Will POC make any difference?
A perspective on EID, CD4 and viral load.

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Diagnostics Advisor
MSF Access Campaign
SA HIV Clinician’s Society Conference 2014
Automation has largely reduced complexity of viral load testing

- Lab-based tests are automated for sample extraction, target amplification and analysis

- Point-of-care tests, some of which will be imminently available, are completely automated “load-and-go” tests that include integrated sample processing but do often require plasma
POC CD4 products: available and pipeline*

*Estimated as of May 2014 - timeline and sequence may change. --- No market launch date set by company.
11% Of CD4 Tests Delivered via SCMS Are POC Based (2013)

Ref: Jason Williams, SCMS
## Country X: Example Of The PIMA POC Utilization (2012)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of sites</td>
<td>269</td>
</tr>
<tr>
<td>Sites with &quot;0&quot; consumption</td>
<td>46</td>
</tr>
<tr>
<td>Sites with consumption ≤ 1/day</td>
<td>91</td>
</tr>
<tr>
<td>% of sites with 0 or consuming ≤1/day</td>
<td>34%</td>
</tr>
<tr>
<td>% of sites with access to referral lab</td>
<td>30%</td>
</tr>
</tbody>
</table>

Ref: Jason Williams, SCMS
Appendix 2: Pipeline for POC diagnostics

**POC viral load & EID products: available and pipeline***

*Estimated as of May 2014 - timeline and sequence may change.  
No market launch date set by company.*
MSF IMPLEMENTATION OF INFANT, VIRAL LOAD AND POC CD4 DIAGNOSTIC TOOLS

Point-of-Care (POC) testing:
- MSF has implemented POC CD4 diagnostics**
- MSF is implementing or planning to implement POC VL / Infant diagnostics
  **Implementation in at least one MSF project in the country

Laboratory-based testing:
- MSF has installed its own VL laboratory**
- MSF conducts referrals to a non-MSF VL laboratory
- MSF conducts referrals to a non-MSF infant diagnostics laboratory

Bangladesh
Cameroon
Central African Republic
Chad
Congo
Democratic Republic Congo*
Guinea
Haiti
India
Kenya
Kyrgyzstan*
Lesotho*
Malawi
Mali
Mozambique
Myanmar
South Africa
South Sudan
Swaziland
Uganda
Ukraine
Yemen
Zimbabwe

*MSF VL lab implementation planned
**MSF provides diagnostics but not treatment

MSF currently provides HIV treatment to people in 23 countries.
**MSF 5-country survey**
http://msfaccess.org/content/issue-brief-getting-undetectable-usage-hiv-viral-load-monitoring-five-countries

