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# DRUG-RESISTANT TUBERCULOSIS IN RUSSIA

## DEFINING THE PROBLEM

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SALMAAN KESHAVJEE, MD, PHD

HARVARD MEDICAL SCHOOL  
BRIGHAM AND WOMEN'S HOSPITAL  
PARTNERS IN HEALTH



GLOBAL HEALTH INITIATIVE  
WOODROW WILSON INTERNATIONAL CENTER FOR SCHOLARS

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# Tuberculosis Facts

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- Caused by *Mycobacterium tuberculosis*
- One third of the world's population infected
- Kills approximately 1.8 million people each year
- Poor and/or immuno-compromised at considerable risk of disease
- TB is acquired when a person with *active untreated* TB spreads the bacteria through coughing or sneezing.
- Infection usually occurs in individuals who have **close, prolonged exposure** to someone with the disease.
- Most people who are *infected* with TB do not get TB *disease*.
- **Increasing number of resistant strains**
- **~400,000 cases of MDR-TB each year**

# Treating tuberculosis: a crash course

## First-line

- ~~INH~~ (H)
- ~~RIF~~ (R)
- EMB (E)
- PZA (Z)

## Second-line

### Injectable

- SM
- KM
- AMK
- CM

### Fluoroquinolone

- OFLOX
- LEVO
- MOXI

### Other 2<sup>nd</sup>-line

- ETH
- CS
- PAS

## Third-line

### Other agents

- AMX/CLV
- Clofazamine
- Clarithromycin

## Multi-drug Resistant TB (MDR-TB):

- Resistant to at least the most effective first-line drugs: isoniazid (INH) and rifampin (RIF)
- Requires 18 to 24 months of treatment with second- and third-line medications given under direct observation and with assistance and aggressive management of side effects



# MDR-TB IN THE WORLD



0 2000 4000 Kilometers

Data Source: WHO/IUATLD Global Project

Map Production:

Public Health Mapping Group

Communicable Diseases

World Health Organization

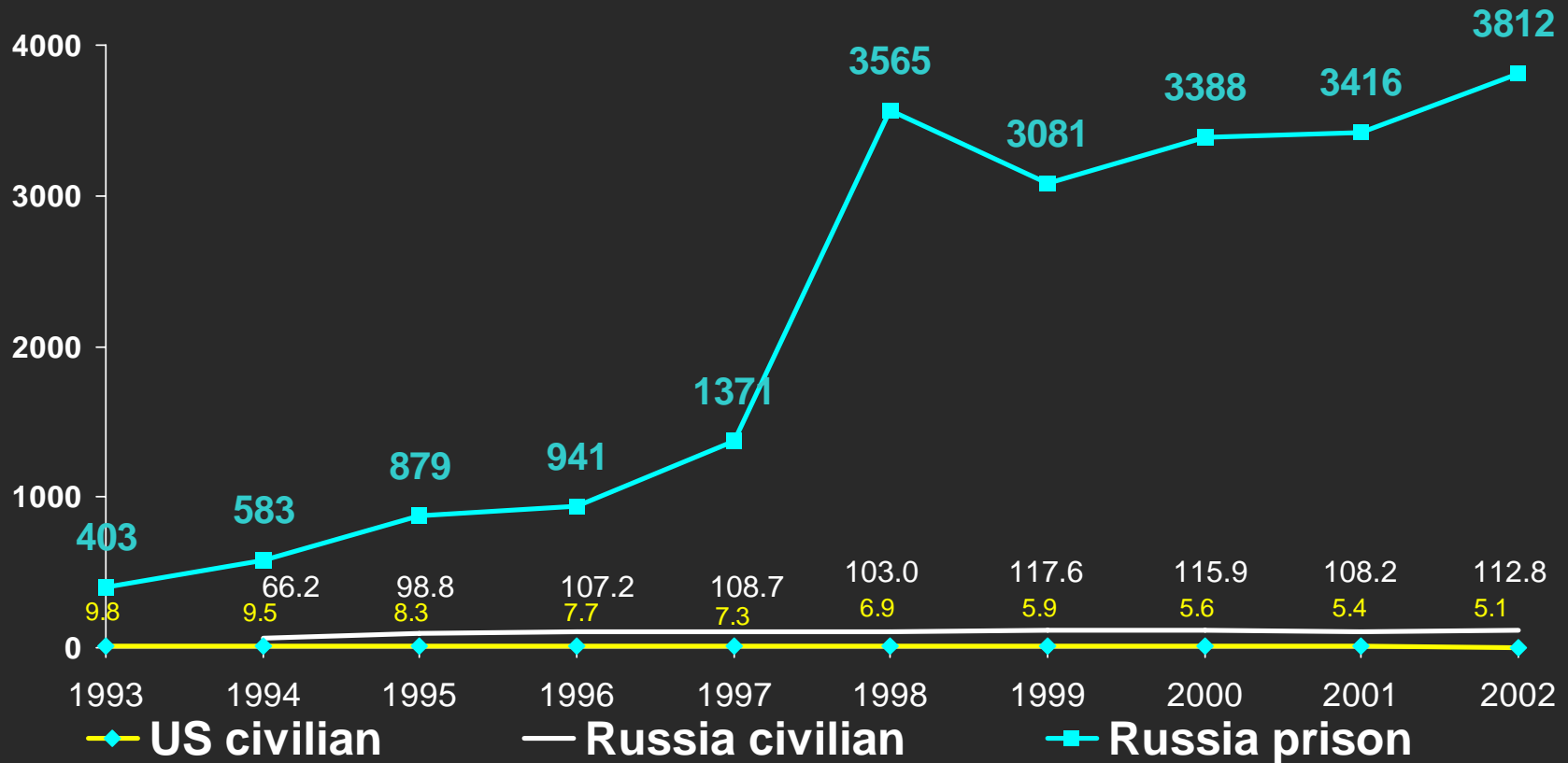
© World Health Organization, October 2003



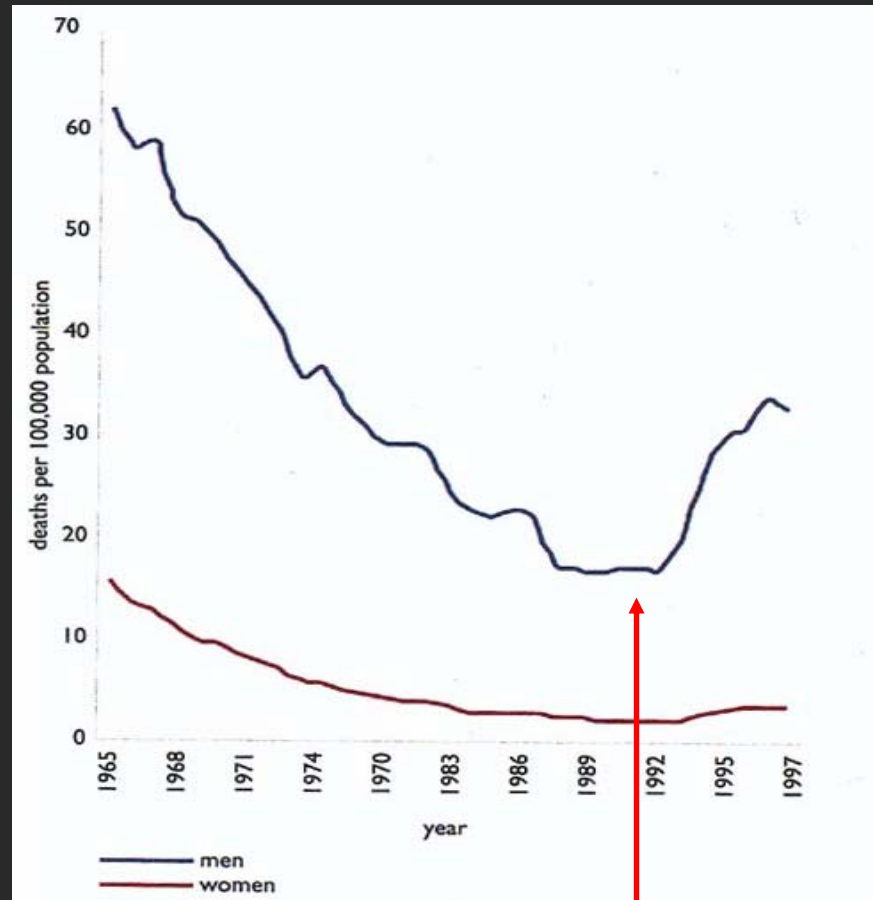
The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delineation of its frontiers or boundaries.



