

Management of patients with rifampicin resistance

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Workshop for Early Implementers

Implementation and roll-out of the Xpert MTB/RIF system for rapid diagnosis of tuberculosis and multidrug-resistance

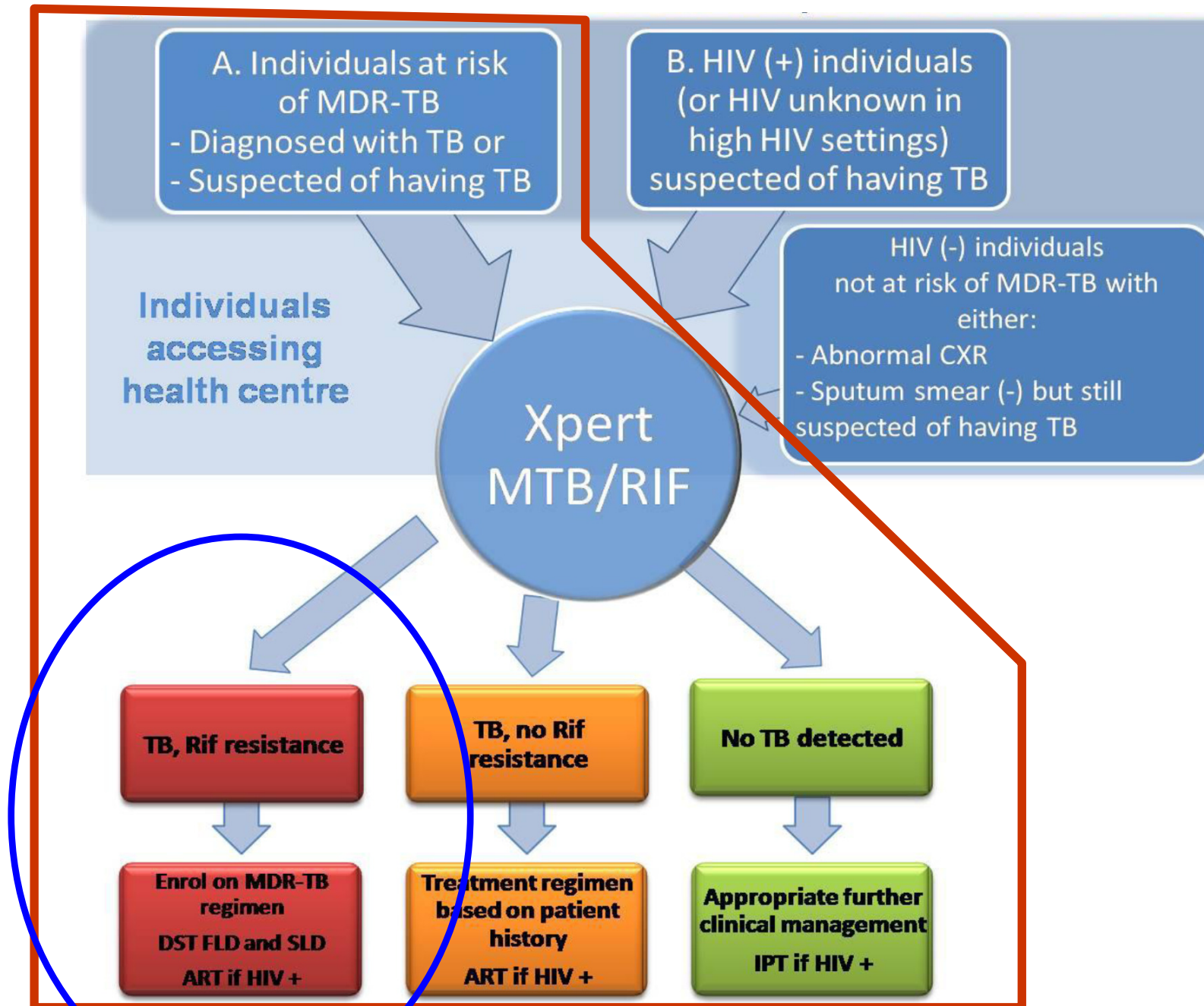
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Topics of presentation

- R-resistant cases post Xpert MTB/RIF algorithm
- The new PMDT guidelines
- MDR-TB regimens & duration
- Recommendations on monitoring



Positive predictive values for R-resistance using Xpert MTB/RIF, at different prevalence of R-resistance (N=1000)



