Point-of Care Technology: Perspective from South Africa

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- South African perspective
- Future Point of Care Viral load testing options
- Two feasibility studies
  - CD4 PIMA
  - GeneXpert TB
Definition

- **Point of Care testing (POCT):** refers to testing that is performed near or at the site of the patient with the result leading to a possible change in the care of the patient.

- **Outpatient clinic, ER, theatre, mobile clinics, PHC clinics, or even small laboratories**

- Small bench top analysers such as blood gas machines or full blood count analyzers, Portable hand held devices such as glucometers, strip based assays

(Warsinke, 2009; Plebani, 2009)
Trends in POC

- Fastest growing segment in diagnostics: 10% annually
- 31000 instruments, 25% of total lab revenue
- **Growth areas**: cardiac, coagulation, HIV testing, drugs of abuse, tight glycaemic control, molecular diagnostics for infections
- Expanded test menus
- Consolidated platforms e.g. glucose, lactate, creatinine
- Self-contained cartridges
- Improved analytical capability
- Improved data management systems, multi-vendor enterprise solutions
### Advantages
- Quality and efficiency of care can be improved in certain scenarios
- Improved accessibility
- Improve patient compliance and LTFU
- Improved turnaround time
- Smaller sample volumes
- Economic benefits – reduced length of stay
- reduced complications and readmission
- Improved patient and clinician satisfaction

### Disadvantages
- Difficulties with quality control/documentation
- Higher unit of cost/reagent
- Greater personnel requirements at clinic
- Longer patient wait times
- Poor regulatory control
- Data management/audit issues
- Slower sequential processing time/throughput in high clinics
- Over-servicing
Specifications for POC

- Rapid
- Results within time-frame of a consultation
- Require minimal training, easy to perform
- Hand held detection device/strip
- No specialised laboratory set-up
- Stable, temp independent
- Affordable
- Quality control
Current Activities in South Africa

- Component of new National laboratory policy (Maputo declaration)
- Establishment of an NHLS POC working group

- **Proposed role in investigation** of:
  - Technologies, equipment
  - Method validation
  - Development of SOP’s, training programs and manuals, checklist
  - Supportive internal QC and EQA programs
  - Ethics clearance for clinical studies and pilot sites
  - CDC support

Recent analysis of rapid HIV VCT testing in South Africa: concerns over performance
The first point of entry for many South Africans to health care is through local primary healthcare clinics or community health centres (1994).

Investigating the development of a pathology formulary for Primary Health Care Clinics:

- may be relatively simple and could be based largely on the clinical care packages mandated by the NDOH for these clinics.
Continued…

- **Two types of facilities:**
  - Tests that can be requested, but need to be referred and thus clinic activity simply involves *specimen collection*
  - Tests that can be *requested and performed on-site*
  - The size and infrastructure of these clinics varies significantly and thus clinics could well be further separated into:
    - **Level 1A:** clinics capable of only conducting rapid, strip based Point of care tests (POC) tests
    - **Level 1B:** clinics capable of conducting more sophisticated POC tests
      - Hb, glucose, creatinine, lactate, ALT
      - Ability to conduct multiple tests in one clinic??
Common themes in Research and Development facilitate new assays…

- Microfluidics for fluid delivery
- Minituarization/ low-cost microfabrication
- Magnetism/magneoresistance
- Efficient, inexpensive light sources (semi-conductor based lighting)
- Affordable microelectronics and digital imaging hardware
- Simplified power sources
- Electromagnetic Actuation of Fluids using Micro/NanoParticles
CD4 testing:

Centralised flow cytometry
Nucleic Acid testing

Centralized automated testing

GeneXpert for POCT
Viral Load: Potential Applications

- Viral load in treatment programs
  - To identify early failure and target non-adherents early (major cost-saving keeping on 1st line regimen as long as possible); and
  - to identify late failure (due to adherence or genotypic failure)
  - To measure programme performance (and site specific performance)

- Potentially diagnosis of acute infection
- Infant diagnosis of HIV
### Available technology for Tiered Laboratory Network

<table>
<thead>
<tr>
<th>Tertiary Reference Laboratory</th>
<th>Nucleic acid Testing strategies</th>
</tr>
</thead>
</table>
| Molecular methods: target or signal amplification | Roche Amplicor (manual and COBAS Amplicor, COBAS Ampliprep/Amplicor)**  
Roche Taqman, vs.1** and 2  
Abbott RealTime** (LCx obsolete)  
bDNA (K-PCR)  
Nuclisens EASYQ (mini-MAG or EASYMAG)*  
In-house assays*  
RNA qualitative screening test |
| Second Tier | May do NAT  
Exavir Load |
| Primary Care | POC*  
Sample collection: DBS |
Technology Landscape for HIV viral load POCT

- LIAT™ analyser (IQUUM)
- mBio System
- Cepheid GeneXpert
- Biohelix RT-HAD
- SAMBA (H. Lee, Cambridge)
- Wave 80: early development
- North Western University

Rapid, nucleic acid isolation modules
- PATH
- FINA
Example 1: LIAT analyzer:

1. Collect sample
2. Scan barcode
3. Insert the tube

Get results

Time to result: 1 hour

Assay chemistry: silica magnetic bead extraction & multiplex real-time PCR detection

