The scale up of TB/HIV collaborative activities in Asia-Pacific

TB/HIV Operational Research: Needs and Recent Advances

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Operational Research: Definition

“Operational research is concerned with the day to day operations of programs. It is intended to provide managers, administrators, and policy-makers with the information that they need to improve service delivery activities and plan future ones. It seeks practical solutions to problem situations and viable alternatives to unsatisfactory operating methods.”

Operational Research should:

- Address country-specific TB/HIV control issues
- Be conducted rapidly, with involvement from programme managers
- Lead to specific recommended interventions, including changes in national policy and national strategies

Examples of Operational Research Questions for TB/HIV in Asia

- In HIV-infected patients diagnosed with TB, how do you reduce mortality?
- What is the best way to screen for and diagnose TB in people with HIV?
- Which TB infection control measures are most effective/cost-effective?
- What is the yield of contact-tracing among patients with pulmonary TB for TB case-finding? HIV case-finding?
- What is the cost-effectiveness of new diagnostic tests?

Need for intensified TB case finding among people with HIV

- Case-fatality rate for HIV-infected TB patients high (up to 25-50% during TB treatment)
- About half of deaths occur within 2 months
- Early diagnosis should decrease case-fatality
- Improve safety of ART initiation
- Improve uptake of IPT
- WHO recommendation

Difficulty of TB screening in HIV-infected persons

- HIV-infected TB patients often lack classic TB symptoms
- Up to 30% of HIV-infected TB patients with pulmonary TB have a normal chest radiograph
- Sputum smears may be negative in 50% or more
- Currently, no internationally accepted, evidence-based approach to screening

Improving the Diagnosis of TB in HIV-infected Persons in SE Asia

- Objectives are to:
  - Develop an evidence-based clinical algorithm with high sensitivity to rule-out TB in HIV-infected persons
  - Develop an algorithm with high specificity to diagnose TB in HIV-infected persons
- Algorithm based on all patients, i.e. no assumptions about importance of cough or other symptoms
- Enroll broad cross-section of HIV-infected persons from multiple settings
- Use a sensitive combination of microbiological tests as the gold-standard

Enrollment Sites & Sample Size

- **Total planned enrollment: 2,050 across 3 countries**
  - **600 in one site in Bangkok, Thailand**
  - **1,000 in four sites in Cambodia**
  - **450 in three sites in Ho Chi Minh City, Vietnam**

Thailand

Bangkok

Cambodia

Phnom Penh

Battambang

Sereysophon

Mongkul Borei

Vietnam

Ho Chi Minh City

Study procedures

- Informed consent
- Questionnaire administered by doctor/nurse
- Patient examined by doctor
- Chest radiograph
- Lab tests: Blood count, CD4
- Microbiology
  - Culture and smear of 3 sputum, 1 urine, 1 stool, and 1 blood specimen
  - Lymph node aspirate cx if enlarged peripheral node
- Optional tests (by site): TST, HIV viral load

