Optimizing Operations for Integrating HIV and TB diagnostics

Professor Wendy Stevens
NPP TEAM

ALL SLIDES ARE PERSONAL VIEWS AND DO NOT ENDORSE ANY PRODUCTS OR NATIONAL POLICIES

CONTEXT COUNTS
HOT TOPICS
in massive scale-up of ART/TB treatment

• Integration of HIV and TB services
• New treatment guidelines
  Drugs, CD4<500, populations started on rapid test alone
  CD4: beginning of the end?
• Global viral load scale-up required is massive
• Linkage to Care and algorithm reviews
• Re-visiting old and new rapid tests, their QA & data collection
• Continuous Monitoring of Quality (CMQ)
• Inter-operability of data systems
• Clinic Performance Monitoring using laboratory data
• Total Coverage Model vs. Total de-centralization
General Integrated Laboratory Network and services

- A network within a country that provides coverage together with a public Health Facility and is sustainable.
- This infrastructure needs to be expanded and co-ordinated to service other diseases: communicable, non-communicable and emerging diseases.

Definitions

- According to Parsons, J.Nkegasong et al 2012:
  "An integrated laboratory network can be defined as one that has the ability to provide all primary diagnostic services needed for care and treatment of patients without them having to go to different laboratories for specific tests"
  OR
  "Integrated network that collects specimens for all tests from a patient at a single site with well-designed logistics network"

- All support services are cross cutting across all sites
- Standardization can be provided
WHO policy in 2004: interim policy on HIV and TB collaborative activities. Updated in 2012

- One health system; yet TB and HIV frequently managed as silos in both clinic and laboratories.

Not simple: several assays required to diagnose and treat both diseases
- In SA, 65% of TB patients are HIV infected
- Run our laboratory implementation program as a silo initially centrally and then integrate horizontally into support services of the integrated network
- Secure political commitment for HIV-TB activities
  - All TB patients have HIV counselling and testing
  - All HIV positive patients needed to be screened for TB
  - NSP SA: Universal testing for HIV and TB
- Standardized Treatment programs for both diseases with linkage to care
- Relevance of DOTS for both diseases.
- M&E improvement is required
- Implement patient and health systems orientated operational search
Expansion of an integrated tiered laboratory service for HIV and TB

Level IV: National/multi-country reference laboratories
- Staff: Senior Health Specialist / lab management, research staff
- Dx: HIV drug resistance testing, HIV viral load, EID PCR, ELISA, CD4 count, chemistry, haem, micro, histopathology

Level III: Regional provincial Laboratory
- Staff: Lab specialists, senior techs, Programme officer
- Dx: HIV Viral Load, qualitative EID PCR, ELISA, CD4 count, chem, haem, micro, histopathology

Level II: District lab
- Staff: Lab specialists, senior techs, Programme officer
- Dx: HIV serology by ELISA, other ELISA, CD4 count, basic chemistry, haematology & microbiology

Level I: Primary Health care laboratory testing
- Staff: Doctors, Nurses, lab or Medical assistants, phlebotomists
- Dx: HIV rapid tests, other point-of-care tests* and DBS collection

Modified from: http://www.who.int/hiv/amds/amds_cons_tech_oper_lab_test.pdf
Introduction to contextual Implementation
“Back to basics and back to reality”

• Previously less stringent ways of test selection or service design; 272 laboratories; arose as clinic services dictated and were implemented; not always logical or efficient

• Arose from the SAIMR to serve mines. NHLS ACT 2000

• Since then, particularly due to volumes, better understanding of best practice, need for affordability, quality and demonstration of impact of any diagnostic intervention this approach is no longer adequate

• All public sector laboratories servicing 87% of the population were made part of one unique, tiered laboratory framework
Significant progress in last 5 years

• National Strategic laboratory Plan for tiered plan
• **National Priority laboratory Program Team** to assist with alignment to clinical needs supported by **expert committees**
• [Roadmap (2014)](#) for more rational, affordable services completed
• Best practice for POCT implementation project completed
• RCT for POCT almost complete
• Realization for national laboratory program implementation: skill sets needed that were not used before: Costing and modelling, engineering, software development, impact
• Test Selection: **VOLUMES** needed: WHERE, WHEN, HOW? Performance, skill set, budget
• **Clinical drivers, technology drivers** and **Information technology changes**
• Development of **Implementation Science course** with fellowships
• New cadre of staff?
Trends in HIV & TB management that will result in major changes in laboratory practice

