NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

February 2013

NATIONAL HEALTH LABORATORY SERVICE

Table of Contents

1. Background to Project

This project was initiated at the request of the Honorable Minister of Health, Dr Aaron Motsoaledi, in early 2011, following the World Health Organization's strong recommendation published in December 2010 which stated that "the new automated DNA test for TB be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB". In essence this comprises the majority of TB suspects in South Africa. A pilot study was proposed by the TB Cluster within the National Department of Health (NDoH) while a project feasibility study was being performed with due diligence.

The pilot study was initiated in microscopy centres. The NDoH requested that at least 1 instrument be placed in each province, preferably in high burden districts. Selections were made by the TB cluster, with twenty-five microscopy centres being selected and a total of 30 instruments placed.

The NDoH funded 9 GX16 and 14 GX4 instruments for the project. FIND (The Foundation for Innovative New Diagnostics) donated 6 GX4 analysers and the Infinity or GX48 was supported by PEPFAR Right to Care funds. All instruments were placed by World TB day March 24th 2011. This placement represented about 10% of national coverage. The basis for the calculations was an assumption that 2 smears at diagnosis would be replaced by 1 Xpert® MTB/RIF assay. All instruments were interfaced to the NHLS Laboratory Information System (LIS) allowing for troubleshooting and data collection.

The remainder of the roll-out is being performed in a phased manner by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 6 below.

2. Assays performed to date

In summary, a total of 1,064,513 specimens have been processed to date (28 February 2013). In February 98,173 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 12.68% (12,445). The percentage positivity has remained on average between 15-16% country-wide. To date Kwa-Zulu Natal (KZN) has performed the greatest number of tests which is probably as a result of the number of instruments placed (refer to tables 1

& 2). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to tables 3 & 4).

Table 1: GeneXpert MTB Results by province (01-28 February 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	2 680	14 954	377	18 011	14.88
Free State	995	7 940	62	8 997	11.06
Gauteng	1 620	11 235	461	13 316	12.17
Kwa-Zulu Natal	2 489	17 147	972	20 608	12.08
Limpopo	898	9 511	502	10 911	8.23
Mpumalanga	419	2 645	155	3 219	13.02
North West	797	5 655	267	6 719	11.86
Northern Cape	586	3 528	220	4 334	13.52
Western Cape	1 961	9 844	253	12 058	16.26
Grand Total	**12 445**	**82 459**	**3 269**	**98 173**	**12.68**

Table 2: Cumulative GeneXpert MTB Results by province (1 March 2011 – 28 February 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grant Total	% MTB Detected
Eastern Cape	25 099	129 524	4 281	**158 904**	**15.80**
Free State	16 760	107 928	413	**125 101**	**13.40**
Gauteng	17 304	112 522	3 492	**133 318**	**12.98**
Kwa-Zulu Natal	44 945	226 014	10 081	**281 040**	**15.99**
Limpopo	8 239	65 077	1 604	**74 920**	**11.00**
Mpumalanga	7 570	39 575	2 489	**49 634**	**15.25**
North West	10 323	54 215	3 169	**67 707**	**15.25**
Northern Cape	8 630	46 314	2 360	**57 304**	**15.06**
Western Cape	19 375	96 173	1 037	**116 585**	**16.62**
Total	**158 245**	**877 342**	**28 926**	**1 064 513**	**14.87**

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-28 February 2013)

Province	Inconclusive	Resistant	Sensitive	No Result	Grand Total	% Rif Resistant
Eastern Cape	65	187	2 398	30	2 680	6.98
Free State	25	44	921	5	995	4.42
Gauteng	34	89	1 493	4	1 620	5.49
Kwa-Zulu Natal	43	209	2 234	3	2 489	8.40
Limpopo	14	59	822	3	898	6.57
Mpumalanga	7	47	363	2	419	11.22
North West	14	48	731	4	797	6.02
Northern Cape	12	39	518	17	586	6.66
Western Cape	32	102	1 827		1 961	5.20
Grand Total	**246**	**824**	**11 307**	**68**	**12 445**	**6.62**

Table 4: Cumulative Provincial GeneXpert RIF Results in MTB detected cases (1 March 2011 – 28 February 2013)

