HIV and Drug-Resistant TB

What do we know?
What do we need to know and do?

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HIV & Drug-Resistant TB Epidemic

- Rise of Drug-resistant TB cases in Africa confirms convergence of HIV & drug-resistant TB epidemics
- MDR TB caseload in Botswana has risen consecutively over past decade
- Explosive MDR and XDR TB epidemics seen in South Africa over past 5 years
  - MDR TB prevalence now exceeds 25 cases per 100,000 population in certain areas

Convergence of HIV & MDR/XDR TB

- Why is the convergence of these epidemics concerning?
  - Usual public health implications: drug-resistant TB is more costly, complex & difficult to treat
  - Two factors especially worse with HIV co-infection:
    - Worse outcomes: dramatically greater mortality
    - Potential for explosive spread due to primary transmission

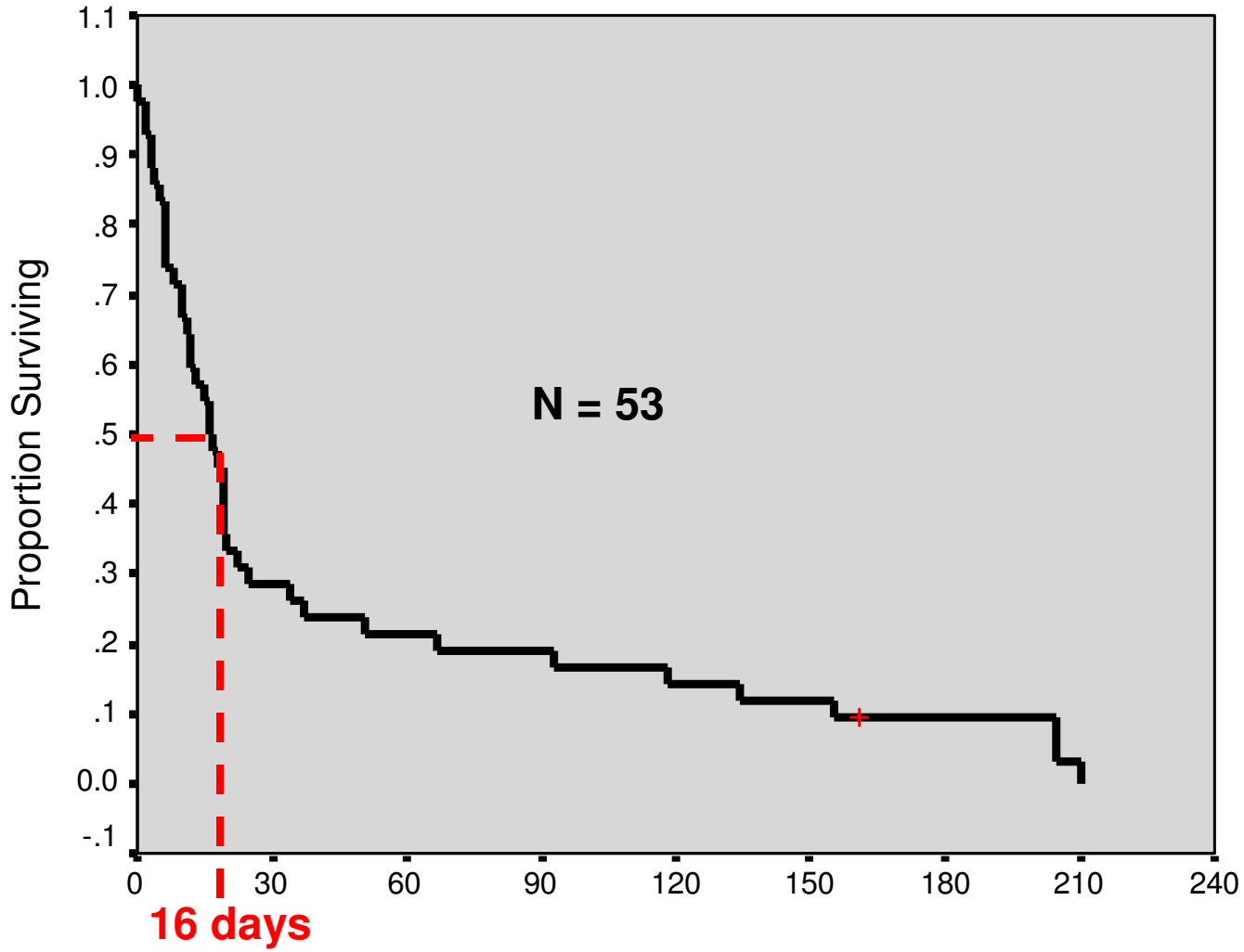
Rise of MDR TB in 1990s

- Numerous outbreaks in congregate settings
- Primarily among HIV co-infected patients
- Characterized by high and rapid mortality

