HIV/MDR-XDR-TB: Implications

• Define and update epidemic in rural South Africa
• List and explore implications
  – Prevention
  – Treatment
• Offer prescription for short and long term solutions
Rural KwaZuluNatal - Tugela Ferry-Msinga District

- TB incidence 1,100/100,000 population
- MDR TB incidence 140/100,000
- HIV antenatal seroprevalence >30%
- M/XDR TB/HIV co infection >90%
MDR and XDR Index Patients Over Time

Tugela Ferry

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<th>Year</th>
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<td>2007</td>
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Tugela Ferry
Continuing Cases with High Mortality
2005 to 2007

• Total Cases MDR / XDR TB = 619
  – MDR TB = 269 (43%)
  – XDR TB = 350 (57%)
  (US: 124 MDR TB cases in 2005; 83 XDR TB cases 1993-2006)

• Mortality
  – MDR TB Deaths = (67%)
  – XDR TB Deaths = (82%)
Recognition that MDR/XDR TB are Widespread in South Africa and Beyond

- By mid 2007, XDR TB ~60 KZN facilities in KZN
- 2005-07-4701 MDR cases; 656 (6%) XDR in KZN
  - 55% of XDR TB cases not from Tugela Ferry
- XDR TB cases found in all 9 South African provinces
- Neighboring countries affected:
  - Botswana, Mozambique, Lesotho, Namibia, ? Zimbabwe
- Full extent unknown; no denominator, culture and DST limited
South Africa MDR XDR 2005-2007

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<td>XDR % total</td>
<td>57%</td>
<td>14%</td>
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Clearer Understanding of Etiology of XDR-TB Epidemic in KwaZuluNatal

- High prevalence *M. tb*; weak TB control program
  - Low cure and completion rates
  - Acquired, previously treated drug resistance
- Absent microbiologic surveillance + empiric Rx
  - Amplified drug resistance
- KZN strain
  - ? Increased virulence?
Clearer Understanding of Etiology of XDR TB Epidemic in KwaZuluNatal (2)

- Arrival and progression of the HIV epidemic
  - Massive increase in TB cases,
  - Rising population/individual immuno compromise
  - Rapid progression to disease
  - New, transmitted drug resistance

- Absent/limited infection control
  - Nosocomial transmission
  - Community transmission
M/XDR TB Mortality
Tugela Ferry 2005-2007

- XDR mortality 82%
- MDR mortality 67%
- Rapid morality first 30 days
- Increasing mortality with each increase in resistance
Patients with MDR-TB treated at the provincial MDR referral hospital

No. patients

Year

2000 2001 2002 2003 2004 2005 2006

0 100 200 300 400 500 600 700 800

686/2476 = 28%
Patients diagnosed and treated at KGV
Patients diagnosed and not treated
Patients seen and not diagnosed
Patients not seen or diagnosed
What can be done in the short term to reduce the impact of XDR-TB epidemic?

- Rapid and massive infusion of resources
  - address epidemic, strengthen TB programs, integrate TB/HIV
- MDR/XDR TB treatment must be expanded but will remain limited
- Fast-track ARV roll out-universal access
  - decrease susceptibles-reduce reactivation and superinfection and rapid disease progression
What can be done in the short term to reduce the impact of XDR-TB epidemic?

- **Focus on TB transmission and preventing new infections**
  - **Earlier diagnosis**
    - New rapid diagnostic tests
    - Active (intensive) case finding
      - Reduce sputum positivity and transmission and improve survival
  - **Implement airborne infection control**
    - Improved isolation facilities and use of available strategies
  - **Decrease reliance on hospital care**
    - Decentralize and provide community based care and treatment
Community Based Treatment: MDR-TB and HIV

• Centralized referral treatment overwhelmed
• Nosocomial spread implicated in spread of MDR/XDR TB
• No follow-up infrastructure
• Community spread < 2%
• Brief admission community hospital
• Daily visit at home
  – MDR-TB and HIV Rx
  – Injection teams
  – Monthly clinic visit
HIV/M/XDR TB: implications

• Need to re think past experience and dogma and about TB and drug resistance and appreciate importance of transmission

