

# HIV INFECTION AND M(X)DR-TB

Associated professor, Vaira Leimane  
WHO International Training Centre on Treatment and  
Management of MDR-TB  
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# Presentation outline

- Introduction
- Recommended collaborative TB, MDR-TB/HIV activities;
- Diagnosis and management of TB and MDR-TB in HIV-infected patients;
- Implications of HIV on infection control.

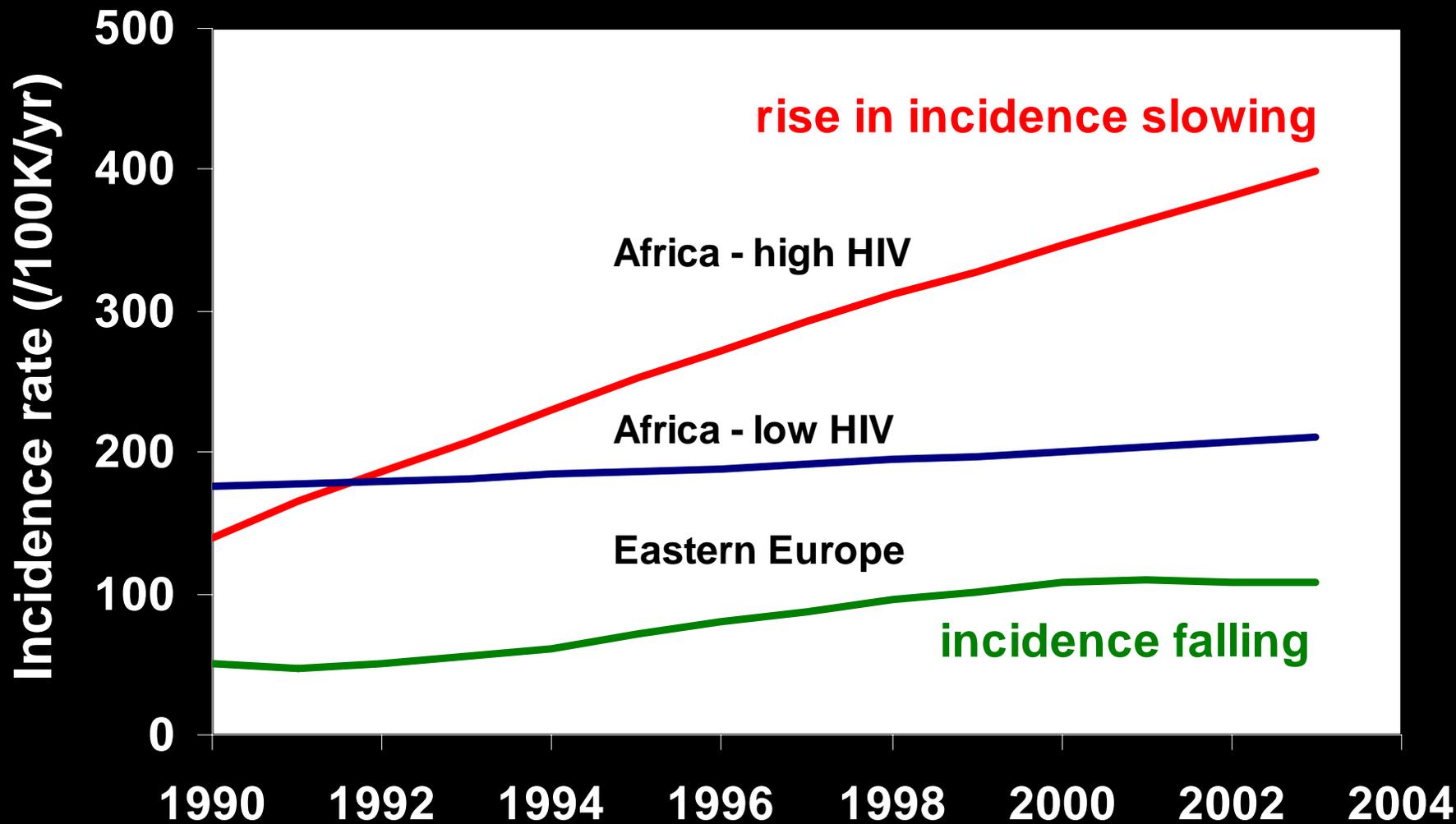
# Global TB/HIV burden in 2004

- 4,1 million new HIV infections;
- 8,9 million new TB cases
- 741 000 PLHIV;
- 37% adult TB patients HIV+ in sub-Saharan Africa – nearly 80% in some East and Southern African countries;
- 50% of all TB deaths in PLHIV in Africa, 7% in South East Asia
- 11% of adult AIDS deaths due to TB globally, one third in worst affected countries