Province	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	357	1 748	22 733	261	**25 099**	**6.96**
Free State	236	996	15 496	32	**16 760**	**5.94**
Gauteng	219	1 153	15 856	76	**17 304**	**6.66**
Kwa-Zulu Natal	674	3 766	40 048	457	**44 945**	**8.38**
Limpopo	113	591	7 425	110	**8 239**	**7.17**
Mpumalanga	103	727	6 655	85	**7 570**	**9.60**
North West	136	801	9 359	27	**10 323**	**7.76**
Northern Cape	118	545	7 937	30	**8 630**	**6.32**
Western Cape	222	979	18 171	3	**19 375**	**5.05**
Total	**2 178**	**11 306**	**143 680**	**1 081**	**158 245**	**7.14**

3. Rif Concordance

Rifampicin concordance is good for both LPA and culture. The national average is 89.4% for DST and 86.7% for LPA. This could be attributed to a number of factors such as geographical variation, laboratory variation, interpretation of LPA, reliability of gold standard or even strain variation.

Testing and clinical algorithms show variation across provinces, requiring standardisation as this leads to significant confusion in all aspects of the testing cycle, as well as in some cases, being more onerous to the TB patients themselves.

Table 5: Rif Concordance by LPA or DST

Province	Rif Resistant Cases	GeneXpert Confirmation & Rif Concordance									
		DST					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Inderterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	1153	47	4.1%	10	21.3%	0	46	4%	45	97.8%	1
Free State	724	15	2.1%	7	46.7%	11	79	11%	64	81.0%	14
Gauteng	895	21	2.3%	16	76.2%	21	90	10%	84	93.3%	2
Kwazulu-Natal	2726	686	25.2%	652	95.0%	0	631	23%	509	80.7%	28
Limpopo	380	28	7.4%	27	96.4%	1	44	12%	39	88.6%	0
Mpumalanga	514	81	15.8%	78	96.3%	1	131	25%	111	84.7%	2
North West	435	8	1.8%	7	87.5%	2	50	11%	47	94.0%	6
Northern Cape	343	24	7.0%	17	70.8%	8	55	16%	47	85.5%	8
Western Cape	782	1	0.1%	0	0.0%	3	235	30%	234	99.6%	0
National	7 952	911	11.5%	814	89.4%	47	1 361	17%	1 180	86.7%	61

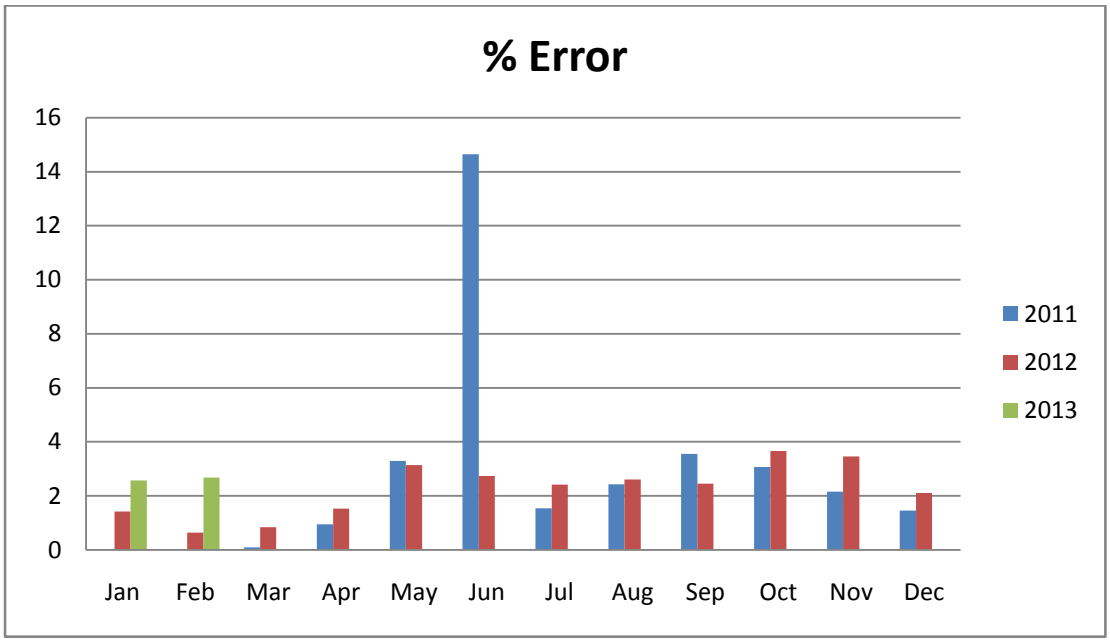
4. Errors

Errors have ranged consistently below 3%. Details of invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