	HIV co-infection	Mortality	Survival (median)
Florida	**93%**	**72%**	**7 weeks**
New York	**95%**	**77%**	**4 weeks**
Argentina	**98%**	**79%**	**4 weeks**
New York	**91%**	**83%**	**4 weeks**
New York	**100%**	**89%**	**16 weeks**
Italy	**98%**	**95%**	**6-8 weeks**
Spain	**100%**	**98%**	**7 weeks**

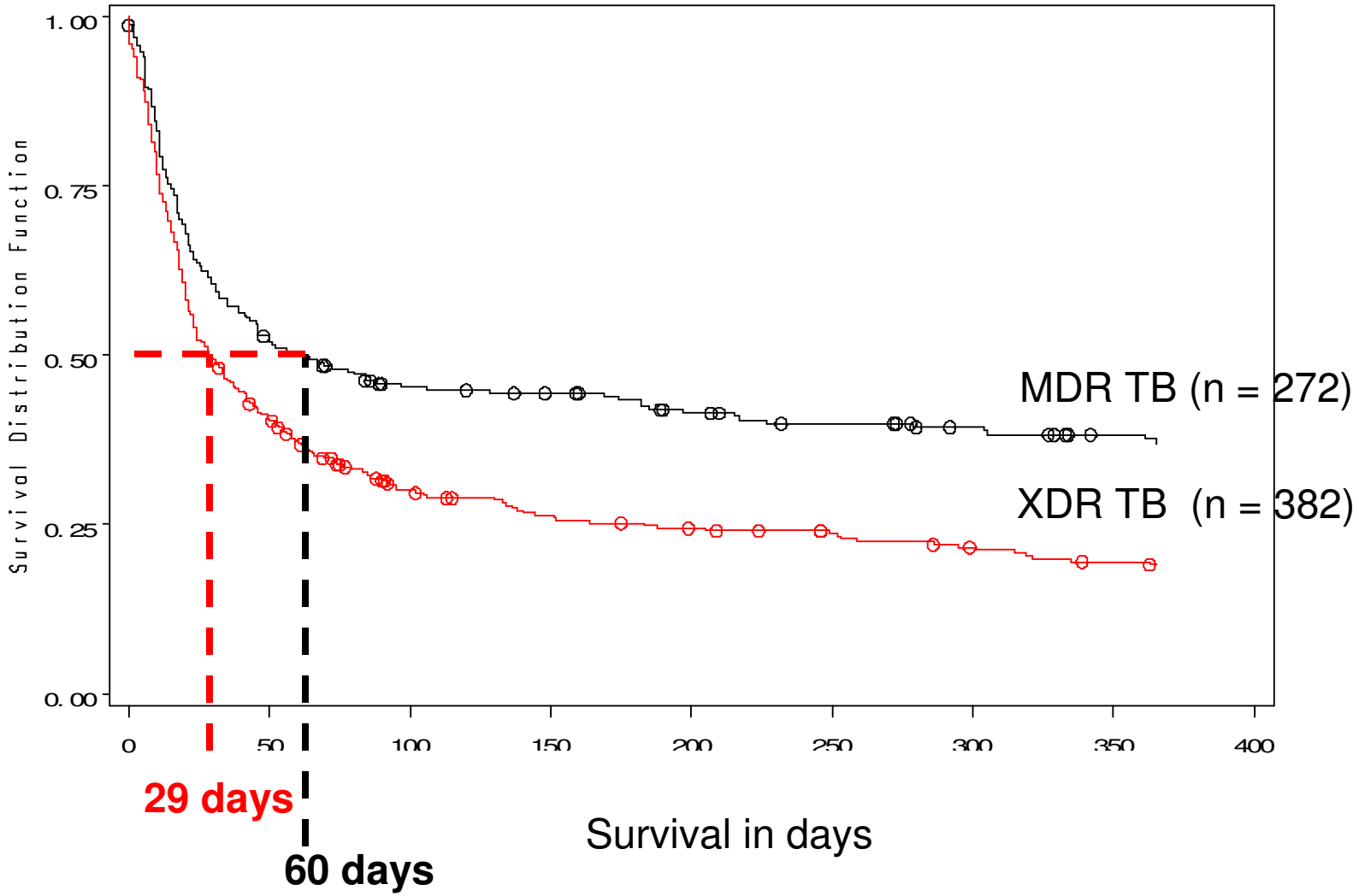
Wells C et al. CID 2007;196:S86-107

Mortality in HIV-Associated XDR TB



Gandhi NR et al. Lancet 2006

HIV-Associated MDR & XDR TB in S Africa



Mortality in HIV & MDR/XDR TB

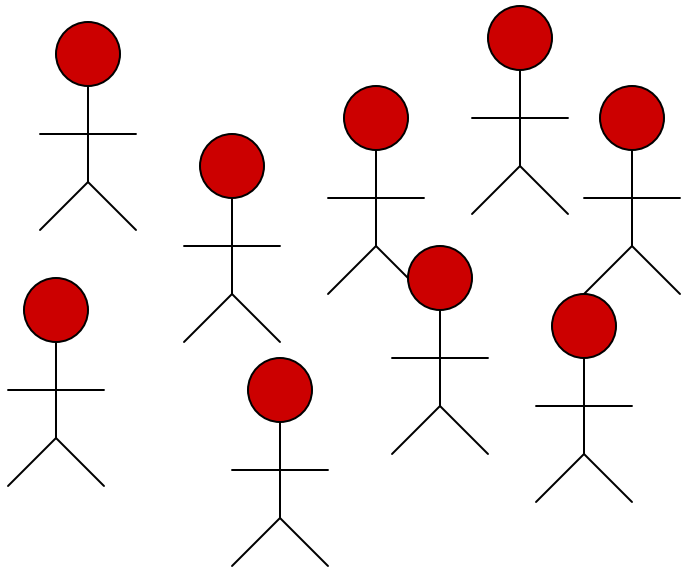
- Successful treatment outcomes possible in low and middle income countries in absence of HIV
- With HIV co-infection, however, drug-resistant TB takes on a different and more aggressive course