*Source: UNAIDS 2001*

# TB cases have been rising in Africa and E Europe



# Extensively Drug-Resistant (XDR) TB

- CDC & WHO report described TB resistant to second line TB medications
  - Extensively Drug-Resistant (XDR) TB
  - Found in 347 isolates worldwide
- Few data regarding presence in Africa and in high HIV prevalence settings

*<sup>2</sup>Emergence of Mycobacterium Tuberculosis with Extensive Resistance to Second Line Drugs—Worldwide 2000-2004. MMWR.2006;55:301-305*

# Definitions

- **MDR-TB** = resistance to at least INH and rifampicin
- **INJ** = second-line injectables including aminoglycosides and capreomycin
- **FQ** = fluoroquinolones
  
- **XDR-TB (revised, WHO)** = MDR-TB with resistance to FQ and one INJ
  
- **XDR-TB (MMWR)** = MDR-TB with resistance to at least 3 second-line drugs

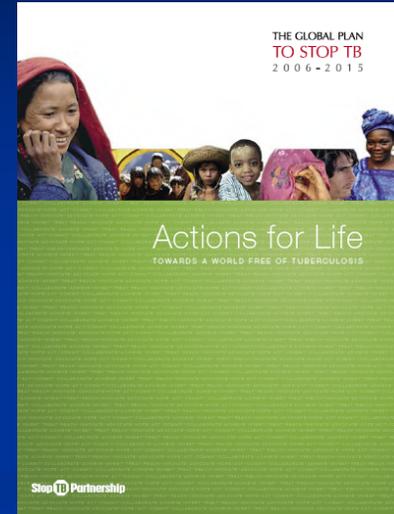
# HIV and TB epidemics in South Africa closely intertwined

- Up to 80% of new TB cases in KwaZulu Natal coinfecting with HIV
- Annual mortality rate among coinfecting patients 40% before antiretroviral (ART) medications, a large proportion of these deaths have been attributed to “end-stage AIDS”
- Reduced mortality rate to 12% in TB/ART integration study in KwaZulu Natal.
- 71% of the deaths in study, were due to multi-drug resistant or MDR TB.

# TB/HIV collaborative activities

## Global policy and implementation tools

- **Goal** - To decrease the burden of TB and HIV in dually affected populations;
- **Objectives** –
  - to establish the mechanisms for collaboration between TB and HIV/AIDS programmes;
  - to decrease the burden of TB in PLWHA;
  - to decrease the burden of HIV in TB patients;



# TB/HIV COLLABORATIVE ACTIVITIES

## **Establish mechanisms for collaboration /Who will be partners?**

- Set up a coordinating body for TB/HIV activities
- Conduct surveillance of HIV prevalence among tuberculosis patients
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation

## **Decrease the burden of tuberculosis in people living with HIV/AIDS/Which is a common strategies?**

- Establish intensified tuberculosis case-finding
- Introduce isoniazid preventive therapy (IPT)
- Ensure tuberculosis infection control in health care and congregate settings

## **Decrease the burden of HIV in tuberculosis patients**

- Provide HIV testing and counselling (VCT)
- Introduce HIV prevention methods
- Introduce co-trimoxazole preventive therapy (CPT)
- Ensure HIV/AIDS care and support
- Introduce antiretroviral therapy

# HIV TESTING OF TB PATIENTS

## RECOMMENDED HIV SURVEILLANCE METHODS (3 SITUATIONS)

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**Generalized HIV epidemic**  
(HIV consistently >1% in pregnant women).

Routine HIV testing of TB patients AND  
Periodic (special) or sentinel surveys to **calibrate the data from routine HIV testing**

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**Concentrated HIV epidemic**  
(HIV consistently >5% in at least one defined sub-population, e.g. IDUs, SWs, MSM; HIV <1% in pregnant women)

Routine HIV testing of TB patients OR  
Periodic (special) or sentinel surveys **in the administrative areas where HIV level unknown. Such surveys can also calibrate data from routine HIV testing.**

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**Low-level HIV epidemic**  
(HIV prevalence has not consistently exceeded 5% in any defined subpopulation, e.g. IDUs, SWs, MSM)

Periodic (special) or sentinel surveys

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# TB/HIV burden, 2003

## Intervention priorities for European countries

Priority for HIV/AIDS prevention/control	High			Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine
	Intermediate		Poland	Kazakhstan, Romania, Tajikistan, Turkmenistan, Uzbekistan
	Low	Andorra, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, San Marino, Slovakia, Slovenia, Sweden, Switzerland, United Kingdom	Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Hungary, Macedonia FYR, Portugal, Serbia & Montenegro, Spain, Turkey	Armenia, Azerbaijan, Georgia, Kyrgyzstan
		Low	Intermediate	High
		Priority for TB control		