# TB Case Notification (Incidence) per 100,000 1993-2002



# Age-Standardized Mortality Rates from TB in Russia, 1965-1997



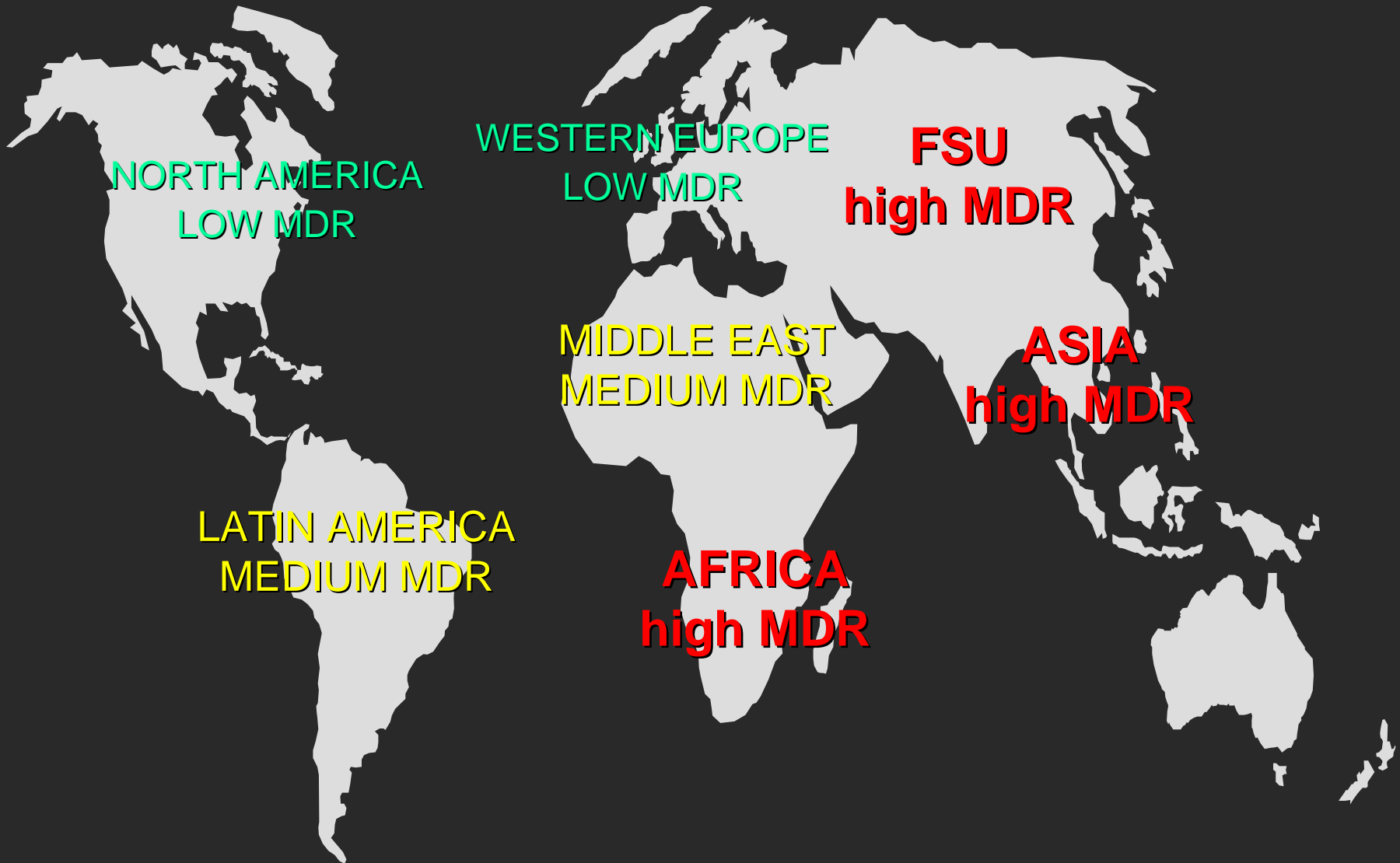
Collapse of FSU

Source: INED/CHDE



# Burden of MDR-TB in World Regions

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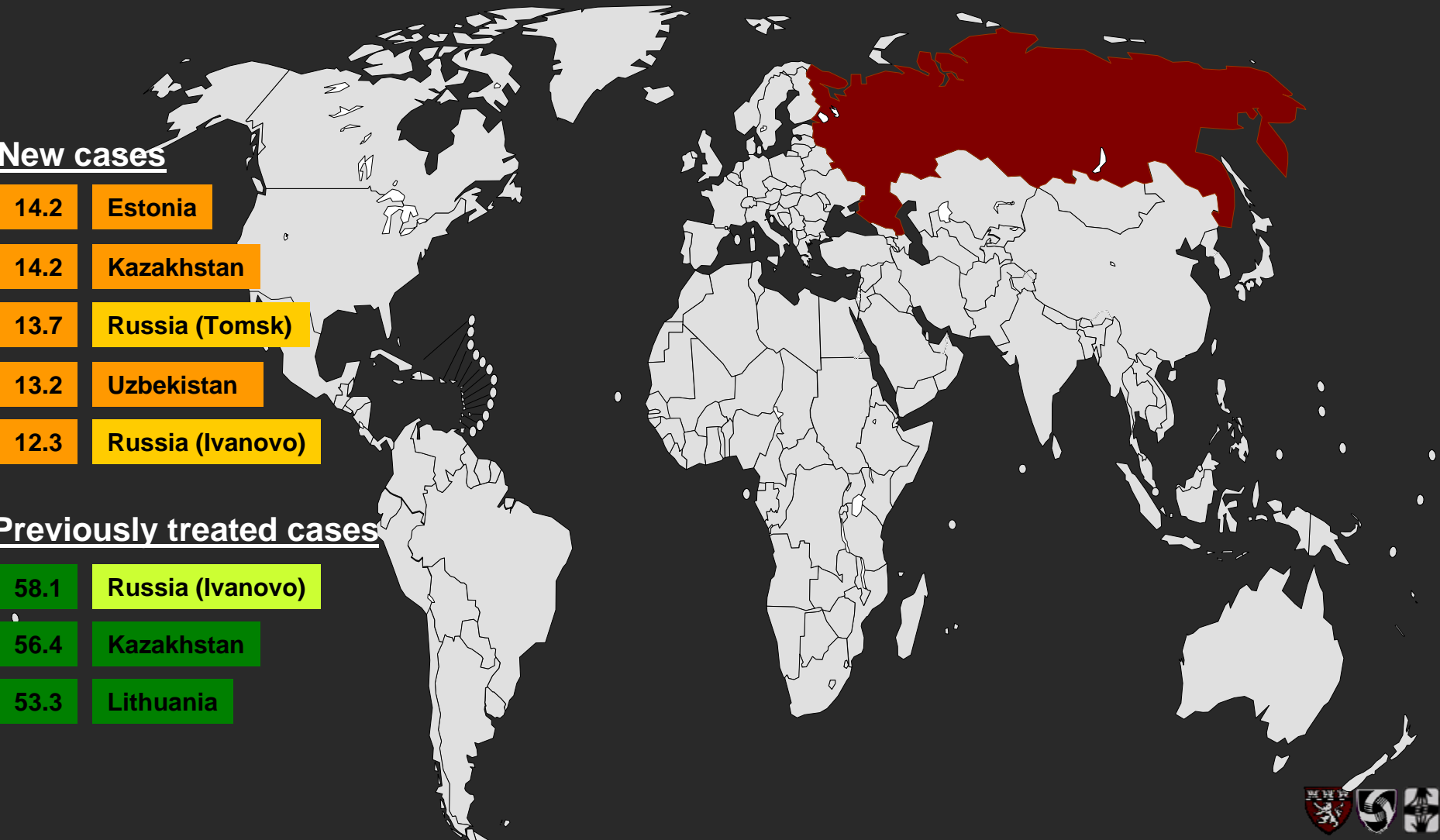


