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Technical Considerations in Implementation of New Diagnostics:

Diagnostic Algorithms

Dr Leigh Berrie

23 September 2014

IMPLEMENTING HIV AND TB DIAGNOSTICS IN RESOURCE-LIMITED SETTINGS
CAPE TOWN – SOUTH AFRICA, 22-23 SEP 2014

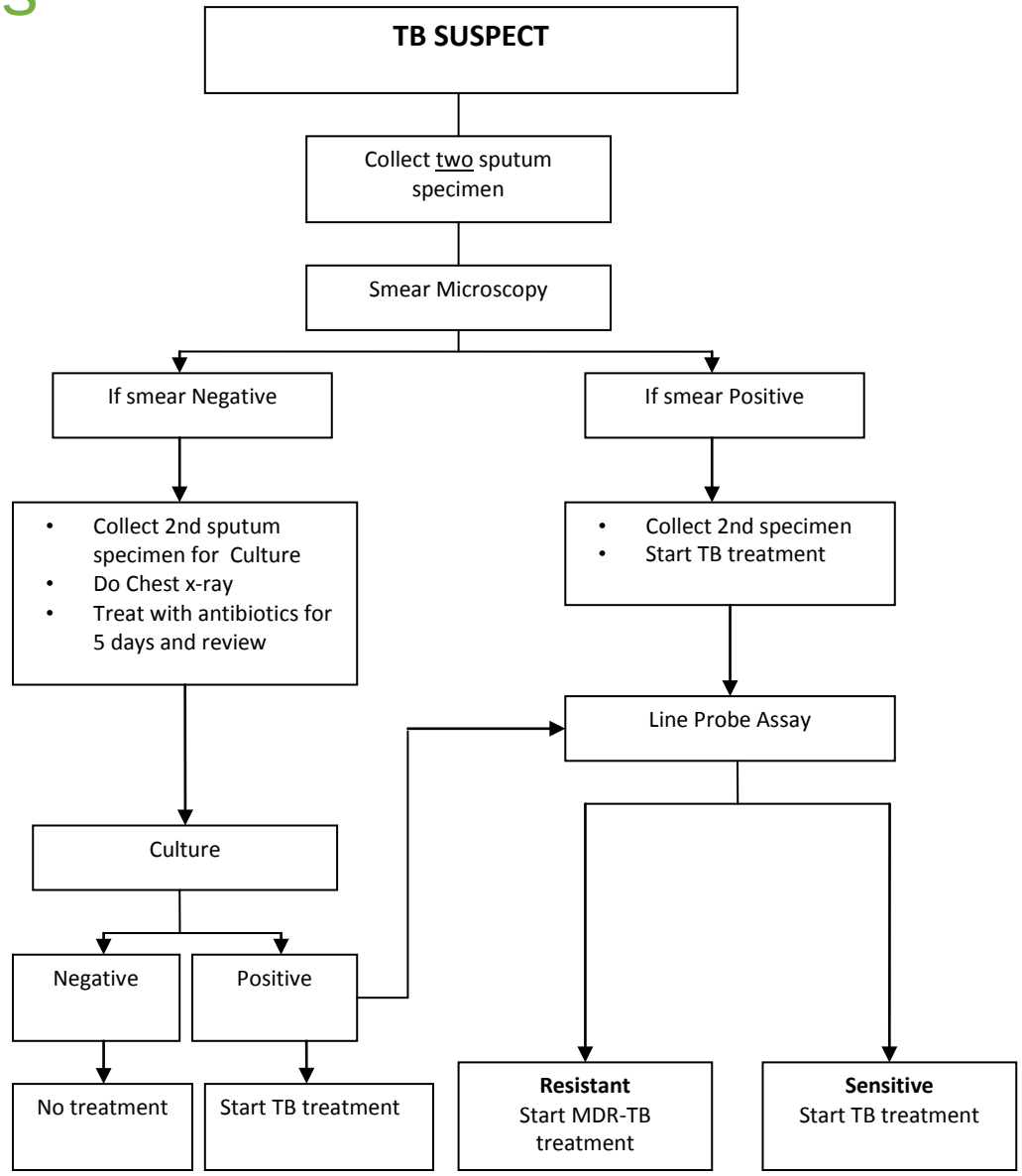
Introduction

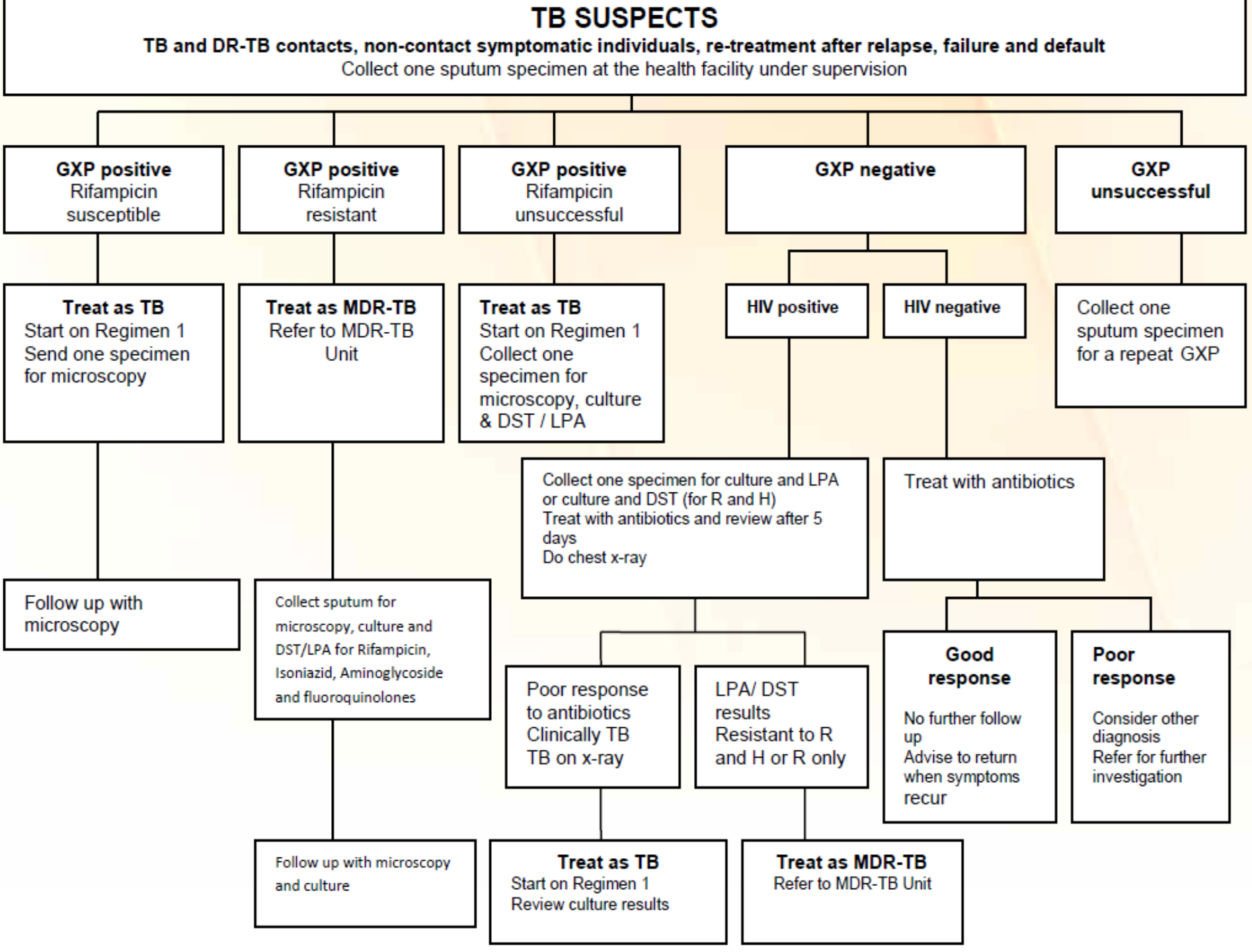
- Need for new and improved diagnostic technologies to reduce morbidity and mortality due to TB and HIV
- Highly sensitive, rapid molecular tests now available- offering improved diagnosis of disease
- Development of new diagnostic algorithms is needed to adapt to changing technology
  - Improvement in HIV/TB treatment outcomes
  - cost effectiveness
  - Integration into existing systems that require flexibility

TB Diagnostic Algorithms

- In 2010, Xpert MTB/RIF ("Xpert"), was endorsed by the WHO for the diagnosis of adult pulmonary TB

- In March 2011, South Africa developed and initiated a National Plan for phased implementation of the technology, as a **replacement for microscopy** as the initial diagnostic screen for TB suspects




TB SUSPECTS
TB and DR-TB contacts, non-contact symptomatic individuals, re-treatment after relapse, failure and default
Collect one sputum specimen at the health facility under supervision
GXP positive Rifampicin susceptible
GXP positive Rifampicin resistant
GXP positive Rifampicin unsuccessful
