TB Update: March 2012

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- IGRAs vs TST
- LTBI – A New Regimen
- NAATs – What is Their Role?
- Rapid Susceptibility Testing
- HIV plus TB: When to Start ART?

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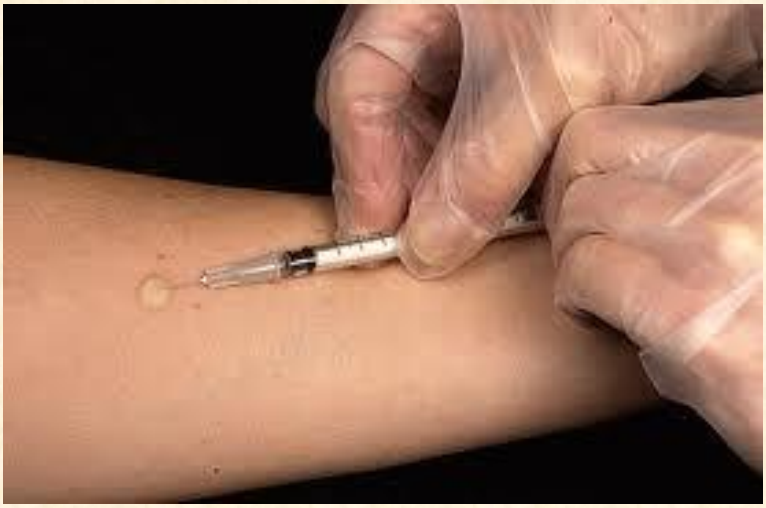

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IGRAs

QuantiFERON® and T-Spot®.TB

Measures IFN-gamma production from sensitized T-cells

- Antigens: ESAT-6, CFP-10, (+ TB-7.7 in QTF)
  - These antigens not found in most NTM, particularly BCG
  - They are found in *M. kansasii*, *M. szulgai* and *M. marinum*
- Sensitivity: comparable to TST
- Specificity: data lacking

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IGRAs

- Advantages
  - Only one office visit
  - Interpretation less subjective
  - Not affected by BCG (most US cases now foreign-born)
  - Not affected by most NTM
- **However:**
  - Need more data: HIV, window period, children, annual testing, immigrants, effect of Rx on test results
  - $$$
  - Results may be indeterminate, discrepant or "wobble"

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IGRAs – CDC Recommendations

- Can use either IGRA or TST in all circumstances, including contacts and periodic screening
- IGRA preferred:
  - BCG vaccinees
    - However – TST wanes with time and is negative after 10 years
  - If less likely to return for TST reading
- TST preferred
  - <5 years of age – few data
- Consider using both
  - High risk with negative result (e.g. HIV or <5)
  - Low risk with positive result
  - To encourage compliance with LTBI Rx
    - e.g., BCG vaccinee with strongly positive TST

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IGRAs. *MMWR* 2010; 59 (No. RR-5): 1-25

Caveats Regarding IGRAs

- TSTcan boost IGRAs
- Conversion can take up to 14-22 weeks
  - vs. 8-10 weeks for TST
- False-positives may occur
- Variability – the Wobble
  - Conversion without TB exposure
  - Reversions without therapy
- Cost: Quest Diagnostics® - $299.00

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IGRA – Bottom Line

Use your judgment – either is acceptable

-- Ultimately a cost-benefit analysis

In Philadelphia we currently use the TST

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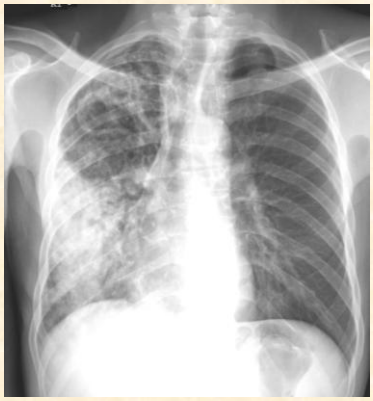
…and remember



In the adult, the TST and IGRA play NO role in the diagnosis of TB **disease**

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Rx of LTBI

- INH x 9 months
- INH x 6 months
  - Not for HIV+, children, healed TB on CXR
- RIF x 4 months (off-label)
- New regimen… (off-label)

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Rx of LTBI – New Regimen

- INH + Rifapentine (RPT) weekly x 12
  - Healthy patients 12 or older
  - HIV+ if not on ART
  - Not in pregnancy
  - Not if INH or rifamycin resistance suspected
  - Only with DOT
  - In largest trial, more permanent discontinuations than with INH9 because of adverse events or hypersensitivity.