# Eastern Europe and Central Asia

## Highest proportion of MDR-TB (of all TB cases)

> 10% among new cases

> 50% among previously treated cases



### New cases

14.2	Estonia
14.2	Kazakhstan
13.7	Russia (Tomsk)
13.2	Uzbekistan
12.3	Russia (Ivanovo)

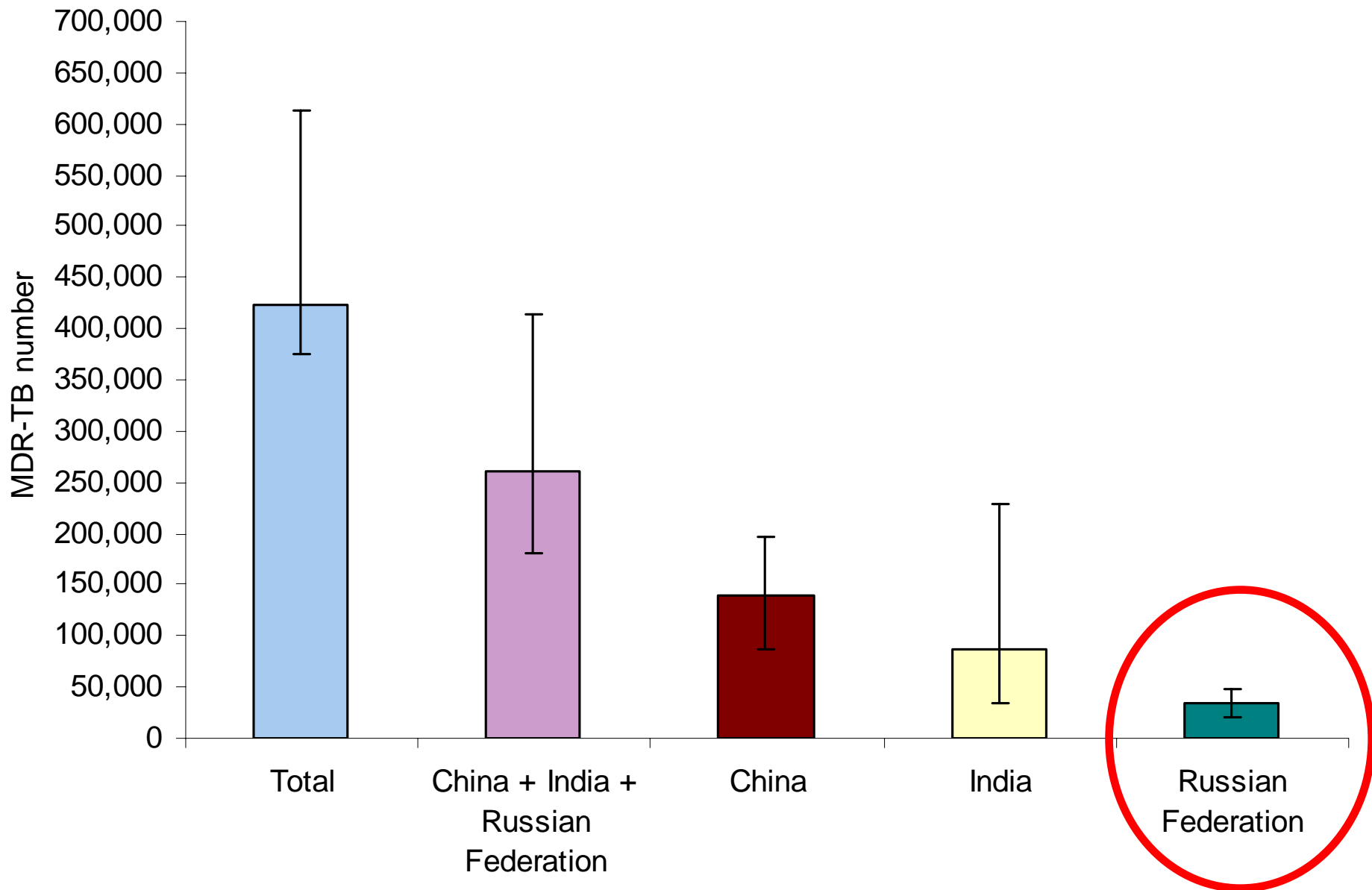
### Previously treated cases

58.1	Russia (Ivanovo)
56.4	Kazakhstan
53.3	Lithuania



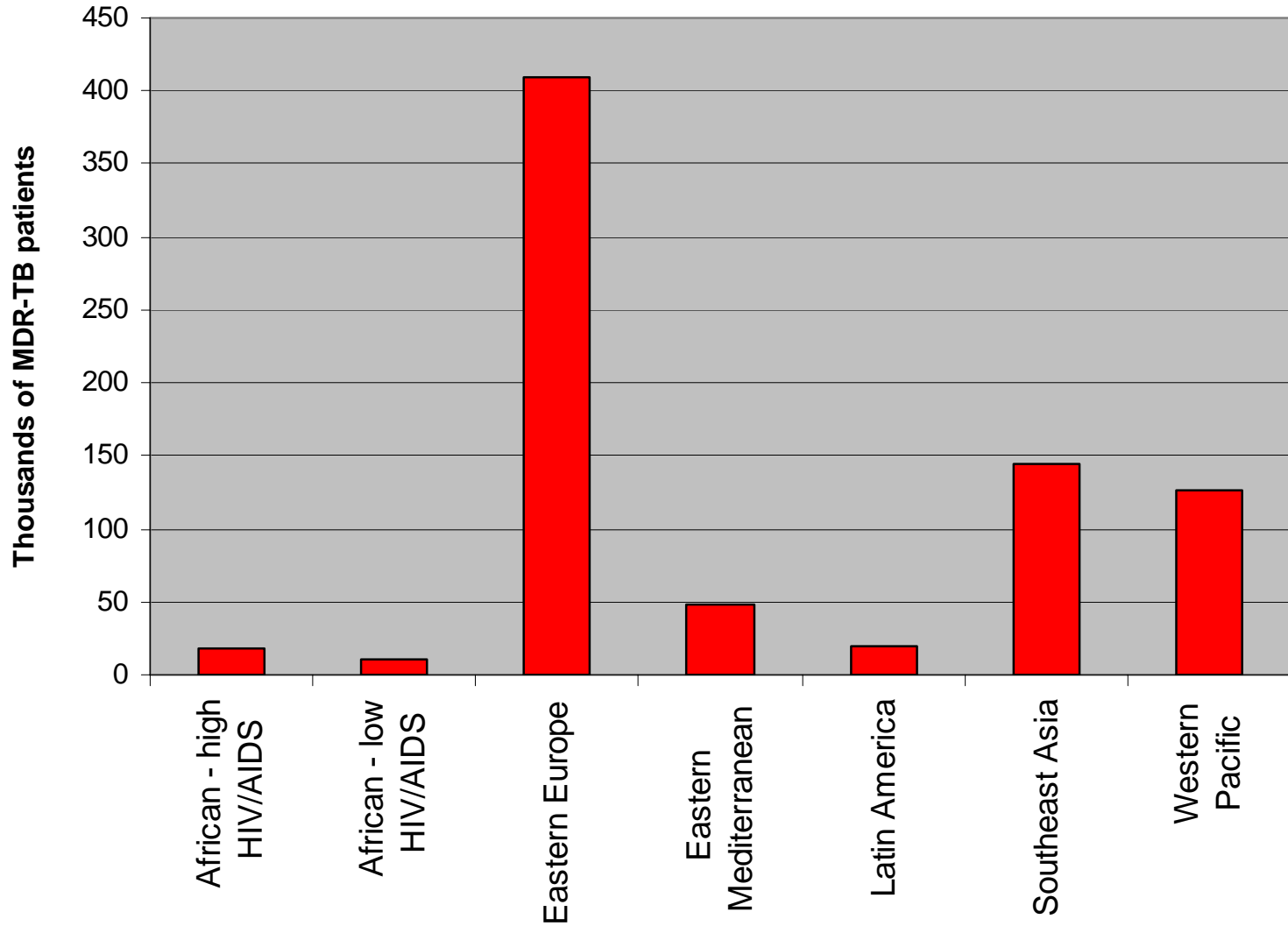


# 62% of new MDR-TB cases expected in 3 countries



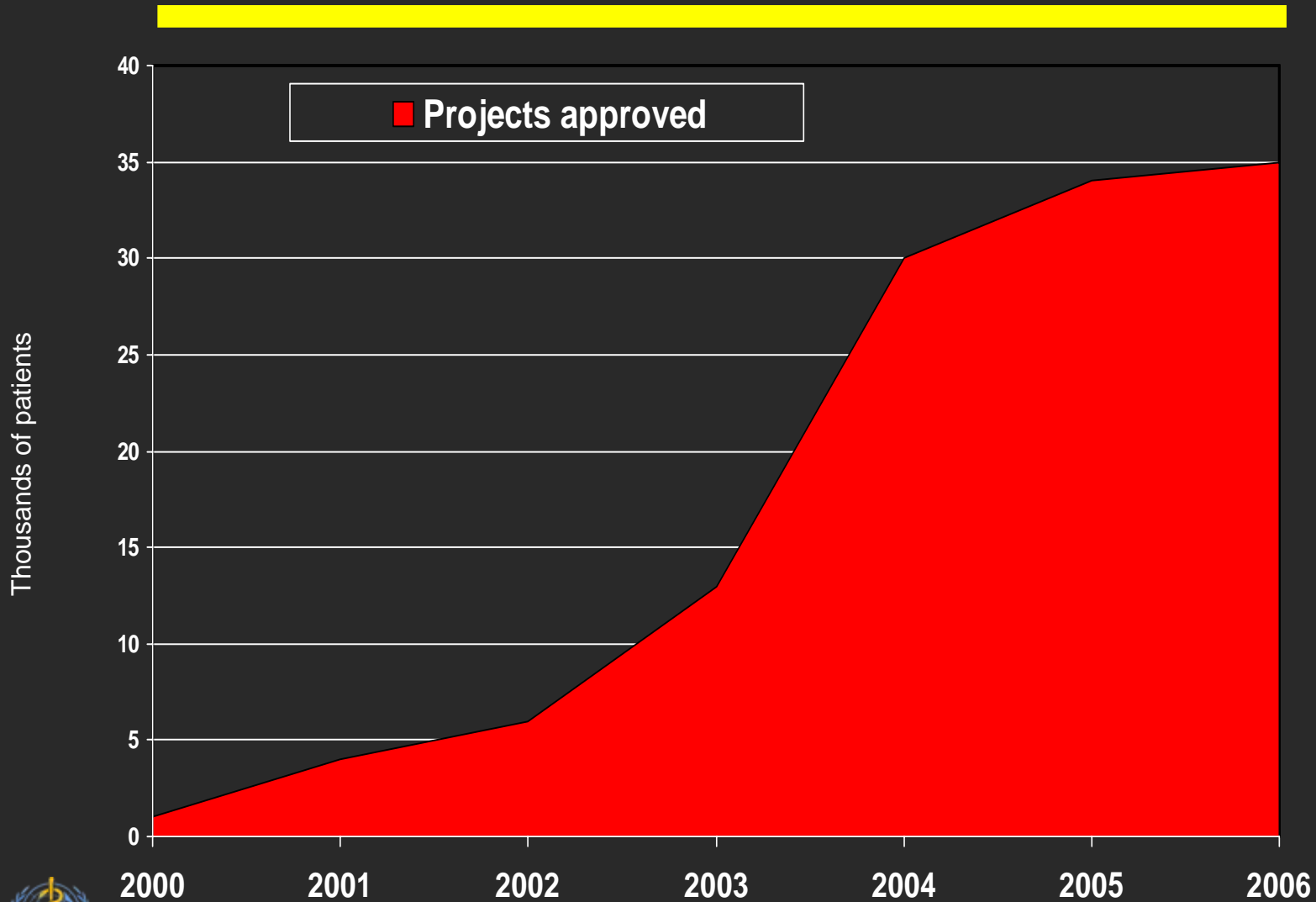


# MDR-TB cases to be treated by Region



# SCALING UP OF MDR-TB TREATMENT GLOBALLY

> 400,000 new MDR-TB cases each year



Source: Green Light Committee/WHO Geneva



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TOMSK OBLAST  
RUSSIAN FEDERATION

