MDR-TB and HIV co-infection in Eastern Europe

Francis Drobniewski MBBS PhD
Professor of Global Health and Tuberculosis
f.drobniewski@imperial.ac.uk
Conflict of interest

In the last year I have been a consultant or I presented talks for: Imperial College, London; Queen Mary College, London, ECCMID, ECDC and WHO
Talk

- Global view and WHO prioritisation outline
- Accuracy of MDRTB HIV data
- EU vs Eastern Europe
- MDRTB
- HIV
- MDRTB+HIV
- Treatment
The WHO End TB Strategy

The End TB Strategy at a glance

| VISION | A WORLD FREE OF TB — zero deaths, disease and suffering due to TB |
| GOAL | END THE GLOBAL TB EPIDEMIC |
| INDICATORS | MILESTONES | TARGETS |
| | 2020 | 2025 | SDG 2030* | END TB 2025 |
| Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline) | 35% | 75% | 90% | 95% |
| Percentage reduction in the TB incidence rate (compared with 2015 baseline) | 20% | 50% | 80% | 90% |
| Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown) | 0% | 0% | 0% | 0% |

PRINCIPLES
1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS
1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION
   A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   B. Treatment of all people with TB including drug-resistant TB, and patient support
   C. Collaborative TB/HIV activities, and management of comorbidities
   D. Preventive treatment of persons at high risk, and vaccination against TB
2. BOLD POLICIES AND SUPPORTIVE SYSTEMS
   A. Political commitment with adequate resources for TB care and prevention
   B. Engagement of communities, civil society organizations, and public and private care providers
   C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   D. Social protection, poverty alleviation and actions on other determinants of TB
3. INTENSIFIED RESEARCH AND INNOVATION
   A. Discovery, development and rapid uptake of new tools, interventions and strategies
   B. Research to optimize implementation and impact, and promote innovations
END TB-Where we are globally

FIG. 2.1
Projected incidence and mortality curves that are required to reach End TB Strategy targets and milestones, 2015–2035

- Incidence rate per 100,000 population per year
  - 20% reduction
  - 50% reduction
  - 80% reduction

- Deaths (million)
  - 35% reduction
  - 75% reduction
  - 90% reduction

TARGET FOR 2035 = 90% REDUCTION
TARGET FOR 2035 = 95% REDUCTION
% of new TB cases which are MDR/RR

Percentage of new TB cases with MDR/RR-TB

Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before 2002 are not shown.
% of previously treated TB cases which are MDR/RR

The most important risk factor for MDRTB
Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap

**WHO High Burden TB, HIV, MDR**
WHO High MDRTB Burden countries (n=30)

The top 20 by estimated absolute number:

Bangladesh
China
DPR Korea
DR Congo
Ethiopia
India
Indonesia
Kazakhstan
Kenya
Mozambique
Myanmar
Nigeria
Pakistan
Philippines
Russian Federation
South Africa
Thailand
Ukraine
Uzbekistan
Viet Nam

Additional 10 by estimated rate per 100,000 population and minimum number of 1000 cases per year (in alphabetical order):

Angola
Azerbaijan
Belarus
Kyrgyzstan
Papua New Guinea
Peru
Republic of Moldova
Somalia
Tajikistan
Zimbabwe

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WHO High Burden TB, HIV, MDR

Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap

But.... What are the main data limitations?
MDR cases: importance of cases as well as rates

Estimated incidence of MDR/RR-TB in 2016, for countries with at least 1000 incident cases

Different numbers as important as rates eg Estonia vs Russia
WHO European High Priority Countries

Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Romania, Russia, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.
Know HIV co-infection rate

Globally in 2016, 57% of notified TB patients had a documented HIV test result (up from 55% in 2015).