• Short term strategies may be effective even in resource limited settings
  – critical need for massive infusion of new resources
  – strong focus on reducing transmission
  – Strengthen and further integrate TB and HIV programs
  – Improve diagnostics
HIV/M/XDR TB: implications

- Global problem, but collision of TB and HIV accelerated TB drug resistance and created a “perfect storm”
- MDR and XDR TB uncovers past and current deficiencies in TB knowledge, strategies, programs and practices
- In high TB and HIV prevalence areas, threatens success of both StopTB and historic ARV roll out programs; low prevalence areas still problematic
HIV/M/XDR TB: implications

• Long term solutions are critical
  – new diagnostics and drugs, an effective vaccine
  – renewed interest in TB and TB/HIV research and care
  – alleviation of social and economic conditions and health disparities that breed TB, HIV, and TB drug resistance
With Acknowledgments

TF CARES
COSH
Philanjalo
KZN Department of Health
Italian Cooperation
Microbiology labs at
Nelson Mandela School of Medicine
Inkosi Albert Luthuli Hospital
Yale School of Medicine
Albert Einstein College of Medicine
Tugela Ferry – COSH

**Rural District Hospital - 350 beds**
- Male & female medical and TB wards
- ~40 beds

**TB DOTS Program**
- >1000 new cases/yr, ~50% completion rate

**HIV Program**
- 2001-HIV clinic, Home Based Care
- 2004- ARV roll out, >3000 on ARVs

**Sizonqoba:**
- 2003-HIV/TB integration study

**TB laboratory/Durban**
- circa 2000-3 laboratories, ~600,000 tests/yr
Special Challenges in M/XDR TB and HIV Co infection

• High and rapid mortality
• Vertical, overburdened, underfunded care systems
• Comprehensive prevention, care and treatment
  • Improved TB diagnostics
  • Interruption of transmission
  • New treatment paradigms
• Ethical issues
THREATSPOSED BY MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (TB) TO ANTIRETROVIRAL THERAPY ROLLOUT AND TB PROGRAMS

- Increased morbidity and mortality among patients with M/XDR TB and HIV coinfection
- Transmission of drug-resistant TB
  - in hospital inpatient and outpatient settings
    - to patients and health care workers
  - in congregate community settings
THREATS POSED BY MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (TB) TO ANTIRETROVIRAL THERAPY ROLLOUT AND TB PROGRAMS

- Further overburdening of TB diagnostic and treatment facilities
  Additive complexities and complications of treatment with antiretroviral agents and second-line TB drugs
- Potential reversal of positive gains in TB and HIV program collaboration and integration
- Competition for human and financial resources
ELEMENTS OF SUCCESSFUL RESPONSE TO MULTIDRUG-RESISTANT (MDR) AND EXTENSIVELY DRUG-RESISTANT (XDR) TUBERCULOSIS (TB) IN SOUTH AFRICA IN THE CONTEXT OF HIGH LEVELS OF HIV INFECTION PREVALENCE

- **Improving diagnosis**
  - Enhancing surveillance for drug-resistant TB
  - Expanding laboratory capacity for first-line and second-line drug-susceptibility testing
  - Testing and deploying rapid diagnostic procedures and strategies to identify MDR-TB and XDR-TB
  - Improving rates of HIV testing among patients with MDR-TB or XDR-TB
  - Enhancing screening for TB among HIV-infected patients
  - Enhancing MDR-TB and XDR-TB contact tracing

- **Reducing transmission**
  - Instituting and monitoring infection-control measures in congregate care settings
  - Encouraging HIV testing for health care workers to reduce the risk of TB transmission

- **Improving treatment**
  - Accelerating universal access to antiretroviral therapy (ART)
Effects of MDR/XDR TB on the HIV Epidemic