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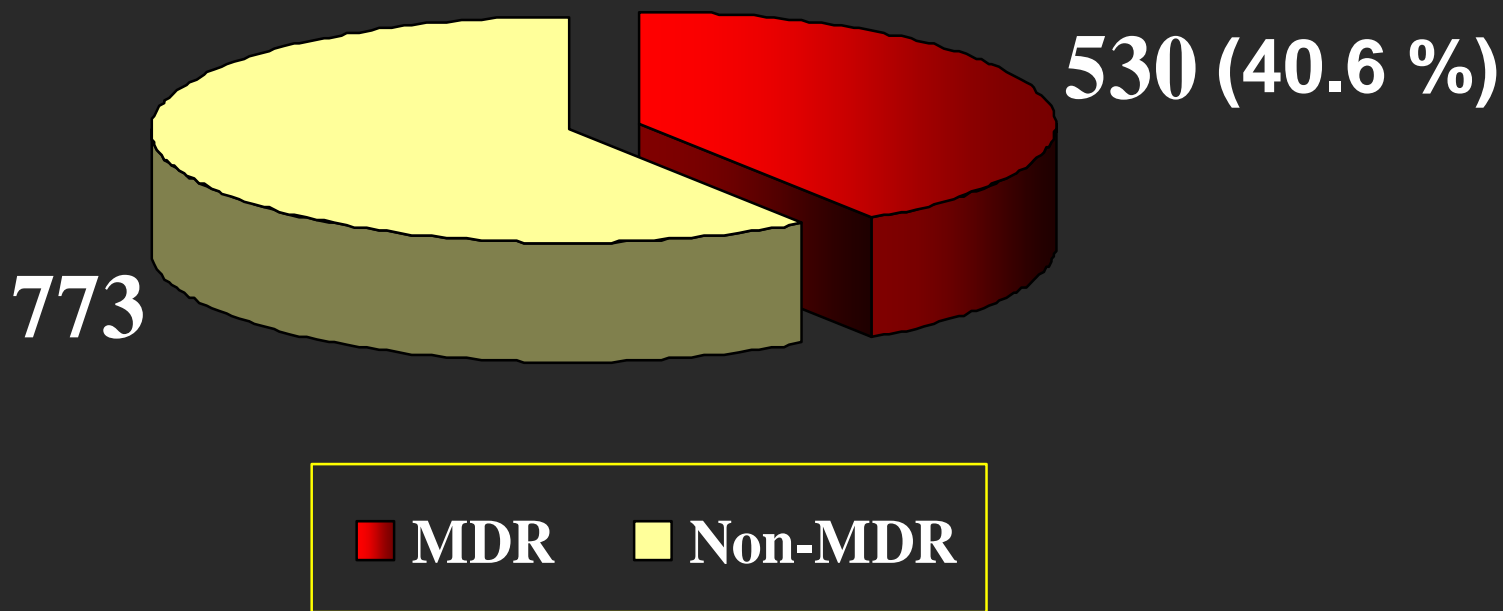
**Saint-Petersburg**

**Moscow**

**Toms Oblast**  
**Population: 1,073,600**

MDR-TB prevalence among all smear-positive new and re-treatment cases  
2001, Tomsk Oblast (n=1303)

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# Factors associated with MDR-TB in Tomsk

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## Treatment Program

- Inadequate drug regimens for re-treatment
- Unsupervised therapy (no DOT)
- Unreliable drug supply
- Limited political will
- Poor management systems

## Transmission

- Excessive incarceration
- High prevalence of drug resistance
- Rising HIV

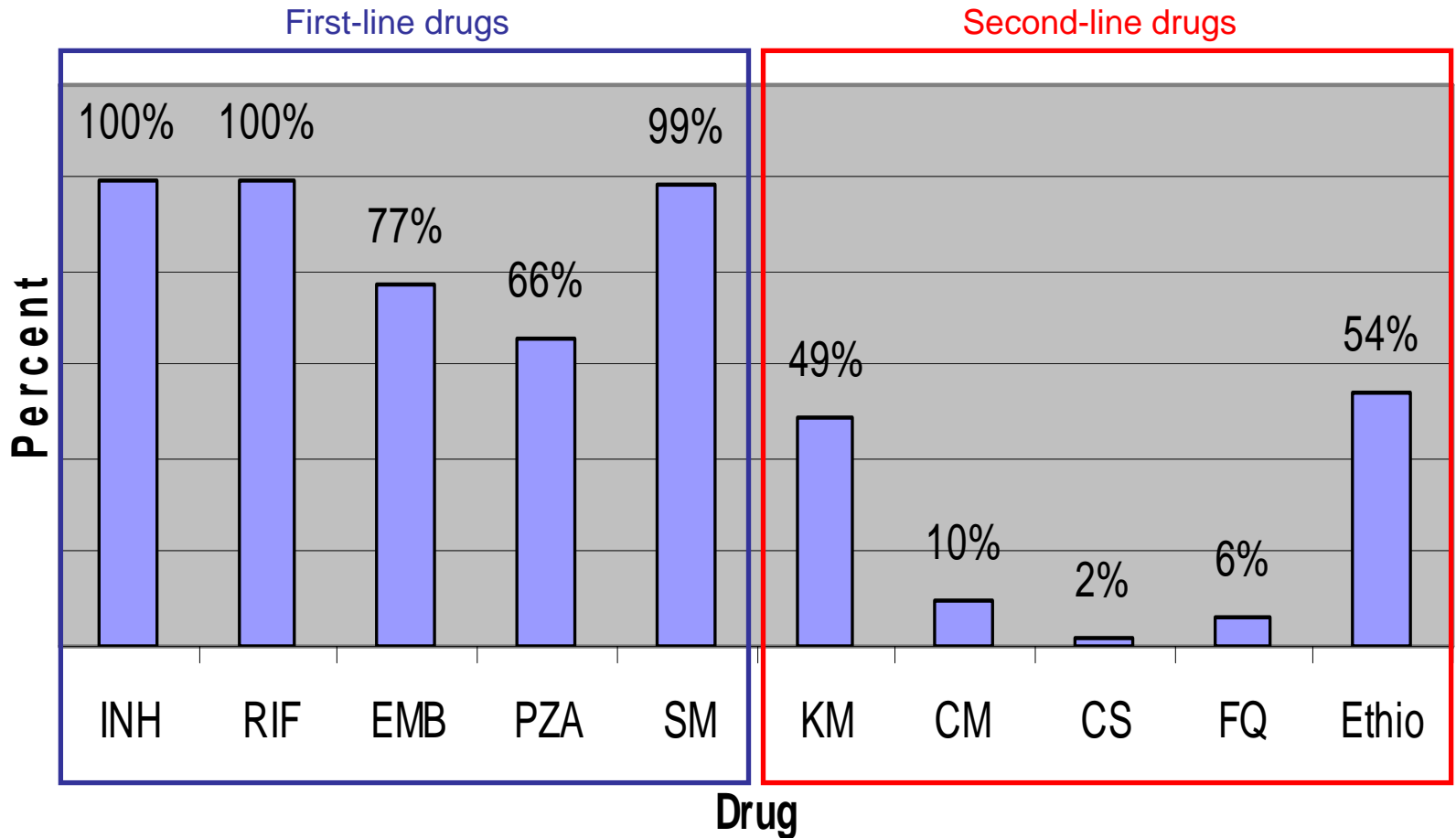
## Social/structural context of the post-Soviet period:

- poverty and unemployment
- breakdown in state structure
- Substance abuse
- breakdown in family structure
- anomie





# Resistance patterns of Tomsk Cohort (244)



Source: Tomsk Oblast Tuberculosis Services, Tomsk, Russian Federation, 2005.

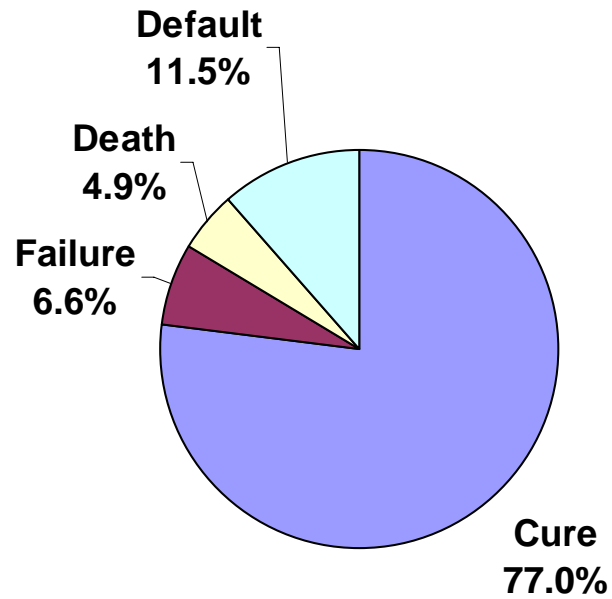






# TREATMENT OUTCOMES (N=244)

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# PROGRAM CHALLENGES

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- Alcoholism
- Drug abuse
- Poverty
- Adverse events
- Long duration of treatment
- Distance from treatment sites





## STRATEGIES (1)

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- Creating an administrative structure to treat MDR-TB that builds on the current health system, and integrates both the civilian and penal sectors
- Ensuring a reliable drug supply
- Training physicians, nurses, and community health workers in both rural and urban areas
- Improving facilities
- Providing transportation assistance for patients and health workers



## STRATEGIES (2)

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- Food assistance for patients
- Choice of treatment site
- Improved side effect management
- Improvement of working hours at medical facilities to make it more convenient for patients
- Treatment at home for patients who are unable to ambulate or who live too far
- Volunteers (e.g. neighbors) for observation of therapy
- Rapid search for non-adherent patients and defaulters
- Social support for patients





## Next Cohort (N=386)

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- Cure rate lower in the civilian sector but not in the prison sector
- Findings:
  - Worse adherence
  - Increased substance abuse
  - More difficult cases being addressed now
  - Longer delays to treatment
  - Increasing resistance due to exposure to 2<sup>nd</sup> line drugs



# Overcoming socio-economic factors: “Sputnik Initiative” for non-adherent patients

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- Started in December 2006
- Non-adherent patients selected by clinical committee
- Patient-oriented approach
  - Place and time preferred by patient
  - Attempts to help in health and social problems
  - Few patients per nurse
- Daily supervision
- Administrative support



## Sputnik Initiative results: first 3 months

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- Success in 13 of 16 patients (81%):
  - 1 patient refused treatment
  - 1 patient transferred to observation
  - 1 patient defaulted
  - 3 out of 5 (60%) patients who initially were registered as defaulters, continued treatment with 100% adherence rate
  - **Adherence increased from 42% to 83%**



# MAIN LESSONS LEARNED FROM TOMSK

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1. Ambulatory care can play a crucial role in successful TB control
2. There are socio-economic barriers to successful treatment that can be overcome





## XDR-TB: CAUSE FOR CONCERN?

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Emergence of XDR-TB

WHO concern over extensive drug resistant TB strain

5 SEPTEMBER 2006 | GENEVA -- The World Health Organization has announced the emergence of virulent drug-resistant strains of tuberculosis, which it has strengthened and implemented to prevent the global spread of the disease. Research showing the extent of XDR-TB, a newly identified TB strain that is virtually untreatable using current drugs (and especially dangerous for many people living with HIV) has prompted WHO to take these steps.