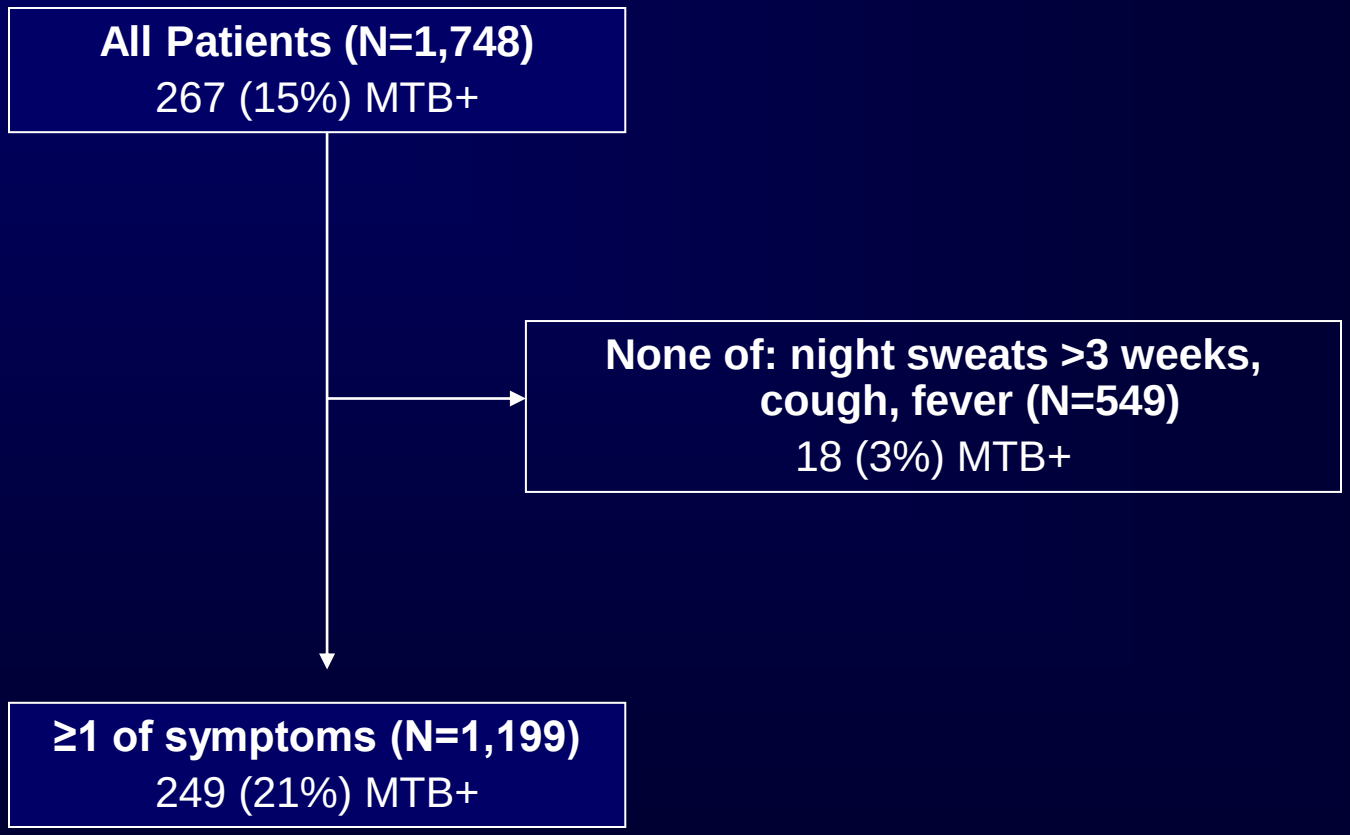
Summary results: TB screening

- Chronic cough, or any other single symptom, is not sufficiently sensitive for TB screening in people with HIV
- Combination of symptoms achieves sensitivity >90%
  - Much better than standard methods
  - Achieving 100% not feasible

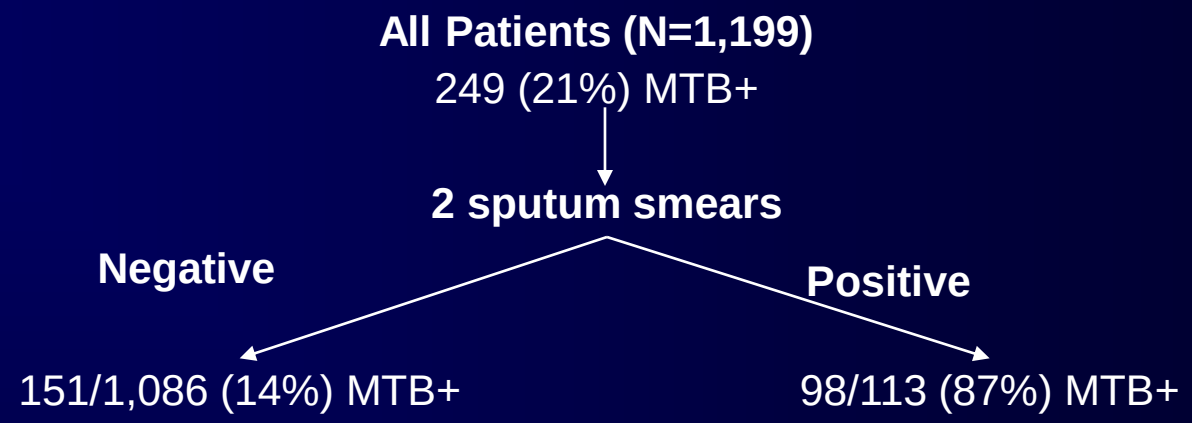
Some candidate combinations

Rule	Sens (%)	Spec (%)
1 of 2 rules		
Cough, fever	91	37
Cough in past 24 hours, fever	88	44
1 of 3 rules		
Cough, fever, drenching night sweats ≥3 weeks	93	36
Cough, drenching night sweats, loss of appetite	93	35
Cough in the past 24 hours, fever, drenching night sweats ≥3 weeks	90	43