Source: INH-RPT regimen for LTBI.
***MMWR* 2011; Vol. 60 (No. 48): 1650-1653**

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Concerns with INH/RPT

- INH resistance
  - In Philadelphia, among foreign-born: 15-18%
- Toxicity: 2 drugs > 1 drug
  - In largest trial, more permanent discontinuations
- More convenient compared to INH x 9 months; less of a difference compared to RIF x 4
- Pharmacy cost: INH x 9 $95
  RIF x 4 $84
  INH/RFP $179

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INH/RPT – Bottom Line

In Philadelphia: Our usual approach is RIFx4

- Resistance
- Toxicity
- Cost
- Compliance

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Caveat regarding LTBI

Rule out TB disease before treating LTBI

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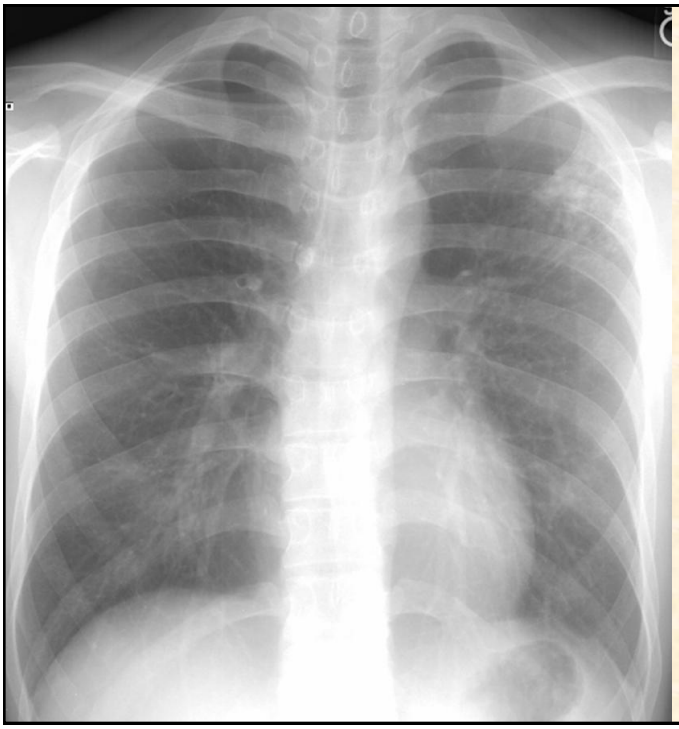

Inactive??

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LTBI = Rule Out Active TB: Beware the Misleading X-ray Reports:

"Stable"
"Inactive"
"Healed"
"Fibrotic"
"Old"
"Scarring"

Cannot tell activity from CXR. Either wait for culture and sensitivity or begin Rx with 4 drugs pending C&S result

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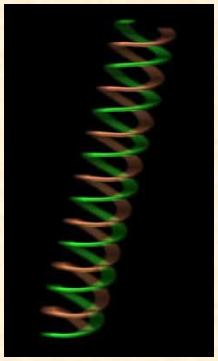

Nucleic Acid Amplification (NAAT)

- Excellent specificity and sensitivity
- However:
  - Can be + with dead organisms
  - Can have false negatives
  - Takes time, money and technical expertise
  - Smear better gauge of infectiousness
- Therefore:
  - Not stand-alone: still need culture
    - Final identification
    - Sensitivity testing
    - More sensitive than NAA
  - Don't use if suspicion very high or very low
  - **Clinical judgment!**

FDA-approved - for sputum only:
MTD (Gen-Probe)

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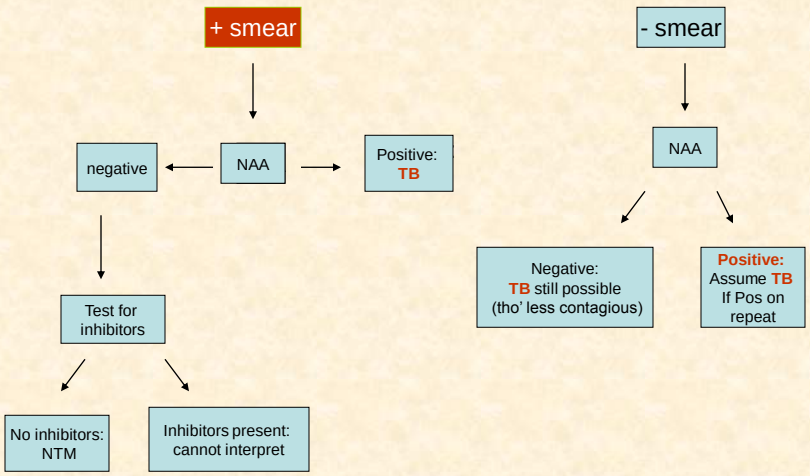
Nucleic Acid Amplification Tests



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CDC: NAAT Recommendation

Should be performed on each patient with signs and symptoms of pulmonary TB, **for whom the test result would alter case management**

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NAAT – Bottom Line

NAAT has not lived up to its promise. It should **never** override clinical judgment; therefore, it rarely if ever changes management.