<table>
<thead>
<tr>
<th></th>
<th>India</th>
<th>Kenya</th>
<th>Malawi</th>
<th>South Africa</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number PLWHA (on ART)</strong></td>
<td>2,085,008 (750,000)</td>
<td>1,646,012 (604,000)</td>
<td>1,129,768 (405,100)</td>
<td>6,070,751 (2,200,000)</td>
<td>1,368,128 (565,700)</td>
</tr>
<tr>
<td><strong>VL tests 2013</strong></td>
<td>6,000 - 7,000</td>
<td>53,000</td>
<td>37,000</td>
<td>2,400,000</td>
<td>30,000 - 48,000</td>
</tr>
<tr>
<td><strong>Gov VL labs (machines)</strong></td>
<td>9 (20)</td>
<td>7 (~15)</td>
<td>5 (6)</td>
<td>17 (17)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Gov EID labs</strong></td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><strong>EID TAT</strong></td>
<td>sample transport: ≥3 days</td>
<td>2-4 weeks (&gt;1 month in rural areas); some access to web-based results, SMS or SMS printers but mostly paper-based</td>
<td>3 weeks - 2 months; some access to SMS and SMS printers but mostly paper-based</td>
<td>1-10 weeks depending on geography; internet-based results possible otherwise SMS printers or hard copies</td>
<td>1-4 months</td>
</tr>
<tr>
<td><strong>POC tests</strong></td>
<td>none</td>
<td>100 Alere PIMA (not in operation)</td>
<td>125 Alere PIMA</td>
<td>A few in the Free State</td>
<td>&gt;250 Alere PIMA</td>
</tr>
<tr>
<td><strong>Interest in CD4 POC</strong></td>
<td>yes, in specifically targeted areas only, based on difficulty of terrain and overload on ART centres only, limited to augment lab system</td>
<td>unsure</td>
<td>unsure, not if CD4 testing is phased out altogether</td>
<td>not currently (awaiting results from evaluation of Free State pilot)</td>
<td>yes, mainly due to quick turn around time and guaranteed results delivery</td>
</tr>
<tr>
<td><strong>Interest in EID / VL POC</strong></td>
<td>not currently, not prior to validation, only limited to augment lab system, depending on cost</td>
<td>not currently, although SAMBA is being evaluated by KEMRI; waiting for tests to become commercially available to gauge performance, usability and price</td>
<td>not currently (except for implementation of SAMBA by MSF); concerns about underuse, incorrect use and capacity for nurses to perform tests</td>
<td>not currently, although some products have been evaluated by the NHLS; possibly for infant diagnosis</td>
<td>not currently, although some products may be validated at the NMRL, and substantial interest to overcome lack of lab and sample transport capacity, and result delivery, including for infant diagnosis</td>
</tr>
</tbody>
</table>
MSF 5-country survey:
Access barriers to viral load testing and subsequent intervention

http://msfaccess.org/content/issue-brief-getting-undetectable-usage-hiv-viral-load-monitoring-five-countries

In most but not all countries:

- India: State AIDS Clinical Expert Panels (SACEPs) as “gate-keepers” for VL testing
- High cost
- Lack of funding
- Limited human resources (and training)
- Poor procurement management e.g. stock outs
- Lack of awareness among civil society, PLWHA, clinicians etc on importance of VL testing
- Geography and distance e.g. sample transport and results delivery
- Poor lab infrastructure and equipment maintenance
- No validation of DBS and POC tests
- Poor record keeping and patient tracking
- Poor follow-up on results and high patient loss to follow-up
- Unequal access within the same country e.g. urban versus rural
- Weak adherence counseling
# POC versus DBS

**MSF 5-country survey** ([http://msfaccess.org/content/issue-brief-getting-undetectable-usage-hiv-viral-load-monitoring-five-countries](http://msfaccess.org/content/issue-brief-getting-undetectable-usage-hiv-viral-load-monitoring-five-countries))

<table>
<thead>
<tr>
<th>Country</th>
<th>Use of DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>only for infant diagnosis; needs validation for viral load use</td>
</tr>
<tr>
<td>Kenya</td>
<td>yes, for infant diagnosis and viral load - although viral load is still controversial and requires further validation due to accuracy issues</td>
</tr>
<tr>
<td>Malawi</td>
<td>yes, for infant diagnosis and, from 2014, for viral load (with a subsequent validation at 1,000 copies/ml)</td>
</tr>
<tr>
<td>South Africa</td>
<td>only for infant diagnosis</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>yes, for both infant diagnosis and viral load</td>
</tr>
</tbody>
</table>

### WHO: Implementing HIV VL Testing (July 2014) – Performance at 1000 copies/mL

<table>
<thead>
<tr>
<th>Assay assessed</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Molecular: Abbott RealTime HIV-1 (manual, m24sp and m2000sp) assays with m2000rt platform</td>
<td>95.24±</td>
<td>91.67±</td>
<td>1529</td>
</tr>
<tr>
<td>Biocentric: Generic HIV Charge Virale</td>
<td>94.86±</td>
<td>55.16±</td>
<td>531</td>
</tr>
<tr>
<td>bioMérieux: NucliSSENS EasyQ® HIV-1 v2.0</td>
<td>84.37±</td>
<td>94.52±</td>
<td>1062</td>
</tr>
<tr>
<td>Roche Molecular Systems: COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0 [free virus elution protocol]</td>
<td>81.02±</td>
<td>96.74±</td>
<td>229</td>
</tr>
<tr>
<td>HIV-1 RNA 1.0 Assay (kPCR)</td>
<td>90.97±</td>
<td>87.76±</td>
<td>144</td>
</tr>
</tbody>
</table>

Meta-analysis in press by Vojnov et al. (CHAI); Roche results by Carmona et al. (NHLS)
Laboratory Systems Approach vs Point of Care Diagnostics?