Application of candidate approach to screening



Diagnostic Algorithm



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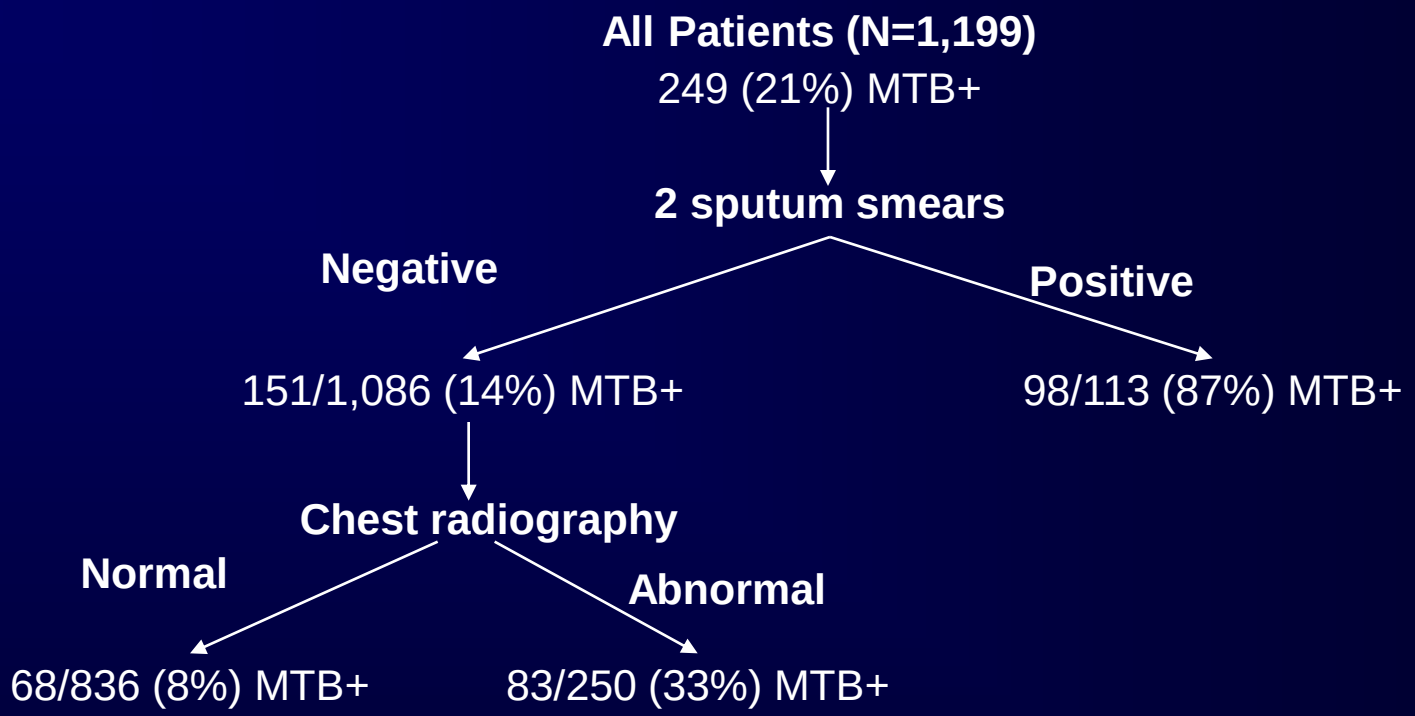

