



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

December 2013





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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 24 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.

Since then, 285 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:3) have been placed in 207 sites – both urban and rural settings, by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 6 below.

The programme is being further expanded to directly support the annual screening for TB and HIV of a quarter of a million people in special risk populations in correctional centres and in peri-mining communities. There are 6 districts with high proportion of mines in South Africa that have been identified for focused attention.



2. Assays performed to date

In summary, a total of 2,606,945 specimens have been processed to date (31 December 2013). In December 113,927 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 13.91% (15,849). As a reflection of Xpert MTB/RIF's superior sensitivity over microscopy, the average national TB positivity rate among suspects was found to be 8% using microscopy but up to 16-18% in the first year and 13-14% in the second and third year, after introduction of Xpert® MTB/RIF assay. 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 (cumulative)

Province	Year	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	2011	3 295	15 463	555	19 313	17.06
	2012	16 040	85 575	2 892	104 507	15.35
	2013	42 190	295 115	9 338	346 643	12.17
Free State	2011	2 844	14 831	33	17 708	16.06
	2012	11 631	77 087	280	88 998	13.07
	2013	14 317	134 986	1 248	150 551	9.51
Gauteng	2011	3 049	18 727	424	22 200	13.73
	2012	10 960	72 367	2 267	85 594	12.80
	2013	29 766	206 050	7 478	243 294	12.23
Kwa-Zulu Natal	2011	12 226	45 944	1 730	59 900	20.41
	2012	24 446	138 967	6 116	169 529	14.42
	2013	42 725	298 036	15 777	356 538	11.98
Limpopo	2011	1 975	17 261	172	19 408	10.18
	2012	3 993	30 710	688	35 391	11.28
	2013	13 476	183 034	6 080	202 590	6.65
Mpumalanga	2011	2 639	12 763	1 107	16 509	15.99
	2012	4 044	21 959	1 118	27 121	14.91
	2013	9 761	59 223	2 297	71 281	13.69
North West	2011	3 476	14 887	657	19 020	18.28
	2012	5 174	29 005	1 976	36 155	14.31
	2013	12 272	93 980	4 876	111 128	11.04
Northern Cape	2011	2 864	16 117	735	19 716	14.53



	2012	4 440	23 653	1 192	29 285	15.16
	2013	7 752	51 022	2 556	61 330	12.64
Western Cape	2011	2 204	10 093	31	12 328	17.88
	2012	13 202	68 428	596	82 226	16.06
	2013	30 621	165 248	2 813	198 682	15.41
Total		331 382	2 200 531	75 032	2 606 945	12.71

Table 2: GeneXpert MTB Results by province (01-31 December 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	2 819	15 542	376	18 737	15.05
Free State	912	6 710	75	7 697	11.85
Gauteng	2 524	14 228	322	17 074	14.78
Kwa-Zulu Natal	3 779	24 045	959	28 783	13.13
Limpopo	1 071	9 544	301	10 916	9.81
Mpumalanga	921	5 028	188	6 137	15.01
North West	984	6 440	281	7 705	12.77
Northern Cape	535	3 079	88	3 702	14.45
Western Cape	2 304	10 731	141	13 176	17.49
Grand Total	15 849	95 347	2 731	113 927	13.91

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-31 December 2013)

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistant
Eastern Cape	41	146	2 630	2	2 819	5.18
Free State	13	40	859		912	4.39
Gauteng	41	154	2 318	11	2 524	6.10
Kwa-Zulu Natal	72	331	3 309	67	3 779	8.76
Limpopo	9	57	1 004	1	1 071	5.32
Mpumalanga	15	83	823		921	9.01
North West	12	61	911		984	6.20
Northern Cape	8	28	498	1	535	5.23
Western Cape	22	120	2 162		2 304	5.21
Grand Total	233	1 020	14 514	82	15 849	6.44

Table 4: Provincial GeneXpert RIF Results in MTB detected cases (cumulative)