Table 6: Number of Unsuccessful Tests and Reasons

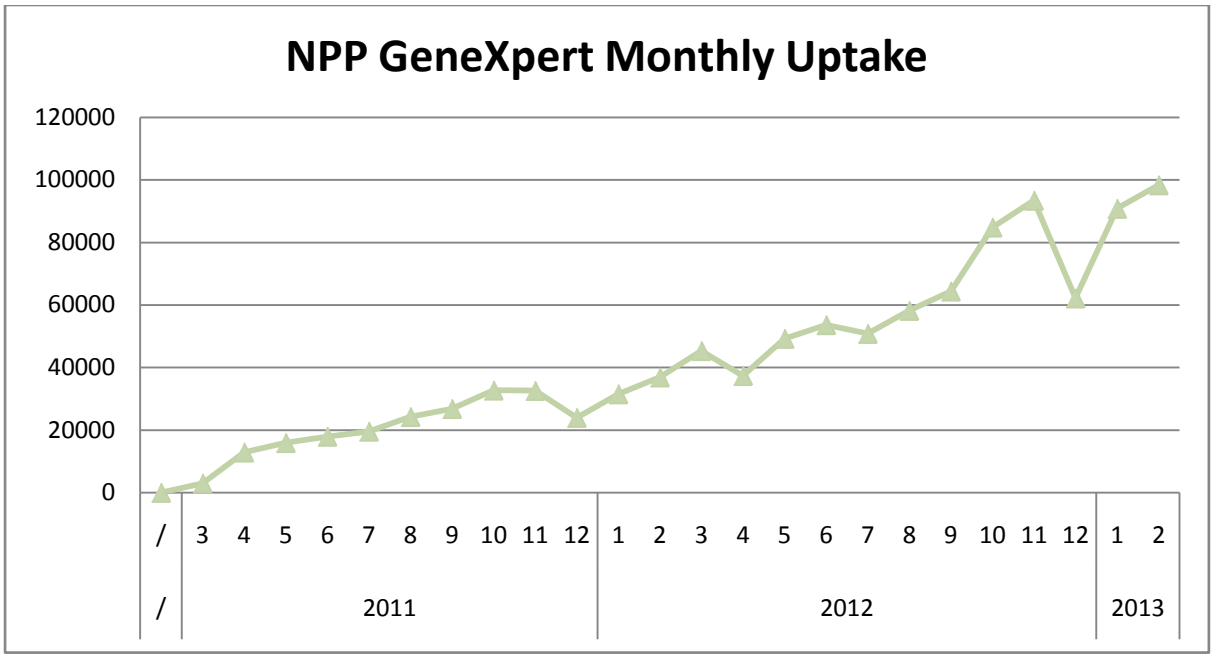
Province	ERR	INVALID	NORESULTS	MTB Result	Grand Total	% Error
Eastern Cape	301	66	10	17 634	18 011	1.67
Free State	52	8	2	8 935	8 997	0.58
Gauteng	401	45	15	12 855	13 316	3.01
Kwa-Zulu Natal	726	127	119	19 636	20 608	3.52
Limpopo	444	45	13	10 409	10 911	4.07
Mpumalanga	136	15	4	3 064	3 219	4.22
North West	236	22	9	6 452	6 719	3.51
Northern Cape	102	1		4 231	4 334	2.35
Western Cape	235	16	2	11 805	12 058	1.95
Grand Total	**2 633**	**345**	**174**	**95 021**	**98 173**	**2.68**

Figure 1: GeneXpert Error rate by Month



5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake



Monthly uptake increased steadily since program inception. The main reason for interruptions is due to the variation in work practices which is expected during the December period. In addition, there was a global shortage in the supply of Xpert MTB/RIF® cartridges in the months of July, October and November 2012. This was resolved in December 2012. Another shortage was experienced this month. We have once again been assured that the NHLS has first priority in the manufacturing and procurement process. Cepheid has also provided a weekly delivery schedule for the NHLS until the end of the year based on the projections provided.

