Evaluations of POCT for EID

ILF, IAS Durban 2016
19 June, 2016
Content

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How many children are living with HIV?

- Of the estimated 35.3 million people worldwide living with HIV, approximately 3.2 million are children under 15 years of age,
- 91% of these children residing in sub-Saharan Africa.
- An estimated 260,000 children were newly infected with HIV in 2012;
- ± 700 children are newly infected with HIV every day.

Source: UNAIDS, Global Report, 2014)
EID testing Algorithm Options

- Birth PCR
- 10 week PCR
- Post cessation of breastfeeding
- 9 month rapid test
- 18 month rapid test
- 6 week PCR
- Post cessation of breastfeeding
- 9 month rapid test
- 18 month rapid test
- 6 weeks post cessation of breastfeeding
- 18 month rapid test

Slide credit : Gayle Sherman
Testing at birth

- Better retention in the cascade
- Earlier ART initiation
- Low sensitivity of virological testing at birth
- Increased cost

Source: Bourne et al. AIDS, 2009

Slide credit: Martina Penazzato, WHO
The % decline in new HIV infections among children in 21 Global Plan priority countries, 2009–2014

- The number of new HIV infections among children in 2014 and % reduction in new HIV infections since 2009 in 21 Global Plan priority countries

### >60% decline
- Ethiopia (65%)
- Mozambique (69%)
- Namibia (64%)
- South Africa (76%)
- Swaziland (63%)
- Uganda (69%)
- United Republic of Tanzania (72%)

### 30–60% decline
- Botswana (58%)
- Burundi (57%)
- Ghana (51%)
- Lesotho (42%)
- Malawi (53%)
- Zambia (38%)
- Zimbabwe (57%)

### <30% decline
- Angola (25%)
- Cameroon (27%)
- Chad (19%)
- Côte d’Ivoire (26%)
- Democratic Republic of the Congo (27%)
- Kenya (29%)
- Nigeria (15%)

Source: 2015 Progress report on the Global Plan UNAIDS / JC 2774/1/E
What does this mean in paediatric care?

- 90% diagnosed
- 90% on treatment
- 90% virally suppressed
PLWHIV that know their status

54% Adults

32% Children
Percentage of infants born to women living with HIV receiving a virological test within the first 2 months of life in 21 Global Plan priority countries, 2014

only 49% of children exposed to HIV received HIV virological testing within the first two months of life in 2014
The volume of EID tests performed has grown from ±200,000 in 2007 to close to 1,000,000 in 2014.

**Total EID Testing Volumes in LMICs, 2007-2014**

- **2007**: ±200,000
- **2008**: ±500,000
- **2009**: ±600,000
- **2010**: ±700,000
- **2011**: ±800,000
- **2012**: ±800,000
- **2013**: ±900,000
- **2014**: ±1,000,000

**Sources:** CHAI annual lab data requests; government reports; UNAIDS data; Global Plan; CHAI-UNICEF Pediatric Project Grant Reports
Lab Evaluations

This have taken place at CDC Atlanta and NHLS, Johannesburg
WHO Prequalification of Diagnostics

**Dossier Review**

- **Objective**: to review the data supporting the design, development and manufacture of the product.
- Review of Safety and Performance data

**Performance Evaluation**

- **Objective**: to independently verify essential, clinically relevant performance and operational characteristics of assays with a focus on resource-limited settings.

**Site Inspection**

- **Objective**: To verify the quality of the product through a Quality Management System audit based on international standards (ISO 13485) with a focus on resource-limited settings.