Province	Year	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	2011	33	251	2958	53	3 295	7.62
	2012	213	1096	14597	134	16 040	6.83
	2013	1178	2774	38100	138	42 190	6.58
Free State	2011	28	154	2661	1	2 844	5.41
	2012	162	736	10707	26	11 631	6.33
	2013	366	793	13138	20	14 317	5.54
Gauteng	2011	25	174	2849	1	3 049	5.71
	2012	135	760	9995	70	10 960	6.93
	2013	860	1895	26946	65	29 766	6.37
Kwa-Zulu Natal	2011	107	923	11134	62	12 226	7.55
	2012	434	2207	21553	252	24 446	9.03
	2013	1090	3696	37534	405	42 725	8.65
Limpopo	2011	25	148	1777	25	1 975	7.49
	2012	52	267	3599	75	3 993	6.69
	2013	295	703	12370	108	13 476	5.22
Mpumalanga	2011	31	210	2392	6	2 639	7.96
	2012	57	407	3504	76	4 044	10.06
	2013	219	979	8536	27	9 761	10.03
North West	2011	40	304	3128	4	3 476	8.75
	2012	66	390	4704	14	5 174	7.54
	2013	284	695	11263	30	12 272	5.66
Northern Cape	2011	28	197	2637	2	2 864	6.88
	2012	64	273	4093	10	4 440	6.15
	2013	177	414	6873	288	7 752	5.34
Western Cape	2011	15	106	2082	1	2 204	4.81
	2012	150	657	12393	2	13 202	4.98
	2013	682	1537	28401	1	30 621	5.02
Total		6 816	22 746	299 924	1 896	331 382	6.86

3. Rif Concordance

Rifampicin concordance is good for both LPA and culture. The data is skewed by reporting the GeneXpert immediately, but still have to wait for MGIT and LPA results.

Table 5: Rif Concordance by LPA or DST

		GeneXpert Confirmation & Rif Concordance									
Province	Rif Resistant Cases	Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Indeterminate
		#	%	#	%		#	%	#	%	
EC	3 814	186	4.9%	109	58.6%	0	648	17%	588	90.7%	2
FS	1 476	78	5.3%	38	48.7%	0	342	23%	233	68.1%	57
GP	2 765	99	3.6%	76	76.8%	0	425	15%	364	85.6%	7
KZN	5 318	1 227	23.1%	1 140	92.9%	0	1 247	23%	981	78.7%	40
LP	998	74	7.4%	66	89.2%	0	184	18%	123	66.8%	2
MP	1 330	232	17.4%	220	94.8%	0	355	27%	286	80.6%	3
NW	1 051	50	4.8%	40	80.0%	0	186	18%	146	78.5%	13
NC	770	65	8.4%	39	60.0%	2	146	19%	100	68.5%	11
WC	1 832	25	1.4%	3	0.0%	0	1 239	68%	1 162	93.8%	4
National	19 354	2 036	10.5%	1 731	85.0%	2	4 772	25%	3 983	83.5%	139

4. Errors

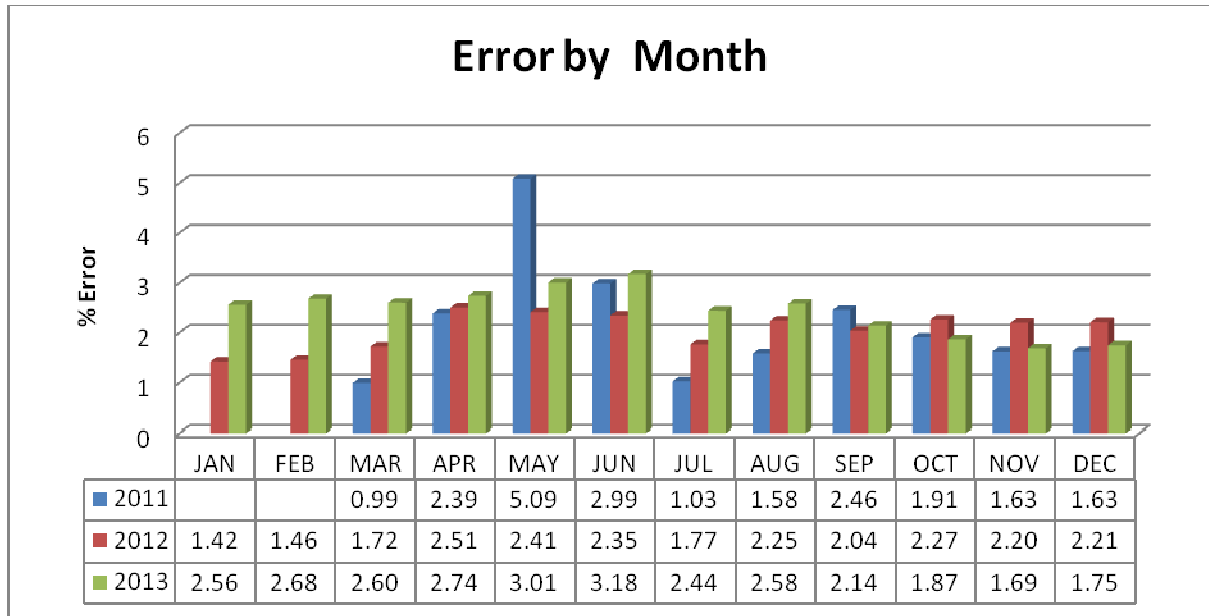
Average error rate has ranged consistently below 3%, however 1/9 provinces reported error rates above 3% in the month of December. Details of the invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