GXP negative
GXP unsuccessful
Treat as TB Start on Regimen 1 Send one specimen for microscopy
Treat as MDR-TB Refer to MDR-TB Unit
Treat as TB Start on Regimen 1 Collect one specimen for microscopy, culture & DST / LPA
HIV positive
HIV negative
Collect one sputum specimen for a repeat GXP
Collect one specimen for culture and LPA or culture and DST (for R and H) Treat with antibiotics and review after 5 days Do chest x-ray
Treat with antibiotics
Follow up with microscopy
Collect sputum for microscopy, culture and DST/LPA for Rifampicin, Isoniazid, Aminoglycoside and fluoroquinolones
Poor response to antibiotics Clinically TB TB on x-ray
LPA/ DST results Resistant to R and H or R only
Good response
No further follow up Advise to return when symptoms recur
Poor response
Consider other diagnosis Refer for further investigation
Follow up with microscopy and culture
Treat as TB Start on Regimen 1 Review culture results
Treat as MDR-TB Refer to MDR-TB Unit

Algorithm debates- too complex?

- Collection of one or two sputums?
- The cost of the further testing recommended in the HIV-positive, *GeneXpert*-negative individual - should a second *Xpert* test be performed, or a more sensitive molecular assay?
- Testing algorithm in children and for extrapulmonary TB
- Previously treated patients- false positivity?
- HAIN GenoType® MTBDRplus v2 (direct and EPTB)
- HAIN GenoType® MTBDR *sl v2* instead of culture and DST