% Prevalence of rifampicin resistance	True Positives*	False Positives*	False Negative*	True Negative*	PPV	NPV
1%	9.5	19.8	0.5	970.2	32.4%	99.9%
2%	19	19.6	1	960.4	49.2%	99.9%
3%	28.5	19.4	1.5	950.6	59.5%	99.8%
4%	38	19.2	2	940.8	66.4%	99.8%
5%	47.5	19	2.5	931	71.4%	99.8%
6%	57	18.8	3	921.2	75.2%	99.7%
7%	66.5	18.6	3.5	911.4	78.1%	99.6%
8%	76	18.4	4	901.6	80.5%	99.6%
9%	85.5	18.2	4.5	891.8	82.4%	99.5%
10%	95	18	5	882	84.1%	99.4%
11%	104.5	17.8	5.5	872.2	85.4%	99.4%
12%	114	17.6	6	862.4	86.6%	99.3%
13%	123.5	17.4	6.5	852.6	87.7%	99.2%
14%	133	17.2	7	842.8	88.5%	99.2%
15%	142.5	17	7.5	833	89.3%	99.1%

* Sensitivity (95%) and specificity (98%) for Xpert MTB/RIF rifampicin resistance, compared with reference method

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Second test for R-resistance

Re-testing

In "low MDR prevalence" setting

(THRESHOLD determined by country)

- Recommended to confirm new cases by LPA or conventional DST
- Sample is also referred for SLD testing
- MDR-TB regimen started immediately and modified if necessary based on second DST

Revised regimens for MDR regimens (1)

- Guidelines on PMDT updated between 2009-2011
- Key questions on MDR regimen composition and duration of treatment
- Systematic review with individual patient data
- 32 case series with >9,000 treatment episodes
- No RCTs

Revised regimens for MDR regimens (2)

Regimen composition for treatment of MDR-TB (1)

- 1) a fluoroquinolone should be used (**strong recommendation** / very low-quality evidence)
- 2) a higher generation fluoroquinolone rather than a lower generation fluoroquinolone should be used (conditional recommendation, very low-quality evidence)
- 3) ethionamide (or prothionamide) should be used (**strong recommendation**, very low-quality evidence)

/...

Revised regimens for MDR regimens (3)

Regimen composition for treatment of MDR-TB (1)

4) four second-line anti-TB drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, very low-quality evidence).

5) regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, very low-quality evidence).

Revised regimens for MDR regimens (3)

Odds of success by duration of intensive phase (left)
and total treatment (right)

INTENSIVE PHASE			TOTAL TREATMENT*		
Duration in months	Observations	Adjusted** Odds Ratio (95% CLs)	Duration in months	Observations	Adjusted** Odds Ratio (95% CLs)
1- 2.5	308	1.0(ref)	6.0-12.5	743	1.0 (ref)
2.6 -4.0	1406	1.2(0.5, 2.9)	12.6- 15.5	384	2.4 (1.5,3.6)
4.1 -5.5	481	2.4(1.3,4.3)	15.6- 18.5	1646	4.6 (2.0,10.4)
5.6 -7.0	377	3.7(1.9,7.1)	18.6-21.5	612	9.3 (5.8,15.0)
7.1- 8.5	172	5.1(2.1,12.7)	21.6-24.5	435	6.8 (4.2,11.1)
8.5 -20	792	2.2(1.2,3.9)	24.6-27.5	207	8.2 (4.2,15.9)
			27.6-30.5	106	2.4 (1.2,5.0)
			30.5 - 36	48	1.3 (0.6-2.7)

* only in patients without prior treatment for MDR

** adjusted for age, sex, HIV, past TB treatment, past MDR treatment, and extent of disease

Shorter regimen for MDR : Bangladesh

- Also observational study
- The most effective regimen was 9 months (minimum) with gatifloxacin, clofazimine, E and Z throughout treatment + prothionamide, Km, and high-dose H during intensive phase (minimum of 4 months)
- Relapse-free cure of 88% (95% CL: 82.7–91.6) in 206 patients
- RCTs recommended especially in settings with high prevalence of HIV & resistance to SLDs

Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, Rieder HL. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010 Sep 1;182(5):684-92

Monitoring of response to second line treatment

- The use of sputum smear and culture over smear alone is recommended for monitoring patients with MDR-TB during treatment (conditional recommendation/very low quality evidence).
- Recommendation based on data pooled from 10 observational studies
- Modelling different testing strategies
- Sputum smear and culture monthly until conversion performed best at identifying failures earlier