In the WHO African Region, (highest burden of HIV-associated TB), 82% of TB patients had a documented HIV test result (up from 81% in 2015).
% of TB cases with known HIV status

Percentage of new and relapse TB cases with documented HIV status, 2016

- 0-24%
- 25-49%
- 50-74%
- ≥75%
- No data
- Not applicable

* 2015 data were used for 9 countries.
Know MDRTB infection rate

In 2016, global coverage for rifampicin resistance testing = 33% for new TB patients and 60% for previously treated TB patients, So 41% overall (up from 31% in 2015).
Culture positive TB cases tested for Rifampicin resistance (2016)

Percentage of bacteriologically confirmed TB cases tested for RR-TB, 2016

Among new laboratory confirmed and previously treated cases; cases with unknown previous treatment history are not included. 2015 data were used for 19 countries.
Euro: % Notified Pulmonary TB cases proven to have MDRTB (lab testing)
TB in the EU (2016 data)

- 30 x EU/EEA countries reported 58,994 TB cases, 11.4 cases per 100,000 population.
- Overall notification rate and most country-specific rates continued their declining trend,
- But annual rates of decline mostly too low to reach the UN’S Sustainable Development Goal target (80% reduction in TB incidence by 2030 compared with 2015).
- Foreign-origin TB cases accounted for 33% of cases overall and over 50% of cases in 15 EU/EEA countries, mainly in the north and west of Europe.
In 2016, 5 cases of XDR TB were linked to a cluster originally detected in foreign medical students at a Romanian university in 2015 (ECDC Communicable Disease Threats Report. Week 43, 23–29 October 2016) On 25 October, Finland reported an XDR-TB case linked to this cluster.

A cluster of 29 cases of MDR TB among refugees from the Horn of Africa and Sudan was detected in six EU Member States and Switzerland (Walker et al. Lancet Infect Dis 2018 Apr;18(4):431-440). In 2016, and 2017, 29 patients were diagnosed with MDRTB in 7 European countries. All originated from the Horn of Africa or Sudan, with all isolates two SNPs or fewer apart. Data suggested that source cases are linked to an M tuberculosis clone circulating in northern Somalia or Djibouti and that transmission probably occurred en route before arrival in Europe.
%MDRTB trends for 18 HPC and EU (2)

ECDC 2018 Report and WHO Euro
%MDRTB trends for 18 HPC and EU (1)
TB in Eastern Europe and Central Asia

• Rates of new TB infections are declining in many countries in the region, both EU and outside
  • Often at a far higher rate than the global decline of 1.9%.
• The highest annual rates of decline between 2007 and 2017 were in Kazakhstan (-9.4%) and Tajikistan (-7.4%).
• Around 36% of new and relapse cases come from Russia, even though Russia only accounts for 16% of the Region’s population

MDRTB in E Europe

- 9 of 30 of world’s highest MDRTB burden countries are in Eastern Europe/Central Asia:
- In 2015, an estimated 16% of people newly diagnosed TB and 48% of people previously treated for TB had multi-drug resistant TB (MDR-TB), accounting for an estimated 74,000 cases.
MDRTB in Europe 2

• TB mortality rate highest in Ukraine (9.5 deaths per 100 000), followed by Russia (8.2 deaths per 100 000).

• Of estimated 74 000 cases of MDRTB in 2015, only 60% were diagnosed (limited access to rapid and quality diagnosis) and treated.

• XDR-TB is increasing. Over 2000 cases of XDR-TB detected in MDRTB patients in 2015, ie 1 in 4 MDR-TB patients had XDR-TB; most XDR-TB cases occur in countries with a high burden of MDR-TB.
% TB patients hospitalised for 1\textsuperscript{st} or 2\textsuperscript{nd} line (2016) therapy
% TB patients hospitalised for 1\textsuperscript{st} or 2\textsuperscript{nd} line (2016) therapy

What problems does this create?
Trend in treatment success for new+relapse cases (non MDRTB)
Trend in treatment success for new+relapse cases (non MDRTB)

If treatment rates for sensitive TB are low then cannot expect MDRTB treatment success either...and prior treatment main reason for new MDRTB plus transmission
MDRTB in Europe

Treatment success rate in MDR-TB patients increased from almost 49% in 2011 to over 51% in 2015, and 54.7% in 2016.