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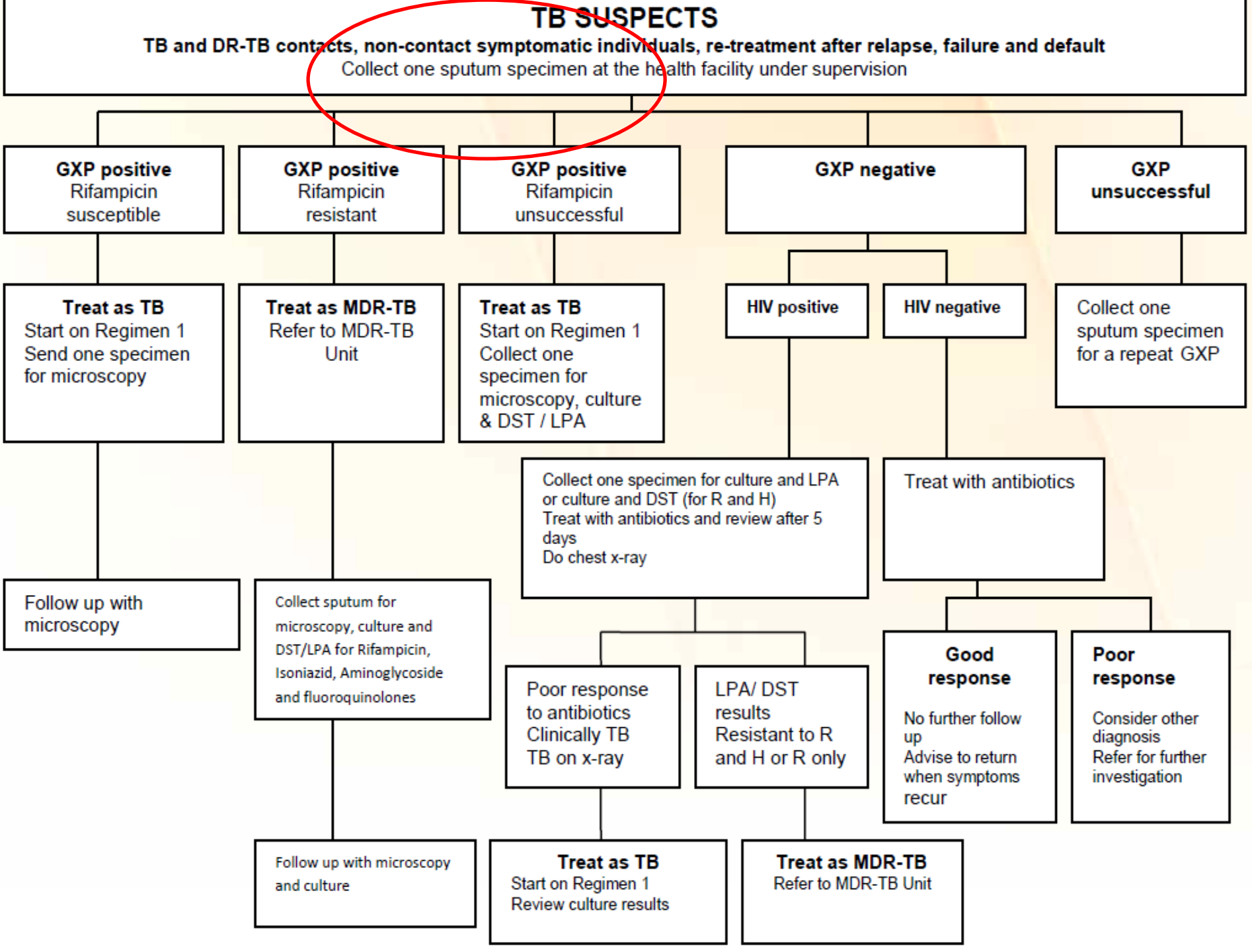
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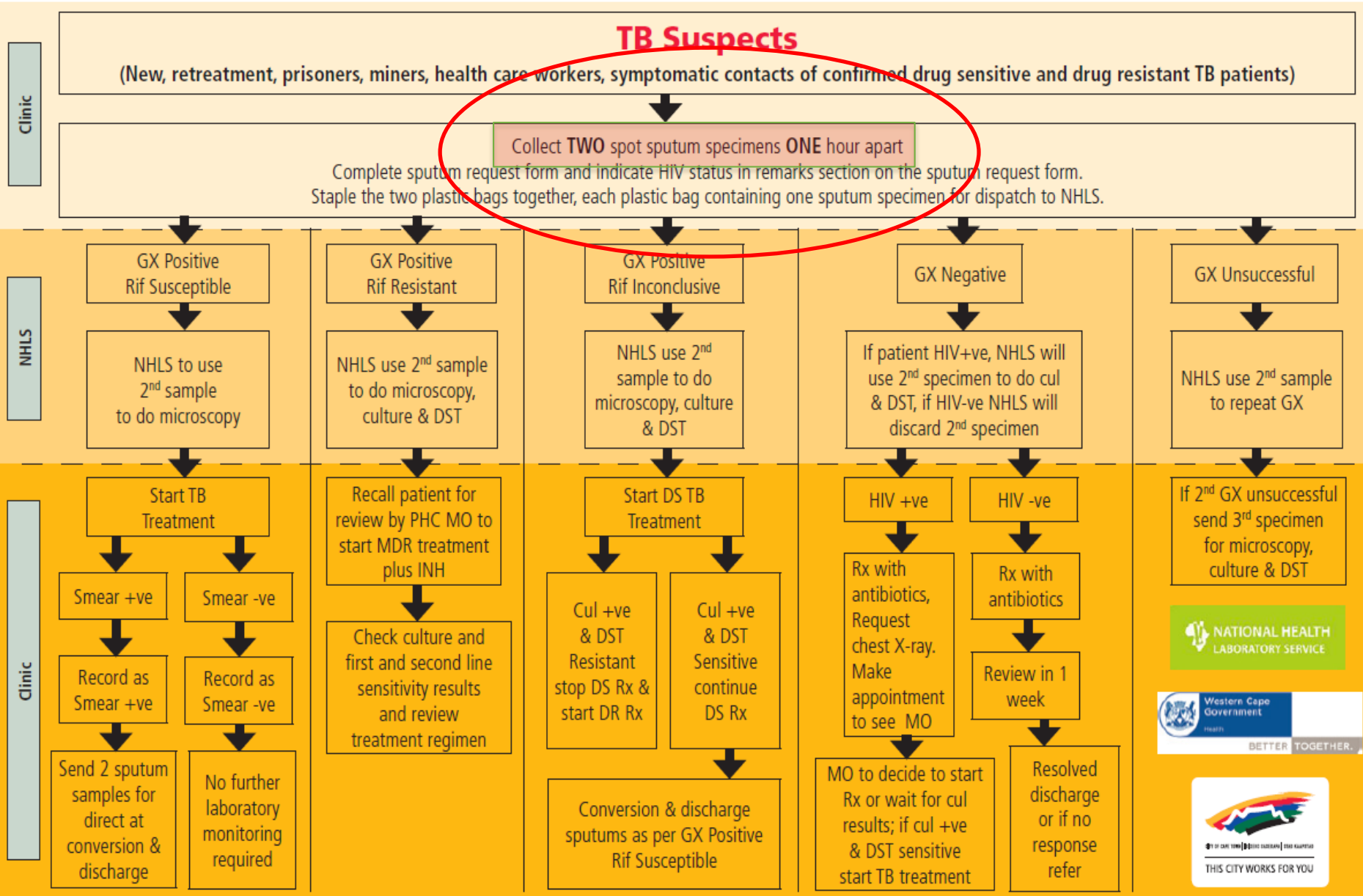
GeneXpert Diagnostic Algorithm