6. Further project phases as defined in the NTCM model

Phase I has been completed and has been reported on in the section above.

Phase IIa involves full capacitation of existing labs: Completed

Phase IIb: Full capacitation of high burden districts. Completed

Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Phase 3a Completed

Phase IIIc: ensuring all districts have a minimum of 1 instrument per district: In Progress

Phase IIId: Completion of all current microscopy and clinic sites: In Progress

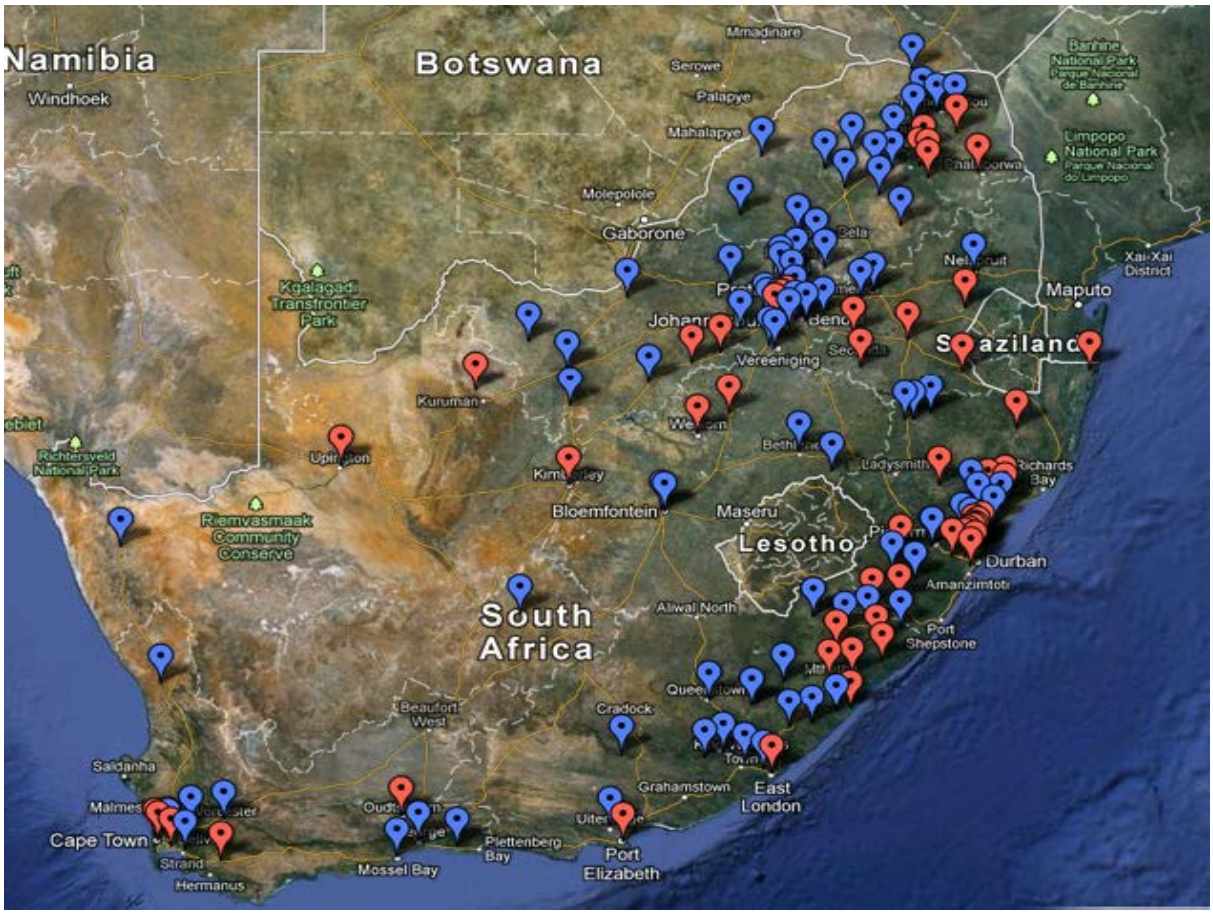
7. Phased Implementation Progress

Table 7: Phased Implementation Progress

Phase	GX4	GX16	GX48	TOTAL	Placed	% Completion
Phase 1/2a	7	30	1	38	38	100
Phase 2b	22	23	1	46	46	100
Phase 3a	3	10	0	13	13	100
Phase 3b	2	11	0	13	13	100
Phase 3c	6	28	0	34	28	82
Phase 3d	41	83	0	124	54	44
TOTAL	**81**	**185**	**2**	**268**	**192**	**72**

To date implementation is 72% complete.