...but remains far below the 75% target set out in the TB action plan for the WHO Euro Region 2016–2020.
Large population cohorts: MDR/XDR TB survival analysis Lithuania (TB PANNET)

All culture-confirmed cases of TB (2002-2008) (n=10,664)

- Not diagnosed with MDR/XDR (n=8,823)
  - Diagnosed after death or missing data (n=34)

Diagnosed with MDR/XDR at any point of treatment, complete data (n=1,807)

- MDR TB 95.7% (n=1,729)
  - Primary 40.2% (n=726)
  - Acquired 55.5% (n=1,003)
- XDR TB 4.3% (n=78)
  - Primary 1.5% (n=28)
  - Acquired 2.8% (n=50)
Survival of MDR TB and XDR TB patients

Median survival
• MDR TB: 4.1 (95%CI 3.7, 4.4) years
• XDR TB: 2.9 (95%CI 2.2, 3.9) years

• Balabanova et al ERJ 2012
• Balabanova et al BMJ Open (2011)
HIV in Eastern Europe

- 1.4 million people were living with HIV (PLHIV) in Eastern Europe and Central Asia (2017).
- Only WHO region where HIV epidemic continues to grow rapidly: 30% increase in annual HIV infections between 2010 and 2017.
- In 2017, approx 190,000 new HIV infections - 80,000 more than in 2013.
- In 2017, 40,000 AIDS-related deaths: a 22% increase from 2010.
- In 2017, 73% of PLHIV were aware of their HIV status, a 4% increase from 2016.
- The vast majority of PLHIV in Eastern Europe + Central Asia live in Russia (70%), (new infections are rising), followed by Ukraine.
- Outside of Russia, the rate of new HIV infections is stable.

HIV in Eastern Europe 2

- Epidemic is concentrated among key affected populations – people who inject drugs (PWID)
- BUT there is low coverage of harm reduction and other HIV prevention programmes in key countries in region.
- Conservative legislation around same sex relationships, drug use and sex work continues to fuel stigma = obstructing the HIV response in some countries
- **ARV coverage remains below the global average at 36%**.
- New infections outpace ARV enrolment. Unprotected sex is increasing number of HIV infections and is now leading cause of transmission in some countries.
- New HIV infections through heterosexual sex increased by 150% between 2002 and 2012 in region

Late presentation rates as high as 60–80% reported in Georgia, and Albania. (Gokengin, D et al (2018) *HIV care in Central and Eastern Europe: How close are we to the target*? Internat J Infect Dis:70, 121-130)

A 2018 analysis found overall percentages of late presentation and advanced disease in the region to be 40.3% and 25.4%, respectively. (Gokengin, D et al (2018)

Main barriers to effective provision of HIV testing services in the region relate to a lack of community-based testing services
TB, TB+MDRTB-HIV in the EU

- MDRTB was reported for 4% of all tested cases.
- But for 10–20% of cases tested in Baltic countries.
- XDRTB was reported for 20% of MDR TB cases that underwent second-line drug susceptibility testing.
- Treatment success was achieved in 72% of all TB cases, 62% of HIV-co-infected TB cases, 38% of MDRTB cases notified in 2014, and 34% of XDRTB cases notified in 2013.
- Estimated TB mortality rate in the EU/EEA was 0.8 deaths per 100,000 population, with 4,270 estimated deaths overall.
TB and HIV co-infection E Europe

• Proportion of people with TB co-infected with HIV was highest in Ukraine (21%) and Russia (19%).
• Russia had the largest number of people with TB in 2016 at 94,000, followed by Ukraine (39,000),
• TB remains the leading cause of death for people living with HIV in the region.
• TB mortality rate highest in Ukraine (9.5 deaths per 100 000), followed by Russia (8.2 deaths per 100 000).
% HIV co-infection among new and relapse for 18 HPC + EU
Risk groups

• What are the major risk groups for MDRTB and HIV coinfection?
Prisoners and HIV East Europe and Central Asia

- Prisoners are at particular risk of HIV infection in Eastern Europe and Central Asia.
- Data about this population is currently scarce.
- Criminalisation of drug use resulted in very high levels of incarceration.
- In 2016, estimated that IVDU more than a third of prisoners across the region; but level could be as high as 50-80% in some countries.