Clinical drivers
- Massive scale-up required; additional 2.4 million; de-centralised care
- Rapid tests have a more important role to play in treatment initiation and alternative approaches being considered: self-testing, opt out implementation, more convenient sites
- Universal screening of TB to accompany all HCT; and the reverse
- Initiation without CD4 for a large number of patients: pregnant women, TB patients, children<5, sero-discordant couples
- Lifelong treatment for pregnant mothers
- Treatment simplification: FDC drugs and massive price reductions
- CD4: Gatekeeper for initiation, cryptococcal meningitis
- Viral load more important in measuring treatment success
- The need for routine HIV drug resistant testing (2nd line)
- ARV treatment as prevention, or Test and Treat

Technology drivers
- Move towards same technology able to test for HIV and TB
- Catalyzation of POC assays for HIV and TB
- Analyzers with Massive automation
- Highly sensitive assays; earlier diagnosis
- Improvement in DBS results for VL and EID
- Random access and multiplexing

Improved laboratory data collection tools
- Integration and co-ordination, e-Health and m-Health solutions
- Need for BIG data collection: e.g. Next gen Sequencing
- Integration to clinical data with a unique number is essential
Game-changer volumes for SA and other countries

Predicted VL scale up will not meet the need at the current laboratory growth with the technology available. A global push to build laboratory capacity to achieve the 90–90–90 targets.
**AS IS:** Largely centralized PCR (HIV), CD4, TB (GeneXpert) laboratory footprint

**CD4 labs**
The NHLS enumerates CD4 for the public sector at **62 labs** – current footprint for >3.8m test. Beckman Coulter, PLG CD4

**HIV viral load labs**
17 laboratories
8 sites with Abbott m2000 system
9 sites with Roche CAP/CTM
Current instrument capacity (8 hour shift)
6888 samples/day = 1,818,432/annum

**GeneXpert TB testing labs**
National policy
Roll out March 2011, testing at smear microscopy labs
>4.2 million tests to date.
Gx at POC:NTCM=too costly

**Testing centres:** 207
Analysers: 286
Clinic placements: 20
Gx4: 95
Gx16-8: 1
Gx16: 186
GX80-48: 1
GX80: 4

Scott, L.E; Stevens, W et al. Comparison of Xpert MTB/RIF with other Nucleic acid technologies for diagnosing pulmonary tuberculosis in a high HIV prevalence setting: A prospective study. PLoS Medicine, July 2011 8:(7) e1001061

Volumes... moving towards consolidation
### Rapid Rate of Scale up Scenario: Eligibility at 500 CD4 cells/ microl + PMTCT Option B+

#### Capacity Utilisation Analysis

<table>
<thead>
<tr>
<th>Year</th>
<th>CD4 Vols</th>
<th>Current Adjusted Capacity*</th>
<th>Capacity Utilisation</th>
<th>VL Vols</th>
<th>Current Capacity</th>
<th>Capacity Utilisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014/2015</td>
<td>3,484,757</td>
<td>5,665,248</td>
<td>62%</td>
<td>3,589,938</td>
<td>3,047,676</td>
<td>118%</td>
</tr>
<tr>
<td>2015/2016</td>
<td>1,502,379</td>
<td>5,665,248</td>
<td>27%</td>
<td>3,833,688</td>
<td>3,047,676</td>
<td>126%</td>
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<tr>
<td>2016/2017</td>
<td>1,109,244</td>
<td>5,665,248</td>
<td>20%</td>
<td>4,056,075</td>
<td>3,047,676</td>
<td>133%</td>
</tr>
<tr>
<td>2017/2018</td>
<td>983,484</td>
<td>5,665,248</td>
<td>17%</td>
<td>4,315,782</td>
<td>3,047,676</td>
<td>142%</td>
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</table>

* CD4 capacity adjusted due to labs planned for consolidation

### Analysis of additional systems required

<table>
<thead>
<tr>
<th>Year</th>
<th>CD4 Capacity Gap</th>
<th>CD4 System Capacity (BHR 2+2)</th>
<th>Additional Systems Required</th>
<th>VL Capacity Gap</th>
<th>VL System Capacity (24HR)*</th>
<th>Additional Systems Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014/2015</td>
<td>-2,180,491</td>
<td>259,200</td>
<td>None</td>
<td>542,262</td>
<td>86,184</td>
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<td>2015/2016</td>
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<td>None</td>
<td>786,012</td>
<td>86,184</td>
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<tr>
<td>2016/2017</td>
<td>-4,336,004</td>
<td>259,200</td>
<td>None</td>
<td>1,008,399</td>
<td>86,184</td>
<td>12</td>
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<td>2017/2018</td>
<td>-4,681,764</td>
<td>259,200</td>
<td>None</td>
<td>1,268,106</td>
<td>86,184</td>
<td>13</td>
</tr>
</tbody>
</table>