Increased risk of DR TB compared to HIV uninfected individuals
Increased mortality among HIV patients co-infected with DR TB
Potential morbidity from drug toxicities of second line TB drugs and antiretrovirals
Nosocomial transmission of DR TB to HIV patients in hospitals and clinics
Risk to health care workers caring for HIV patients
Strain on national TB control programs and DOTS programs
Unmet demand for laboratory services and specialized treatment referral
Rivalry for resources between HIV and TB programs
Growing stigma of TB and HIV co-infected patients comparable to early HIV epidemic
Overall reversal of gains from historic antiretroviral rollouts
Rural KwaZulu-Natal - Tugela Ferry-Msinga District

- Population 200,000
- 1800 sq km rural district

**TB burden**
- TB case rate >1,000/100,000 population
- >90% HIV co-infected

**HIV burden**
- 30% in antenatal attendees

----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
Progressive increase in resistance

Drug Resistance Patterns in XDR TB Cases by 6 Month Interval

- 4 Drug: HRCK
- 5 Drug: HRECK, HRSCK
- 6 Drug: HRESCK
Amplified Resistance and Mortality

- XDR TB is more common than MDR TB in Tugela Ferry.
- A 6 drug resistance pattern has become predominant over time in XDR TB cases.
  - Likely secondary to suboptimal treatment with empiric MDR TB regimens in the presence of existing XDR drug resistance.
  - Amplification of resistance further limits treatment options for patients with XDR TB.
- Two phases of mortality seen in both MDR and XDR TB:
  - An early rapid decline in survival may reflect advanced disease at presentation.
  - The difference seen between MDR and XDR TB in the second phase may reflect the contribution of treatment (TB and HIV) or specific organism properties linked to resistance.
Dire TB warning to SA
South Africa must declare emergency, says World Health Organisation

Super resistant TB rife in KZN

A Kenzul-Natal study has revealed a super strain of tuberculosis — XDR TB — that is resistant to all first and second-line drugs and that a high death rate. South Africa does not have any drugs to treat patients with XDR TB.

Tugela Ferry unites to fight double disease crisis

Outbreak of killer TB at Tugela Ferry

KERRY CULLINAN

There has been an outbreak of a multi-drug-resistant (MDR) strain of tuberculosis in the Tugela Ferry area of the Eastern Cape. About 30 patients from the area have been referred to King George V Hospital in Durban, the province's only facility dealing with MDR TB, but their chances of recovery are low.
Ethical Dilemmas
Public Health vs. Individual Rights

49 TB patients escape from S. African hospital

Patients cut wire fencing and fled isolation unit to spend holidays at home

Associated Press
updated 4:19 p.m. ET, Tues., Dec. 18, 2007

JOHANNESBURG, South Africa - Forty nine highly infectious tuberculosis patients cut through wire fencing and broke out of a hospital isolation unit, apparently because they wanted to spend Christmas with their families.

The mass escape highlights the problems faced by South Africa as it struggles to cope with an epidemic of virtually incurable TB that feeds off the AIDS virus and kills most of its victims. South Africa has an estimated 5.4 million people living with the AIDS virus.

There have been around 400 confirmed cases of the incurable strain known as XDR-TB, or extremely drug resistant TB. But activists say the actual number is probably much larger, because testing methods are not sophisticated enough to detect the new strain and many people die before they can be diagnosed.
## Poverty

### 200- M/XDR TB families

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<th>Characteristic</th>
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Intensive case finding sites

• Health care facilities
  – Primary care clinics, ARV clinic

• Community sites
  – Household contact tracing
  – Community treatment sites
  – Congregate settings
    • Pension pay points, taxi ranks, markets
  – Door to Door screening

SHOW EXAMPLES
XDR TB Cases Averted 2007-2012
Available Combinations of Strategies


28% (365)
37% (482)
48% (625)
• **Staff cases**
  – Jan 2005-07 8 confirmed M/XDR TB staff deaths
  – 39 of 1300 (3%) expected cumulative cases by 2012
  – 75% can be prevented with use of N95 masks with enforcement and HIV VCT with redeployment of HIV positive staff

• **Involuntary confinement**
  – Increase in transmission of 3%

• **Community cases**
  – ARVs to eligible HIV+ would avert 24% of new cases
Decentralized Community based Care
Greytown TB Hospital
Community Based MDR TB/HIV Treatment
M/XDR TB in US