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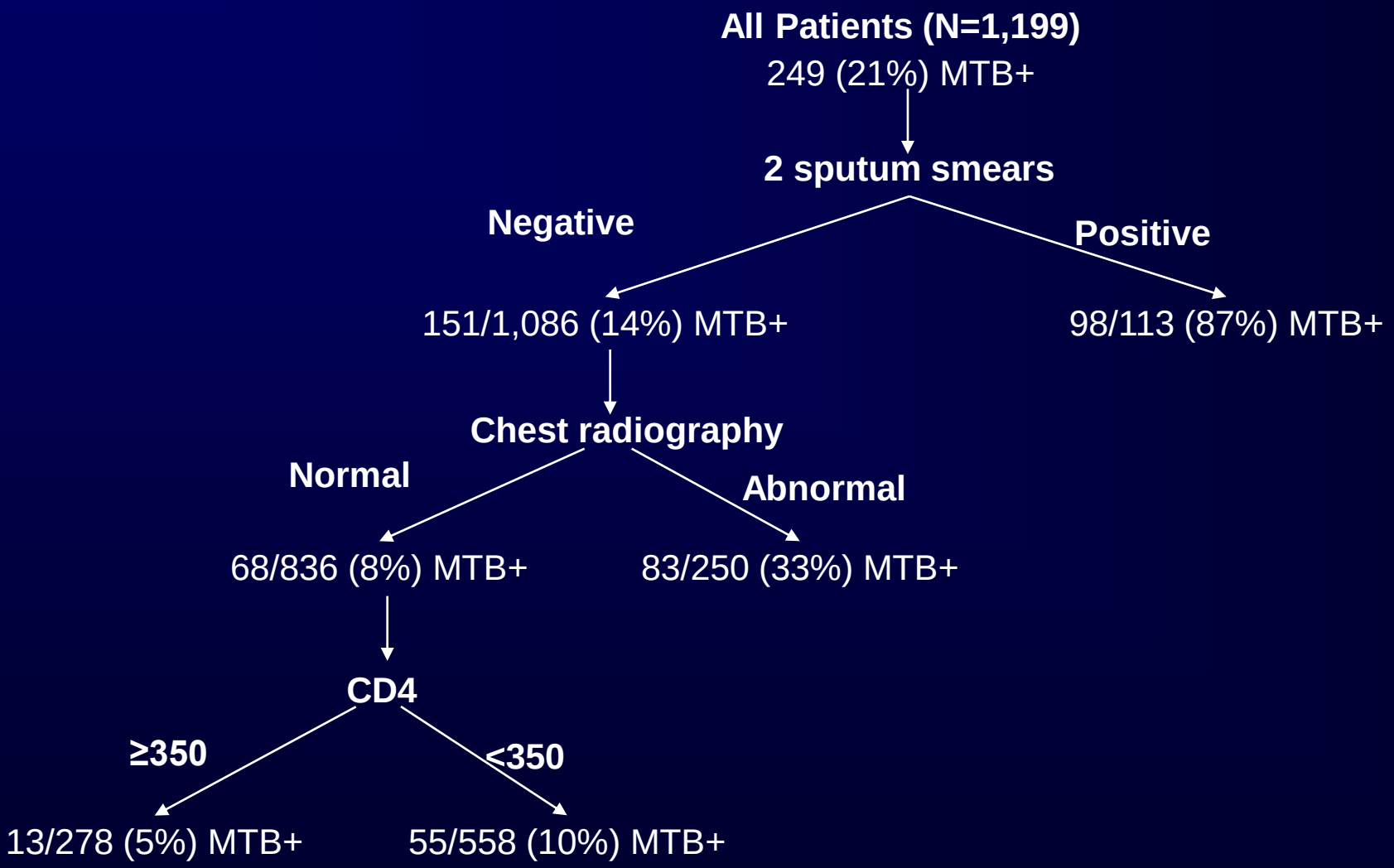