* Based on Roche capacity, minimal difference at 24 hours between Roche and Abbott

### Total Number of Instruments required (high capacity CD4 system and 24 hour Viral Load laboratories)

<table>
<thead>
<tr>
<th>Year</th>
<th>CD4 Vols</th>
<th>CD4 System Capacity (BHR 2+2)</th>
<th>No of Systems required</th>
<th>VL Vols</th>
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<td>42</td>
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<td>1,502,379</td>
<td>259,200</td>
<td>6</td>
<td>3,833,688</td>
<td>86,184</td>
<td>44</td>
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<td>2016/2017</td>
<td>1,109,244</td>
<td>259,200</td>
<td>4</td>
<td>4,056,075</td>
<td>86,184</td>
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<tr>
<td>2017/2018</td>
<td>983,484</td>
<td>259,200</td>
<td>4</td>
<td>4,315,782</td>
<td>86,184</td>
<td>50</td>
</tr>
</tbody>
</table>

* Based on Roche capacity, minimal difference at 24 hours between Roche and Abbott
Significant effort on work flow efficiency: increase 1 million tests without adding additional equipment

Currently 17 functioning laboratories
- 8 sites using the Abbott m2000 system
- 9 sites using the Roche Cobas Ampliprep/Cobas TaqMan system

Current instrument capacity (8 hour shift)
- 6888 samples per day = 151,536 per month = 1,818,432 per annum

Currently 2 HIV viral load systems as per tender agreement:
- Abbott m2000
- Roche Cobas Ampliprep/Cobas TaqMan
First 96 results
In less than 3.5 hrs

Number of Tests

4 hours
Work-away time

Method comparison (local HIV-1 cohort)
cobas® HIV-1 correlation to TaqMan® HIV-1 v2

Data under analysis

The cobas® HIV-1 test is currently in development and not commercially available.

Courtesy of Roche and Sergio Carmona
Large - standalone

Complete automation of manual tasks

Challenges addressed

• Single point of entry
• Continuous sample loading
• Load balancing
Large - connected
Reduce hands-on time to a minimum

Challenges addressed
• Higher throughput
• Predictable TAT
• Full sample traceability
The Liat™ HIV Quantitative VL (low volume POCT)

- Quantitative POC instrument
- Fully automated
- Lab in a tube technology
  - Sample extraction by magnetic silica beads
  - Multiplex amplification of what region???
  - Real-time detection
- LOD: 81 cp/ml in plasma,
- Dynamic Range: $10^2$ - $1.5 \times 10^6$ c/ml
- Sample types:
  - Blood – 75ul
  - Plasma – 150ul
- TAT:
  - Blood – 35 minutes
  - Plasma – 30 minutes

- Plasma testing as good as lab (<1000c/ml) **but** requires phlebotomy and centrifugation: ?POC.
- Whole blood uses finger stick, but is TNA so threshold becomes 5000c/ml. ?clinical interpretation and second plasma follow up. Same as DBS.

Increased detection by LIAT in lower VL ranges: good for diagnostic assay using whole blood, but needs interpretation with finger stick.
Drug Resistance Phenotyping

A. Perform Assay

B. Quantitate viral replication

C. Quantitate viral resistance

Varying drug concentration

2000 TCID₅₀ virus

1 x 10⁵ cells/ml
## The Sequencing Revolution: Integration of HIV and TB resistance and typing

<table>
<thead>
<tr>
<th></th>
<th>Trugene/ABI</th>
<th>454 Junior/FLX</th>
<th>MiSeq</th>
<th>Ion Torrent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>2nd Generation</td>
<td>3rd Generation Emulsion PCR</td>
<td>3rd Generation Sequence by synthesis</td>
<td>3rd Generation Semiconductor</td>
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<tr>
<td><strong>Read Length</strong></td>
<td>~900 bp</td>
<td>~500 bp</td>
<td>2x300 bp</td>
<td>~400 bp</td>
</tr>
<tr>
<td><strong>Sequence Output</strong></td>
<td></td>
<td></td>
<td>Up to 15Gb</td>
<td>Up to 1Gb</td>
</tr>
<tr>
<td><strong>Raw read Quality</strong></td>
<td>NA (cons only)</td>
<td>Error ~1%</td>
<td>Error&lt;1%</td>
<td>Error&lt;1%</td>
</tr>
<tr>
<td><strong>Variant detection limit</strong></td>
<td>≥20%</td>
<td>~2% and above</td>
<td>~0.8% and above</td>
<td>~1% and above</td>
</tr>
<tr>
<td><strong>Sample throughput /multiplexing</strong></td>
<td></td>
<td>25</td>
<td>48-96</td>
<td>16, or customer-designed e.g. 40.</td>
</tr>
<tr>
<td><strong>Sample Drop out</strong></td>
<td>Rare</td>
<td>Yes (10-30%)</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Hands on time</strong></td>
<td>2 days</td>
<td>5 days</td>
<td>1 day</td>
<td>1 day</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>~USD 150</td>
<td>~USD 75</td>
<td>~USD 75 -100</td>
<td>~USD 75-100</td>
</tr>
</tbody>
</table>
Not only addressing the “what and where” but also the “how” through technology integration