Table 6: Number of Unsuccessful Tests and Reasons (1-31 December 2013)

Province	ERR	INV	NORES	MTB Results	Grand Total	% Error
Eastern Cape	239	107	30	18 372	18 748	1.27
Free State	50	20	5	7 624	7 699	0.65
Gauteng	265	45	12	16 773	17 095	1.55
Kwa-Zulu Natal	698	223	38	27 831	28 790	2.42
Limpopo	227	62	12	10 618	10 919	2.08
Mpumalanga	137	45	6	5 951	6 139	2.23
North West	233	39	9	7 425	7 706	3.02
Northern Cape	38	48	2	3 615	3 703	1.03
Western Cape	106	32	3	13 291	13 432	0.79
Grand Total	1 993	621	117	111 500	114 231	1.74

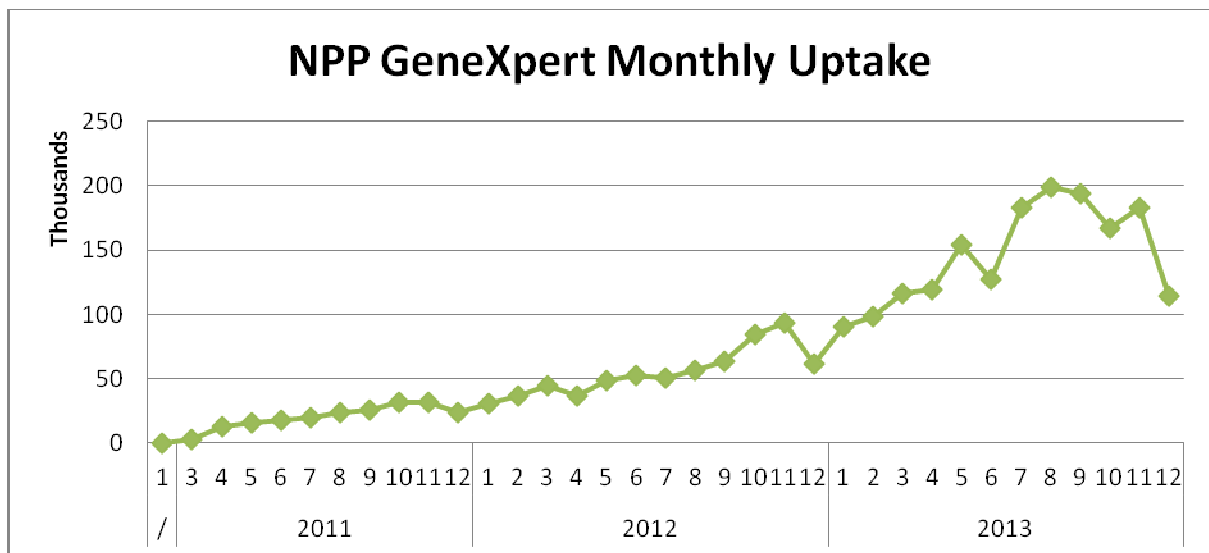


Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake

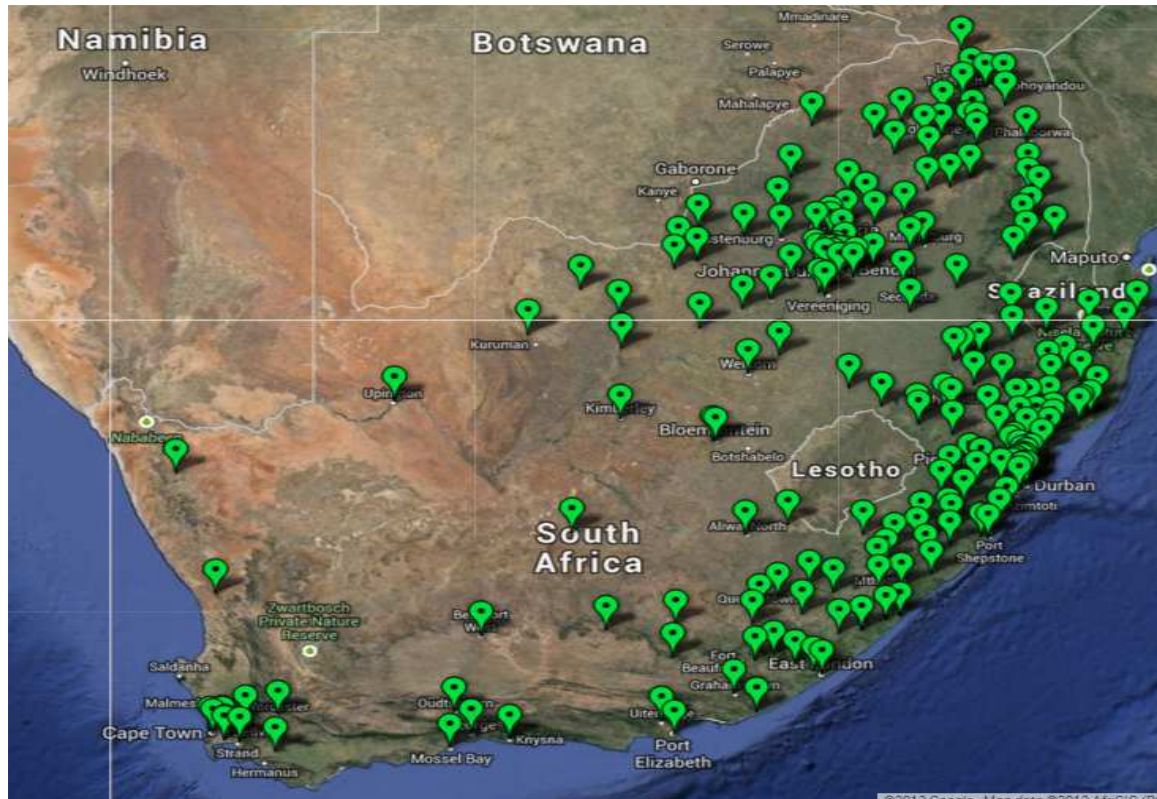


Monthly uptake increased steadily since program inception. The main reason for interruptions is due to the variation in work practices which is expected during the December period.



6. Phased Implementation Progress

Figure 3: Current GeneXpert Placement (207 testing centers, 285 analysers, Gx4: 95; Gx16-8: 1; Gx16: 185; GX48:1; GX80-80: 3) *20 clinic placements



7. Training: Laboratory and Clinical

A total of 1,035 laboratory staff and 5,332 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.

8. 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
- Rollout of EGK to avoid duplications
- Multiple specimens submitted for initial diagnosis using the GeneXpert in the Kwazulu Natal: being addressed with the provincial coordinator.



9. Literature Update For GeneXpert

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

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

Manuscript	Aim/Sample population and specimen type (n=...)	Results	
		Sensitivity	Specificity