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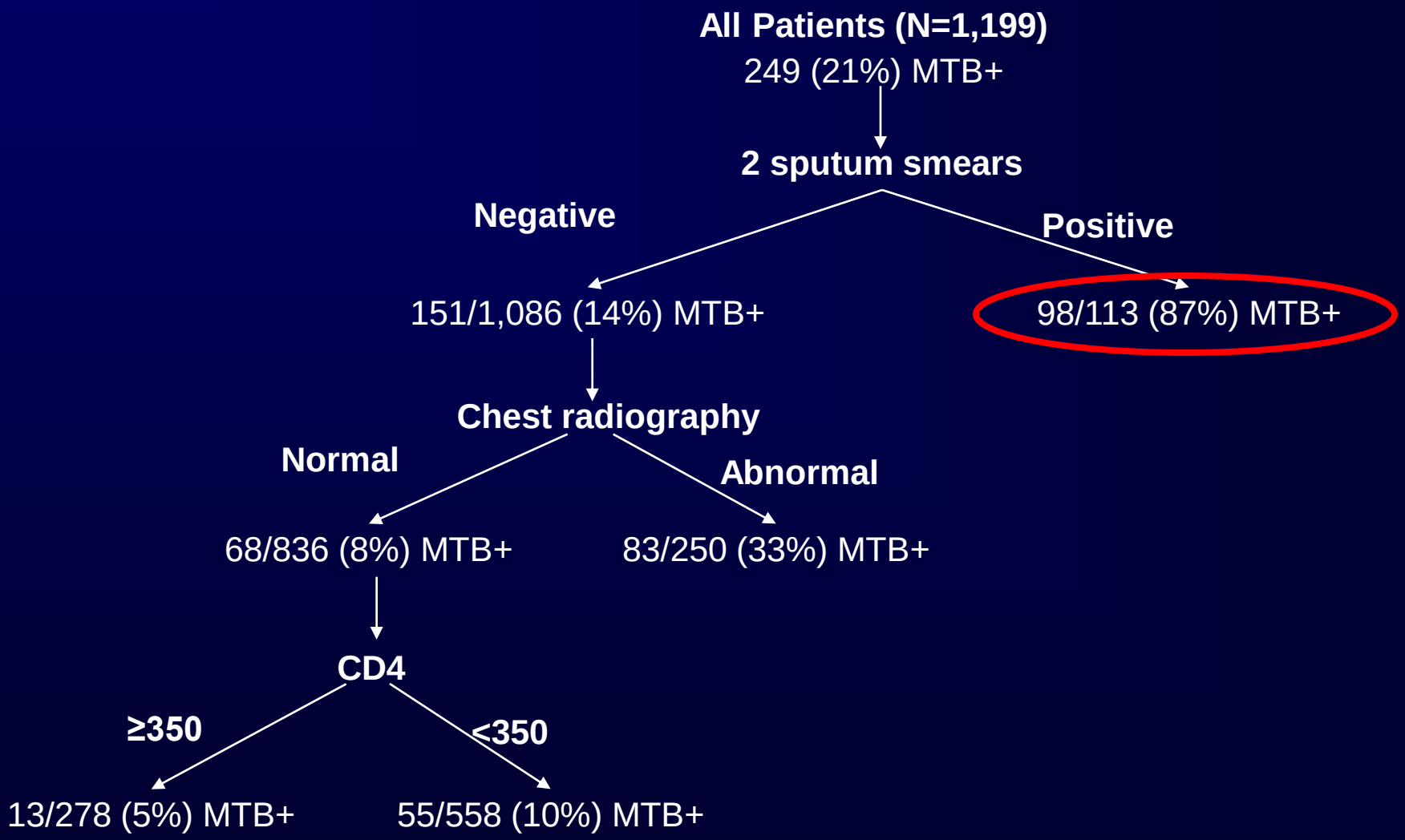

