Evaluation of quality, performance and operation of diagnostics

UN Meeting with Manufacturers
23-25 September 2013, Copenhagen

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World Health Organization

World Health Organization
Diagnostics at point of care

- POC = *where the patient is or where the treatment/care is*

- Critical features of diagnostics for use at POC
  - No venipuncture required
  - No electricity required for test procedure or storage of reagents
  - Robustness and portability
  - Can be operated by non-lab user, minimal training/installation
Serological RDTs

- Multiple formats
  - Immunochromatographic RDTs
  - Immunofiltration RDTs

- Multiple analytes detected
  - Combined (2 line test) HIV-1/2 Ab
  - Discriminatory (3 line tests)
    - HIV-1 and HIV-2 Ab
    - HIV-1/2 Ab and HIV-1 p24 Ag
    - HIV/syphilis
    - HIV/HCV
    - HIV/HCV/HBV
New POC CD4 diagnostics

*Estimated as of March 2013 - timeline and sequence may change.
UNITAID technical report June 2013, 3rd edition
New POC EID/VL diagnostics

- Liat™ Analyser
- Alere Q
- EOSCAPE HIV™ Rapid RNA Assay System
- LYNX Viral Load Platform
- Alere
- NWGHF
- Wave 80 Biosciences
- RT CPA HIV-1 Viral Load Ustar
- NWGHF
- Cepheid
- Gene-RADAR® Nanobiosym
- Gene Xpert® System
- Cavidi AMP
- Viral Load Assay with BART
- Lumora
- Micronics
- ALL
- BioHelix

SAMBA VL
- DDU/Cambridge

SAMBA EID
- DDU/Cambridge

Truelab™ PCR
- Molbio/bigTec

*Estimated as of March 2013 - timeline and sequence may change. No market launch date set by company.*

UNITAID technical report June 2013, 3rd edition

UN Meeting with Manufacturers, Copenhagen 23-25 September 2013
Performance characteristics – serology

- Clinical sensitivity
  - Other measures: analytical sensitivity, seroconversion sensitivity

- Clinical specificity
  - Other measures: cross-reactivity, interfering substances, concomitant infections

- Lot-Lot variability

- Inter-reader variability, if subjectively read

- Invalid rate (or no result obtainable)
Performance characteristics – CD4

- Precision
  - Intra-assay (within run) variability = repeatability
  - Inter-instrument (between run) variability = reproducibility
  - Inter-assay (between run) variability = reproducibility

- Accuracy = bias and misclassification
  - Compared to reference results (i.e. gold standard)

- Invalid rate (or no result obtainable)
Performance characteristics – VL

- **Precision**
  - Within run variability = repeatability (same specimen, same run)
  - Between run variability = reproducibility (same specimen, different run)

- **Accuracy** = bias and misclassification
  - Compared to reference results (i.e. gold standard)

- **Limit of detection** (analytical sensitivity)

- **Linearity**

- **Invalid rate** (or no result obtainable)
## Performance acceptance criteria - serology

<table>
<thead>
<tr>
<th></th>
<th>EIA (Laboratory)</th>
<th>RDT (Point of Care or Laboratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>100%</td>
<td>Sensitivity ≥ 99%</td>
</tr>
<tr>
<td>Specificity:</td>
<td>≥ 98%</td>
<td>Specificity ≥ 98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inter-reader variability ≤5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invalid rate ≤5%</td>
</tr>
<tr>
<td><strong>HCV serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>100%</td>
<td>Sensitivity ≥ 98%</td>
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<tr>
<td><strong>HBsAg serology</strong></td>
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</tr>
<tr>
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Performance acceptance criteria - CD4

<table>
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<tr>
<th>Laboratory (conventional instruments)</th>
<th>Point-of-care (dedicated cytometers)</th>
</tr>
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<tbody>
<tr>
<td><strong>Intra-assay variability (CoV) same specimen, same instrument, same day</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;15% at 200 cells/µl</td>
<td>&lt;20% at 200 cells/µl</td>
</tr>
<tr>
<td>&lt;10% at 350 and at 500 cells/µl</td>
<td>&lt;15% at 350 and at 500 cells/µl</td>
</tr>
<tr>
<td><strong>Inter-instrument variability (CoV) same specimen, same day, different instruments</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;15% at 200 cells/µl</td>
<td>&lt;20% at 200 cells/µl</td>
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<td>&lt;15% at 350 and at 500 cells/µl</td>
</tr>
<tr>
<td><strong>Carryover</strong></td>
<td></td>
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<tr>
<td>&lt;2%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: differences between venous vs. capillary whole blood should be characterised
Taken from draft meeting report of WHO technical advisory group meeting on performance and quality criteria of POC CD4 technologies, May 2013
Performance acceptance criteria- CD4