# WHO recommendations

- Establish a national-level TB/HIV coordination committee
- Establish HIV surveillance among TB patients
- Screen for TB all people attending for HIV services

# The role of TB program in HIV prevention

- **HIV counselling and testing - standard of care for TB** (including MDR-TB) patients, Offer HIV testing and counseling to all patients with TB
  - 106 countries already implementing HIV C&T
  - **Malawi in 2005** - 47% of all TB patients and 92% who started CPT;
    - 18% of TB patients on ART
  - **Rwanda** 53% TB patients HIV tested in 2005;
  - **Kenya** increasing up to 50% of all TB patients in 2005
    - 67 000 patients registered
    - 56% tested HIV positive
    - 30% started ART
    - 80% CPT

# Strategies to decrease TB/HIV in addition to DOTS

- **Active or intensified tuberculosis case-finding (ICF)**
  - To identify TB cases transmitting infection, and who may die of TB infection
  - Household case finding to TB and HIV prevent HIV transmission
- **Introduce isoniazid preventive therapy (IPT)**
  - To prevent disease in HIV+ (and HIV-) persons
  - Combined ARV and IPT to reduce probability of developing of primary TB or reactivation TB
- **Ensure tuberculosis infection control in health care and congregate settings**

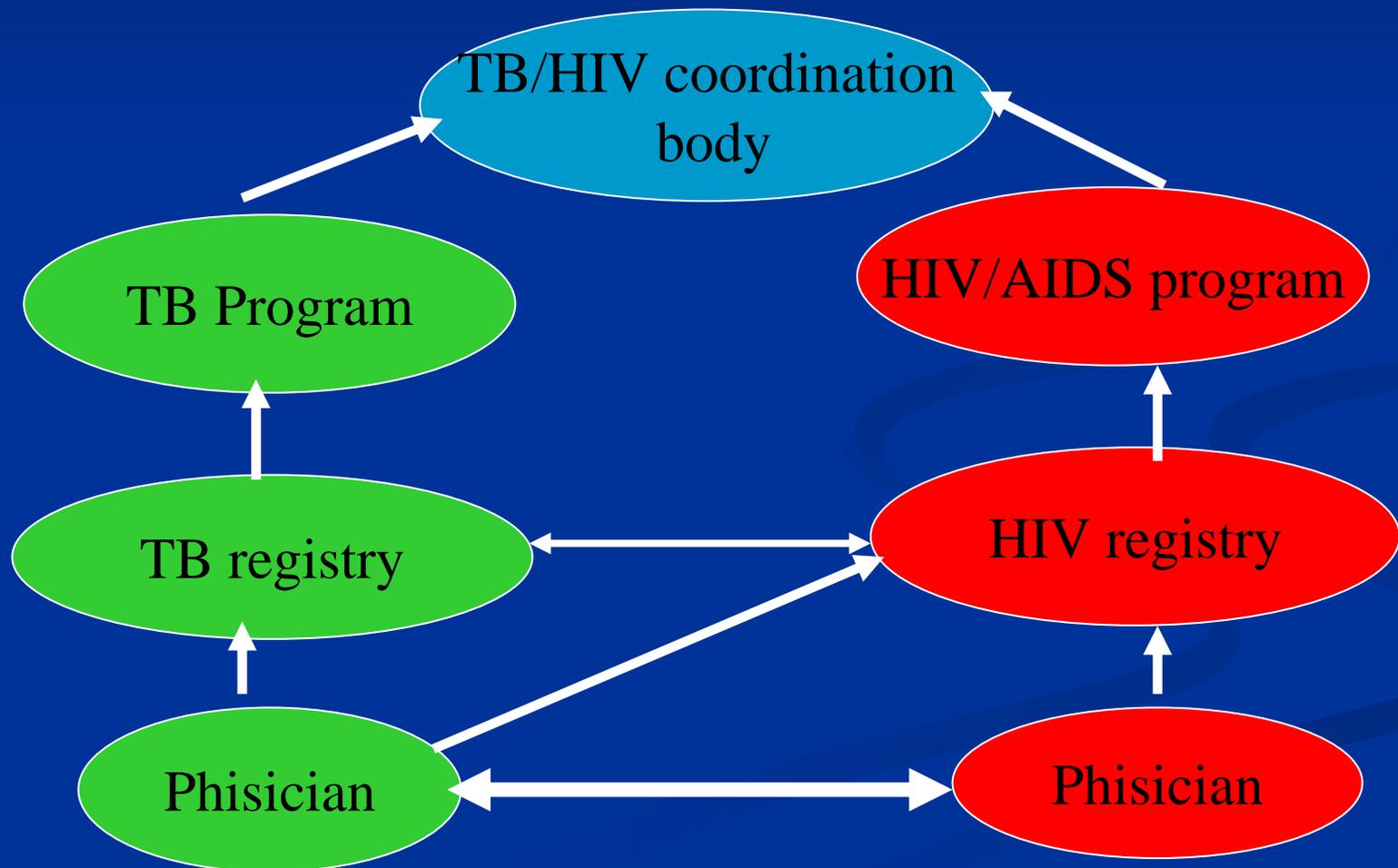


# Intensified TB case finding – counselling on TB in harm reduction programs





# Surveillance for TB/HIV, Latvia



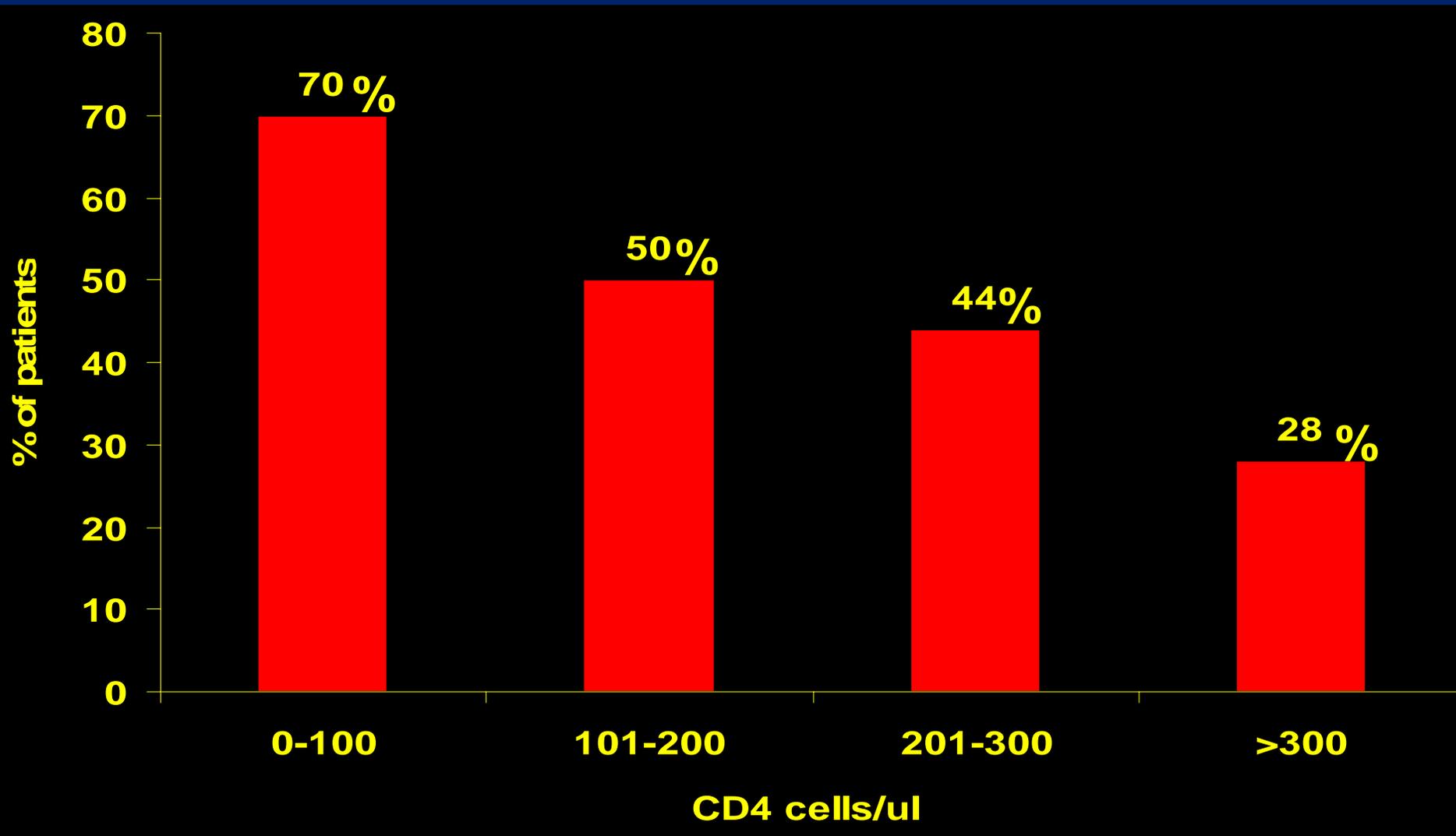
# The WHO recommendations to MDR-TB/HIV activities

- **Basic TB/HIV activities should be in place before embarking on HIV/MDR-TB activities;**
- Involve the TB/HIV coordinating body in the area with the planning and monitoring of HIV/MDR-TB activities and programs.
  - Use culture and DST to improve the diagnosis of TB in HIV individuals.
  - Introduce ART promptly in MDR-TB/HIV patients.
  - Close treatment follow up should be with a specialized team.
  - Implement additional socioeconomic support
  - Ensure strict infection control.