Source: González 2016 EID Consortium Meeting
EID Laboratory Evaluation Protocol (CDC-NHLS-WHO PQ)

USG/WHO QA Procurement Alignment

Development of Evaluation Protocol (CDC/WHO/NHLS)

First EID POC Evaluations Started

First EID POC Evaluations Completed

- 2014-Q3
- 2014-Q4
- 2015-Q1
- 2015-Q2
- 2015-Q3
- 2015-Q4
- 2016-Q1
- 2016-Q2

Slide credit: Mackenzie Hurslton, CDC Atlanta
Protocol Objectives

Primary objective of the study

✓ To independently evaluate NAT based HIV qualitative assays undergoing prequalification assessment

Specific objectives of the study

✓ To evaluate the performance of the assays in different subtypes near the limit of detection
✓ To determine the performance of the assays at the manufacturer’s stated lower limits of detection
✓ To determine the inter- and intra-device precision of assays
✓ To determine the specificity, sensitivity, negative and positive predictive values of assays in relation to the benchmark assay
✓ To assess potential cross-contamination
✓ To evaluate device failure rates as well as additional operational characteristics
## Division of Responsibilities

<table>
<thead>
<tr>
<th>Protocol Component</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carry-over</td>
<td>ILB</td>
</tr>
<tr>
<td>Limit of Detection</td>
<td>ILB</td>
</tr>
<tr>
<td>Subtype Coverage</td>
<td>ILB</td>
</tr>
<tr>
<td>Precision</td>
<td>NHLS, ILB*</td>
</tr>
<tr>
<td>Accuracy</td>
<td>NHLS</td>
</tr>
<tr>
<td>Coordination</td>
<td>WHO</td>
</tr>
</tbody>
</table>
HIV-1 Isolates Used in the Evaluation

<table>
<thead>
<tr>
<th>Source</th>
<th>Sub-type</th>
<th>Isolate Name</th>
<th>GenBank No./Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>A</td>
<td>KER2008 (KE_KER2008)</td>
<td>AF457057</td>
</tr>
<tr>
<td>NIH</td>
<td>B</td>
<td>Ba-L (85US_Ba_L)</td>
<td>AY713409</td>
</tr>
<tr>
<td>NIH</td>
<td>C</td>
<td>97USNG30</td>
<td>AF096349</td>
</tr>
<tr>
<td>NIH</td>
<td>D</td>
<td>A03349M1</td>
<td>AY736834</td>
</tr>
<tr>
<td>NIH</td>
<td>F</td>
<td>BR112-D6</td>
<td>AF113560</td>
</tr>
<tr>
<td>NIH</td>
<td>AG</td>
<td>CAM0002BBY</td>
<td>AY371122</td>
</tr>
<tr>
<td>NIH</td>
<td>AE</td>
<td>NP1251 (98th_NP1251)</td>
<td>AY13422</td>
</tr>
<tr>
<td>NIBSC</td>
<td>B</td>
<td>WHO 3rd International Standard (10/152)</td>
<td>KJ019215</td>
</tr>
</tbody>
</table>
## Methods Summary

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Specimen Type</th>
<th>Number of Replicates</th>
<th>Evaluation Assay</th>
<th>Reference Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carry-over Assessment</strong></td>
<td>C</td>
<td>97USNG30</td>
<td>20 High positive (10⁶), 20 Negative</td>
<td>Confirmed on Roche in triplicate</td>
</tr>
<tr>
<td><strong>Performance Across Representative Subtypes</strong></td>
<td>A, B, C, D, F, AG, AE</td>
<td>Isolates grown in ILB (previous slide)</td>
<td>3 replicates of each subtype</td>
<td>3 replicates of each subtype</td>
</tr>
<tr>
<td><strong>LOD Verification</strong></td>
<td>B</td>
<td>3rd International WHO Standard</td>
<td>30 replicates of 5 separate dilutions 150 total</td>
<td>10 replicates of 5 separate dilutions 50 total</td>
</tr>
<tr>
<td><strong>Precision: Repeatability and Reproducibility</strong></td>
<td>unknown</td>
<td>3 Adult HIV-1 Positive Remnant Specimens</td>
<td>42 total (14 replicates of each donor)</td>
<td>NA; confirmed HIV-1 positive with viral load</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>unknown</td>
<td>Infant remnant specimens collected in South Africa</td>
<td>150 individual; positives, 150 individual negatives</td>
<td>150 individual; positives, 150 individual negatives</td>
</tr>
</tbody>
</table>
Routine EDTA whole blood EID Roche CAPCTM