Prof Andrew Whitelaw, SA TB conf 2014

Date: 24/01/2013

GeneXpert confirmation by LPA or DST (March 2011-June 2014)

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Probabilistic matching: No unique identifier for patients in SA

GeneXpert to end June 2014

		GeneXpert Confirmation & Rif Concordance									
Province	Rif Resistant Cases	Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Indeterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	4 960	184	3.7%	116	63.0%	4	1 228	25%	1 129	91.9%	6
Free State	1 745	153	8.8%	86	56.2%	0	713	41%	463	64.9%	134
Gauteng	3 638	147	4.0%	103	70.1%	4	947	26%	849	89.7%	17
Kwazulu-Natal	8 515	1 895	22.3%	1 760	92.9%	0	1 825	21%	1 528	83.7%	61
Limpopo	1 284	87	6.8%	69	79.3%	2	294	23%	221	75.2%	7
Mpumalanga	2 073	468	22.6%	459	98.1%	0	750	36%	650	86.7%	2
North West	1 940	92	4.7%	69	75.0%	0	588	30%	467	79.4%	24
Northern Cape	878	187	21.3%	136	72.7%	3	357	41%	250	70.0%	21
Western Cape	2 846	78	2.7%	20	0.0%	0	2 248	79%	2 091	93.0%	2
National	**27 879**	**3 291**	**11.8%**	**2 818**	**85.6%**	**13**	**8 950**	**32%**	**7 648**	**85.5%**	**274**

Sue Candy, CDW NHLS

- **Only 43.8% confirmed by culture or LPA**
- **Western Cape is the role model: 82% confirmation**
- **Where in algorithm should second sputum be taken? Patient follow-up systems/ logistical challenges/ electronic gatekeeping**

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Treat as TB
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Follow up with microscopy

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Collect sputum for microscopy, culture and DST/LPA for Rifampicin, Isoniazid, Aminoglycoside and fluoroquinolones

Follow up with microscopy and culture

GXP positive
Rifampicin unsuccessful

Treat as TB
Start on Regimen 1
Collect one specimen for microscopy, culture & DST / LPA

GXP negative

HIV positive

Collect one specimen for culture and LPA or culture and DST (for R and H)
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Poor response to antibiotics
Clinically TB
TB on x-ray

Treat as TB
Start on Regimen 1
Review culture results

LPA/ DST results
Resistant to R and H or R only

Treat as MDR-TB
Refer to MDR-TB Unit

HIV negative

Treat with antibiotics

Good response

No further follow up
Advise to return when symptoms recur

Poor response

Consider other diagnosis
Refer for further investigation

GXP unsuccessful

Collect one sputum specimen for a repeat GXP

HIV infected, GXP negative cases- ~50%

- Second sputum sample to be sent for culture. Undergo a clinical examination and chest X-ray and start on presumptive antibiotic therapy

- Schnippel et al SAMJ, 2013: Cultures amount to 60% of total cost of diagnosing PTB in SA, but 10% of TB cases diagnosed. More cost effective to perform 2nd GXP

- Black SAMJ, 2013: History and examination crucial for further management to diagnose and treat the patient, further algorithms that address the patient's major symptoms or signs need to be developed

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2013- New WHO policy recommendation – **paediatric** Xpert MTB/Rif

- Initial diagnostic test in children presumed to have MDR-TB or HIV-associated TB
  - (**strong recommendation**, very low-quality evidence).
- Initial diagnostic test in all children presumed to have TB
  - (**conditional recommendation** acknowledging resource implications, very low-quality evidence).
- Single Xpert MTB/RIF -negative result
  - further diagnostic testing,
  - high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available
- SA algorithm- Culture in parallel

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Xpert MTB/RIF Algorithm: Paediatric Samples

Xpert for all childhood TB suspects (<13 years old)

Submit one sample per child (Gastric Washing, Induced or E Sputum)

- Xpert
  - Xpert Pos/Rif Resistant (2nd sample for LPA to get INH)
  - Xpert Pos/Rif Inconclusive (2nd sample)
  - Xpert Negative
  - Xpert Unsuccessful (2nd sample)
- Culture

Culture already in system

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2013- New WHO Policy Recommendation: EPTB

- Xpert In preference to conventional microscopy and culture as the initial diagnostic test in testing CSF
  - (**strong recommendation** given the urgency of rapid diagnosis, very low quality of evidence);
- Replacement test (for microscopy, culture, histopathology) for specific non-respiratory specimens (lymph nodes and other tissues)
  - (**conditional recommendation**, very low quality of evidence).
- For CSF specimens, Xpert preferentially used over culture if the sample volume is low in order to reach quick diagnosis.
- Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method (but for consideration).
  - A pleural biopsy is the **preferred** sample.
  - The sensitivity of Xpert MTB/RIF in pleural fluid is very low.
- These recommendations **do not apply** to stool, urine or blood (under investigation and for paeds)