  - Nearly two decades of experience demonstrating rapid and high mortality
  - Majority die within 6-8 weeks, before diagnosis can be made by conventional culture and DST
    - Thus, majority die before treatment with second-line TB drugs can be initiated

Predictors of Mortality: HIV & MDR/XDR TB

	Adjusted Hazard Ratio	**p**
CD4 Count: <50 cells/mm3	**5.1**	**0.002**
51-200 cells/mm3	**4.0**	**0.006**
>200 cells/mm3	ref	ref
ARVs before MDR/XDR TB diagnosis	**0.4**	**0.027**
Extrapulmonary TB	1.5	0.27
Admission within last year	1.4	0.30
Smear Positive	2.1	0.04

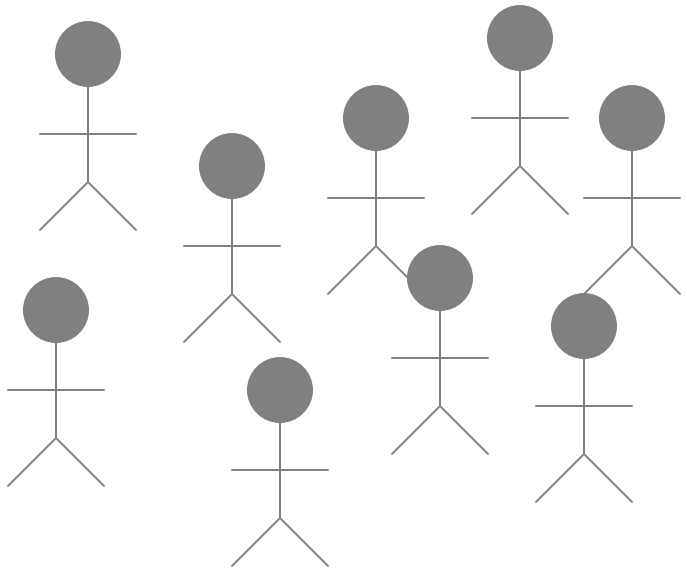
How do HIV-infected patients develop MDR/XDR TB?