1993-2007

- 3,379 cases with MDR TB; 83 cases with XDR-TB
- Among those with known HIV results, 53% HIV-positive
- Mortality XDR-TB > MDR-TB > drug-susceptible TB cases
- Patients diagnosed and treated at KGV
- Patients diagnosed and not treated
- Patients seen and not diagnosed
- Patients not seen or diagnosed
King George V XDR-TB Known Outcomes
2000-2007, n=64 (42%)
Philanjalo
Tony Moll
Staff at Church of Scotland Hospital, Philanjalo

Nelson Mandela School of Medicine
AW Sturm
Prashini Moodley
Staff of the TB research laboratory
Umesh Lalloo

KZN Department of Health
Bruce Margot
Claudio Marra
Venanzia Vella
IALCH TB Laboratory

Yale School of Medicine
G Friedland
Jason Andrews, Sanjay Basu
Alison Galvani, Palav Barberia, Zahir Kanji, Tracey Thomas

J and J Scholars
Leo Calo, Tania Thomas, Scott Heysell
Sarah Apgar, Daimani Piggott, Tania Thomas

DDCF Student fellows
Palav Babaria, Michelle Scott (Harvard)
Krisda Chayacheti (Michigan)

ID Fellows
Sheela Shenoi

Albert Einstein College of Medicine
Neel Gandhi, Sarita Shah, James Brust

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Figure 1: Common and Alternative TB and HIV Program Paradigms

A Common TB and HIV Paradigm

National TB Program

TB Services
- Sputum collection
- DOT
- Treatment Support
- Contact Tracing
- LTBI Screening
- IPT

National HIV Program

HIV Services
- C&T
- Antiretrovirals
- OI Rx and Px
- Adherence Support
- Community Support
- HIV Prevention

An Alternative TB and HIV Paradigm

Collaboration of Programs

Communication

National TB Program

TB Services
- Sputum collection
- DOT
- Treatment Support
- Contact Tracing
- LTBI Screening
- IPT

Integration of Services

National HIV Program

HIV Services
- C&T
- Antiretrovirals
- OI Rx and Px
- Adherence Support
- Community Support
- HIV Prevention

TB = Tuberculosis  HIV = Human Immunodeficiency Virus  DOT = Directly Observed Therapy  LTBI = Latent Tuberculosis Infection  IPT = Isoniazid (INH) Preventive Therapy  C&T = Counseling and Testing  OI = Opportunistic Infection  Rx = Treatment  Px = Prophylaxis
Definitions

- **MDR-TB**: multiple drug resistant TB
  resistance to at least **isoniazid and rifampin**
  two most potent first line TB therapies

- **XDR-TB**: extensively drug resistant TB
  MDR+ resistance to **fluoroquinolones and injectables** (aminoglycosides and capreomycin)
  two most potent second line therapies
Fig 1. Resistance development in the KZN family of strains of *Mycobacterium tuberculosis* from 1994 till 2006

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Resistance found for the first time in:

- DOTS, Smear,+, standardized Rx
- DOTS+, no SLD testing, standardized Rx

(Pillay and Sturm, CID, Dec. 2007)
Definitions (cont)

• **Acquired resistance**
  – Resistance as a result of treatment failure
    • The predominant mechanism in past and many areas
    • A consequence of program and/or patient limitations

• **Primary resistance**
  – Resistance resulting from transmission of resistant organisms
    • The predominant mechanism in areas of high HIV prevalence
    • A consequence of increased susceptibility, rapid progression to disease and absence of infection control
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Treatment of HIV-related MDR-TB

• Consider initiating antiretroviral therapy as soon as possible once anti-TB regimen is documented to be tolerated
• More ARVs choices as no rifampin
• IRIS may occur and be severe-be prepared
• Practice airborne infection control
• Use therapeutic drug monitoring if malabsorption is suspected
Integrated MDR TB/HIV Community Treatment
Msinga sub District KZN

• Centralized referral treatment overwhelmed
  – Limited bed capacity at KGVH
  – Distance and transportation costs
  – High loss to follow-up rate