Walters, Padiatr Pulmon, 2013	To evaluate the feasibility of Xpert on bronchoalveolar lavage (BAL) samples in children. n=14 children from Tygerberg Children's Hospital. Obtained 2 sputum specimens and a BAL	<ul style="list-style-type: none"> • TB was confirmed by either culture or Xpert from any sample in 11 (78%) children. • Among 9/14 (64%) cases confirmed by culture, BAL Xpert was positive in 7 (78% sensitivity). • Xpert confirmed 2 cases who had negative culture (14% additional diagnostic yield). 	
Kerkhoff et al, J Acquir Immune Defic Syndr. 2013	To assess the prevalence of TB among those with HIV-related anaemia and evaluate new means of rapid TB diagnosis. N=485 paired sputum specimens from HIV-related anaemia patients	Sensitivities of diagnostic assays were much higher among those with moderate/severe anaemia compared to those with no/mild anaemia: <ul style="list-style-type: none"> • Sputum microscopy (42.9% vs 15.4%); urine LAM (54.8% vs 0%); • Sputum microscopy plus urine LAM (71.4% vs 15.4%) • Sputum Xpert (73.8% vs 41.0%) 	
Van'T Hoog et al, PLoS 2013	Explored combinations of sensitivity, specificity and cost at which a hypothetical triage test will improve affordability of the Xpert assay.	A triage test with sensitivity equal to Xpert, 75% specificity, and costs of US\$5 per patient tested reduced total diagnostic costs by 42% in the Uganda setting, and by 34% and 39% respectively in the India and South Africa settings	

10. Update on GeneXpert Research projects:

11.1. GeneXpert Verification and EQA program using Dried Culture spots (DCS)

- Phase 3 of the national NHLS GeneXpert EQA program has been distributed to the sites and the submission deadline is 31 December. Thereafter the results will be analyzed and a national report submitted.