Acquired Resistance

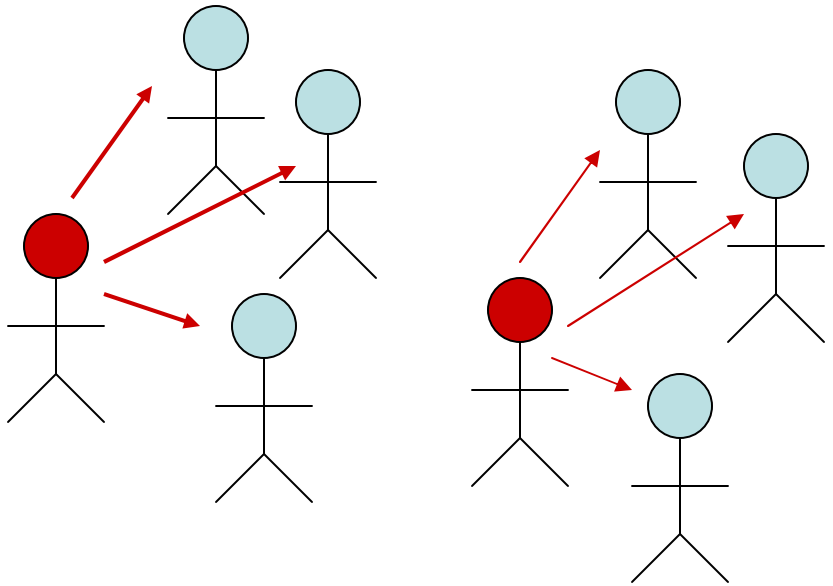


Acquired resistance:
Patient develops resistance due to incomplete or <u>inappropriate treatment</u>