- HIV began with **cumbersome phenotypic** assays: replaced with molecular Cobas series, Abbott,
- TB had **phenotypic assays (culture)**: first sensitive enough molecular assay launched in 2011: GeneXper with some fast followers
- **Further integration**: HIV and TB assays on same platforms: Cepheid, Abbott together with others like HPV, HBV
- Trend is for **amalgamation of instruments and assays** and move away from conservative laboratory disciplines in pathology
- Same tests can be done in same lab; reduction of infrastructure
- HIV and TB drug resistance testing: molecular; final place may well be with Next Gen Sequencing (cost, pooling and volumes); whole genome sequencing for TB
- **Information technology** is facilitating this through mechanisms such as cloud computing; either real-time monitoring or BIG DATA
- MIx and match based on different country business models
Do we go BIG or SMALL or both?

Selection based on volumes and level of healthcare, technical skill and cost

UNITAID LANDSCAPE DOCUMENTS for HIV and TB in packs
Implementation is recommended to follow a phase approach: across all assays.

**Phase I: Planning**
- Policies and leadership
- Harmonization with stakeholders*
- Algorithm & Plan
- Mapping and forecasting**
- Assess capacity
- Costing
- Specimen and product selection***
- Equipment procurement

**Phase II: Scale Up**
- Phase In
  - Human resources
  - Training and supervision
  - Quality management system
- Verification on site
- Standardisation of quality
- May need to interface if LIS
- Equipment implementation

**Phase III: Sustainability**
- Partner harmonization
- Regular supplier interactions
- M&E
- Data collection
- Operational research
- Implementation science training

- Stakeholders may include NDoH, NHLS, funders, suppliers, clinicians, economists etc
- ** Intervention affects the whole continuum of care
- *** Require evaluation and validations for performance, SLA, & maintenance negotiation

Source: WHO 2014 - Technical and operational considerations for implementing HIV viral load testing

14 October 2014    page 22    © 2014 Roche
Figure 1

Accurate GIS Mapping
Accurate volumes
Site and logistics
Figure 2: CD4 example: volumes

Legend:
- Current Community Labs
- Current District Labs
- Current Centralised Labs

CD4 Tests per day:
- 11 POC
- 12 - 100 Community
- 101 - 300 District
- 301 - 765 Centralised
- 766 - 1296 Centralised
Figure 3

% of reports with < 48-hour TAT

Legend
- Current Community Labs
- Current District Labs
- Current Centralised Labs

- 34
- 35 - 85
- 86 - 95
- 96 - 100
Figure 4

Distances between clinic and labs

Legend
• Health Facilities
○ Current District Labs
○ Current Centralised Labs
Models for POC implementation: using 2 GIS models

Totally Centralised model (4hr)

Solution:
15 Labs
No POC

Decentralised model (1hr)

Solution:
127 Labs
190 POC

Summary of initial findings

Current

Total Running Costs

Centralised

3 Tier

4 Tier

Decentralised

Centralise ➔ Decentralise

Causer: poor sample integrity
100% Coverage as per NDoH plan in public sector.

- Implementation in all original smear microscopy centres: in a 3 phased approach, HBD first
- 207 centers across the 9 provinces
- Phased implementation started March 24th, 2011
- To date >3,2 mill tests performed to date; 60% of global cartridges procured
- **289 analyzers**: GX4 (95); GX16(186);GX48(1)
- 7 GX 80’s have been purchased and 5 installed to improve capacity, but also assist with increased no”s expected for high risk populations
- **4th phase: High risk populations**: correctional services, mines and peri-mining communities and MDR/XDR
Map of all DCS facilities and all NHLS GXP labs: No separate network; integrated into current

Total DCS facilities- red
Total NHLS GXP labs (207)- green
## Existing Mobile-based Rapid Strip Readers