• Nosocomial spread of MDR/XDR TB

• No infrastructure established for follow-up

• Limited/no community hospital isolation facilities

• Community spread in our setting found to be < 2%
Injection teams

• MDR TB patient seen at home by visiting nurses
  – Injections 7 days/wk
  – Contact screening of family members
  – Side effect monitoring
  – Infection control at home (masks supplied for patient and carer)
  – Education of family members
  – Social support assessment
  – Family and patient prepared for continuation phase medication
  – VCT offered at home
Conclusions

• Drug resistant tuberculosis has emerged as a major global public health threat and clinical challenge.
  – Primary as well as acquired resistance
• Available drugs for M/XDR TB are variable in potency, toxic, expensive and limited in availability.
• Evidence based treatment lacking—but more drugs, longer treatment and supportive treatment program important
• M/XDR TB/HIV raise additional treatment challenges
• New drugs, regimens and comprehensive treatment programs needed
Comprehensive Response

• Prevention
  – Strengthen TB DOTS program to curb creation of drug resistance
  – Create & Implement comprehensive Infection control program to prevent transmission of drug-resistance

• Improved Diagnosis
  – Intensified case finding: active screening and surveillance
    – Reduce time to diagnosis: Rapid diagnostic assay

• Treatment
  – Faster initiation of second line drugs (decentralized treatment centre)
  – Improved Patient support
  – Community management of MDRTB
Eastern Cape officials said 49 patients with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) escaped last week from the Jose Pearson Hospital near Port Elizabeth.

Patients escaped from medical isolation through a hole cut in wire fencing around the hospital's perimeter.

–Apparently, they wanted to see their families for Christmas.

The state attorney's office issued notices to the patients' homes appealing for their return. "So far 20 have returned; we are expecting more to come back soon."

Forced confinement violates most medical ethics; however, officials say they have no choice but to put the good of public health above individual rights. XDR
KGV Durban (160 beds)
TYPICAL HOUSEHOLD
Reason for Community Management

- Centralized referral treatment overwhelmed
  - Limited bed capacity at KGVH
  - Poor records and communication
  - Distance and transportation costs
  - High loss to follow-up rate

- Nosocomial spread implicated in spread of MDR/XDR TB

- No infrastructure established for follow-up

- No community hospital isolation facilities

- Community spread in our setting found to be < 2%
Greytown TB Hospital
Current Decentralized Protocol

Patients identified

MDR TB to Greytown MDR TB Clinic
XDR TB to KGVH

Hospitalization at Greytown
(Length of stay Multifactorial, ~2w)

Directly initiated on outpatient basis

Discharged to the community
COSH patients followed by integrated MDR TB/HIV injection teams
**Community based treatment of MDR TB**

**DESIGN:**
- Non-randomized, open-label trial comparing a program for community-based co-treatment of HIV and MDR TB with standard centralized care.

**DURATION:**
- Subjects will be followed from enrollment until one year after completion of their treatment for MDR TB. The study is expected to accrue over 30 weeks and last a total of 3 years.

**SAMPLE SIZE and POPULATION:**
- This study will enroll 30 HIV-infected adults with a CD4 \( \leq \) 200 cells/mm\(^3\) or WHO stage 3 / 4 disease presenting to CoSH with a new diagnosis of MDR TB.

**INTERVENTION:**
- Study subjects will receive home-based, directly observed therapy for both MDR TB and HIV by community health workers and assisted by family members. Adherence, cure rates, hospitalizations and survival will be measured and compared with those who receive usual centralized care.
Preparation

- DOH buy in
- Staff training
- Patient literacy
- Household infection control
- Injection teams created.
- Screening tools for adverse events created.
- Response system for adverse events instituted.
- Initiation of weekly district MDR TB clinic to provide monthly outpatient clinical follow-up.
Injection teams

- MDR TB patient seen at home by visiting nurses
  - Injections 7 days/wk
  - Contact screening of family members
  - Side effect monitoring
  - Infection control at home (masks supplied for patient and carer)
  - Education of family members
  - Social support assessment (identification of OVC)
  - Family and patient prepared for continuation phase medication
  - VCT offered at home
Community Based MDR TB/HIV Treatment