Prisoners and HIV in E Europe (2)

• Detention facilitates HIV transmission among IV users:

• HIV prevalence in prisons exceeds 10% in Latvia (20.4%), Ukraine (19.4%), Estonia (14.1%), and Kyrgyzstan (11.3%) UNAIDS (2017) Ending AIDS: Progress towards the 90-90-90 Targets’

• Prison surveillance studies: HIV prevalence 22X, 19X, and 34X higher in prisons than in corresponding communities in Ukraine, Azerbaijan and Kyrgyzstan, respectively. Altice et al 2016

• In Russia (2010) (most recent data), 55,000 of 846,000 inmates thought to be HIV positive. (WHO) (2007) 'Effectiveness of interventions to address HIV in prisons'
IV Drugs and HIV Eastern Europe and Central Asia

• Approx 3.1 million people who inject drugs (PWID) in Eastern Europe and Central Asia.

• Region has approx one in four people who inject drugs worldwide. Harm Reduction International (2016) *Regional Overview: 2.2 Eurasia*

• Russia has the highest number of IVDU (1.8 million), about 2.3% of the adult population.

• Moldova (1%), Belarus (1.1%) and Ukraine (0.8-1.2%) also have significant numbers of the adult population. United Nations Office on Drugs and Crime (UNODC) (2016) *World Drug Report 2016'*
MDRTB+HIV Treatment—a few points

• Treat MDRT with TB drugs..and ARV
• Multiple TB drugs to which organism is susceptible eg molecular, phenotypic testing
• For non MDR—RIF is a minimum of 10 mg/kg
ARV in Eastern Europe/Central Asia 1

• Majority of countries have officially adopted a test-and-treat policy
• Just 36% of all people living with HIV in the region accessing ART in 2017, with key populations most likely to miss out. (UNAIDS (2018) *Global AIDS Update: Miles to go: closing gaps, breaking barriers, righting injustices*)
• In 2017, ART coverage ranged from 29% in Ukraine to 65.4% in Tajikistan among HIV positive sex workers for example. (UNAIDS (2018) ‘*Global AIDS Update: Miles to go: closing gaps, breaking barriers, righting injustices*)
• Despite high ARV adherence, low HIV testing +treatment coverage means that only 26% of all PLWHIV in the region were virally suppressed in 2017. UNAIDS (2018) ‘*Global AIDS Update: Miles to go: closing gaps, breaking barriers, righting injustices*
## Modified WHO MDRTB Regimens

<table>
<thead>
<tr>
<th>GROUP</th>
<th>MEDICINE</th>
<th>Abbreviation</th>
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</table>
| **Group A:**  
Include all three medicines (unless they cannot be used)  
Levofloxacin **OR**  
Moxifloxacin  
Bedaquiline\(^1,4\)  
Linezolid\(^2\)  
Clofazimine  
Cycloserine **OR**  
Terizidone | Levofloxacin  
Moxifloxacin  
Bedaquiline  
Linezolid  
Clofazimine  
Cycloserine  
Terizidone | Lfx  
Mfx  
Bdq  
Lzd  
Cfz  
Cs  
Tmd |
| **Group B:**  
Add both medicines (unless they cannot be used)  
Ethambutol  
Delamanid\(^3,4\)  
Pyrazinamide\(^5\)  
Imipenem-cilastatin **OR**  
Meropenem\(^6\)  
Amikacin **(OR Streptomycin)**\(^7\)  
Ethionamide **OR**  
Prothionamide  
*p*-aminosalicylic acid | Ethambutol  
Delamanid  
Pyrazinamide  
Imipenem-cilastatin  
Meropenem  
Amikacin  
Ethionamide  
Prothionamide  
*p*-aminosalicylic acid | E  
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Modified WHO MDRTB Regimens