<table>
<thead>
<tr>
<th>Name</th>
<th>Number of tests</th>
<th>Platform</th>
<th>Additional Hardware</th>
<th>Central Repository</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fio Corp.</td>
<td>‘near universal’</td>
<td>Mobile, Android</td>
<td>Deki Reader</td>
<td>Yes</td>
</tr>
<tr>
<td>Holomic LLC</td>
<td>‘near universal’</td>
<td>Mobile</td>
<td>RDT Reader</td>
<td>Yes</td>
</tr>
<tr>
<td>MobileAssay™</td>
<td>‘near universal’</td>
<td>Mobile &amp; Tablet Apple, Android, Windows</td>
<td>None required</td>
<td>Yes</td>
</tr>
<tr>
<td>Global Solutions for Infectious Disease (GSID)</td>
<td>‘near universal’</td>
<td>Mobile</td>
<td>Phone stand</td>
<td>Yes</td>
</tr>
<tr>
<td>BBI Solutions and Albagaia</td>
<td>Custom per test</td>
<td>Mobile Apple, Android, Windows</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Not entire list of available devices*
Smart Phone: data and graphic uploaded to cloud for analysis

- 61 million active sim cards in SA
- 14 million smart phones

1. Capture sample
   - Manual Entry
   - Take picture of barcode
2. Take picture of rapid test
3. Enter result

Automatic upload to Cloud Server for analysis and Verification of result
Rapid HIV Test

1. Detect Presence of Control Line

2. Detect Presence/Absence of Target
Potential value

- QC/QA of rapid testing nationally: strategy being developed.
- Centralised reporting and operational data.
- Monitoring of operator performance and identification of individuals/clinics which require (re)training.
- Automatic resulting of strips (no operator interpretation required).
- EQA sample processing, resulting and reporting.
- Configuration of system to be able to identify:
  - Multiple control lines
  - Multiple target lines
  - Multiplex Rapid Tests
- Support Home based self testing

- New thinking: Incentivized based activities in the continuum of care. Eg. Testing, adherence, DOTS, service delivery....
Community involvement through incentivization

The Market: specific to South Africa

- Official unemployment is 25.5%,
- 69.2 million active sim cards
- 32.9 million people with some form of telephony
- 14.1 million smartphones (estimated)
- Data cost declining, free WIFI penetration increasing
- Advertising & market research on the decline
- Tougher legislation changing the landscape for marketers
- Social engagement continues to grow
- Chat based platforms: highest levels of engagement

www.m4jam.com
Digitally Enabled **Micro Jobbing**

Breaks large projects into small tasks, empowering many geographically dispersed people to quickly and independently complete the tasks using their phones in exchange for payment.

**The Flow:**

1. Enterprise (client): Project
2. M4JAM Jobbers: Grab a micro job
3. Race against the clock to complete the micro job
4. Jobber gets paid
5. Submit the Job for client approval
6. Meet your Jobber and your new customer!
Feasibility of performing multiple POCT for HIV/TB ART initiation

- **POC operators: 2 sites, with previous research experience**
  - Nurses are “easily trained” and can accurately perform multiple POCT (n=364 validation study) and carry out QC/EQA, but are too busy to add an extra 22 POCT duties to their hectic schedule.
  - 2 ½ staff required for GeneXpert POCT to ensure 15 patients have same day treatment.
  - Hb POCT placement in hospital wards did not reduce lab testing volumes

- **Patients and POCT**
  - >69% patients require 3 or more POCT per visit.
  - Patients prefer finger stick to venous puncture blood draw and 150ul can be obtained from a single finger stick for accurate multiple POCT.
  - Patient flow is not randomly distributed over the day – puts pressure on HCW and POCT design: Majority POCT performed before midday. (re-engineering)

- **Existing lab testing environment**
  - 75% specimens collected form clinic and received in the lab same day
  - 72% results received back in clinic within 1 day.
Components for POC Best Practice

- Suitable POC platforms and assays are available (CD4, Hb, ALT, Cr, TB and now VL).
  - A checklist and validation protocol is unique to POCT and a “starter kit” required to ensure safe GCLP.
  - Selected POCT are as accurate as laboratory tests.
  - Sample throughput must be matched to testing arena
  - Support laboratory
- Clinic staff and infrastructure:
  - GIS mapping of POCT/integrated existing lab services is valuable to determine gaps and ensure NSP for universal testing/screening HIV/TB).
  - Infrastructure is lacking in several clinic sites – and temperature fluctuations are a reality.

