

# **Screening for Multidrug-resistant Tuberculosis and Extensively Drug-resistant Tuberculosis in High HIV Prevalence Settings**

**Timothy H. Holtz & J. Peter Cegielski**

**International Research and Programs Branch  
Division of Tuberculosis Elimination**

**National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention  
CDC, US Department of Health and Human Services**



# Outline

- **Importance of HIV/TB interaction**
- **Associations between HIV and drug-resistant TB**
- **Screening for MDR/XDR TB**
- **Algorithm for screening TB suspects at risk for drug-resistant TB in HIV high-burden settings**

# Public Health Importance

- HIV as strongest risk factor for those infected with *M. tuberculosis* (MTB) to develop TB
  - 10-fold increased risk
- TB as leading opportunistic infection / cause of death for PLWH
- Excessive TB burden from HIV
  - Overwhelmed health services
  - Poor adherence and high default rates
  - Drug and lab supply issues
- Low cure rates in programmes → anti-TB drug resistance

# Known Risk Factors for Drug Resistance

- Previous treatment for TB:
  - Chronic TB > previous treatment failure > previous default > relapse
- Contacts of MDR TB cases
- Sputum smear-positive at 2 (3) months of standard course chemotherapy
  - May be predictive of imminent treatment failure

\*Table 5.1, Guidelines for the Programmatic Management of Drug-resistant TB, WHO, 2005



# Reported Risk Factors for Drug Resistance

- TB treatment in private sector
- Exposure in institution with MDR TB outbreak
- Poor quality anti-TB drugs
- Treatment in programmes with low cure rates
- Treatment in non-DOTS programmes
- Hospitalization or incarceration
- Residence in high MDR TB prevalence area
- HIV in some settings

# Important Issues Between HIV and Drug-resistant TB

- **High mortality rates in persons with MDR/XDR TB and HIV/AIDS**
  - **> 70% death rates**
- **Mortality occurs rapidly**
  - **As short as 4-8 weeks from TB diagnosis, possibly even before diagnosis of DR**
- **HIV/AIDS often is undiagnosed**
- **HIV-infected patients at risk of MDR TB need most rapid diagnosis**

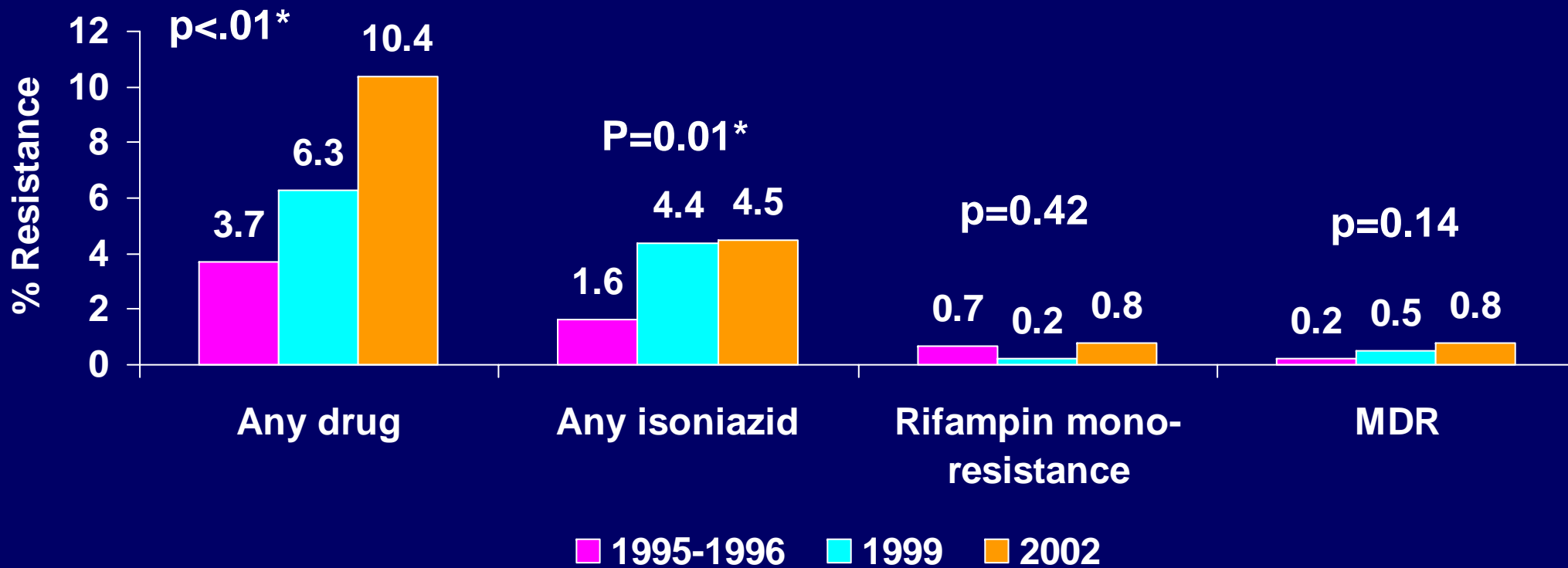
# Associations Between HIV and MDR- and XDR TB