Primary Resistance

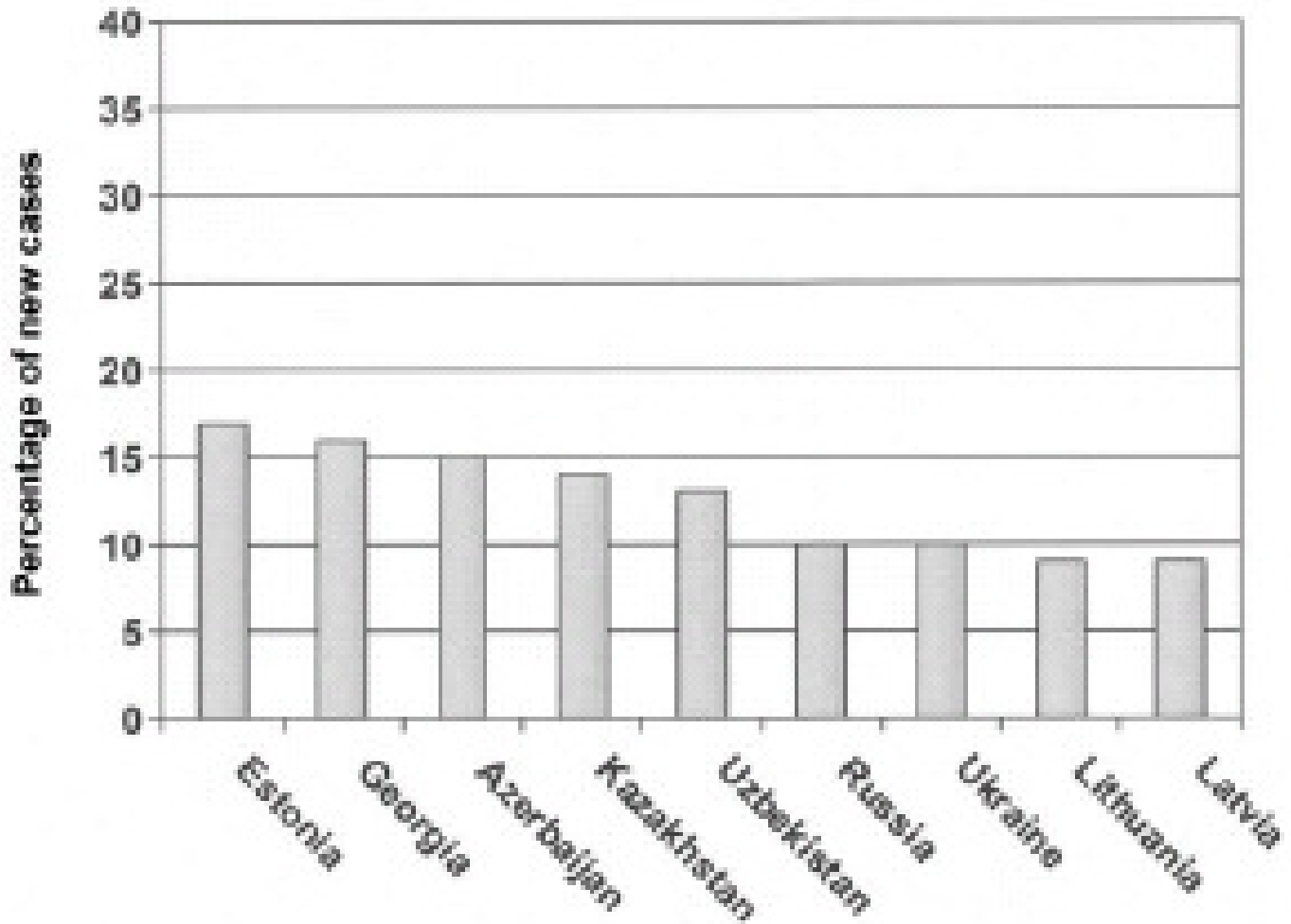


Acquired resistance:
Patient develops resistance to drugs due to incomplete or inappropriate treatment



Primary Resistance:
Patient develops resistance due to transmission of drug-resistant strain