# Clinical presentation of HIV-related MDR-TB

- **Signs and symptoms of MDR-TB are the same for HIV- and HIV+**
  - influenced by the degree of underlying immunodeficiency.
- Increasingly, the presentation is extra-pulmonary (pleura, the lymph nodes and the pericardium).
- Misdiagnosis may lead to higher morbidity and mortality.

# Frequency of extrapulmonary TB in patients with HIV infection and TB



# Relationship between HIV and site of TB

<i>Site</i>	<i>HIV-negative (n=67)</i>	<i>HIV-positive (n=182)</i>
<b>Pulmonary</b>	<b>48 (72%)</b>	<b>72 (40%)</b>
<b>Extrapulmonary</b>	<b>11 (16%)</b>	<b>62 (34%)</b>
<b>Both</b>	<b>8 (12%)</b>	<b>48 (26%)</b>
<b><i>Individual site compared with all other cases</i></b>		
<b>Pulmonary</b>	<b>56 (84%)</b>	<b>120 (66%)</b>
<b>Pleural</b>	<b>13 (19%)</b>	<b>57 (31%)</b>
<b>Lymph node</b>	<b>2 (3%)</b>	<b>34 (19%)</b>
<b>Pericardial</b>	<b>2 (3%)</b>	<b>27 (15%)</b>
<b>Multiple sites</b>	<b>9 (13%)</b>	<b>53 (29%)</b>

**14% chest X-ray is normal in culture positive cases**

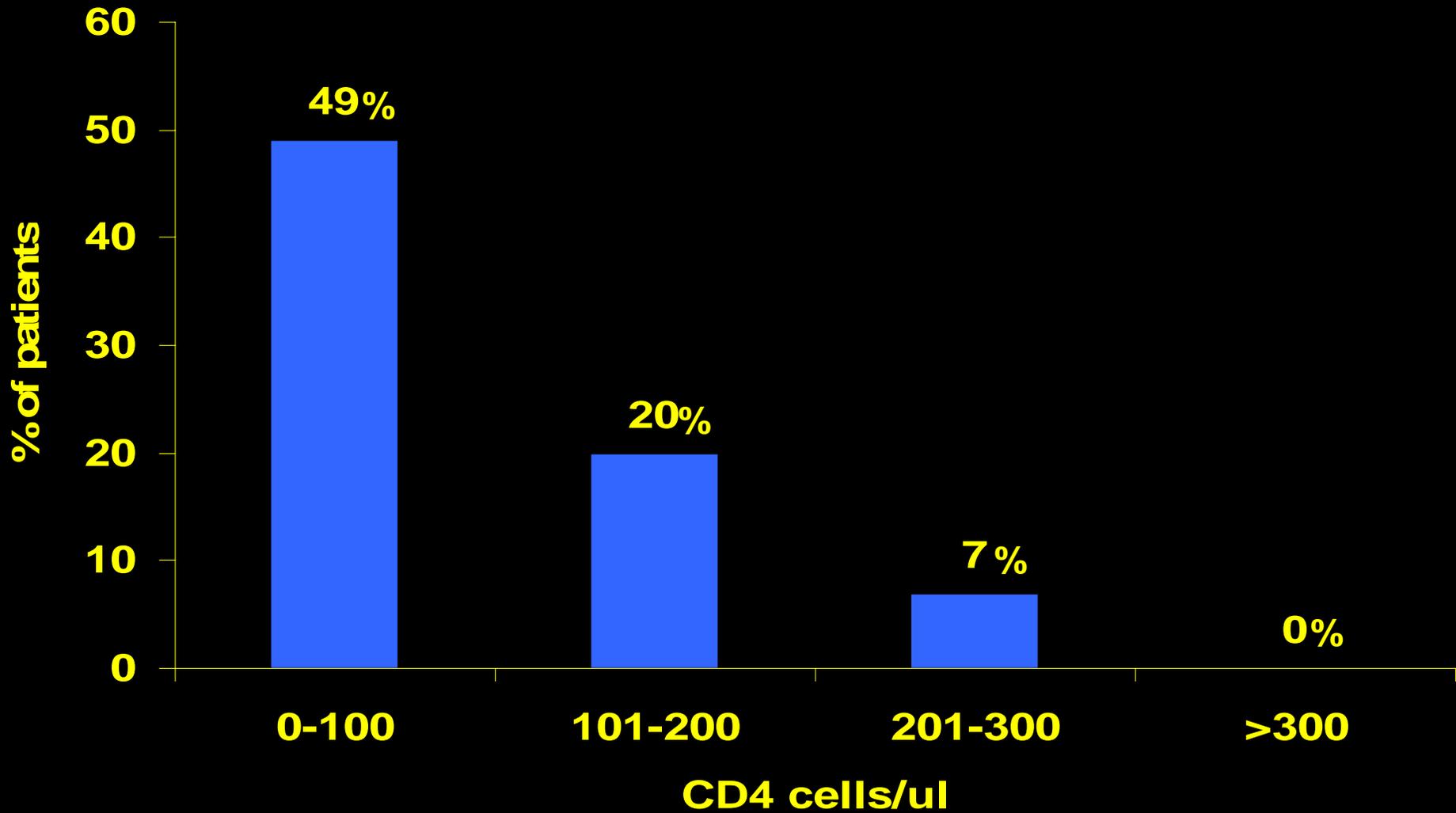
# Smear microscopy is the mainstay of TB diagnosis in resources limited testing