<table>
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<th>Point-of-care technologies</th>
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<tbody>
<tr>
<td><strong>Accuracy, if quantitative, compared to the reference method</strong></td>
</tr>
<tr>
<td>Standard deviation of 40 cells at &lt;200 cells/µl</td>
</tr>
<tr>
<td>Standard deviation of 50 cells at 200 - 500 cells/µl</td>
</tr>
<tr>
<td>Standard deviation of 75 cells at &gt;500 cells/µl</td>
</tr>
<tr>
<td><strong>Misclassification, if qualitative, compared to the reference method</strong></td>
</tr>
<tr>
<td>Sensitivity &gt;90%</td>
</tr>
<tr>
<td>Specificity &gt;90%</td>
</tr>
</tbody>
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Note: overestimation could be permitted, but underestimation will affect decision to initiate ART

Taken from draft meeting report of WHO technical advisory group meeting on performance and quality criteria of POC CD4 technologies, May 2013
Operational characteristics

- Characteristics of the technology (equipment/instrument)
  - Including throughput, time to result, parameters available, power source, portability

- Characteristics of the reagents
  - Including stability/shelf life for storage and in-use stability

- Specimen preparation
  - Including specimen type & volume, number of steps, precision of measurement, specimen stability after application to device
Operational characteristics cont'd

● Quality control
  – Including internal QC (software and instrument), external QC specimens, compatibility with known EQA schemes

● Regulatory, cost & other operational aspects
  – Including regulatory version, cost of instrument and/or reagents, connectivity & data management, maintenance, training, technical support
Evaluations performed

- WHO evaluation protocols followed, based on existing international standards and best practice

- WHO Collaborating Centres performs evaluation under supervision of WHO

- WHO Composite Reports of all products evaluated
  - Report 17 to be released

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<tr>
<th></th>
<th>RDTs</th>
<th>EIAs</th>
<th>CD4</th>
</tr>
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<tbody>
<tr>
<td>HIV</td>
<td>21</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hep C</td>
<td>2</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Hep B</td>
<td>2</td>
<td>1</td>
<td>N/A</td>
</tr>
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</table>
Common issues related to evaluation

- Delivery of test kits and/or platforms took longer than expected
  - Importation, customs delays
  - Unreasonable time extensions requested for RDTs

- Request for two distinct production lots not always followed
  - Verification of batch manufacturing records during site inspection
Information sources

- WHO Prequalification of Diagnostics Public Reports for each individual product

- WHO composite comparative report of performance and operational characteristics
  - Report 17 for HIV serology assays,
  - Report for CD4
  - Report 18 HIV serology assays (in preparation)
Product selection

- Which technology and where
  - Based on performance & operational characteristics
  - Trade-offs may need to be made

- Different technologies for different levels of the health systems
  - Depending on the needs and available resources
Product selection cont'd

- Assess facility needs
  - Required through-put required at the testing facility
    - High volume facilities
      - Many low volume TP instruments or few high volume TP instruments
    - Low volume facilities
      - Low volume TP instruments
  - Opening hours of facility
  - Number of staff
  - Other services required during the same visit to facility

- Are more people likely to visit if POC is available?
Product selection cont'd

- Determine key aspects of POC technologies that will relate to the facility needs
  - Specimen type and volume required
  - Specimen preparation and precision required
  - Stability of specimen once collected into device/cartridge
  - Time to result
  - Random access capability
    - Or must wait for one specimen to be run before next specimen can be run

- Other factors
  - Storage/stability of reagents, life span of instrument, data capture, quality control
Our Website

- Information, documents & much more are on our website
  
  www.who.int/diagnostics_laboratory/en/

- We have an email address
  
  diagnostics@who.int

Thank you