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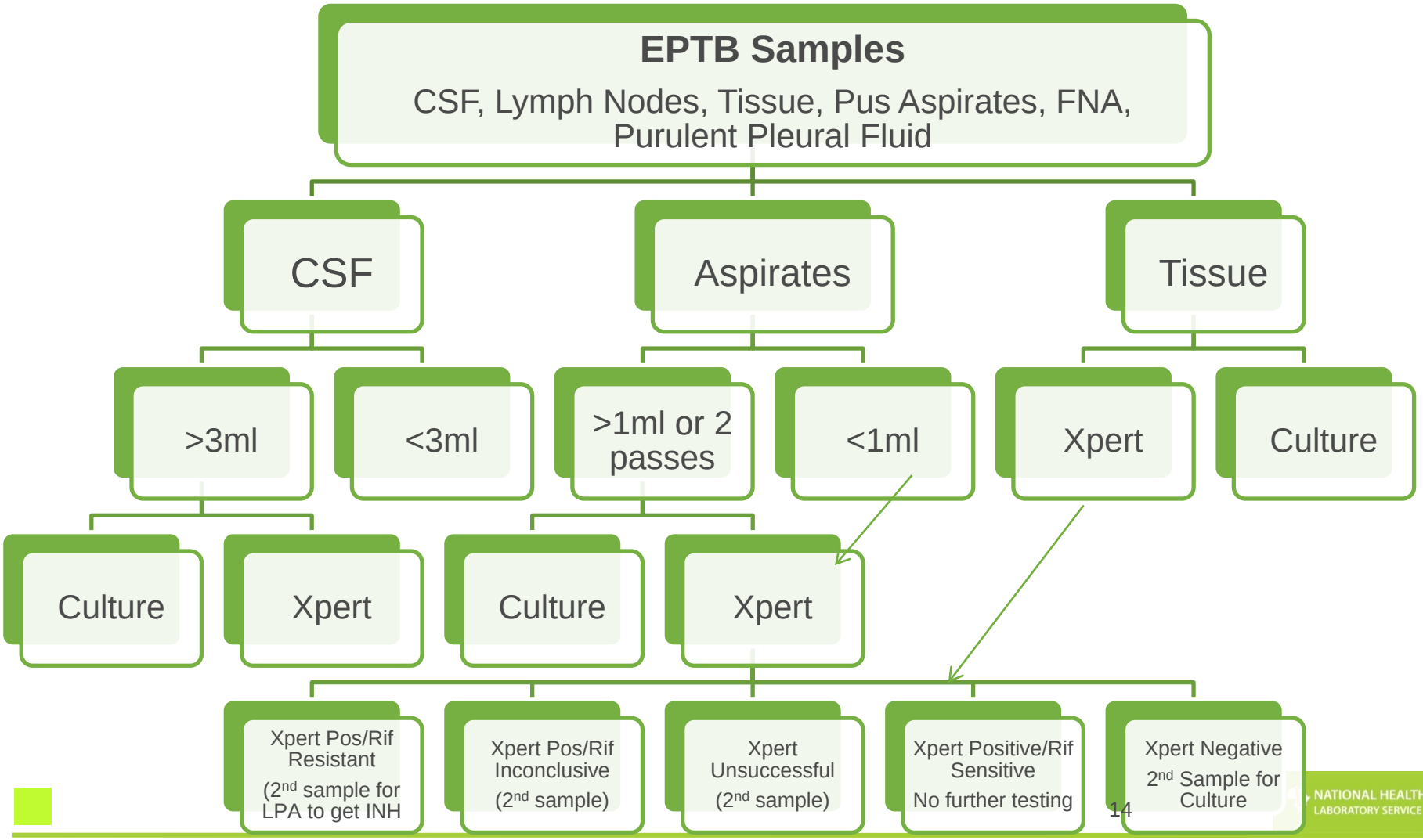
Xpert MTB/RIF Algorithm: EPTB Samples



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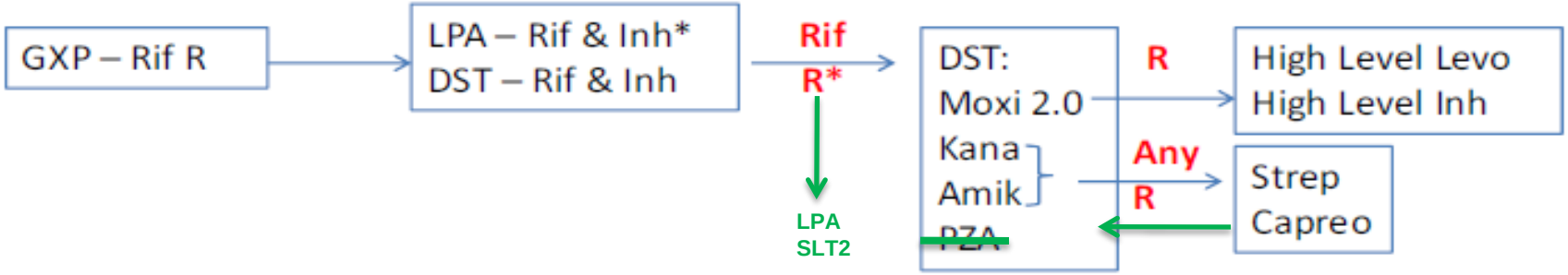
HAIN GenoType® MTBDR*sl v2- under investigation*

Rifampicin trigger

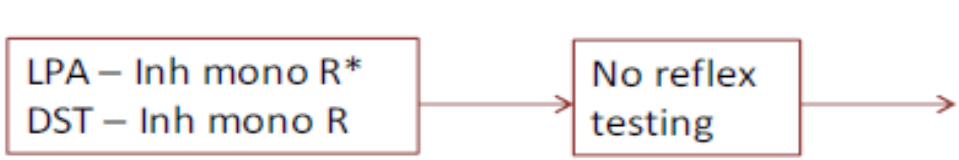


*irrespective of Inh R or S

*Report LPA
KatG and inhA mutations

Special Request offered
Ethionamide
Ethambutol

Isoniazid mono R trigger



Special Request offered
PZA
Ethambutol
High level Inh

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Division of the National Health Laboratory Service

Courtesy Nazir Ismail, NICD

HIV Diagnostic Algorithms

Massive Clinical Changes in Global ARV Treatment Programs

- **Treatment Simplification**
  - Fixed dose combination (single pill)(e.g. TDF/FTC/EFV)
  - Massive Price Reductions in ARVs
- **Trend towards ARV initiation at higher CD4s** and **greater value placed on use of viral load**
- **Life-Long treatment for pregnant women**
- **Treatment in all children <5 years**
- **Treatment as Prevention? Discordant couples, PEP and PREP**
  - HPTN052
  - ACTG5202
  - PREP
- **Integrated response**
  - Move towards Consolidated Guidelines: WHO 2013/ 2014 supplement
  - Programme managers to collaborate with clinicians for country-specific algorithms
- **De-centralization of care and Task shifting**