- In collaboration with PATH we are in the process of commercialization of the verification and EQA material for TB Xpert testing globally. This has the support of both the NHLS and the University of the Witwatersrand, the WHO and the CDC.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification is currently being finalized for implementation.
 - The first of the minor updates has been completed.
 - The national reporting template has been finalized and will be implemented as part of the finalization of the specification.
 - Additional reporting features and an investigation report procedure for samples which do not score 100% has been included in the development scope.
 - Seriu are currently generating a quote for approval to allow development to commence in February 2014.
 - ACTG EQA submission deadline closes 31 December and the reporting template generated for these results will form the basis for the NHLS result template.

11.2. Diagnosis of Extrapulmonary TB (EPTB) using the GeneXpert MTB/RIF

A study to determine whether a modified GeneXpert protocol which will not involve addition of SR buffer, can be used to increase the diagnostic sensitivity of the Xpert MTB/Rif assay for clear watery fluid types among aspirates and fluids.

- This study is complete and data analysis is underway. Abstract submitted to CROI.

11.3. Connectivity solutions for the GeneXpert

- Connectivity: Collaboration with Cepheid ongoing
 - i. Remote connectivity – System deployed on 180 instruments to date with over 1,400,000 results live on the dashboard. Enrolment for all sites, nationally, has been completed. Cepheid and the NHLS are currently resolving instruments which have moved and duplicate enrolments on the system.



- ii. Testing of the new Cepheid Xpert Monitor is currently underway. The system is being tested and troubleshooting is commencing through both the WITS and NHLS networks for compatibility for with the proxy servers.
- iii. Site selection has been finalized for the pilot trial in January at 10 sites. The pre-trial troubleshooting is to ensure the systems can simply be deployed for trials and evaluated without requiring technical interventions.

11. Update on other projects

Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility project

GCC is a three year project to investigate the feasibility of integrating multiple POC testing for HIV and TB (using the Xpert MTB/RIF test) integration of services in an active ARV treatment clinic. This will involve a randomized controlled trial at 3 clinic sites to compare standard of care and Point of care. As of September 2013, the recruitment target was reached with a total of 717 patients enrolled into the study; 344 on the POC arm and 373 on the SOC arm. Of the total enrolled patients, n=399 had a CD4<350 (250 on POC; 149 on SOC) and were eligible for ART initiation. Patient follow-up is continuing.

- *Sub-studies within GCC*
 - **Paediatric stool protocol:** A study to evaluate the Xpert MTB/RIF assay on paediatric stool specimens (In collaboration with David Alland and FIND). Protocol and ethics application development underway.
 - **Investigating blood volumes obtained from finger stick:** The study is complete and result being written up for publication to SAMJ.
 - Investigating **alternative media** (Hemaform plates, Primestore tubes and a thicker DBS cards) **for blood specimen collection/storage and transport** to centralized laboratories for VL testing: Data analysis is underway.
 - **Laboratory validation** of a rapid strip based test for **HIV/Syphilis** (SD Bioline): Study complete. Data analysis underway.
 - **Clinical validation** of nurse operated **Liat (IQuum)** VL testing at POC on finger stick specimens: Study complete and Data analysis is underway.
 - **Laboratory validation of Primestore technology with flocked swabs** to determine the ease and accuracy of flocked swab technology for collecting and



transporting finger stick blood specimens for centralized VL testing. Patient recruitment complete, testing ongoing.

- **Laboratory Comparison of Genotype MTBDRplus v1 and 2 using DCS.** This comparison will be performed using DCS material in order to determine the reproducibility of results using either version of the MTBDRplus assay. Version 1 testing complete. Awaiting version 2. Interim results submitted to SA TB conference 2014.
- **GCC Connectivity**
 - The captured data via **TBGxCompanion** has been cleaned based on the initial feedback from the study coordinator and sent to the HERO group for analysis.
 - The **SMS-randomization** gateway has been closed down since no further patients are being enrolled.
 - The **AegisPOC-Conworx** user evaluation and transcription error investigation has been completed on the AegisPOC data showing that manual data transcription has a high error rate.

12. 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.

13. Recent Campaigns

To mark the 25th annual World Aids Day on Sunday, 01 December 2013, NHLS and the NDOH participated in the re-launch of the country's HIV counseling and testing campaign in Piet Retief in Mpumalanga. NHLS provided a mobile unit equipped with a GeneXpert system for TB testing on-site, as well as consumables for collecting samples for CD4 testing and pap smears.