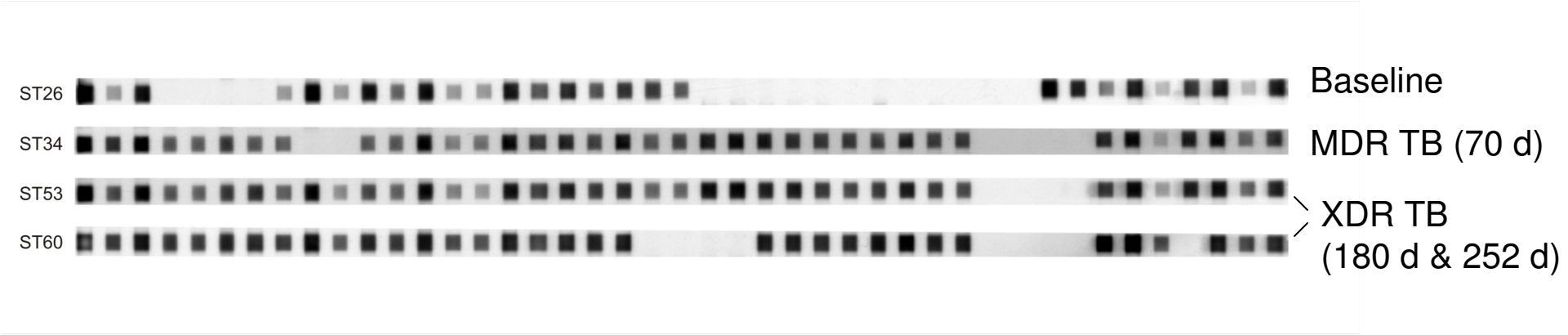
MDR/XDR TB among New TB Cases



Wells C et al. CID 2007;196:S86-107

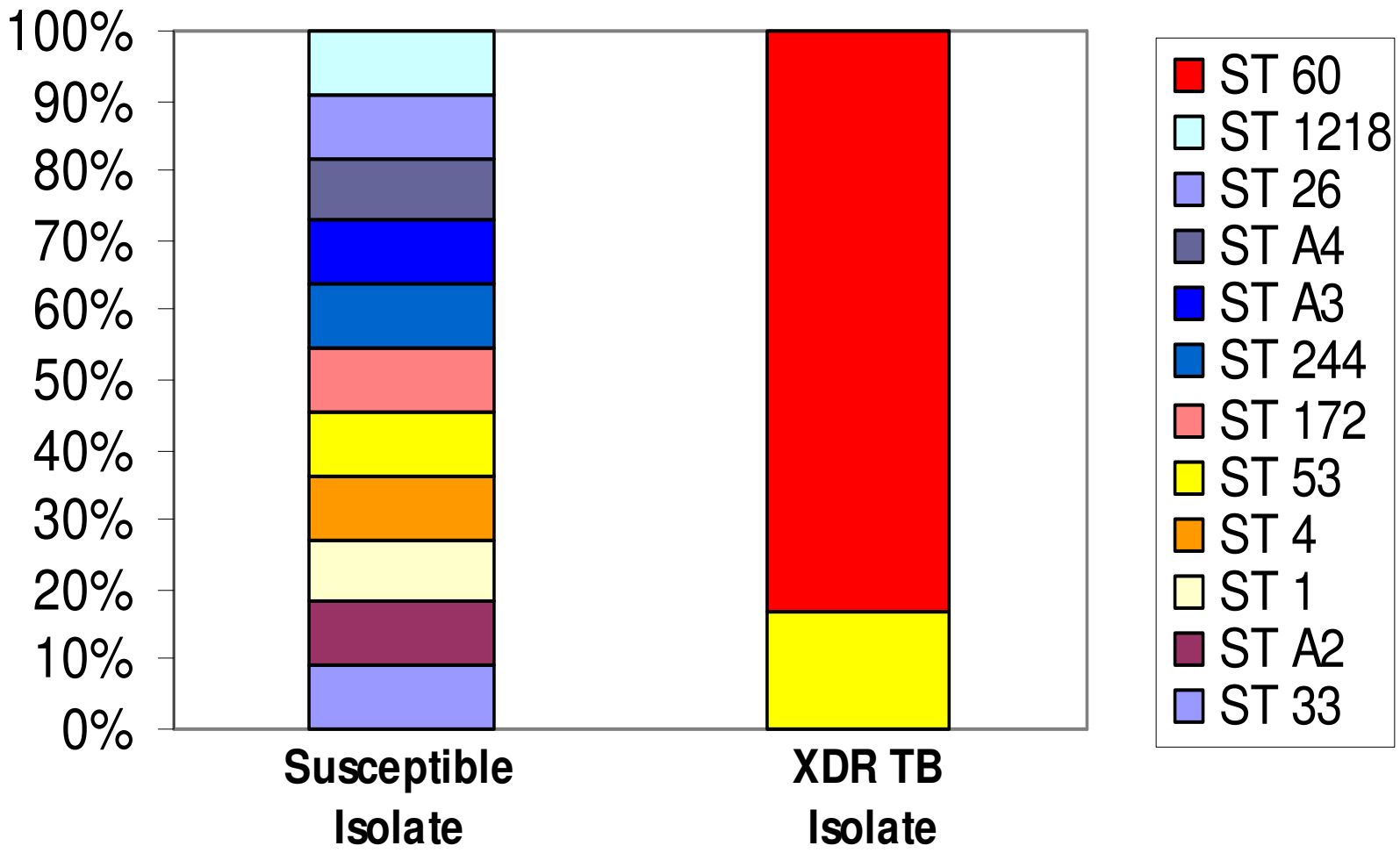