Flexibility required for hurdles encountered

Challenges experienced throughout study at 3 clinical sites

Key:

Clinic issues: HR shortages/stock shortages/infrastructure problems
National policy changes: Change in guidelines /no eligible patients/campaigns
POC issues: instrument downtime/errors/invalids/QC failures

2010, 2013 treatment guidelines/FDC: shift away from CD4 for initiation and VL for monitoring but not yet available at POC
Enrollment (Mid August 2014)

Total HCT: 9495
HIV positive: 1367
Enrolled: 717
Branch of care: 368 (POC) 51.3%
CD4 <350 ART eligible: 226 (61.4%)
Initiated on ART: 196 (86%)
Median days to initiation: 1 day

Initiated on ART:
- 196 (86%)
- 136 (72%)

Completed 6 months:
- 108 (47.8%)
- LTFU 80 (35%)
- 88 (46.6%)
- LTFU 44 (23%)

1.21 (95% CI (1.09-1.34)) 1.03 (95% CI (0.84-1.26))

Difference due to misclassification of PIMA CD4 (over classify up to 8%)

- More patients identified as eligible for ART initiation by “Pima effect”.
- Significantly more patients initiated using POC
- But increased LTFU in POC arm (?adherence)

Are patients being pressurised
Role of CD4 testing questioned

• Under scrutiny beyond role of establishing patient wellness and gatekeeper for resources
• Guideline changes: <200 (2002); <350 (2010) and <500 (2013)
• Change in SA: August 2014
• Starting high risk patients: pregnant women, TB, hepatitis B, sero-discordant couples, children <5 years. (greater emphasis needed on HIV rapid test; hepatitis B?)
• Use CD4 <100 cells/ul to screen for meningitis with cryptococcal antigen (11%)
• 2013/2014 fiscal year: >6 million tests-not feasible
• Treatment not changed based on poor sensitivity of CD4 for treatment failure
• Testing after year 1 only if patient ill or not virologically suppressed
• Savings of over 167 million rand  (K.Schnippel)

- Stevens. W, Ford, N. SAMJ. 2014. CD4 testing for the management of ART in HIV infected individuals: is it the beginning of the end.
POCT principal components

- Connectivity: critical to POCT
  - A universal bi-directional multi-functional (clinic and lab) connectivity solution for POCT is lacking but “cloud-based” SaaS promising (eg PIMA data point – Dashboard and novel approach: Cepheid Remote monitoring).
  - Some areas require signal boosting and internet policing is essential.
  - Computer literacy is currently lacking by many staff.
  - Novel approaches: SMS printers shown to extend services and shorten TAT and being modified to encompass “linkage to care” and modified for bidirectional communication and expanded test repertoire.

Connectivity Data Analysis

- Automated results:
  - GeneXpert
  - Hemocue
  - PIMA
- Manual entry for Reflotron (Creatinine and ALT) - AegisPOC
- Analysis performed on manual entry
  - Transcription error of results
  - Incorrect patient ID used
  - Duplicate entry
  - Results not captured

62% of overall results captured correctly

Connectivity at POC

Centralised data for decentralised testing

Reality of Connectivity for multi-disciplinary POCT

Available Options for POC Connectivity
PIMA connectivity:

<table>
<thead>
<tr>
<th>Operational Dashboard</th>
<th>Middleware</th>
</tr>
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<tbody>
<tr>
<td>Interface single instrument type/s from a specific vendor</td>
<td>Interfaces 100’s of instruments and types – vendor neutral</td>
</tr>
<tr>
<td>Limited, more basic reports</td>
<td>Flexible, extensive reporting</td>
</tr>
<tr>
<td>Non-patient identifiable</td>
<td>Patient Identifiable</td>
</tr>
<tr>
<td>Unlinked</td>
<td>Linked to LIS &amp; HIS</td>
</tr>
<tr>
<td>Free (generally)</td>
<td>High cost – but high cost saving</td>
</tr>
</tbody>
</table>
LIS extended to the clinic: SMS printers

- SMS printers to **improve** turn-around-time of results back to facilities from the labs
- **Beneficial in remote**, far-reaching areas where no internet access is available
- SMS is automatically generated from the lab’s LIS
- **Result printed on paper** and to be stored in patient’s file
- Initial roll-out in 2009 (1990 SMS printers in the field nationwide (~4500 DoH facilities)
  - Services available for: CD4 Count, HIV VL, EID, GeneXpert TB and TB Microscopy.
  - Training on installation (uses a manual and with regional coordinators to train)
  - Monitor and follow up with dashboard
- In 2013: 2096 new bi-directional printer purchased by NHLS for implementation.