Later this week, WHO will join other TB experts at a two-day meeting in South Africa (7-8 September) to assess the extent of XDR-TB and to discuss ways to prevent its spread. The meeting is being held in Durban, South Africa, at the invitation of the South African government.



# XDR-TB

## First-line

• ~~INH~~ (H)

• ~~RIF~~ (R)

• ~~EMB~~ (E)

• ~~PZA~~ (Z)

## Second-line

### Injectable

• ~~SM~~

• ~~KM~~

• ~~AMK~~

• ~~CM~~

### Fluoroquinolone

• ~~OFLOX~~

• ~~LEVO~~

• ~~MOXI~~

### Other 2<sup>nd</sup>-line

• ~~ETH~~

### Weak Agents

• ~~PAS~~

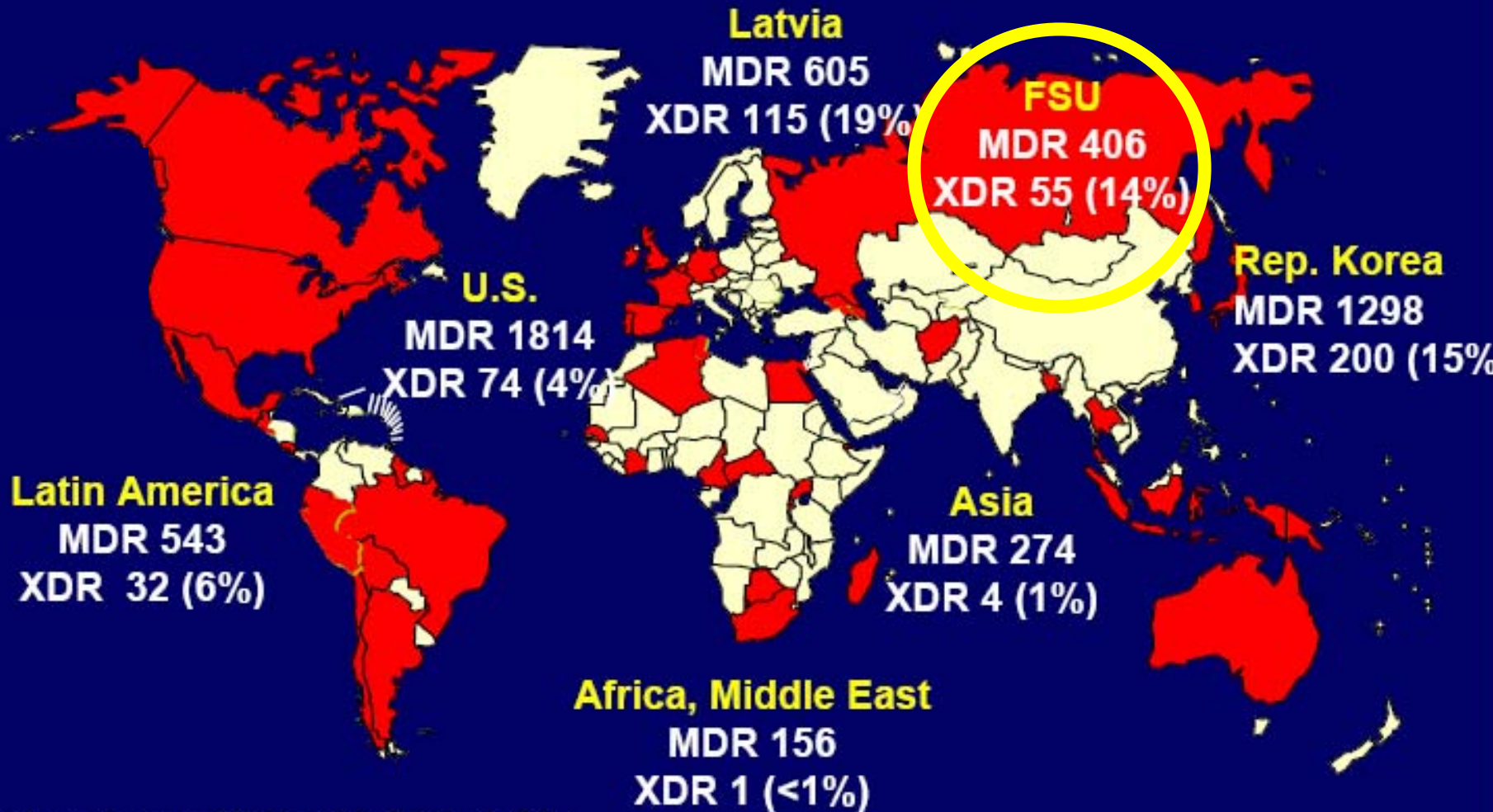
## Third-line

### Other agents

- ~~AMX/CLV~~
- ~~Clofazamine~~
- ~~Clarithromycin~~

- Resistant to at least the two most effective first-line drugs: **isoniazid (INH)** and **rifampin (RIF)**
- Also resistant to at least the most effective second-line drugs: a **fluoroquinolone** and an **injectable agent**

# Number of MDR TB and XDR TB Cases by Region, 2000–2004 (N=347)



# XDR-TB

THE LANCET.com

## Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

### Summary

**Background** The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

**Methods** We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

**Results** From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR



drug resistant TB strain

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sistant strains of tuberculo  
prevent the global spread  
R-TB, a newly identified T  
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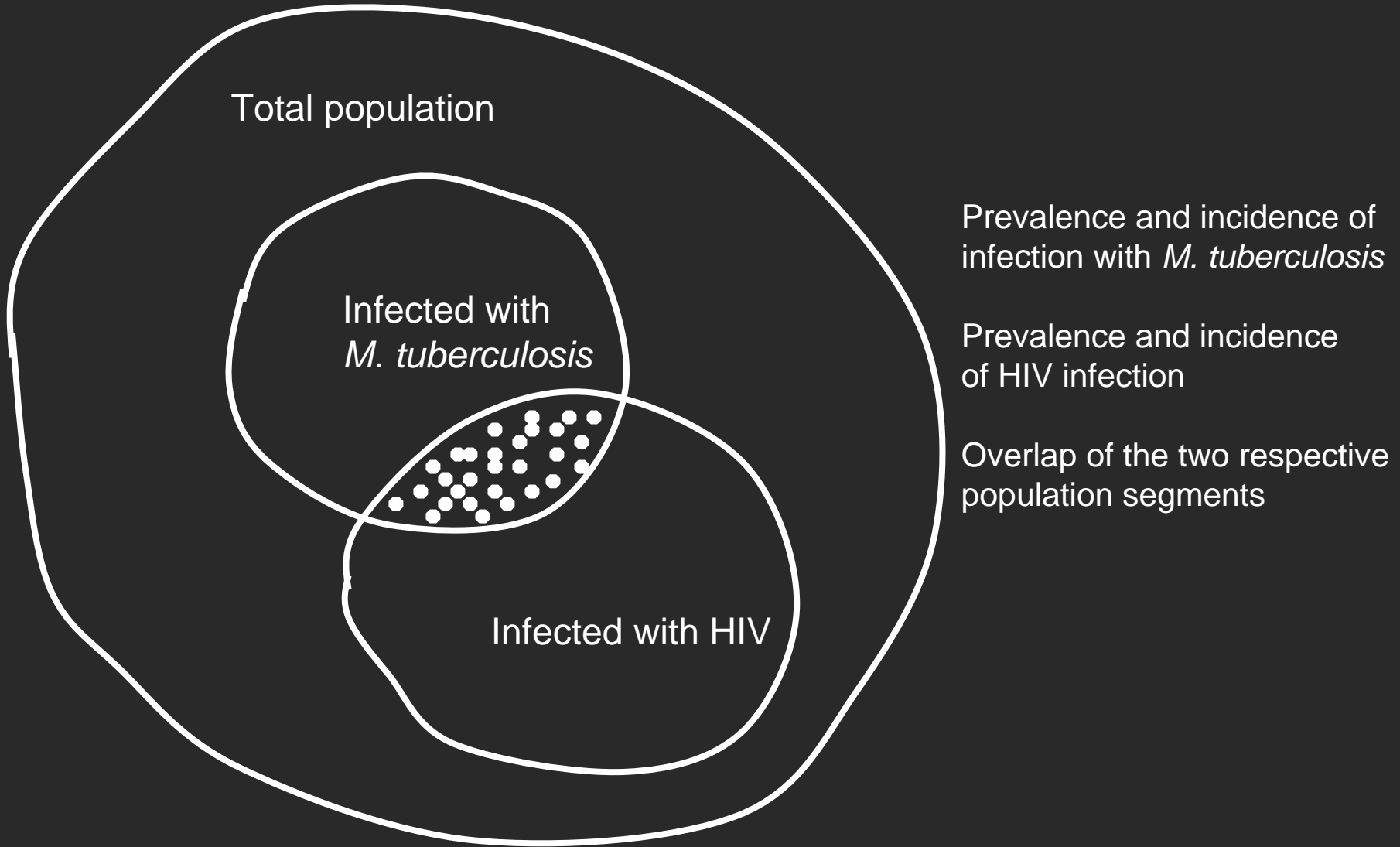
# XDR-TB – KwaZulu Natal, Republic of South Africa