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Rapid Susceptibility Testing

CDC – molecular testing

- Performed on cultures
- Performed on NAAT-positive clinical specimens, e.g., sputum
- Send via state or local lab
- Results available in days
- Confirm with conventional in vitro testing

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MDDR Service: Drugs and Genes for Panel

Rifampin	MDR TB	*rpoB* (81bp region)
Isoniazid	MDR TB	*inhA* (-15)
Isoniazid	MDR TB	*katG* (Ser315)
Fluoroquinolones	XDR TB	*gyrA* (coding region)
Amikacin, Kanamycin, Capreomycin	XDR TB	*rrs* (nt1401/1402,1484)
Kanamycin	XDR TB	*eis* (promoter region)
Capreomycin	XDR TB	*tlyA* (coding region)
Ethambutol		*embB* (Met306, Gly406)
Pyrazinamide		*pncA* (promoter and coding regions)

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Results for Molecular Detection of Drug Resistance; Conventional Drug Susceptibility Test in progress.

Locus (region) examined *	Result	Interpretation (based on in-house evaluation of 254 clinical isolates)
rpoB (RRDR)	No mutation	Probably Rifampin susceptible. (96% of RIF-R isolates in our in-house evaluation of 254 clinical isolates have a mutation at this locus.)
inhA (promoter)	No mutation	Isoniazid resistant. (100% of isolates in our in-house evaluation of 254 clinical isolates with this mutation are INH-R.)
katG (ser315 codon)	**Mutation:** AGC>ACC; Ser315Thr	

*A negative results (e.g., no mutation) does not rule out contributory mutations present elsewhere in the genome.

Source: Unpublished data from Beverly Metchock, CDC

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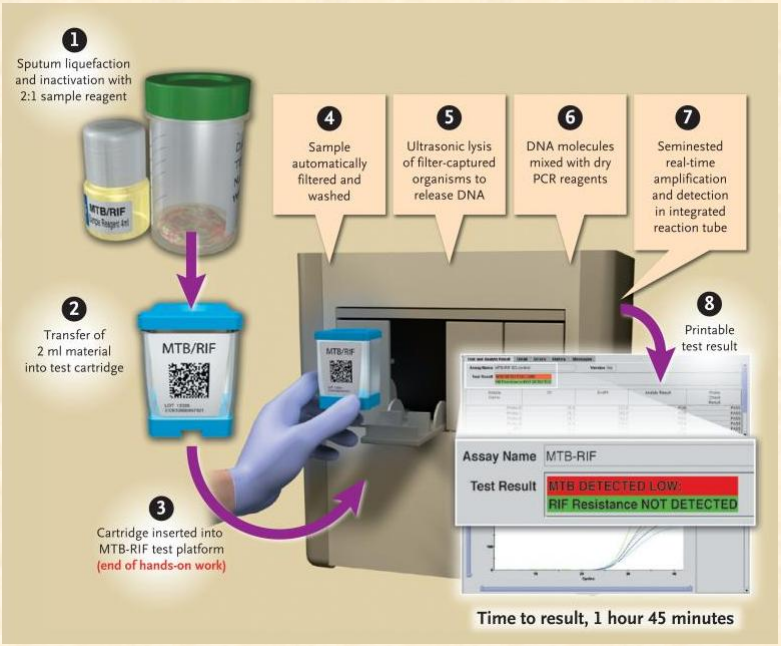

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance – GeneXpert®, Cepheid

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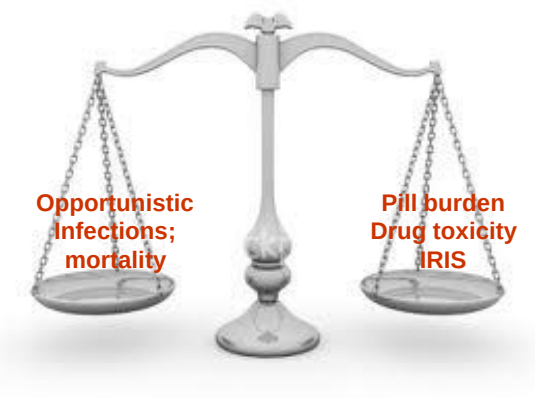
Timing of ART



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Timing of ART: Synthesis of Current Data

Treat early (2 weeks):

- **Especially if CD4<50 cells/mm^3**
- **Consider if CD4 <200 cells/mm^3**

Defer until 8 weeks (but not beyond):

- **Higher CD4 counts**
- **If at risk for dangerous IRIS e.g. CNS disease**

WHO: As early as possible

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Thank You!

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