**Dashboard**

Connectivity = service expansion, quality and training maintenance.
Challenges, barriers and opportunities

- Poor infrastructure.
- Costs of maintenance to systems and instrumentation.
- No incentive schemes to invest in electronic capture of data.
- Fragmentation of systems; SA full of legacy systems.
- Limited use of standards (Some Well-established systems. e.g. SNOMED).
- Systems are often complex and require vendor support (*No access to proprietary communication standards making interfacing difficult*).
- No standardized physical connectivity (infra-red, serial, direct network etc.)
- Bi-directional communications support with DMS or host LIS is not supported by all devices (especially for POC).
- IN SA, a unique identifier is needed and connection to EMR is essential.
- Numerous based technical standards (*CIC 1999 – communication protocols*) to ensure stability e.g. HL7 (health), CLIA etc.
- Many are adding **SLAMs** (stand alone add on modules (apps)) to LIS; specific modules with specific functions e.g. web portals, management, QA/QC, telepathology etc to fill the LIS functionality gap.
- Software delivery has a thin client application; remote server, frequently accessed by web browser. Service investment rather hardware investment (*SaaS = software as a service*)
Cloud computing

- **Cloud computing** is emerging as a new paradigm in healthcare.
- simple means of the **delivery of a service rather than a product**.
- The main enabling technology Virtualisation is the ability to allow the system to operate independently of the hardware.
- From the Cloud via the internet, one can provide information to other users of hardware or software
- resources can be shared within and between organisations to improve economies of scale. Data can be transferred in a computer network that is able to compartmentalise your needs.
- Advantages cited include increased speed, flexibility and a reduction in costs and labour.
- New work suggests the use of the “mobile cloud” which combines the use of mobile devices and the cloud (PDA’s, smart phones etc.).
- The cloud provides an affordable outsourcing model for whoever has dynamic needs for scalable computing.
- Cloud computing could facilitate global disease surveillance.
A new Era in Lab services: “the cloud”

Gx verification (on installation, module maintenance) and EQA 3 x per year, but third quality monitoring component = real time monitoring.

- Operational dashboard for real-time monitoring of results, errors, resistance and positivity rates
- Pre-configured on all newly installed GeneXperts

Training needs and managing staff turnover

Alpha and beta testing completed, National Priority Program
Appropriate, controlled placement is required

1. **Total Coverage model**: where Point of Care added to ensure complete coverage of laboratory services in a tiered laboratory service, focussing on remote, low volume sites. Equipment selection: based on volumes largely and gaps.

2. **Point of Treatment (total decentralized)**
   - Disease specific e.g. HIV treatment initiation, TB diagnosis, diagnosis of diarrhoea, non-communicable e.g. glucose, HbA1c
   - Assay specific e.g. Hb, or GeneXpert, cryptococcal antigen or POC CD4 for wellness testing

3. **Product niching**: VL/EID maternity wards,

**Needs**
Accreditation of sites: staff, quality and connectivity with appropriate checklists.
An extension of the existing laboratory infrastructure/footprint.

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Trends in “supplier business models”: Partnering is essential.

Multiple suppliers with Single platform solution for POCT. Numerous examples in UNITAID development pipeline documents 2014 (HIV and TB).

Single supplier with multiple separate platform solution for POCT eg Alere (HIV Determine, PIMA CD4 and now EID/VL, ePOC for Hb and Cr)

Single supplier with high/ultra throughput analysers, with extension to low throughput at POC, eg. Roche (8800 to the “LIAT” and/or DBS).

Single supplier with high throughput analysers with multiplexing of assays (HIV, TB, HPV, HBV…..Roche, Abbott)

Single supplier with modular approach (single cartridge across all volume testing) and multiplex, Eg. Cepheid

Now there is an increase in options which facilitates competition and innovation.
Future work

• **HIV rapid tests: Quality concerns**
  • HIV misclassification study (impact on test and treat - CD4 to 500c/ul): pilot underway
  • Reader/smartphone use for quality
  • EQA needed for national program: protocol design to include whole blood material and result capture managed by SaaS (SMS printers and/or cell phone technology).

  😡 Community involvement for expanded access

• **Linkage to Care**
  • MDR TB project (Gates funded)
    – Principles likely to apply to HIV

• **Complete CD4 and viral load validations.**

• **Draft policy: difficult as guidelines, technology and regulatory changes.**

• **Investigation of new cadres of staff with official training and registration and “implementation science” course,**

• **Role of Incentivization: previously absolute refusal via ethics: more open to approaches**

• **Pilot project: investigation of solutions such as m4JAM and expand connectivity applications**
Acknowledgements

- National Department of Health
- NHLS National Priority Program staff (led by Prof Wendy Stevens and Dr. Leigh Berrie)
- NHLS POCT working group.