Result is available and sufficient left over blood remains

Sample is retrieved for study

150 µL are temporarily stored

Assay under Evaluation

DBS cards are prepared with 5 x 70 µL Spots

Assay under Evaluation

Discrepant Resolution

Results Compared to Roche

EiD Consortium
Maximizing Resources
The CDC-NHLS-WHOPQ collaboration

Capillary whole blood

EDTA Whole Blood Exposed <18 months old infants

150 # Positives specimens

± 150 # Positives

± 150 # Positives

± 150 # Positives

Munktell or 903 Free virus elution protocol

Roche

Alere

Cepheid

150 # Positives specimens
This is a lab (phase 2) assessment of EID POCT devices to be conducted both in CDC Atlanta and an NHLS lab in Johannesburg. The intention is WHO PQ listing and NHLS HTA qualification too.

- Lab testing completed
- Data analysis completed
- Report draft completed
- Internal verification and approval in progress.

Acknowledgment: Lucia Hans Mackenzie Hurlston, MSPH - CDC
Mercedes Perez Gonzales - WHO
FIELD PERFORMANCE OF POINT-OF-CARE HIV TESTING FOR EARLY INFANT DIAGNOSIS: Pooled analysis from six countries from the EID Consortium

S. Carmona1,2, C. Wedderburn1, W. Macleod4,5, M. Hsaio2,6, I. Jani7, M. Kroon8, D. Maman9, J. Maritz2,10, B. Meggi7, F. Mosha11, V. Muchunguzi11, E. Munemo12, T. Murray13, R. Mwenda14, L. Myer15, A. Nelson16, V. Opollo17, G. Sherman18,19, R. Simbi12, K. Technau20, L. Vojnov21 and members of the Early Infant Diagnosis (EID) Consortium

1University of the Witwatersrand, Molecular Medicine and Haematology, South Africa, 2National Health Laboratory Service, South Africa, 3London School of Hygiene & Tropical Medicine, United Kingdom, 4WITS Health Consortium, South Africa, 5Boston University, Center for Global Health, United States, 6University of Cape Town, Medical Virology Division, South Africa, 7Instituto Nacional de Saúde, Mozambique, 8University of Cape Town, Neonatal Medicine, South Africa, 9Médecins Sans Frontières, Epicentre, South Africa, 10University of Stellenbosch, South Africa, 11Ministry of Health and Social Welfare, Tanzania, 12National Microbiology Reference Lab, Zimbabwe, 13WITS Health Consortium, South Africa, 14Ministry of Health, Malawi, 15University of Cape Town, South Africa, 16Médecins Sans Frontières, South Africa, 17CDC/KEMRI, Kisumu, Kenya, 18National Institute of Communicable Diseases, South Africa, 19University of the Witwatersrand, South Africa, 20Empilweni Services and Research Unit, South Africa, 21Clinton Health Access Initiative, Malawi
There are at least 20 sites either in progress to or already evaluating EID POCT devices such as Alere, Cepheid or Samba.
BACKGROUND

The expansion of prevention of mother-to-child transmission programmes has resulted in a reduction in paediatric HIV infections. However, HIV transmissions still occur requiring accurate early infant diagnosis (EID) and early treatment initiation. Evaluations of new technologies for EID are essential to inform national regulatory approval and implementation, but the low HIV incidence in infants limits timely, adequately sized evaluation studies. The EID Consortium is helping to accelerate the evaluation and subsequent implementation of EID point-of-care (POC) diagnostics across Africa; here we report on field performance of HIV qualitative assays from Alere and Cepheid in exposed infants < 18 months of age.

www.eidconsortium.org
METHODS

Data from 9 independent field evaluations of Alere q HIV-1/2 Detect and Cepheid Xpert HIV-1 qual assays were pooled from ongoing studies in Kenya, Malawi, Mozambique, Tanzania, South Africa and Zimbabwe. A range of health professionals from nurses, laboratory technicians to medical doctors operated the devices.
Results