Figure 3: Current GeneXpert Placement (142 testing centers, 203 analysers, Gx4: 65; Gx16: 136; GX48:2) ***20 clinic placements**



8. Training: Laboratory and Clinical

A total of 348 laboratory staff and 1430 health care workers have been trained since December 2011. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff received both clinical and technical training.

9. Challenges identified during the course of the project to date

- Delay in training health care workers, especially doctors whose availability is limited, on clinical algorithm: is being addressed
- Global shortage of GXP cartridges
- Rollout of EGK to avoid duplications

- Laboratories using GXP for monitoring treatment (and not just diagnosis): is being addressed through training
- Under expenditure on the GeneXpert: resolved at the TB/HIV quarterly meeting.
    - Reduction in the price of the cartridge.
    - Delay in release of funds by Global Fund
    - Global shortage of cartridges
    - Delay in implementation of the automated billing system by the NHLS which will only be operation from the 1st of September 2012.
    - Delay in setting up billing accounts: KZN, Northern Cape and Free State

10. Literature Update For GeneXpert

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in table 8 below:

Table 8: Recent publications (GeneXpert for pulmonary TB and extrapulmonary TB)

Manuscript	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Munoz et al, DiagnMicrobiol Infect Dis. 2012	Performed a retrospective analysis of costs and time to treatment (TT) of 150 culture-confirmed TB cases: 100 sputum smear (SS) (+) and 50 SS(-). This group underwent GeneXpert® (GX) assay.	Expenditures and TT of SS(-)/GX(+) cases were inferred from the SS(+) group. GX detected 68% of SS(-) cases.	
Nhu et al, BMC Infectious Diseases. 2012	Performed an evaluation on stored paediatric specimens comparing the MODsassay to the GeneXpert, in a cohort of Vietnamese children.	The sensitivity of MODS vsXpert were 51.7% and 50.0% respectively. The PPv and NPV were higher for Xpert than for MODS.	

Steingart K.R. et al Cochrane Systematic Review	Systematic Review, pooling data from multiple studies to assess the Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults, against replacing smear, then phenotypic DST in people with and without HIV	Identified 18 eligible studies, about half from low-income countries. Alone pooled sensitivity = 88% and pooled specificity = 98%; as an add on to negative smear pooled sensitivity and specificity were67% and 98%, respectively. Pooled sensitivity of 68% for sm-vecult+ve TB; 80% pooled sensitivity in those with HIV. Regarding rifampicin resistance, pooled sensitivity of 94% and specificity of 98%. Assay showed very high accuracy to distinguish between NTM and MTBC.
Bates M, O'Grady J, Maeuer M et al LID Jan 2013	Study conducted at a teaching hospital in Zambia in children < 15 years, in order to compare the analytical performance of Xpert on Gastic Washings against culture..	Sensitivity of GW was 68% and the specificity was 99.3% compared to sputum samples. They demonstrated a statistically significant increase in GW Xpert compared to microscopy. No significant differences were found between HIV infected and non-infected individuals. This needs further study, as the authors caution that this was a single site study.
Schippel K, Meyer-Rath G, L Long, WS Stevens, I Sanne, S Rosen SAMJ Feb 2013	Diagnosing Xpert MTB/RIF negative TB: Impact and cost of alternative algorithms for SA	Cost of using an additional Xpert as opposed to the standard regimen of culture, LPA and DST was modelled. Very important for HIV positive population. It was found that using a second Xpert would be less expensive than culture, even though 2% of TB cases would be missed. But the authors point out that as 1% more would be initiated on Rx due to faster TAT, this may off-set this initial loss. Overall the cost per initiating patients on Rx by using a second Xpert would save 12% per patient.