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- HERO: Professor Sydney Rosen, Dr. Lawrence Long, Kate Schnippel
- CD4 working team (Prof. Debbie Glencross), viral load and resistance working group (Dr. Sergio. carmona)
- Special thanks to Trevor Peter, Maurine Murtagh, Rosanna Peeling, Tim Tucker,

- Funders (GCC, PEPFAR (CDC, USAID), FIND, Bill and Melinda Gates foundation. CHAI
- Clinical partners (CHRU/RTC, WRHI, PHRU)
- Patients and participants
- Suppliers (hardware and software)
- Centre for Excellence for Biomedical TB Research
- CHAI team, Trevor Peter, Jonathan Lehe
Integrated services for HIV/TB

Integrated diseases

Requires Integrated services

Where does integration already exist:
- Pharmacy,
- Phlebotomy

What must change
- Clinic workflow
- Infection control

Where does integration already exist:
- Courier
- LIS reporting

What must change
- Access
- Technology

Where does integration already exist:
- Household
- Schools
- Retail
- Business

What must change
- Linkage to care
- Ownership
<table>
<thead>
<tr>
<th>Year</th>
<th>Guidelines</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>National ARV Treatment guidelines (2004)</td>
<td>• Baseline CD4 for initiation at CD4 &lt; 200</td>
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<tr>
<td></td>
<td></td>
<td>• Baseline VL, then 6 monthly monitoring</td>
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<tr>
<td>2008/2009</td>
<td>Removal of baseline viral load, except for infants</td>
<td>• Baseline and 6 monthly CD4 count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 6 monthly VL</td>
</tr>
<tr>
<td>2010</td>
<td>The SA Treatment guidelines 2010</td>
<td>• Baseline CD4 for initiation CD4 &lt; 200, then 6, 12 months and annually thereafter</td>
</tr>
<tr>
<td></td>
<td>Baseline viral load for infants and children</td>
<td>• Baseline CD4 &lt; 350 for initiation of TB/HIV and pregnant pts, then 6, 12 and annually thereafter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• VL at 6, 12 months, then annually thereafter</td>
</tr>
<tr>
<td>2011</td>
<td>Circular for initiation of all patients at CD4 counts &lt; 350</td>
<td>• Baseline CD4 initiation CD4 &lt; 350, 6, 12 months and annually thereafter</td>
</tr>
<tr>
<td></td>
<td>Baseline viral load for infants and children</td>
<td>• VL at 6, 12 months and annually thereafter</td>
</tr>
<tr>
<td>2012</td>
<td>Accelerating access to ART services (circular)</td>
<td>• CD4 &lt; 200, fast tracked for same day treatment</td>
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<tr>
<td></td>
<td>• Eligible pregnant mothers to be started on same day</td>
<td>• All new pts should not have CD4 at 6 months, but at 12 months and then annually</td>
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<tr>
<td></td>
<td>• All TB patients initiated on ART (irrespective of CD4 count)</td>
<td>• VL at 6, 12 months and annually thereafter</td>
</tr>
<tr>
<td></td>
<td>• Baseline VL for infants and children</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>FDC combination</td>
<td>• CD4 &lt; 350; CR clearance &lt; 50 ml/min</td>
</tr>
<tr>
<td></td>
<td>All pregnant women</td>
<td>• CD4 baseline 6 months and 12 months in first year, after that in ill patients</td>
</tr>
<tr>
<td></td>
<td>All children &lt; 5 years</td>
<td>• Viral load 6 and 12 monthly in first year and then annually thereafter</td>
</tr>
<tr>
<td></td>
<td>Baseline VL for infants and children</td>
<td>• Hiv genotyping for 2nd line failures</td>
</tr>
<tr>
<td>2014</td>
<td>New WHO guideline 2013 applied</td>
<td>• Initiation CD4 &lt; 500 cells/ul</td>
</tr>
<tr>
<td></td>
<td>UNITAID: 90:90:90</td>
<td>• Plans underway for massive scale-up</td>
</tr>
</tbody>
</table>

**CLINICAL DRIVERS**

- Removal of baseline viral load, except for infants
- The SA Treatment guidelines 2010
- Circular for initiation of all patients at CD4 counts < 350
- Accelerating access to ART services (circular)
- FDC combination
- New WHO guideline 2013 applied

**UNITAID: 90:90:90**