- Poorly performing TB programs
- Undiagnosed or inadequately treated HIV infection
- Poor infection control practices
- Inadequate treatment for drug-resistant TB
- Acquired rifamycin resistance
- Malabsorption of anti-TB drugs
- Uncontrolled use of 2<sup>nd</sup>-line anti-TB drugs

\*Wells CD, et al. HIV infection and MDR TB – the perfect storm.  
JID 2007;196:S86-107



# Prevalence of Drug Resistance Among New Patients, Botswana, 1995–2002



\* $\chi^2$  for trend

\*Nelson LJ, et al. Lancet 2005;366:488-490



# Screening for MDR- and XDR TB

HAVE A NICE  
FLIGHT, SIR.

HA! HE MISSED  
THE TB.



# Screening for MDR/XDR TB

- Active screening of population: drug resistance *survey*
  - Health system identifies and tests representative sample of TB patients with adequate sample size
- Passive screening of population: *surveillance* for drug resistance
  - Policy + practice for universal culture + DST or culture and DST in well-defined groups
  - Results reported to TB program, TB program receives, combines, analyzes, interprets
- Active screening of individuals: contact investigation
  - Public health system tracks down contacts of patients with drug-resistant TB and tests close contacts
- Passive screening (case finding) of individuals: each health care provider tests symptomatic patients on a case by case basis

# Considerations for Rapid MDR/XDR TB Identification

- Rifampicin resistance (RR) testing as critical entry point
  - Most important of 1<sup>st</sup>-line drugs
  - RR = MDR TB in many settings
- Negative predictive value of rapid RIF tests high
- HIV+ suspects with + rapid test for RR need treatment while awaiting final DST
- Evidence-based policy for empiric treatment and access to array of drugs
- HIV+/AFB- contacts of persons with MDR/XDR TB also need rapid diagnosis and possible treatment
- HIV+ suspects with EP TB and children (HIV+/-) need further consideration

# Newer Resistance Test Methods

- **Non-culture methods**
  - Phage: 2 day result, RIF only
  - Molecular genotypic tests directly on sputum (1-3 days)
  - Manual and automated NAAT (molecular) tests, highest performance with RIF
    - *rpoB* (Innogenetics)
    - *katG+rpoB* (Hain Lifescience GmbH)
    - Others (Cepheid)
- **Commercial automated liquid culture & DST**
  - Standard in developed countries
  - AFB+ and AFB- sputum
  - Results in 3-4 weeks, although higher contamination rates
  - SLD DST validated in two studies, use supported by STAG March 2007
- **Other culture methods**
  - Direct testing on solid media: LJ, Griess
  - Direct testing in liquid media, MODS
  - Non-commercial, cheaper, need culture-capable lab

# Challenges of Rapid Diagnosis

- For many countries, 1<sup>st</sup>-line DST on solid media is not readily accessible
- Liquid culture only available in reference labs
- Some technologies are point of care (microscopy center), versus others that are lab based (referral clinic/hospital)
- What is the expected outcome?
  - Earlier diagnosis, earlier culture conversion, lower mortality, higher cure rate, reduced transmission?
- Role of empiric treatment

# Proposed Algorithm for TB Suspects at High Risk of MDR/XDR TB

- Ensure infection control precautions
- Perform AFB smears (2)
- Conduct HIV testing (provider initiated) on all TB suspects, especially those at risk of RR