Need to Strengthen Functional Tiered Laboratory Health Systems and Networks

Ref: John Nkengasong (CDC)
Beyond the lab: preparing the clinicians with a new VL algorithm

Algorithm For Routine Viral Load Testing

**Viral load to be tested on:**
- Any patient with clinical or immunological failure
- 4 to 6 months after starting ART
- 12 months after starting ART and then every 12 months (24 mo, 36 mo, etc)

**VL > 1000 copies/ml**
- Continue current regimen and routine yearly VL monitoring
- At each subsequent yearly VL → follow algorithm from the top

**VL = 1000**
- Refer for enhanced adherence counselling (EAC)

1st EAC session on day of result

2nd EAC session after 4 weeks (If required additional EAC sessions may be given)

Repeat VL 12 weeks after 1st EAC if EAC has been successful and adherence has improved

**VL < 1000**
- Continue current regimen
- Repeat VL at month 12, 24, 36, etc
- At each subsequent yearly VL → follow algorithm from the top

**VL > 1000 copies/ml**
- Refer to clinician experienced in switching to second line
- Gather information on patient from both clinicians and counsellors
- If VL > 2000 copies/ml but >0.5 log drop → Repeat VL after 3 months
- If VL > 2000 copies/ml and <0.5 log drop, and if no outstanding adherence challenges, consider switch to second line if >6 months on ART

**Early Viral Load**
- Zimbabwe Month 3
- Malawi Month 6

**Frequency of Viral Load**
- Zimbabwe Month 12 then yearly
- Malawi 2 yearly

**CD4 Tx monitoring**
- Zimbabwe: Stopped
- Malawi: Never started
Acting on the result: training and supervision is essential

- Flagging of results
- Person in clinic delegated to be responsible for filing
- Automatically generated lists of results from VL database per clinic sent as well as individual results-highlighting those with VL > 1000 copies/ml
- Easy lookup in database
- VL SMS result delivery of >1000 copies to the clinics: plan to SMS all results to patients
Task shifting point-of-care testing to alleviate HR shortages

In Malawi, MSF is investigating whether point-of-care testing can be task-shifted to lay workers (PIMA, SAMBA*)

In Swaziland, MSF has set up “mini-labs” at clinics, where lay workers have been trained to perform point-of-care testing (RDTs, PIMA, HemoCue, Reflotron)

*Performance data on the SAMBA may be found at: Ritchie et al., J Clin Microbiol, 2014
Barriers to implementation of task shifting include:

- **Professional protectionism** – where doctors feel that their many years of training count, and not just anyone can do their work. Nurses too feel that their profession is being invaded by nursing aides. As a result, community health workers are not embracing task shifting.

- **Professional boundaries and regulations** – while the regulatory environment in some countries is permissive of task shifting, the cadre has no legal protection for additional tasks if anything was to go wrong.

- **Poor salaries and working conditions** – most doctors are not willing to be deployed to rural areas and the public sector, where the impact of the shortage is most felt. Task shifting is therefore still seen as a government ploy to avoid paying the right people to do their rightful jobs.

- **Perceived focus on HIV and AIDS** - task shifting tends to be viewed as another HIV and AIDS initiative, and hence a challenge that will weaken the health systems.

- **Prohibitive policies and laws** – some countries still have outdated policies or laws that prevent lower level cadres from carrying out particular tasks.

Ref: Sagie Pillay (NHLS)
How can the laboratory improve access to testing and treatment?