Courtesy Prof Wendy Stevens

WHO 2014 technical update- TECHNICAL AND OPERATIONAL CONSIDERATIONS FOR **IMPLEMENTING HIV VIRAL LOAD TESTING**

Developing an algorithm for HIV viral load:

- Frequency of targeted and routine viral load testing (such as six months after initiating ART and then yearly)
- Definition of viral failure based on testing platform
- Repeat testing interval among people with viral failure (three or six months) and adherence counselling requirements before repeat testing
- Specimen type for testing and repeat testing (plasma or dried blood spots)
- Need for population-specific testing algorithms (such as children, pregnant women and people for whom treatment is suspected to have failed)
- Current and projected numbers for people receiving ART (first-, second- and third-line regimens)
- How, where and when?

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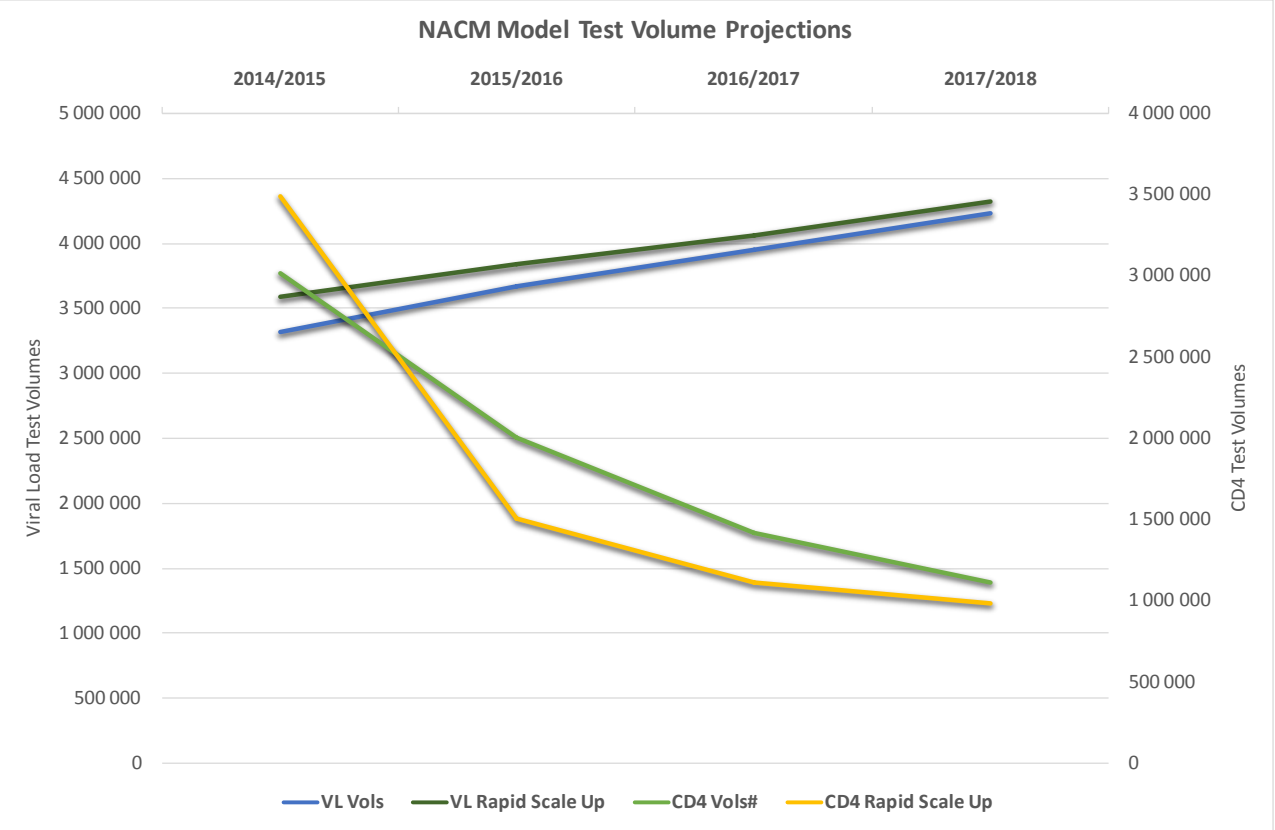
National ARV Treatment Guidelines

Year	Guidelines	Implications
2004	**National ARV Treatment guidelines(2004)**	• Baseline CD4 for initiation at CD4 < 200 • **Baseline VL, then 6 monthly monitoring**
2008/2009	**Removal of baseline viral load, except for infants**	• Baseline and 6 monthly CD4 count • **6 monthly VL**
2010	**The SA Treatment guidelines 2010** **Baseline viral load for infants and children**	• Baseline CD4 for initiation CD4<200,then 6, 12 months and annually thereafter • Baseline CD4<350 for initiation of TB/HIV and pregnant pts, then 6, 12 and annually thereafter • **VL at 6, 12 months, then annually thereafter**
2011	**Circular for initiation of all patients at CD4 counts <350** Baseline viral load for infants and children	• Baseline CD4 initiation CD4<350, 6,12 months and annually thereafter • **VL at 6, 12 months and annually thereafter**
2012	**Accelerating access to ART services (circular)** • Eligible pregnant mothers to be started on same day • All TB patients initiated on ART (irrespective of CD4 count) • Baseline VL for infants and children	• CD4<200, fast tracked for same day treatment • All new pts should not have CD4 at 6 months, but at 12 months and then annually • **VL at 6, 12 months and annually thereafter**
2013	**FDC combination** Baseline VL for infants and children **Identified strong need for evidence- based monitoring**	• CD4<350 • CD4 baseline and 12 months in first year, after that in ill patients • **Viral load 6 and 12 monthly in first year and then annually thereafter** • **>1000 virological failure, repeat VL at 2 months** • HIV genotyping for 2nd line failures