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<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines (unless they cannot be used)</td>
<td>Levofloxacin OR Moxifloxacin</td>
<td>Lfx Mfx</td>
</tr>
<tr>
<td></td>
<td>Bedaquiline(^1,(^4)</td>
<td>Bdq</td>
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<tr>
<td></td>
<td>Linezolid(^2)</td>
<td>Lzd</td>
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Emphasis on oral regimens. Kanamycin out. Streptomycin in, Greater role for clofazamine, cycloserine, delamanid, bedaquiline, levofloxacin equal to moxifloxacin

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<tr>
<td></td>
<td>Amikacin (OR Streptomycin)(^7)</td>
<td>Am (S)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide OR Prothionamide</td>
<td>Eto Pto</td>
</tr>
<tr>
<td></td>
<td>p-aminosalicylic acid</td>
<td>PAS</td>
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</table>
1. Evidence on the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow ‘off-label’ use best practices.

2. Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit its use.

3. The position of Dlm will be re-assessed once individual patient data from trial 213 has been reviewed; these data were not available for the evidence assessment in July outlined above. Evidence on the safety and effectiveness of Dlm beyond 6 months was insufficient for review; extended use of Dlm in individual patients will need to follow ‘off-label’ use best practices.

4. Evidence on concurrent use of Bdq and Dlm was insufficient for review.

5. Z is only counted as an effective agent when DST results confirm susceptibility.

6. Amoxicillin-Clavulanic acid is administered with every dose of Imp-Cln or Mpm but is not counted as a separate agent and should not be used as a separate agent.

7. Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used and if DST results confirm susceptibility (S resistance is not detectable with 2nd line molecular line probe assays and phenotypic DST is required).
Shorter TB Regimen 1

• May 2016, WHO conditionally recommended standardized, shorter regimen MDRTB.

• Regimen includes kanamycin (injectable), moxifloxacin (MFX), prothionamide (PTO), clofazimine (CFZ), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB), given together: initial phase 4 months (extending to 6 months if patients remain sputum smear-positive at end of month 4) +5 months of treatment 4 drugs (MFX, CFZ, PZA, and EMB)

• Attractive, as shorter treatment duration, considerably lower cost, better patient adherence and comparable outcomes

• Strict criteria for use: exclusion includes confirmed resistance to any drugs in regimen, (apart from isoniazid) no prior use of regimen drugs, no resistance to FQs, AGs, pregnancy etc ie “simple MDRTB cases”

By 2016, 35 countries, mostly in Africa and Asia, introduced shorter regimen for MDR-TB/RR, with high success rates (87 to 90%)

China, with one of highest estimated numbers of MDR-TB patients, the shorter regimen has not been applied (Liu et al Clinical Microbiology and Infection 24 (2018) 1035e1036)


High-dose INH, which is probably effective against isolates with low-level INH resistance caused by mutations in the inhA promoter region [Dominguez et al TBNET/RESIST-TB consensus statement. Int J Tuberc Lung Dis 2016;20:24e42].

Little supportive data data for use of high-dose INH for isolates with high-level INH resistance mutations in KatG at position 315: these are dominant E Europe (up to 90%)
Conclusions

- Consider HIV issues, MDRTB issues, joint issues
- MDRTB treatment-challenging changes...read footnotes to WHO guidance
- WHO EURO shows declining TB but not enough
- Too much late diagnosis and presentation HIV, TB and HIV-TB
- HIV spread via IVDU, prisons encourage this
- Now increasing heterosexual spread
- Too low ARV coverage; ARV=treatment for MDRTB
- Better integration of TB and HIV services needed
- Insufficient funds for treatment and research
- Better POC diagnostics needed
• Thanks for listening......

• Any questions?