Four TB Strains in Single Patient

Susceptible TB → MDR TB → XDR TB



Andrews J. et al. JID 2008

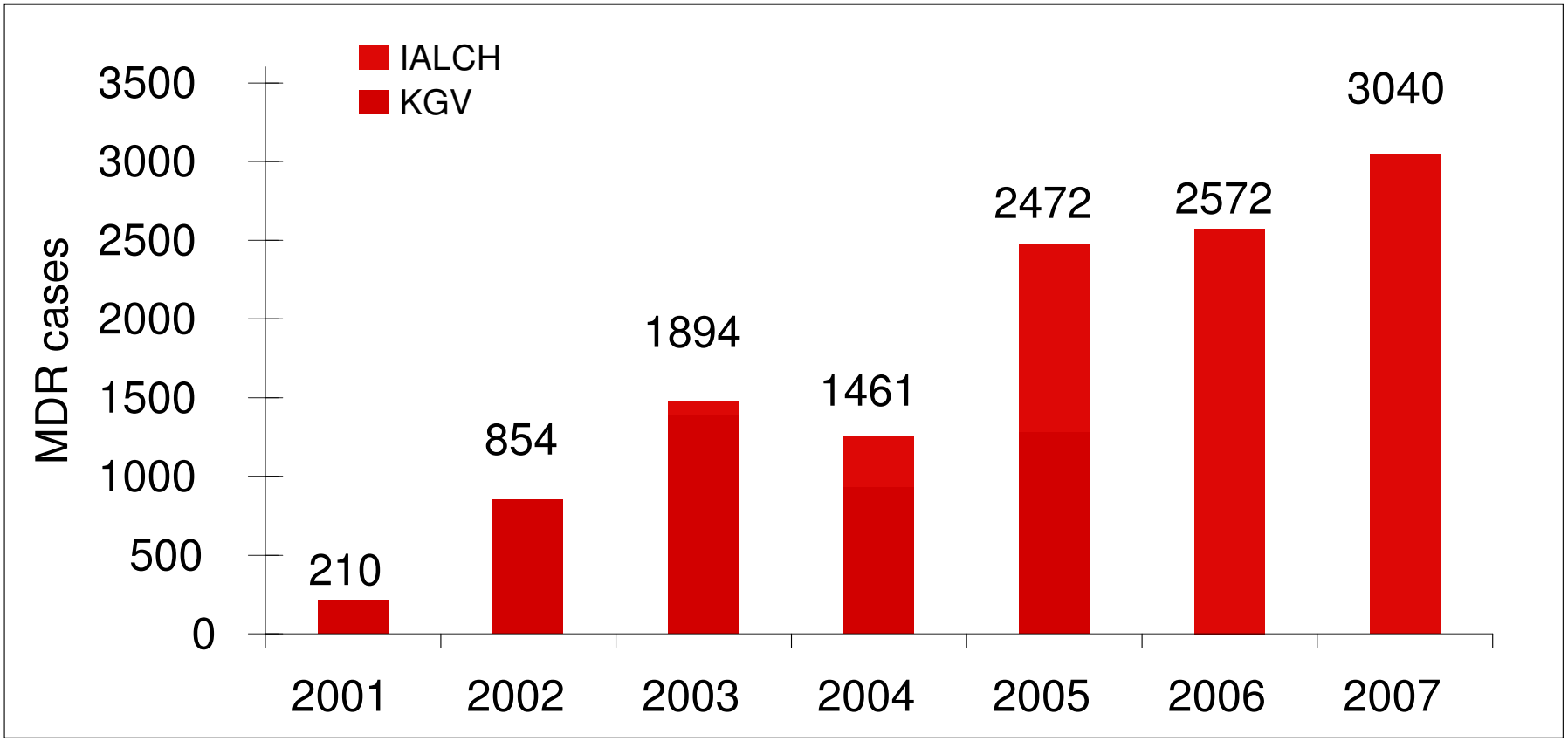
Genotypes of Patients with XDR TB Relapse