2015 SA National guidelines

- Initiation onto treatment CD4 <500
- Move from the B option to the B+ option for the PMTCT programme (B+ option is that all HIV positive pregnant women go onto lifelong ART).
- 2.4 million people on treatment in 3 years

•CD 4 tests expected to decrease from 3.8 million tests in 2014 to ~ 1 million by 2018
•HIV viral loads expected to increase from 2.6 million tests to 4.2 million by 2018



Gesine Meyer-Rath, Boston University

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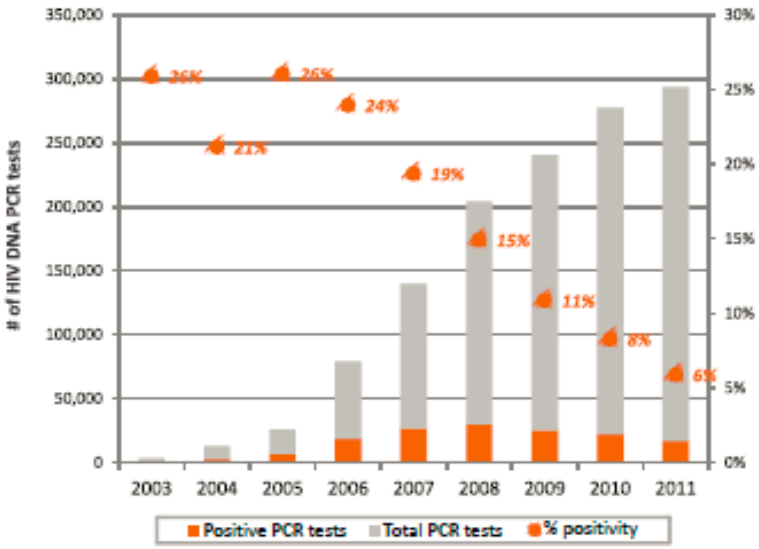
Early Infant Diagnosis

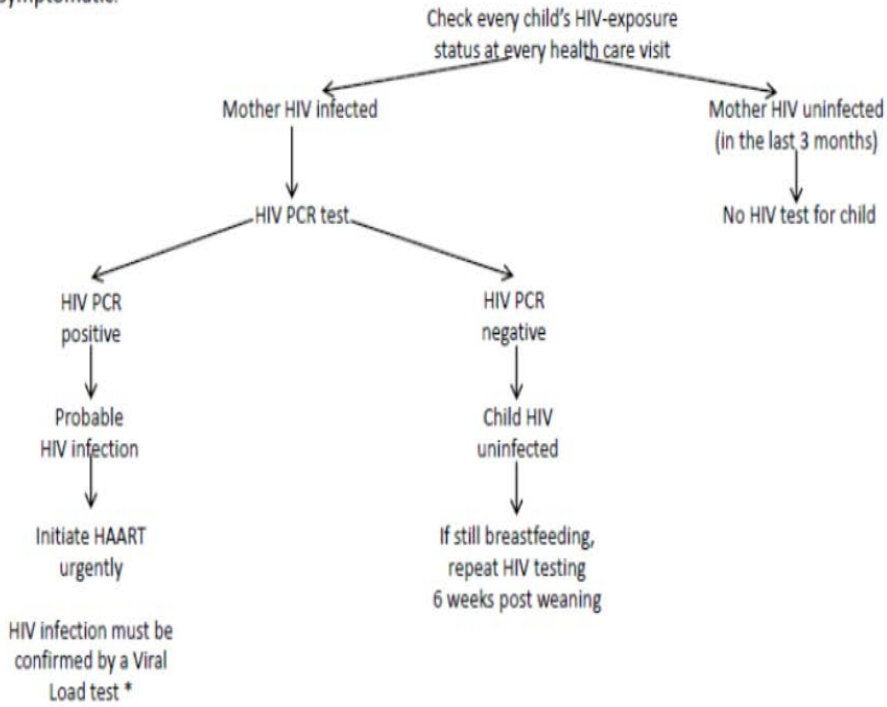
- PCR tests increased from 3370 in 2003 to 293786 in 2011
- Percentage positivity declined from 16.4% in 2006 to 2.8% in 2011



Diagnosis of HIV infection in infants and children

1. Children <18 months old

- All HIV-exposed infants require PCR testing at 6 weeks of age, 6 weeks post weaning and at any age if the child is symptomatic.



- A detectable Viral Load confirms HIV infection. HAART initiation should not be delayed by waiting for the Viral Load result.

If the HIV infection status of an infant initiated on HAART is in doubt, discuss further HIV testing required with your nearest HIV PCR laboratory

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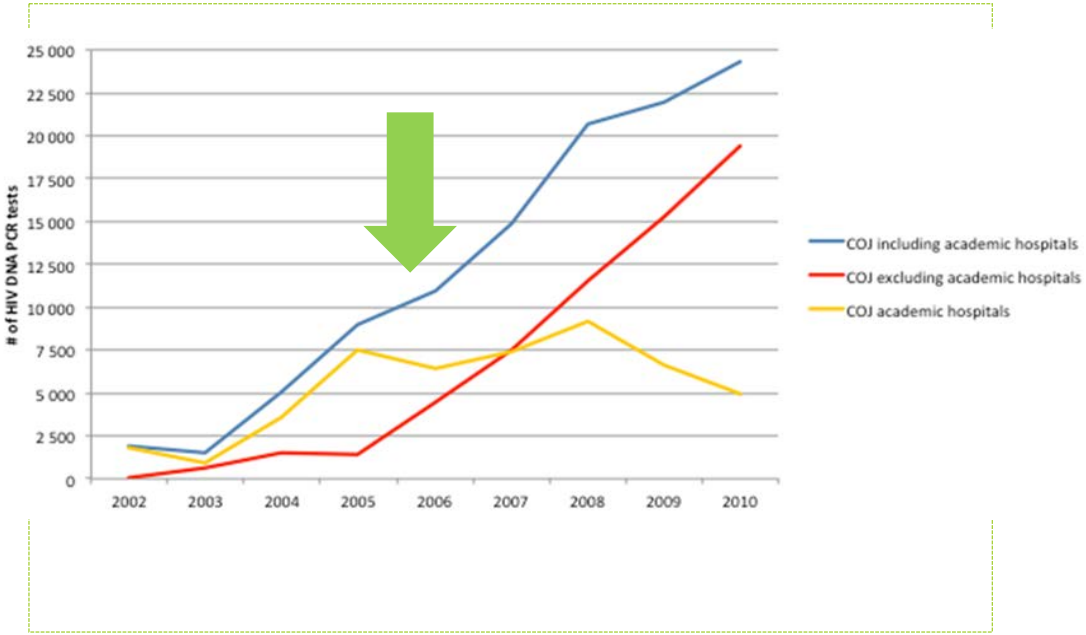
Sherman et al, IAS 2012