- In HIV+ smear microscopy are more likely to be negative or scanty –
- Diagnosis improves
  - Concentrated specimens,
  - Use of fluorescent microscopy,
  - Sputum culture,
  - Rapid cultures.

# Diagnosis of HIV-related **MDR-TB**

- The use of culture for the diagnosis of TB in HIV patients is recommended as the **standard of care**
- Protocols for diagnosis of MDR-TB in HIV follow the same principles as for HIV-negative patients.
- Culture and DST should always be performed, even if extra-pulmonary MDR-TB is suspected.
- Blood cultures for tubercle bacilli sometimes yield positive results.

# Frequency of mycobacteremia in patients with HIV infection and TB



# Radiological features of pulmonary TB in 963 HIV+ adults compared to 1000 HIV- adults with TB

<i>Radiological feature (n=1000)</i>	<i>HIV-positive (n=963)</i>	<i>HIV-Negative</i>
<b>Cavitation</b>	<b>319 (33%)</b>	<b>784 (78%)</b>
<b>Lymphadenopathy</b>	<b>253 (26%)</b>	<b>131 (13%)</b>
<b>Pleural effusions</b>	<b>159 (16%)</b>	<b>68 (7%)</b>
<b>Miliary pattern</b>	<b>94 (9.8%)</b>	<b>52 (5%)</b>
<b>Atelectasis</b>	<b>112 (12%)</b>	<b>237 (24%)</b>
<b>Consolidation</b>	<b>94 (10%)</b>	<b>32 (3%)</b>
<b>Interstitial changes</b>	<b>120 (12%)</b>	<b>68 (7%)</b>

Tshibwabwa-Tumba, et al. *Clinical Radiology* 1997;  
52:837-841.

# Goals of antiretroviral therapy

- The primary goal of antiretroviral therapy is to decrease HIV-related morbidity and mortality:
- The patient should experience fewer HIV-related illnesses;
- The patient's CD4 count should rise and remain above the baseline count;
- The patient's viral load should become undetectable ( $< 400$  copies/ml) and remain undetectable on ART.

International guidelines refer to clinical staging and CD4 count as criteria to initiate ART in drug-susceptible TB patients ([URL to WHO ART Guidelines](#));

### ■ **Reasons to start ART early**

- To decrease HIV/AIDS associated morbidity and mortality.
- ART in HIV co-infected MDR-TB patients has been associated with improved survival and decreased acceleration to AIDS.

### ■ **Reasons to delay initiating ART**

- Overlapping side effects from ART and MDR-TB drugs;
- Complex drug-drug interactions;
- Occurrence of immune reconstitution syndrome;

# WHO criteria for clinical staging and CD4 count for consideration of ART in drug susceptible TB patients are as follows:

- WHO clinical stage 4, irrespective of CD4 count
- WHO stage 3 and CD4 < 350/mm<sup>3</sup>
- WHO stage 1 or 2 with CD4 < 200/mm<sup>3</sup>

# MDR-TB treatment in HIV+

- MDR-TB treatment is the same for HIV-positive and HIV-negative patients,
- **Exception of thioacetazone, which should not be used in the HIV-positive patient.**
- MDR-TB treatment is much more difficult and adverse events much more common in HIV-positive patients.
- Deaths during treatment, partly due to MDR-TB and partly due to other HIV-related diseases
- Patients already on antiretroviral treatment when MDR-TB is diagnosed should immediately be started on appropriate MDR-TB treatment.