• New POC staff cadres need to be defined
• Regulatory barriers for these new professionals need to be overcome
• Improve transport infrastructure and telecommunications can make access to centralized laboratories more attainable, reducing the burden on the nurse for POC
• Lab personnel can provide support in areas of training and quality assurance (at site or through remote connectivity)

Ref: Sagie Pillay (NHLS)
Can POC testing decrease LTFU?

For infants, rates of LTFU are quite significant – in a 4 country review by UNICEF almost ¾ of all positive infants were not on treatment at 1 year.

Greatest loss point is between a positive test and the return of results where as much as 51% of infants are lost.

Source: Chatterjee et al. BMC Public Health, 2011

Slide Ref: Shaffiq Essajee (CHAI)
For adults, rates are not that much better overall... so the problem is not unique to the pediatric population. Average rates of LTFU at various points along the continuum from Testing to Treatment:

- Testing to staging: 41%
- Staging to eligibility: 56%
- Eligible to initiation: 32%

A large meta-analysis found that overall only 1/3 of people who test HIV+ and are eligible are ultimately started on treatment. Source: Rosen and Fox, Plos Med (2011)

Slide Ref: Shaffiq Essajee (CHAI)
Many tests are performed but results are never delivered to patients

Ref: National volumes for Mozambique, Malawi and South Africa based on CHAI data
In Mozambique, POC CD4 testing decreased LTFU

- LTFU between CD4 staging and Rx initiation fell from 64 to 33%
- Proportion starting ART doubled from 12 to 22%
- Median time to ART start fell by half

*Ref: Jani et al., Lancet, 2011*
POC CD4 has now been widely implemented and many pilot programs showed marked reduction in LTFU and increase in initiations.

Malawi
- **PMTCT LTFU**: PMTCT initiation during pregnancy increase from 51 to 78%
- **Time to CD4 result**: time from CD4 blood draw to result reduced from 11 to 0 days

Uganda
- **Time to ART initiation**: Reduced from 59 to 11 days

Source: ¹MOH Uganda; ²MOH Malawi
The Alere Q is one of the VL / EID PoC platforms that is at the more proximal end of the pipeline

Specifications

• Battery Operated, no cold-chain needed
• No sample preparation. Direct sampling
• Processing time: 45 minutes
• Results stored in the device or printed out
• Internal modem for connectivity
• Capillary whole blood EID read outs

Slide Ref: Shaffiq Essajee (CHAI)
When used for EID, the Alere Q had an overall agreement of more than 99% compared with the reference Roche technology.

- Total of 827 HIV-exposed infants were enrolled and tested on both the Alere Q and the Roche reference technology.
- 60% were tested between 1-2 months of age.
- Only 2 discordant samples were found.

### Sensitivity and Specificity of Alere Q

<table>
<thead>
<tr>
<th>POC NAT Results</th>
<th>Conventional Results</th>
<th>Overall agreement</th>
<th>Positive percent agreement</th>
<th>Negative percent agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positives</td>
<td>64</td>
<td>99.8%</td>
<td>98.5%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Negatives</td>
<td>1</td>
<td>95.1 - 100%</td>
<td>95.5 - 100%</td>
<td>99.3 - 100%</td>
</tr>
</tbody>
</table>

Cohen's Kappa: 0.981, 95% C.I. 0.960 - 1.000
McNemar's Test: 0.500, p-value: 0.480

Sensitivity of the Alere Q was 98.5%, specificity was 99.9%

Ref: Jani et al., *J Acquir Immune Defic Syndr*, 2014

Slide Ref: Shaffiq Essajee (CHAI)
MSF lessons learnt

– Assess your context to establish what sample type and platform will be feasible

– Training of clinicians and counsellors essential

– Having the viral load test is not a magic bullet

– Supervision is essential using your Laboratory and M and E tools

– Empower the patient to ask for and be able to act on their viral load result

– More information: http://msfaccess.org/undetectable
Thank you — Ngiyabonga — Enkosi — Ke a leboga — Dankie

Acknowledgements:
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MSF colleagues, PLWHA, Ministries of Health and Laboratories with which we work
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http://www.fixthepatentlaws.org/

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