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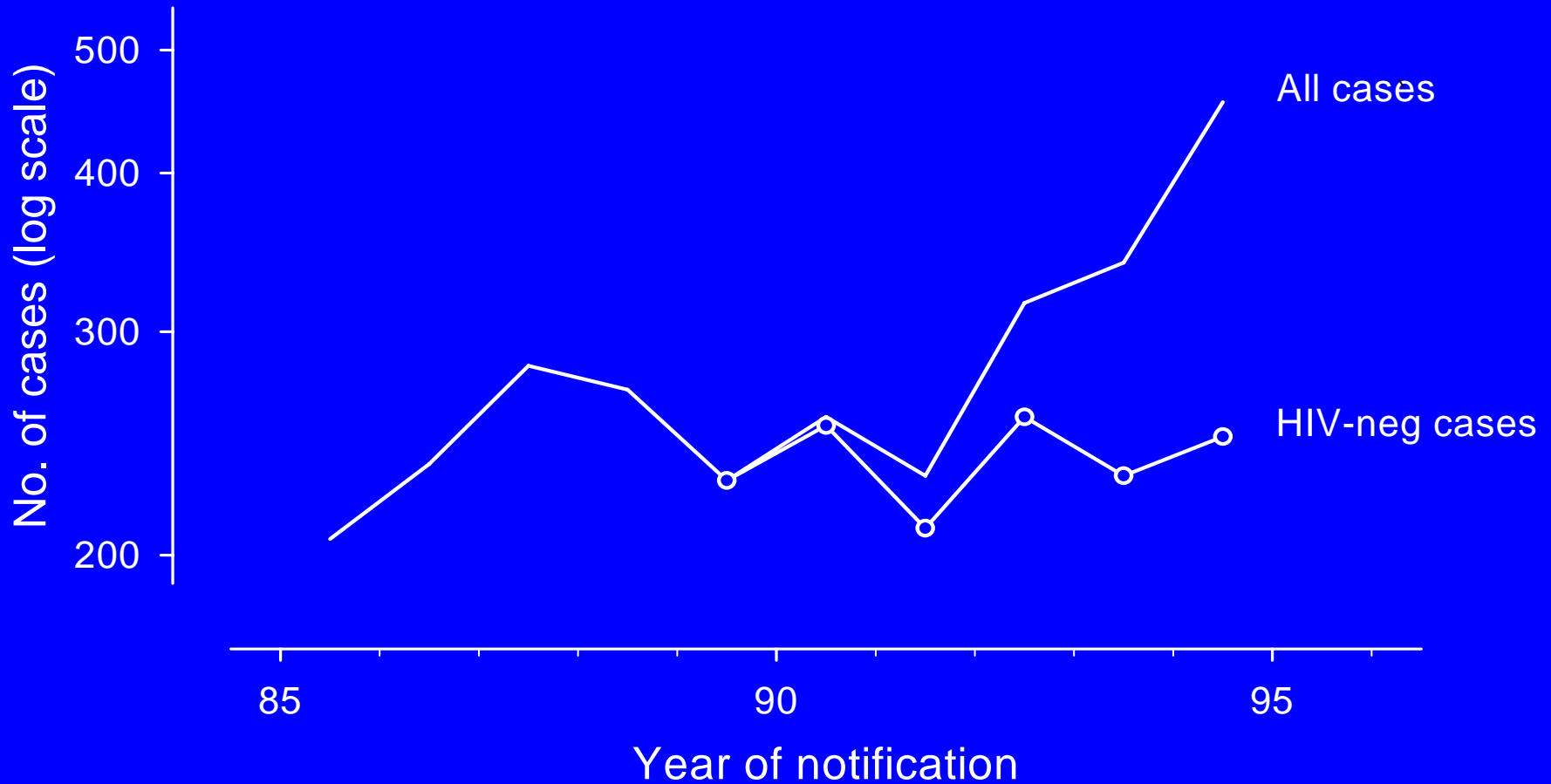
- January 2005 – March 2006: 1539 Patients
  - 221 MDR-TB (14.4%)
  - 53 of MDR-TB patients had XDR-TB (3.4% of total; 24% of MDR-TB patients)
- Of the XDR-TB patients:
  - 55% had never been treated for TB
  - 67% had had a recent hospital admission
  - All tested were HIV positive (44/53 were tested)
  - Median survival from XDR-TB diagnosis: 16 days
  - 85% had similar strains (by genotyping)
  - 98% case fatality



# Determinants for the Frequency of HIV-Associated Tuberculosis in a Community



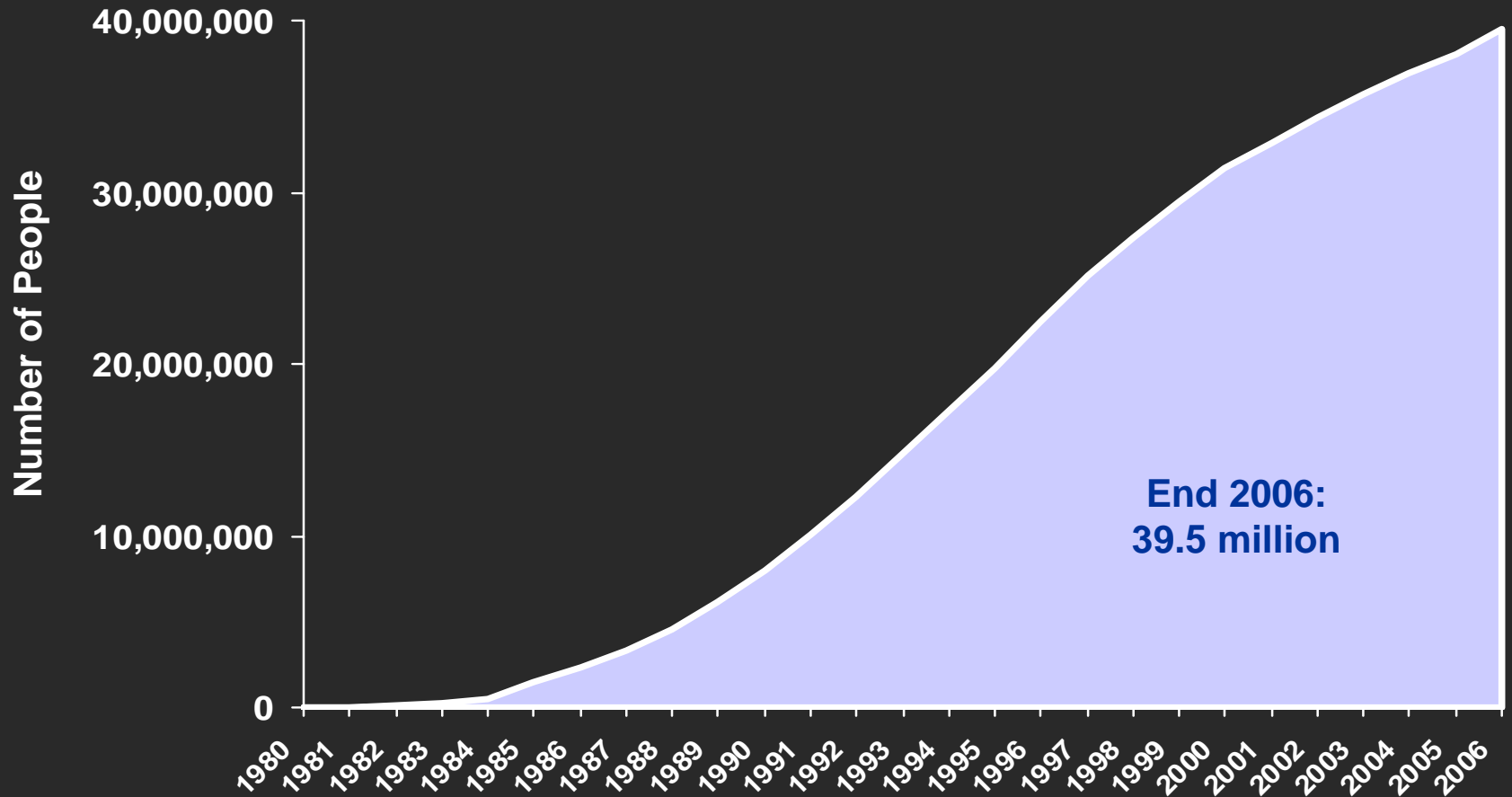
# Impact of HIV Infection on Tuberculosis Notifications in Chiang Rai, Thailand, 1985 - 1994