# Patient develops MDR-TB while on ART

- MDR-TB develops while on ART
  - Continue ARV therapy throughout MDR-TB treatment
  - Patients on first-line therapy containing nevirapine should generally be swapped to efavirenz as follows:
    - **First-line therapy:**
      - 1. **Stavudine** 40mg (or 30mg if <60kgs) every 12 hours +
      - 2. **Lamivudine** 150mg every 12 hours +
      - 3. **Efavirenz** 600mg at night

# Optimal time for initiating ART in MDR-TB patients is not defined, simultaneous initiation of both treatments is discouraged

- MDR-TB treatment should be started first
- ART according to the patient's clinical condition and CD4 levels
- In countries with a high HIV burden - ART in the first few months of MDR-TB treatment in patients with low CD4 counts
- ART can be deferred in MDR-TB patients with relatively high CD4 counts

# Treatment of adult patients with concomitant MDR-TB

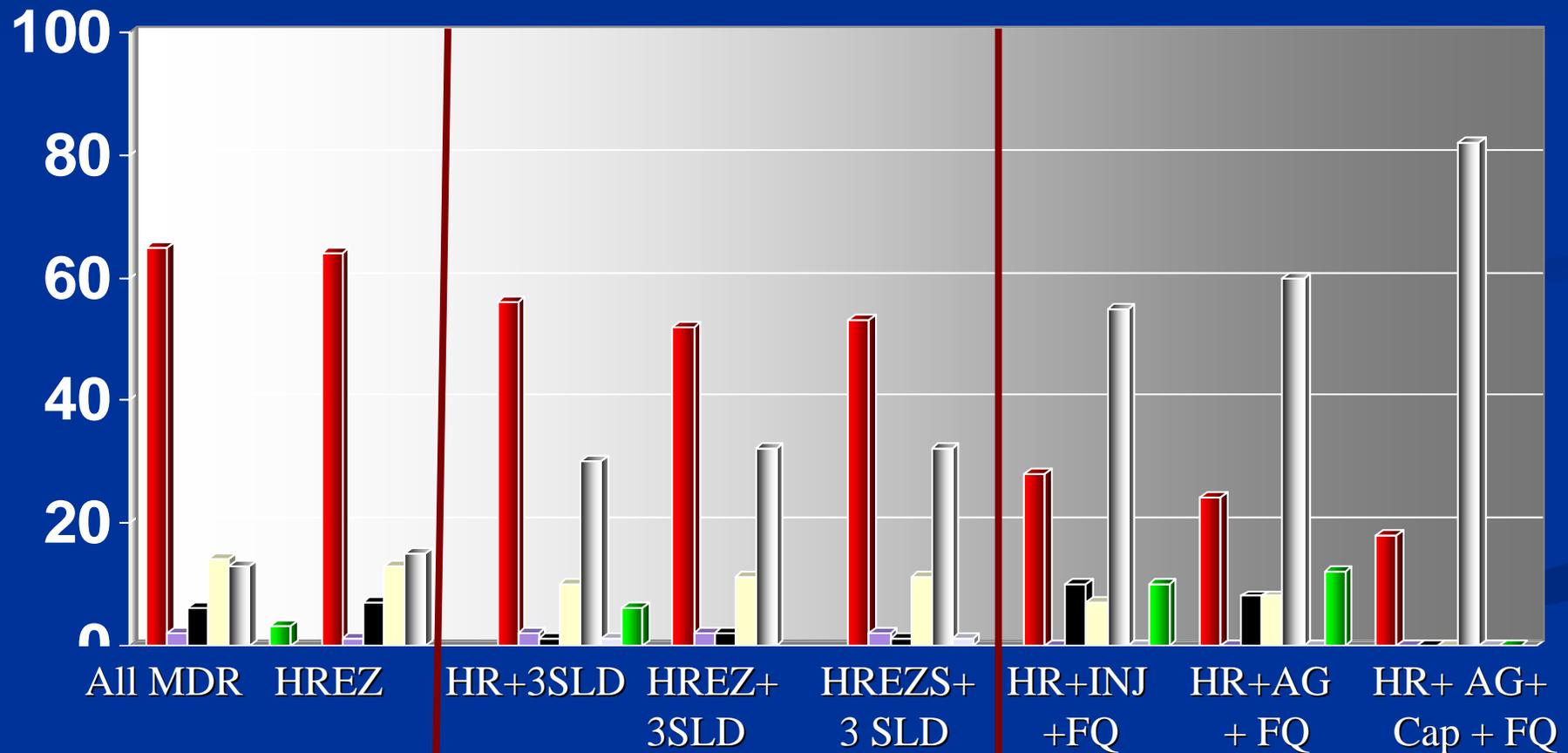
- MDR-TB is present before starting ART
  - CD4+ count > 200/mm<sup>3</sup> (and no other HIV-related symptoms):
    - Start MDR-TB treatment. Assess the need for ART after completing MDR-TB therapy, using CD4 and clinical criteria
  - CD4+ count < 200/mm<sup>3</sup>:
    - Delay ARVs until after 4-months of MDR-TB therapy.
    - Then start first line therapy as outlined below.
  - CD4+ count of < 50/mm<sup>3</sup> or other serious HIV illness: introduce ART as soon as the patient is stabilized on MDR-TB therapy (no less than 4 weeks between starting MDR-TB therapy and starting ART).
  - **First-line therapy::**
    - 1. Stavudine 40 mg (or 30mg if <60kg) every 12 hours +
    - 2. Lamivudine 150mg every 12 hours +
    - 3. Efavirenz 600mg at night