Andrews J. et al. JID 2008

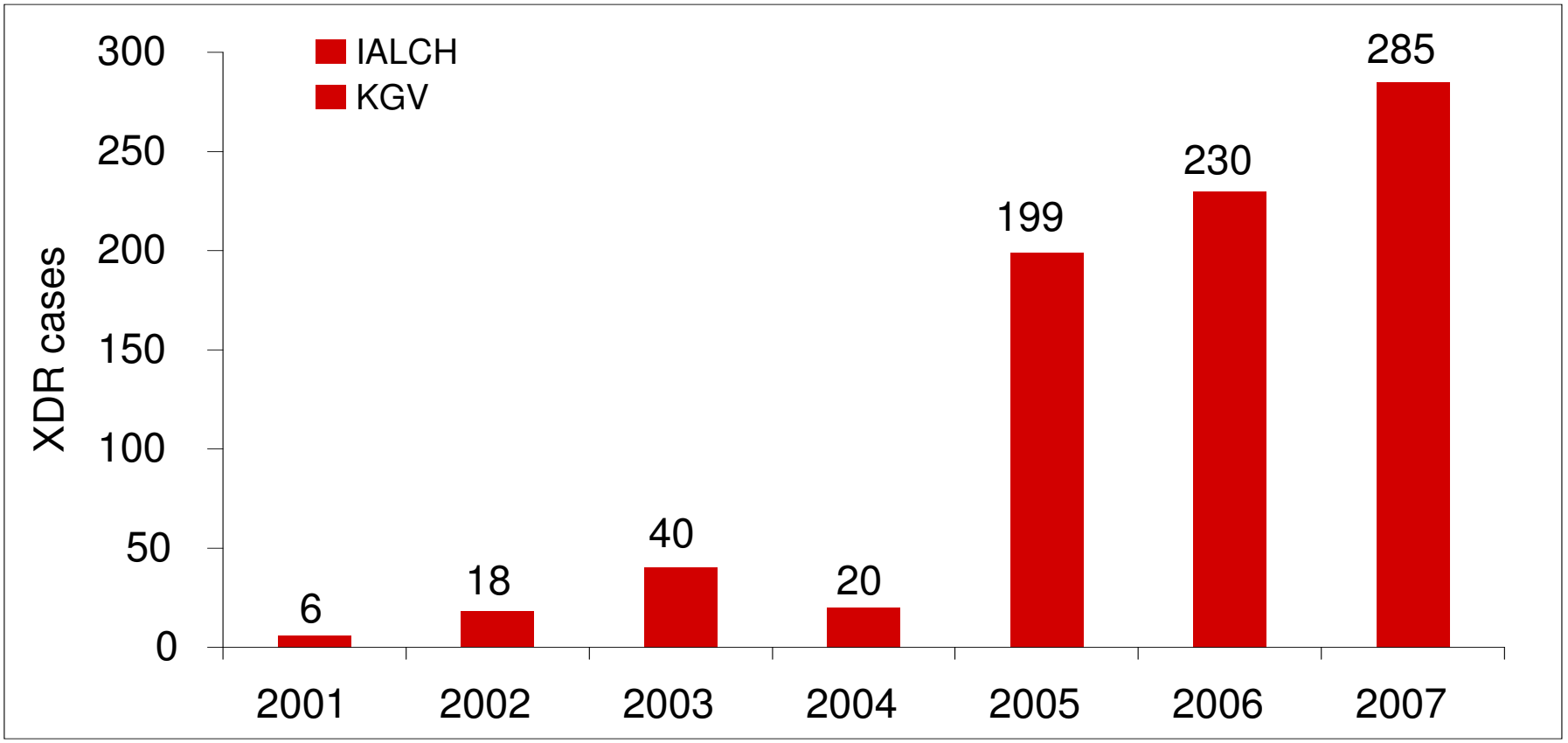
Transmission of MDR & XDR TB

MDR TB cases in KwaZulu-Natal



SSS Buthelezi. XDR TB Task Force 2008

XDR TB cases in KwaZulu-Natal



Why is Primary Transmission Occurring?

- Long delays in diagnosis of drug-resistant TB
  - Average time to diagnosis is 6-12 weeks by conventional TB culture and susceptibility testing
- Inadequate treatment options
  - Patients with MDR and XDR TB remain infectious longer
- Lack of Infection control facilities
  - Congregate wards without any isolation possible

What do we need to do?

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
- Diagnosis
  - Develop and implement rapid diagnostic assays to reduce time to diagnosis from 6-8 weeks to 1-3 days
  - Use intensified case finding to find patients at earlier stages of disease

Comprehensive Response cont'd

- Treatment
  - Decentralize to reduce referral delay, increase capacity and improve treatment completion rates
  - Use SLDs empirically in HIV-infected patients suspected of MDR or XDR TB
  - Integrate antiretroviral therapy into MDR/XDR TB treatment programs to facilitate early and widespread use

What are the gaps in knowledge?

Research Priorities: Early Mortality

- **Develop and test rapid drug-resistance assays**
  - Must perform well in pauci-bacillary TB and HIV
  - Must be useful in peripheral healthcare settings
    - Ideally, point of care
  - Must provide initial results in 1-2 days
- **Examine the effectiveness and safety of integrated antiretroviral and SLD TB therapy**
  - Impact on mortality
  - Timing of ARV initiation
  - Drug-drug interactions
  - Overlapping toxicities
  - Incidence of IRIS in MDR or XDR TB

Research Priorities: Transmission

- Transmission studies
  - Identify locations of transmission
    - Healthcare settings: both inpatient & outpatient
    - Community transmission
  - Test interventions to interrupt transmission in both healthcare and community settings
- Treatment of contacts exposed to MDR or XDR TB to prevent progression to active disease

Research Priorities: Epidemiology

- Systematic TB drug-resistance surveys in high HIV prevalence settings
  - Actual burden of disease still unknown due to lack of lab capacity

Summary

- Convergence of HIV and Drug-Resistant TB epidemics has highlighted inadequacies in TB control
  - Mortality rates with MDR & XDR TB significantly higher and more rapid than in absence of HIV
  - Emphasize need for better, more rapid diagnostics
  - Use of empiric second-line TB treatment and integration of antiretroviral therapy necessary
- Large pool of vulnerable HIV-infected patients leads to rapid propagation of MDR & XDR TB strains
  - Further studies of transmission dynamics and interruption needed

Implications

- Rise of HIV epidemic in Eastern Europe and MDR/XDR TB epidemics in Africa suggest that we are just at the beginning of this catastrophic convergence
- Significant efforts are needed to understand the implications of these dual diseases and to develop the tools to address them effectively

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