*Yanai H, et al. AIDS 1996;10:527-31*



# Global Estimates of People Living with HIV/AIDS, 1980–2006



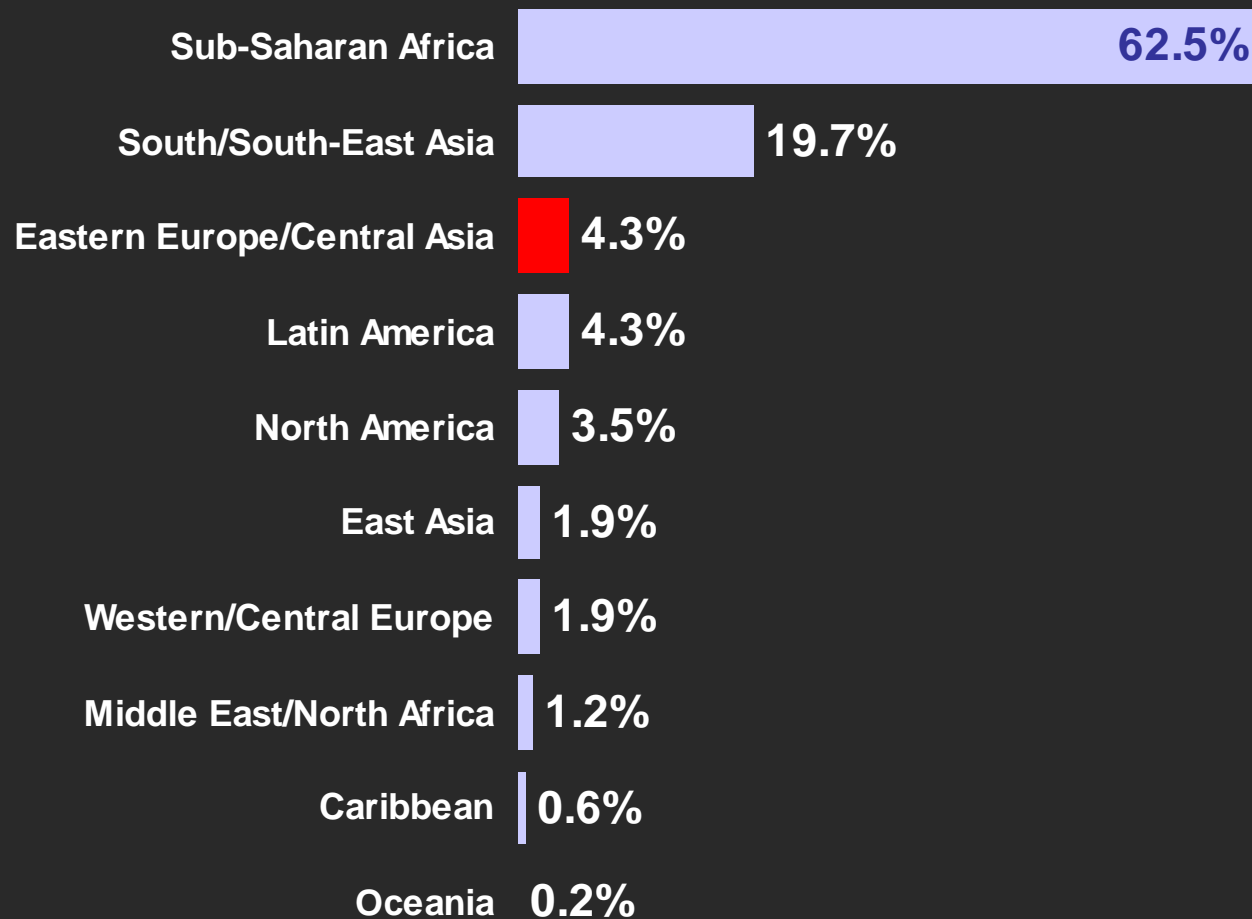
From: Jennifer Kates, KaiserEDU.org

Sources: UNAIDS, *2006 AIDS Epidemic Update*, December 2006; UNAIDS, Data Request, June 2006.



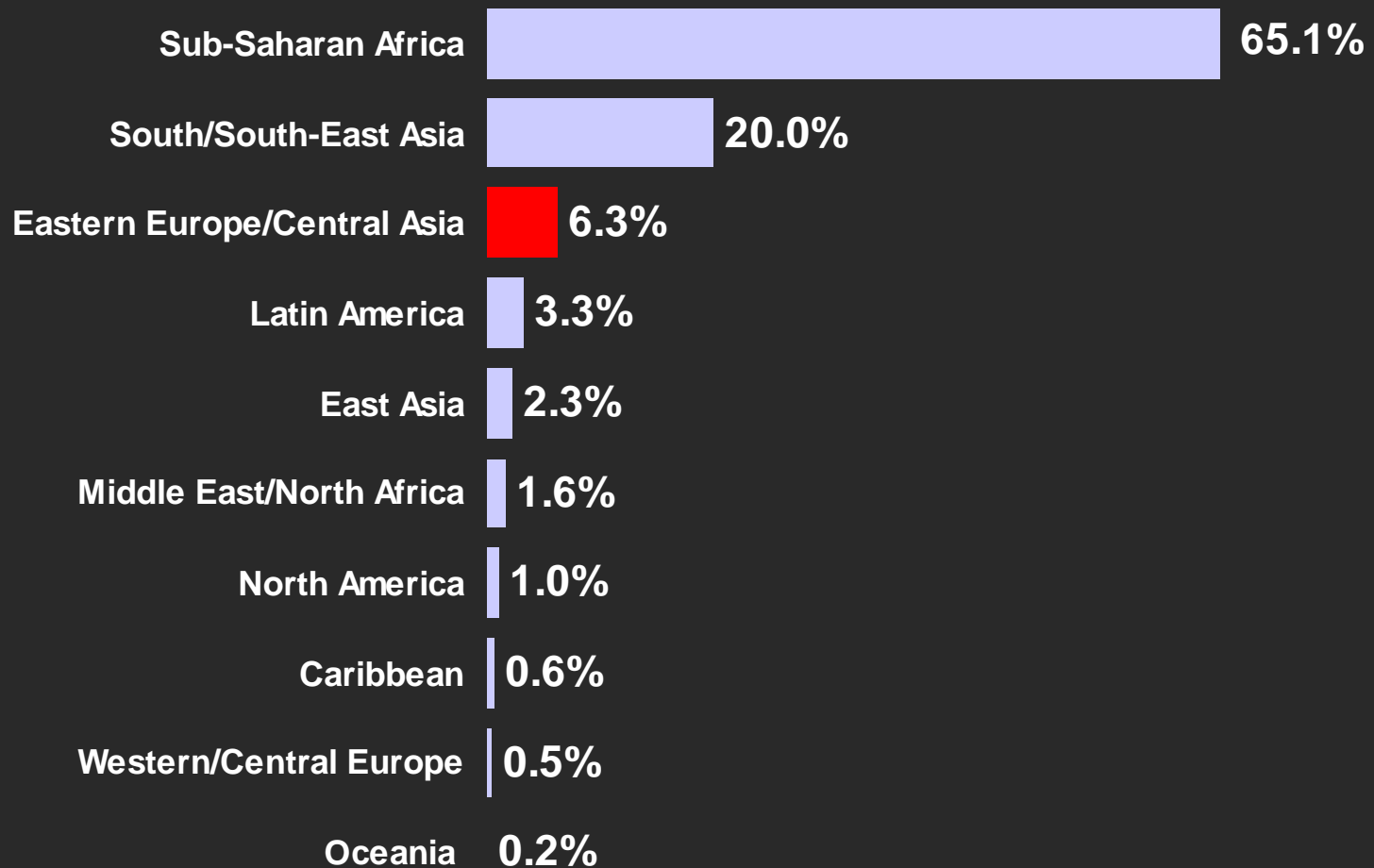
# People Living with HIV/AIDS by Region, as Percent of Global Total, 2006