- Scaling up EID in South Africa has been made possible not only by increasing the laboratory infrastructure but by circumventing the need for venesection

- In 2012: 75% samples arrive in dried blood format, Results are delivered by sms printer

HIV EID PCR testing in Gauteng COJ district 2002-2010



Extensive use of DBS at EC clinic

Courtesy Sherman and Carmona

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Early Infant Diagnosis

- Currently testing at 6 weeks
- Lilian el al 2012, JCM- earlier diagnosis to reduce infant mortality- birth testing?
- Effect of sdNVP on PCR sensitivity? Mother on treatment?

JCM
Journals.ASM.org

Early Diagnosis of *In Utero* and Intrapartum HIV Infection in Infants Prior to 6 Weeks of Age

Rivka R. Lilian,[a] Emma Kalk,[a,b]* Kapila Bhowan,[a] Leigh Berrie,[c,d] Sergio Carmona,[d,e] Karl Technau,[b] and Gayle G. Sherman[a,d,e]

Paediatric HIV Diagnostic Syndicate, Wits Health Consortium, Johannesburg, South Africa[a]; Empilweni Services and Research Unit, Department of Paediatrics, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa[b]; Centre for HIV/STIs, National Institute for Communicable Diseases, Johannesburg, South Africa[c]; National Health Laboratory Service, Johannesburg, South Africa[d]; and Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa[e]

Early initiation of antiretroviral therapy reduces HIV-related infant mortality. The early peak of pediatric HIV-related deaths in South Africa occurs at 3 months of age, coinciding with the earliest age at which treatment is initiated following PCR testing at 6 weeks of age. Earlier diagnosis is necessary to reduce infant mortality. The performances of the Amplicor DNA PCR, COBAS AmpliPrep/COBAS TaqMan (CAP/CTM), and Aptima assays for detecting early HIV infection (acquired *in utero* and intrapartum) up to 6 weeks of age were compared. Dried blood spots (DBS) were collected at birth and at 2, 4, and 6 weeks from HIV-exposed infants enrolled in an observational cohort study in Johannesburg, South Africa. HIV status was determined at 6 weeks by DNA PCR on whole blood. Serial DBS samples from all HIV-infected infants and two HIV-uninfected, age-matched controls were tested with the 3 assays. Of 710 infants of known HIV status, 38 (5.4%) had *in utero* ($n = 29$) or intrapartum ($n = 9$) infections. By 14 weeks, when treatment should have been initiated, 13 (45%) *in utero*-infected and 2 (22%) intrapartum-infected infants had died or were lost to follow-up. The CAP/CTM and Aptima assays identified 76.3% of all infants with early HIV infections at birth and by 4 weeks were 96% sensitive. DNA PCR demonstrated lower sensitivities at birth and 4 weeks of 68.4% and 87.5%, respectively. All assays had the lowest sensitivity at 2 weeks of age. CAP/CTM was the only assay with 100% specificity at all ages. Testing at birth versus 6 weeks of age identifies a higher total number of HIV-infected infants, irrespective of the assay.

J. Clin. Microbiol. 2012. 50(7):2373.

6 weeks PCR: TOO LATE and TOO EARLY

- **Too late to prevent early mortality:**
  - Unable to initiate HAART early enough (7 weeks of age) to prevent ±20% early mortality by 13 weeks of age
  - IU-infected infants (±20%) go undetected because of LTFU or death before 6-weeks

- **Too early to detect all IP infections:**
  - Maternal ARV and infant NVP delay detection of HIV at 6 weeks because of a low target of virus (esp on DBS) failing to detect 10-20% of early infections

- **6 weeks: miss up to ±30-40% of all early HIV+**
- **Place for niched POC vl?**

Courtesy Gayle Sherman

Challenges and impact experienced with the implementation of new diagnostic algorithms within a national programme- Disruptive!

Implementation, training, SOPs, request forms, LIS, HR and adherence (hidden costs)

- Keeping pace with the roll-out of instruments
- High staff turnover-continuous training
- Resistance to change
- HCW misunderstanding of the technology and it's role in the entire lab cycle
- Misinterpretation of results (e.g. GeneXpert and still requiring a smear for monitoring)
- Updating of registers (e.g. no place for Xpert result)- need for electronic databases
- Healthcare worker preferences and patient behaviour
- Takes time to embed a diagnostic into a healthcare system

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Conclusion

- Modifying diagnostic algorithms to adapt to changes in technology and national guidelines is required in order to provide rapid results, simplify diagnostic processes, improve HIV/TB treatment outcomes, and generate cost savings

- Ongoing review and modelling of the impact and cost of algorithms is essential to guide policy decisions

- Simplified clinical algorithms are needed (e.g. GeneXpert) and a massive scale-up in training for both laboratory and clinical staff is essential for implementation and adherence.

- Algorithm needs linkages to clinical health systems

Acknowledgements

- Prof Wendy Stevens and the NPP team
- Dr Sergio Carmona
- Prof Lesley Scott
- Prof Gayle Sherman
- Mr Sebaka Molapo
- Sue Candy and NHLS CDW
- Centers for Disease Control
- National Department of Health

Thank You

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