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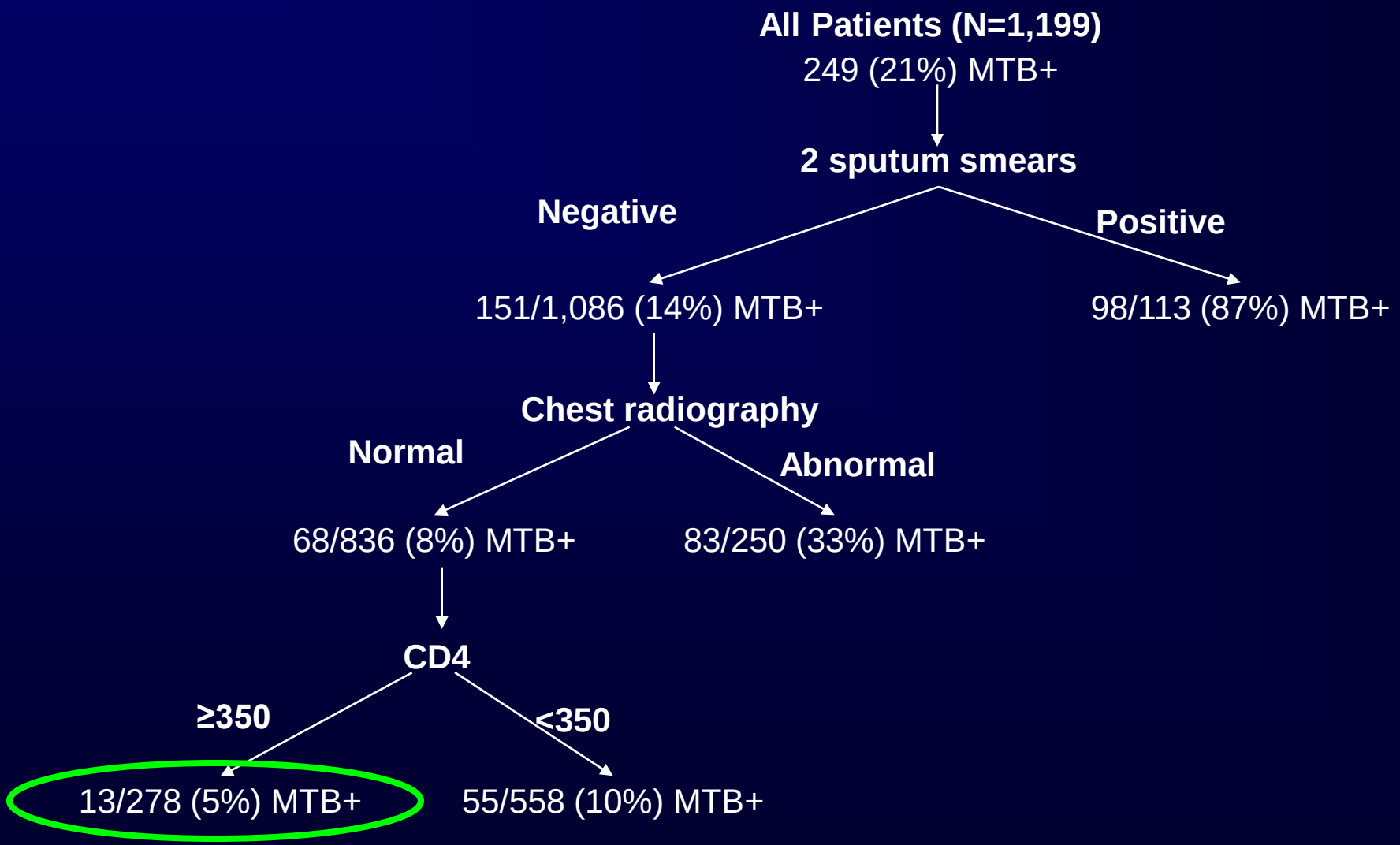

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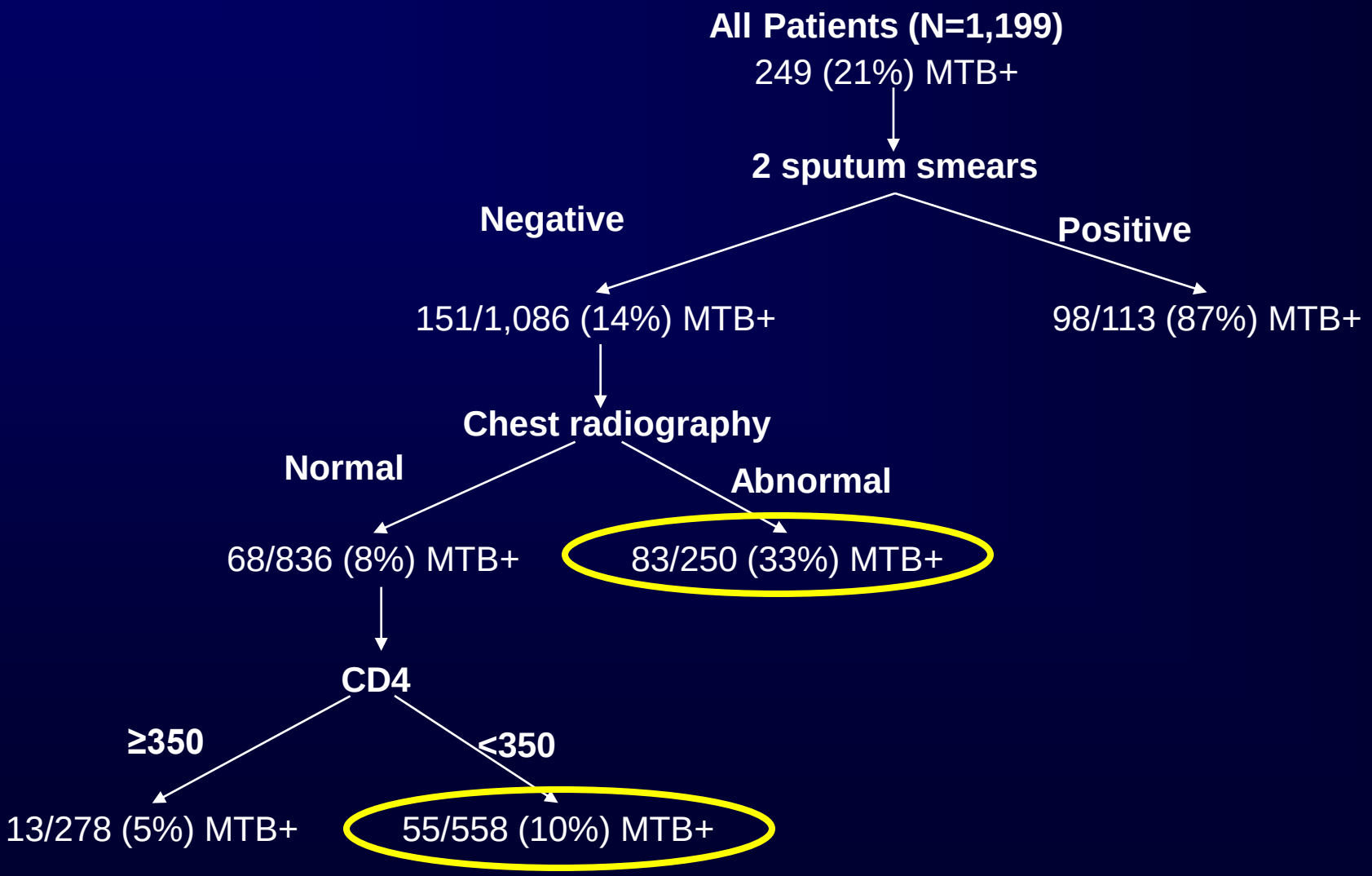