# Treatment outcomes for TB/HIV

	HIV-infected non MDR-TB patients n=98 (%)	HIV-infected MDR-TB patients n=23 (%)	
Treatment success	74 (76%)	13 (56%)	
Defaulters	15 (15%)	5 (22%)	} Relative risk=1.8 (1.0 -3.2) p=0.07
Failure	2 (2%)	3 (13%)	
Death	7 (7%)	2 (9%)	

# Treatment outcomes stratified by different resistance patterns 2000-2003, 820 patients, Latvia

■ Cure 
 ■ Completion 
 ■ Death 
 ■ Default 
 ■ Failed 
 ■ Continue Tx 
 ■ HIV+



# HIV associated XDR-TB in KwaZulu-Natal, South Africa

- 221 MDR-TB patients detected from January 2005 to March 2006;
- 53 (23%) were also resistant to Kanamycin and Ciprofloxacin = XDR-TB;
- 44 (100%) were tested for HIV and was HIV+;
- 52 (98%) patients died median in 16 days of initial sputum collection;
- 16 (30%) of them who died were received ART;

# Co-management of HIV and XDR-TB

- Prolonged co-administration of SLDs and ARVs
  - intolerance and adherence
  - drug-drug interactions (initial and cumulative)
  - is cure possible?
- Potential impact of immune restoration with
  - unrestricted TB multiplication
  - when to start ART with suspected XDR-TB
  - ART in patient with undiagnosed XDR-TB
  - any role for steroids?
- *Identification of XDR-TB and prompt, appropriate action may be significantly compromised by HIV will add significant challenges to the clinical management of XDR-TB*

# Immune reconstitution syndrome

- Reactions usually occur within a median of 15 days after initiation of ART.
- Usually in patients with advanced AIDS CD4 count  $< 50$  cells/mm<sup>3</sup>
- **It is not a reason to stop either MDR-TB or ART**
- Management includes high doses of corticosteroids
- Risk development of complications due to prolonged use of steroids (eg. *Cytomegalovirus* infections).
- Non-steroidal agents tend to not be helpful

# General challenges: lack of tools

## 1. Diagnosis of (M)DR/XDR

- Rapid and accurate diagnostic tests
- Laboratory capacity and strengthening

## 2. Treatment of (M)DR/XDR patients

- Cannot survive with existing drugs
- Lacking new effective drugs

# Monitoring of drug resistant TB and HIV therapy in co-infected patients

- Patients must receive HIV medicines everyday (MDR-TB treatment can be skipped on Sundays)
- While on treatment of MDR-TB, DOT of ART should be included.
- In some patients, DOT or a modified form of it may need to continue with ART after the MDR-TB treatment has finished.
- ART and drug resistant TB treatment, each with its own toxicity profiles
- HCW knowledge needed in both drug resistant TB and HIV
- Viral loads and CD4 counts should be measured to ensure that the patient is improving; if test results suggest virological HIV treatment failure, there needs to be an assessment of adherence, regimen potency, adequate absorption, or determination of possible ART resistance.

# XDR Focus on implementation of existing IC guidelines

- Endorse existing IC international guidelines – focus on implementation
- Establish IC Teams with clear responsibility
- Implement early detection (smear proficiency and turn-around, connect to existing ref. lab, explore rapid tests) and triage suspects
- Implement basic environmental controls – space use, open windows, etc.
- Remove barriers to prompt effective treatment
- Require worker HIV testing to work in high-risk situation
  - Consult implementation experts
  - Identify barriers to implementation and find solutions