critical to monitor test kit quality post-introduction
Contact us

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- Sign up to our mailing list
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