**Total = 39.5 million**

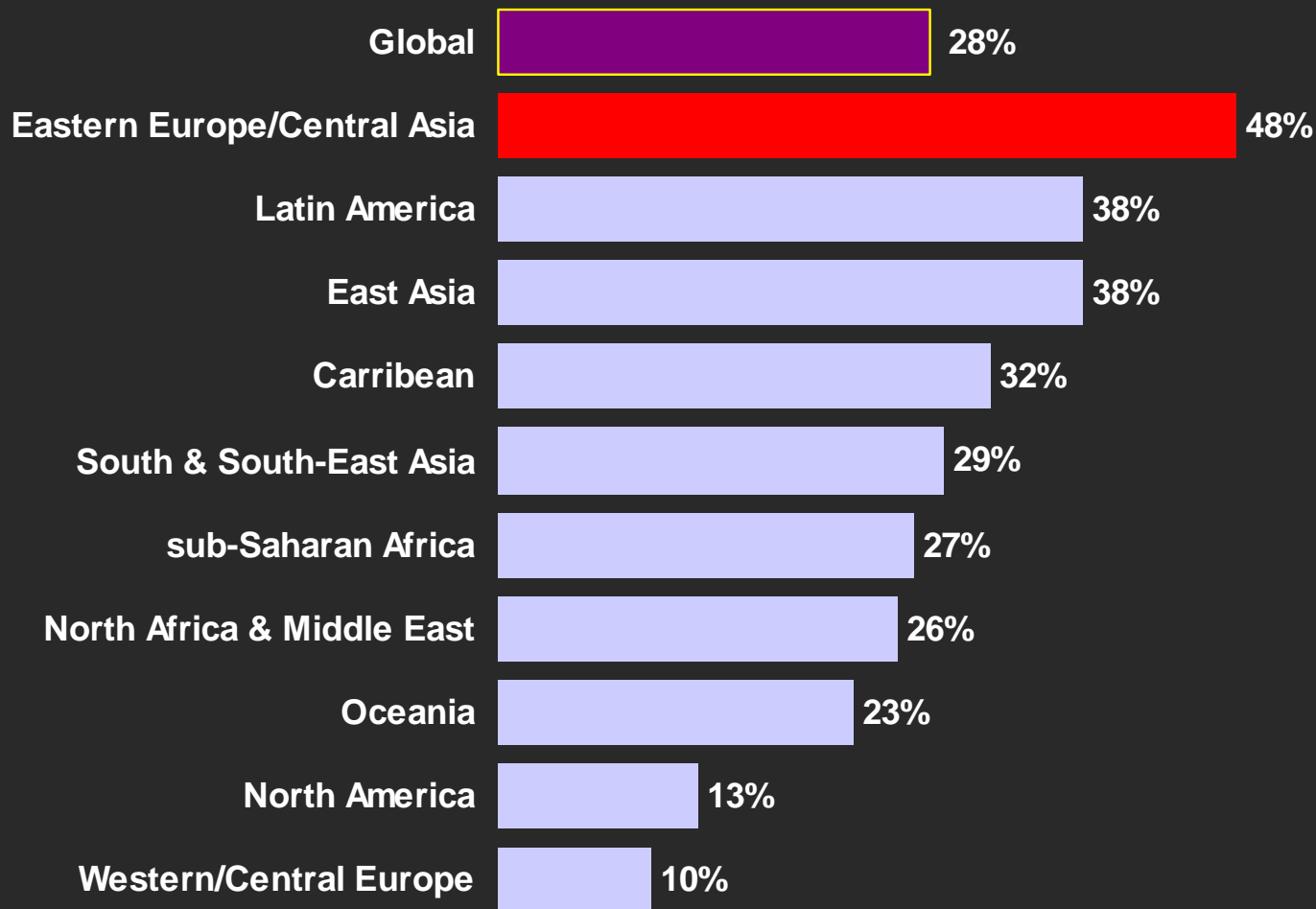


# People Newly Infected with HIV by Region, as Percent of Global Total, 2006

**Total = 4.3 million**



# Young People, Aged 15–24, as Share of People Living with HIV/AIDS by Region, 2003



From: Jennifer Kates, KaiserEDU.org

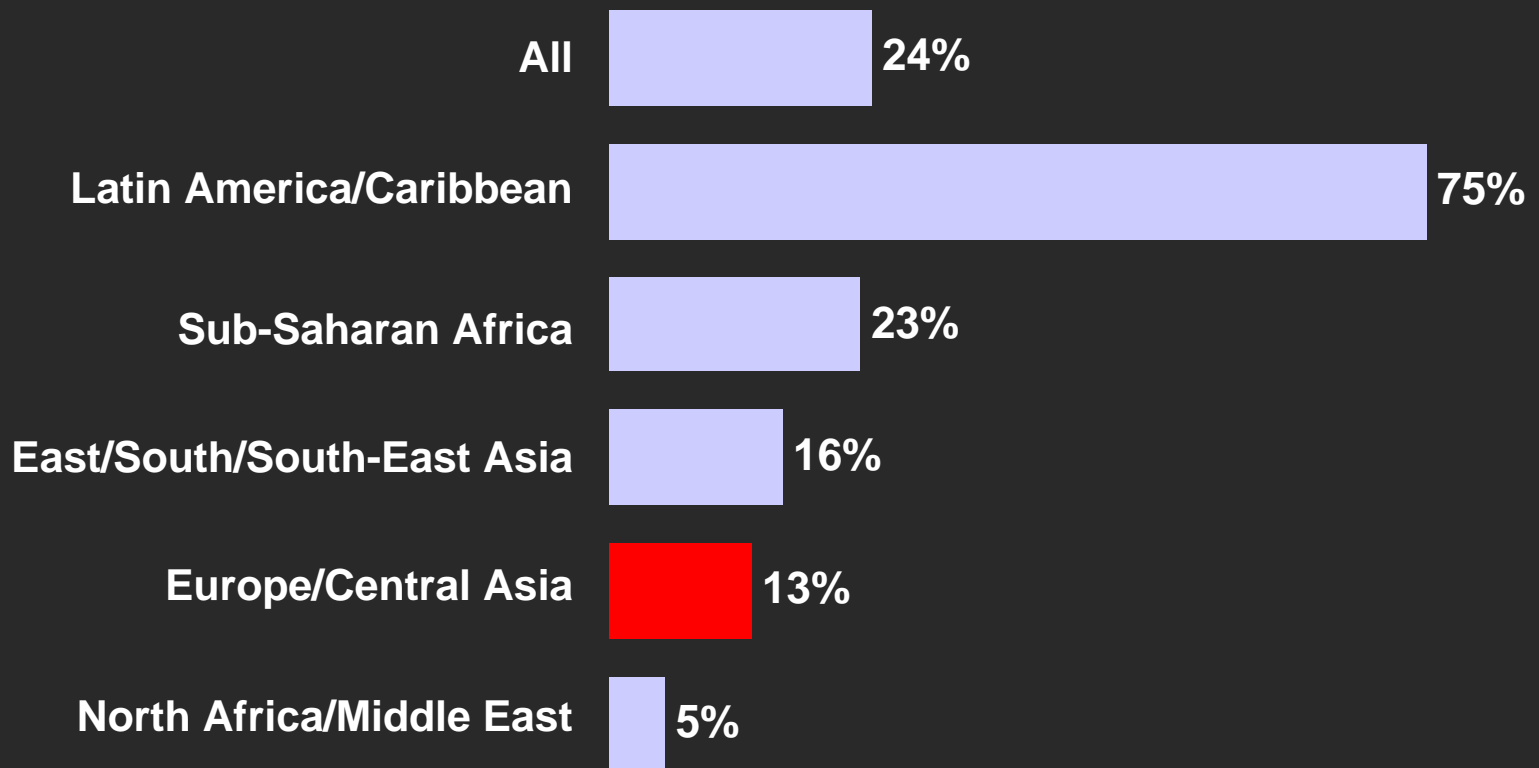
Note: As a share of 15-49 year olds

Sources: UNAIDS, *2004 Report on the Global AIDS Epidemic*, July 2004; UNAIDS Data Request, 2004.



# Antiretroviral (ART) Use among People with HIV/AIDS in Low & Middle-Income Countries, 2006

Percent on Anti-retroviral Therapy (of those who need them):



From: Jennifer Kates, KaiserEDU.org

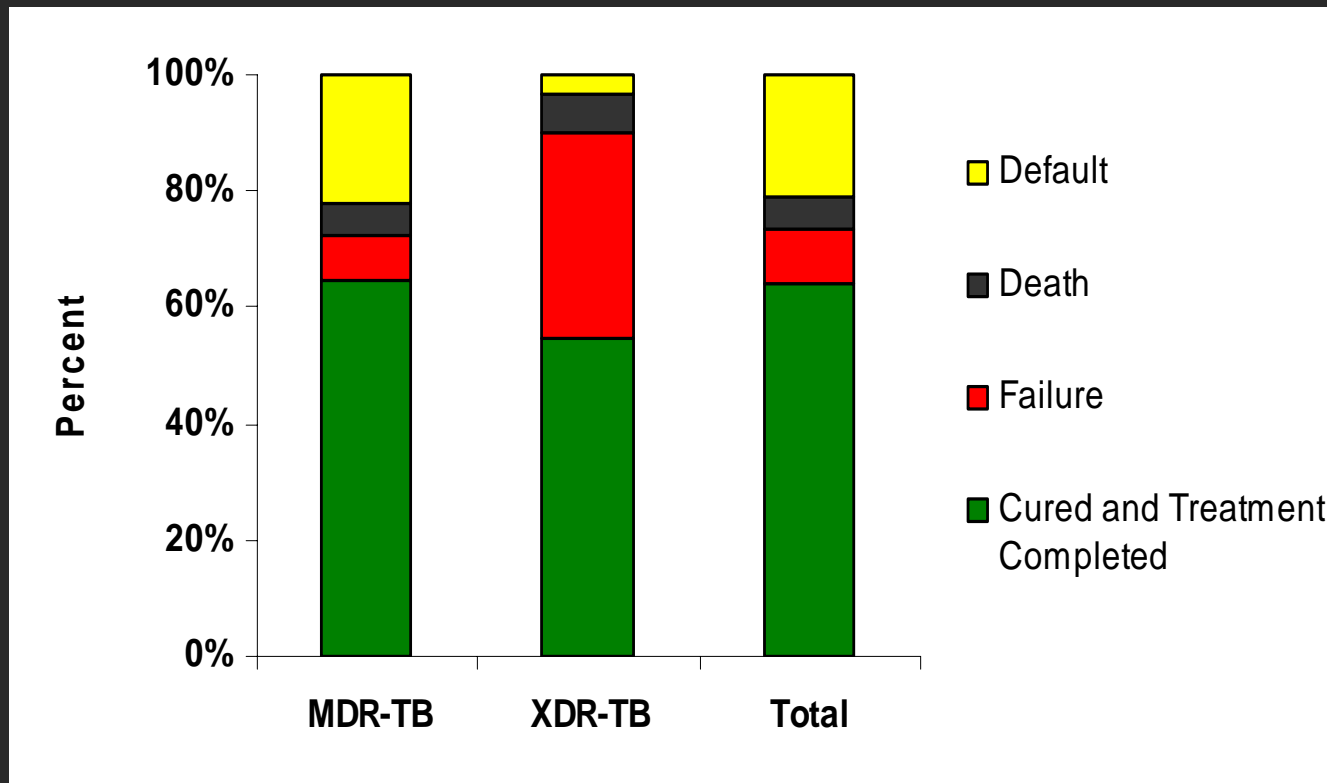
Source: WHO/UNAIDS, Progress in Scaling Up Access to HIV Treatment in Low and Middle-Income Countries, June 2006, Fact Sheet, August 2006.





# XDR-TB in Tomsk

- In a cohort of 611 patients enrolled between 9/2000 and 9/2004, the percentage with XDR-TB at start of treatment: **5.1% (31 patients)**
  - Associated with: previous tuberculosis treatments, previous fluoroquinolone exposure, previous injectable agent exposure, and alcoholism



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