**Identification of persons at high risk needing rapid test for RR and DST**



**Ensure infection control**



**AFB test, HIV test**

**AFB-**



**Management of AFB- TB suspects based on HIV status  
?RR test**

**AFB+**



**RR test**

**HIV+**

**RR+**

**HIV+**

**RR-**

**HIV-**

**RR+**

**HIV-**

**RR-**

# HIV+ / RR+

- Perform rapid liquid-based culture and DST for 1<sup>st</sup>/2<sup>nd</sup>-line drugs
- Rapid transport to reference lab if full DST not yet available locally
- Solid media culture and confirmation of DST
- Treat with 4 or more effective 2<sup>nd</sup>-line drugs for empiric therapy based on lab/survey data and history of 2<sup>nd</sup>-line drug use in the patient, await full DST
- Consider auxiliary drugs
- Ensure adequate ARV treatment
- Ensure infection control
- Initiate contact investigation

# HIV+ / RR-

- Population at risk of MDR/XDR TB
- Perform rapid liquid-based culture and DST for 1<sup>st</sup>/2<sup>nd</sup>-line drugs
- Rapid transport to reference lab if full DST not yet available
- Solid media culture and confirmation of DST
- Follow WHO TB treatment guidelines (2003)
- Start ARVs
- Adjust treatment according to WHO Guidelines for Programmatic Management of DR TB if DR found later

# HIV- / RR+

- Perform rapid liquid-based culture and DST for 1<sup>st</sup>/2<sup>nd</sup>-line drugs
- Rapid transport to reference lab if full DST not yet available
- Solid media culture and confirmation of DST
- Treat with 4 or more effective 2<sup>nd</sup>-line drugs for empiric therapy based on lab/survey data, await full DST
- Adjust treatment according to WHO Guidelines for Programmatic Management of DR TB
- Ensure infection control
- Initiate contact investigation

# HIV- / RR-

- Follow WHO TB treatment guidelines (2003)
- Solid media culture and DST

# Limitations

- **Availability of test**
- **Lab infrastructure, biosafety issues, and number/training of lab personnel**
- **General infrastructure for transportation and telecommunication**
- **Cost vs. available resources vs. need**

# Conclusions

- **HIV testing of all TB suspects combined with rapid detection of RR can lead to earlier diagnosis, treatment, and reduced transmission**
- **Simple algorithm ensuring adequate infection control, rapid detection of RR and HIV can identify those requiring empiric therapy**
- **Institution of rapid diagnosis of HIV-MDR/XDR TB poses several challenges**

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# **MDR TB Outbreaks in Industrialized Countries, 1988-1995**

## **High Mortality with HIV Infection**

<b>Facility</b>	<b>% HIV-infected</b>	<b>% Mortality</b>	<b>Median survival (weeks)</b>
<b>Hosp. Florida</b>	<b>93</b>	<b>72</b>	<b>7</b>
<b>Hosp. NYC</b>	<b>100</b>	<b>89</b>	<b>16</b>
<b>Hosp. NYC</b>	<b>95</b>	<b>77</b>	<b>4</b>
<b>Hosp. NYC</b>	<b>91</b>	<b>83</b>	<b>4</b>
<b>Hosp. Italy</b>	<b>98</b>	<b>95</b>	<b>6-8</b>
<b>Hosp. Spain</b>	<b>100</b>	<b>98</b>	<b>7</b>
<b>Hosp. Argen.</b>	<b>98</b>	<b>79</b>	<b>4</b>

# Impact of HIV on MDR TB Treatment Mortality

- HIV-infected TB patients by MDR TB status
  - NYC, 1997\*
    - 62% (MDR) vs. 26% (non-MDR)
- MDR TB patients by HIV status
  - NYC, 1996†
    - 72% (HIV+) vs. 20% (HIV-)
  - Eastern Cape, South Africa, 2002‡
    - 41% (HIV+) vs. 20% (HIV-)

\*Mannheimer et al, IJTL D 1997; † Park et al, AJRCCM 1996; ‡ Finlay et al, IDSA 2004



# **HIV and Acquired Rifamycin Resistance Among TB Patients**

- **Poor treatment adherence**
- **Advanced immunosuppression**
- **Treatment of other opportunistic infections**
- **Co-treatment with antiretroviral medications**
- **Treatment with intermittent TB treatment regimens**

# Diagnosing Drug-Resistant TB

**From Months – solid culture systems**

**to**

**Weeks – liquid and direct culture**

**to**

**Days – phage assays**

**to**

**Hours - NAATs**

**to**

**Minutes – integrated NAT**

*Adapted from R. O'Brien, December 2006*



# Screening for MDR- and XDR TB

- Active and passive screening (point of view of health system doing the screening)
  - Active: Health system identifies who to test and seeks to test them
  - Passive: Patient identifies health services provider and seeks services
- Population-level or individual-level
  - Population: Drug resistance surveys, surveillance system
  - Individual: Culture and DST