11. Update on GeneXpert Research projects:

- Dried Culture Spot (DCS) for verification of GeneXperts to be rolled out for quarter 1 of 2013: ~700 DCS have been shipped with the instruments placed.
- Stock for Quarter 2 is being prepared.
- The following potential EQA materials are being investigated through a pilot, feasibility study (n=11 sites):
    - DCS EQA panel

i. Liquid EQA panel (Vircell)
ii. Lyophilised EQA panel from the CDC
iii. Liquid EQA panel from WHO-

The feasibility pilot is complete. At present the data is being analysed and results written up for publication as well as, more importantly, presentation to QAD in order to choose the most suitable panel.

- DCS EQA & verification program development - ACTG (6 sites) and MSF included in program: first batch of verification and pilot EQA material have been shipped to ACTG sites. n=2 site results have been returned. Rwanda has received both EQA and Verification Material to aid in their initial setup. The Feedback received, was that the DCS performed well according to both users and the providers at that side.
- TBGxMonitor™ (www.tbgxmonitor.com) automated GeneXpert Verification and EQA reporting platform has been upgraded to include full EQA report processing. Both Verification and EQA components have been completed. The next major upgrade Phase 3 has been completed and is currently undergoing validation testing. Phase 4 scope of work has been generated. Awaiting finalization of specification.
- Alternative specimen preparation protocols:
    - Protocols being developed for Extra-pulmonary TB diagnosis
    - Protocols under development for EPTB: A GeneXpert room has been refurbished at the Braamfontein TB referral lab for the study. A laboratory technician has been recruited and trained. The R&D GeneXpert has been placed for study commencement. The study commenced in the last week of August, investigating 0.5ml of un-centrifuged or concentrated residual EPTB specimens. The activity is ongoing. Thus far about a 20% positivity has been observed on just over 1000unprocessed specimens. Analysis regarding comparison to culture is underway. The phenotypic DST culture confirmation is waiting for about 1/2 of the results.

- Connectivity: Collaboration with Cepheid ongoing
    - Remote connectivity – System deployed on more than 100 sites by Cepheid and the NHLS. More than 334,445 results reported to date. The pilot has reached maximum capacity and no further routine sites will be added until the full product launch. The

current pilot system cannot handle the additional testing capacity which will be addressed in the full product version.

- The first point of care site (Botshabelo Clinic, North West Province) has gone live on the Cepheid Dashboard with an additional 2 sites to be connected. These sites are using Metacom-sponsored routers (3G) connection for reporting.

12. HIV/TB Integration

- Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility project
  - Phase I complete
  - Phase II: Evaluation of nurse operated POC versus routine lab completed at HJH ThembaLethu clinic (n=326) complete.
    - Manuscript in progress.
  - RCT: ~n=452 patients (POC arm =226; SOC =226) recruited into the study.
  - Data audit on the 452 patient files has been completed (14 March)
  - A sub-study to investigate feasibility and patient acceptance of multiple finger sticks for POC testing has been completed at Tshwane District Hospital (n=300). Submitted for publication to Journal of Infectious Diseases.
  - A 2nd sub study protocol to investigate various blood specimen storage and transport options is being developed. This study will compare Viral load testing on Dried Blood Spots (DBS) to new technologies/alternatives such as Hemaform plates, Primestore tubes and a thicker DBS card.
    - Protocol currently being drafted.
    - Initial R&D underway
- Connectivity:
  - Conworx (POCcelerator) and LDS (AegisPOC) to be trialed in 2 sites during RCT. AegisPOC was installed at the first connectivity on 15 September, 2012. The Conworx solution was installed on the 14th of December, 2012. An antennae was installed and sufficiently boosted the signal. Conworx now running routinely at Tigane Clinic.

13. Grants Submitted

None

14. Funding

Table 9: Total and Percentage Contribution to date by Donor

Donor	% Contribution
NDoH	24.04
Bill & Melinda Gates Foundation	7.20
TB Reach	1.42
MSF	0.90
FIND	0.45
USAID	2.45
CDC NHLS 2010/11	14.78
CDC NDoH	0.72
CDC NHLS 2011/12	1.39
Dr. Niebauer	0.20
Gobal Fund NDOH	40.91
Global Fund RTC	2.78
CDC NDoH	2.77
Subtotal	**100**

CDC has contributed 19, 65% towards the program to date.

15. Recent Campaigns

None in February