Internal control strategy: RNA process control to minimize likelihood of a false negative readout
Early validation studies

Liat HIV Quant Assay (59 mins) compared to Abbott m2000 HIV Assay

- 93 HIV clinical samples tested
- 1 sample is Abbott assay low positive, Liat Assay negative
- 1 sample is Liat assay low positive, Abbott Assay negative
- For concordant samples, the viral load result had a 96.5% correlation coefficients between the 2 assays

- US based studies ongoing

Shugi Chen, 2010, IQUUM
Summary

- **Turnaround time** of 1 hour compared to several hours to days for existing assays
- **Full automation from sample to result for POC** with no sample manipulation, reagent handling, or use of supporting laboratory equipment such as centrifuges, vortexes, pipettes, or computers
- **Able to accept POC compatible sample matrices** such as saliva and whole blood
- **Portable and battery operation** to enable bedside or field use
- **Maintains sensitivity at low sample volume**, ideal for pediatric patients
- Meets requirements of **MSF round-table discussion** document
Example 2: mBio System

- Test panels: multiple markers, 25 minutes
- Disposal cartridge
- Low-cost instrument: High sensitivity
  - 20 pg/ml p24 Ag detection
- Clinical validation: San Diego, Seattle, Maputo
- Potential for RNA validation

Chris Myatt,
Precision Photonics
Infectious Disease Test Example

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antigen</th>
<th>Signal / Cutoff</th>
<th>Status</th>
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<tbody>
<tr>
<td>HIV</td>
<td>gp41</td>
<td>6.7</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>gp120</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p24 v.1</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p24 v.2</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>NS3</td>
<td>0.1</td>
<td>NEGATIVE</td>
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<tr>
<td></td>
<td>NS3,4,5</td>
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<td></td>
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<tr>
<td></td>
<td>Core</td>
<td>0.4</td>
<td></td>
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<tr>
<td>T. pallidum</td>
<td>TmPA</td>
<td>0.0</td>
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<tr>
<td></td>
<td>p17</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p47</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Serum Control</td>
<td>Anti-Hu IgG</td>
<td>2.1</td>
<td>Good Test</td>
</tr>
</tbody>
</table>
Example 3: SAMBA technology

- Isothermal signal amplification: 2 hours from collection to result
- Automation of front end extraction underway
- Preliminary data: sensitivity <400 RNA copies/ml

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
Example 4

Proposal for Developing Manual, Point-of-Care, RT-HDA HIV RNA Test


2) Rapid RT-HDA reaction in water bath (30 min).

In discussion with GE’s to develop Ready-To-Go™ HDA dry reagents

3) Equipment-free, rapid detection using lateral-flow cartridge (5 min)
POC DNA extraction methodology: FINA

- Filtration, isolation of nucleic acids
- Separation membrane and absorbent pad traps DNA from whole blood: 2 minutes
- Sensitivity 20 copies/ml: 100ul blood

Jangam SR et al., JCM, 2009

FIG. 1. (a) Schematic of DNA extraction by FINA; (b) the in-house FINA module; (c) the disk transferred to a tube for PCR.
The NHLS of South Africa has 18 molecular diagnostic laboratories throughout the country to handle over 1.0 M HIV VL determinations per year.
Geographical hubs of molecular laboratories exist in certain regions. These closely reflect densely populated areas where professional expertise are present.

Challenges remain:
- pre- and post analytical
- System inefficiencies
- IT, transport

Numerous clinics outside major hubs remain problematic.
Combination Strategy likely in SA

- HIV testing: 30%-40% of total laboratory costs
- Total Assay numbers in April 09-March 2010:
  - 3,190,668 CD4 assays (63 sites)
  - 1,233,462 viral load assays (18 labs)
  - 254,738 HIV DNA PCR assays
- Point –of- Care throughput:
  - CD4: 20 minutes per assay : 8-10 per day
  - Viral load: 1-2 hours per assay: 8-10 per day
  - Assuming 22 days per month X 12 months
- Total numbers of instruments for POC alone:
  - 1510 analyzers for CD4
  - 704 analyzers for viral load and DNA PCR
Centralization versus de-centralization

- Place for both approaches
  - dependent on population serviced, geographic location, clinical indication, anticipated volume, staff skill, interpretation skills, IT connectivity, transport
- Cost-benefit analysis for each indication
- Successful implementation of both approaches: IT
Guideline Documents

- ISO/FDIS 22870: Point-of-care testing (POCT) —Requirements for quality and competence
- NIH guidelines
- British Society of Haematology (*BJH*, 2008)
Australian POCT study

- Australian government: large POCT in GP practices: To address clinical effectiveness, cost effectiveness and safety in a large number of GP practices

- **Conclusions**: POCT was non-inferior to laboratory based testing, but at a substantially higher cost which should be weighed against overall health benefits

*Shepard et al. 2009*
Challenges for Implementation

- Volume basis: tier by clinic
- Appropriate method validation
  - current VL assays may need to be compared to as discrete (bin/categories), not quantitative values
  - Study design: subtypes
- Appropriate internal quality control
- External quality assurance programs
- Instrument maintenance strategy
- Data retention and consolidation
- Interpretation at clinic sites
- Biohazard disposal
- Regulatory environment
- National POC committee: extension of laboratory service: national tender process
Acknowledgements

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