Comparison to other commonly used approaches

- We compared this algorithm to other commonly used approaches
  - WHO diagnosis of smear-negative TB, recommends initial screening for cough >2 or 3 weeks
  - Alternative: Sputum smears and chest radiography for every patient, TB ruled out if both negative
- Evaluated number of false negatives, resource utilization, and characteristics of false negatives

Comparison of approaches (N=1,748 patients)

	WHO	Smear/x-ray	Algorithm
# excluded by symptom screen	1,393	N/A	549
# patients needing smears	355	1,748	1,199
# x-rays	300	1,748	1,086
# needing TB culture	300	N/A	808
# False negatives	≥179	75	31
False negatives, median CD4	398	146	112

Conclusions: Screening

- Cough ≥2 or 3 weeks insensitive (22-33% sensitivity), should not be used alone as initial screening
  - WHO algorithm for diagnosing smear-negative TB should be modified
- No other single symptom sufficiently sensitive
- Combination of symptoms (1 of 3)
  - Can be highly sensitive
  - Example – any 1 of: night sweats ≥3 weeks, fever, cough
  - Simple, performs as well as or better than other approaches that we evaluated

Conclusions: Diagnosis

- Best approach based on available data
  - Symptom screen, then
  - Sputum smears, then chest radiograph, then CD4 testing
- It is ok if some steps occur at the same time, then this can be used as a decision tree
- Decreases smear and chest radiograph utilization
- Culture required for at least ~45% of people with HIV in order to diagnose TB
- Liquid culture much more sensitive than solid culture (data not shown)

Some next steps

Cambodia

- Cambodian Revised TB/HIV Framework/SOP drafted
- New guidelines to be implemented in next year
- Evaluation of new algorithm in field setting
  - Use new algorithm in selected sites; include IPT track for those eligible
  - Evaluate performance, acceptability, resources

International

- Meta-analysis including this and other studies → expert meeting Oct 2009 to revise WHO guidelines for ICF in PLHA
- Enhanced evaluation of algorithm (Thailand, Viet Nam, Kenya)
- Cost-effectiveness analysis (Thailand)

Summary

- Important new research findings on how to screen for TB among PLHA should reduce deaths
- Ongoing evaluation required to confirm algorithm performance
- High-quality operational research can address important programmatic questions and provide practical recommendations
- Requires:
  - Well-defined questions
  - Engagement of programme managers at all stages of planning, implementation, analysis (partnerships!)
  - Effective, rapid sharing of findings

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