Alereq and Cepheid
RESULTS: Alere q HIV-1/2 Detect

Specimens from HIV-exposed infants < 18 months old, were analysed on Alere q HIV-1/2 Detect

Total number samples run: 1884

Comparator: Roche HIV CAPCTM at all sites with the exception of Malawi which compared to Abbott HIV m2000.
RESULTS: Cepheid Xpert HIV-1 qual

Specimens from HIV-exposed infants < 18 months old were analysed on Cepheid Xpert HIV-1 qual

Total number of samples = 2598 and

Comparator: Roche HIV CAPCTM

<table>
<thead>
<tr>
<th>Reference Assay</th>
<th>Xpert</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Sum (n=)</td>
</tr>
<tr>
<td>Positive</td>
<td>93</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>2500</td>
<td>2503</td>
</tr>
<tr>
<td>Sum (n=)</td>
<td>96</td>
<td>2502</td>
<td>2598</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Point Estimate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>96,88%</td>
<td>91,73%</td>
<td>99,20%</td>
<td></td>
</tr>
<tr>
<td>99,92%</td>
<td>99,74%</td>
<td>99,99%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Device Errors</th>
<th>total #</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>total #</td>
<td>118</td>
<td>4,28%</td>
</tr>
</tbody>
</table>
CONCLUSION

- The EID Consortium has been able to aggregate data from multiple centres across Sub-Saharan Africa. This is vital to accelerate progress in evaluating POC EID testing in the field.

- The analysis of the data shows that both the Alere q HIV-1/2 Detect and Cepheid Xpert HIV-1 qual assays perform well in the field.

- Understanding the performance of these devices in their intended setting provides valuable information to support the implementation of POC testing within existing EID programmes.

- Further work is required to evaluate the impact these new technologies will have on paediatric HIV care. The next question is: “Where to place POC devices for maximum impact?”
The Alere Pima Product Evaluation Story

Slide credit: Lara Vojnov
Lessons learned from past CD4 POC introductions

• Lengthy and unclear introduction/validation process
• Suboptimal instrument procurements and long term planning
  • Optimizing existing lab infrastructure
  • Evidence based POC integration
• Long term impact of new technology not clearly understood
  • Instrument life span
  • Maintenance strategy development
• Uptake – lessons learned
  • Limited government, donor, and technical coordination
  • Competing priorities – treatment agenda (increased access) versus laboratory network development
  • Vendor pressures (misleading)
  • Logistics (SDP not lab)
  • Procurement, quantification, distribution, and maintenance

Slide credit: Jason Williams / personal communication Joel Kuritzky
Rapid CD4 POC instrument growth (Country B)

- **2009**: 0 Instruments
- **2011**: 0 Instruments
- **2015**: 410 Instruments

**Legend**:
- PIMA
- Guava Easy
- Cyflow Partec
- FACSCalibur
- FACScount

Slide credit: Jason Williams / personal communication Joel Kuritzky
Historical example of CD4 POCT placement and usage in 2012 Country X

<table>
<thead>
<tr>
<th>Overall 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of sites</td>
</tr>
<tr>
<td>Sites with &quot;0&quot; consumption</td>
</tr>
<tr>
<td>Sites with consumption ≤ 1/day</td>
</tr>
<tr>
<td>% of sites with 0 or consuming ≤1/day</td>
</tr>
<tr>
<td>% of sites with access to referral lab</td>
</tr>
</tbody>
</table>

- Program expansion driven by PMTC programs
- No MOH laboratory involvement
- Existing warranties expired – no long term maintenance plan/financing
- Maintenance costs needed be negotiated (historically at $1,200/machine)

Slide credit: Jason Williams / personal communication Joel Kuritzky
What are some of the next steps:

• Impact evaluations would provide information on the value of POCT for EID in the context of existing programmes
• Where are these devices best place to provide maximum impact
• Multi-valency? Is this possible
Pooled analysis from six countries from the EID Consortium