Intensified TB Case Finding among HIV-infected Persons in Resource-limited Settings

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Need for intensified TB case finding

- 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

Key research questions

- Is there a clinical algorithm sufficiently sensitive to exclude TB in HIV-infected persons?
- Is there a clinical algorithm sufficiently specific to rule in TB in HIV-infected persons?
- What is the incremental yield of microbiologic tests on sputum in HIV-infected persons?
- What is the incremental yield of microbiologic tests on non-sputum specimens in HIV-infected persons?

Key research questions

- What is the frequency with which screening should be performed?

- Should the type or frequency of screening vary according to CD4, ART, country of origin, and other critical variables?

- What is the impact of implementing evidence-based screening algorithms on reducing TB incidence and mortality in HIV-infected persons commencing ART or IPT?

Review of published studies

- CDC reviewed data on available studies
  - PubMed search
  - Nine published studies identified
- Many do not use culture as gold standard
- Others enroll a limited population (e.g. hospitalized patients)
- Focus on 3 studies
  - Culture as gold-standard
  - Population less limited than some others

Focus on clinical algorithms

- **Primary goal to identify sensitive algorithms for ruling out TB disease, including assessment of predictive value of cough**
  - **This is a main barrier to early identification of TB and safe initiation of ART and IPT**
- **Secondary goal to identify algorithms which were specific for the diagnosis of TB disease**

Day, et.al. – South Africa

Setting	South Africa
Study pop.	899 HIV-infected miners being evaluated for IPT
TB def'n	Culture positive or clinical improvement
# with TB	44 (5%) patients met definition for TB, 35 of these had a positive culture
Cough	Cough >3 weeks 14% sensitive, 88% specific
Algorithm	Best combination of signs and symptoms - any 1 of: night sweats, new or worsening cough, weight loss >5%, abnormal CXR. Sensitivity 91%, specificity 59% Best sx combination: night sweats, cough, reported weight loss. Sensitivity 59%, specificity 76%.

Mohammed, et.al. – South Africa

Setting	South Africa
Study pop.	129 stage 3 and 4 HIV+ referred for IPT (TB suspects were not referred)
TB def'n	Definite = cx confirmed, probable = smear+, possible = clinical dx with response to treatment
# with TB	11 (9%) with TB (10 culture-confirmed)
Cough	Cough >2 weeks 82% sensitive, 79% specific
Algorithm	Two or more of: measured weight loss (>2.5%), cough, night sweats, or fever. Sensitivity 100%, Specificity 88%

Kimerling, et.al – Cambodia, 2002

Setting	Cambodia
Study pop.	441 HIV+ in home-based care
TB def'n	Single sputum culture
# with TB	41 (9%) with culture-confirmed TB
Cough	Cough >3 weeks 65% sensitive, 33% specific
Algorithm	Any 1 of: cough>3 wks, hemomptysis, weight loss, fever, night sweats, or weakness – 95% sensitivity, 10% specificity

Unpublished studies

Kimerling, et.al. - Cambodia

Setting	Cambodia
Study pop.	496 HIV+ and HIV- at VCT in Battambang, Cambodia
TB def'n	Sputum culture
# with TB	29 (6%) with culture-confirmed TB
Cough	Cough >3 weeks 59% sensitive
Algorithm	Any 1 of: Hemomptysis, fever, weight loss – 100% sensitivity

Shah, et.al. - Ethiopia

Setting	Addis Ababa, Ethiopia – community hospital
Study pop.	438 newly diagnosed HIV+
TB def'n	Concentrated sputum smear and culture
# with TB	32 (7%) with culture-confirmed TB
Cough	Cough 44% sensitive, 76% specific
Algorithm	Cough or fever – 75% sensitivity, 57% specificity

Status of current evidence

- **Evidence shows that chronic cough may be insufficiently sensitive, combination of symptoms likely needed**
- **Limitations to previous studies:**
  - **Single-center studies**
  - **Pre-screened patients already defined as "TB suspects"**
  - **Referral patients / hospitalized patients only**
  - **No "gold-standard" evaluation for TB**

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

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**

Study population

- **Persons newly diagnosed with HIV at VCT**
- **Persons with previous HIV diagnosis newly presenting to HIV clinic or CD4 test site**
- **Persons already enrolled in HIV care, some of whom are already on ART**

Eligibility Criteria

- Documented HIV infection
- Age ≥ 7 years
- Not currently being treated for TB
- No TB treatment or IPT within one year
- No TB screening (x-ray or sputum smears) within previous 3 months
- No medications with anti-TB activity within past 1 month

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**

Laboratory procedures

- **U.S. CDC assessed all participating laboratories and worked with them to implement standardized SOPs**

- **One reference laboratory in each country participating in study**

- **All laboratories use LJ for solid culture**

- **Vietnam and Thailand also use liquid culture (MGIT)**

Analysis

- A TB case is any patient with a specimen culture-positive for Mycobacterium tuberculosis
- Characteristics of patients with TB compared to those without TB
- Logistic regression + classification & regression tree analysis

Enrollment to date

Country	Enrolled as of 1/15/2008	Included in this analysis
Thailand*	600	582
Cambodia	750	369
Vietnam	196	0
TOTAL	1,546	951

*Enrollment completed

Patient characteristics

Characteristic	n (%) N=951
Female sex	464 (49)
Median age (range)	33 (7-65)
Hospitalized at enrollment	22 (2)
On ART at enrollment	180 (19)
Median CD4 (range)	291 (1-1,695)

Total number with TB

Country	Total with culture results	Culture-positive for TB	Smear-positive
Thailand	561	27 (5)	10 (37)
Cambodia	360	39 (11)	15 (38)
TOTAL	921	66 (7)	25 (38)

Evaluation of cough as predictor of TB

Criteria	Cx+ TB (N=66) n (%)	No TB (N=861) n (%)	Sensitivity	Specificity
Any cough	47 (71)	382 (44)	71	56
Cough >2 weeks	19 (29)	126 (15)	29	85
Cough >3 weeks	16 (24)	81 (9)	24	91

**Any 1 of: cough, fever, weight loss: 91% sensitive, 33% specific

Other signs, symptoms, and test results associated with TB*

- **Symptoms**
  - Loss of appetite
  - Cough
  - Weight loss
  - Difficulty breathing
  - Fatigue
  - Fever
  - Shaking chills
  - Night sweats
  - Chest pain
  - Abdominal pain
  - Nausea / vomiting

- **Signs**
  - Temp > 37.5 (or 38)
  - BMI < 18.5
  - Lymphadenopathy of head & neck
- **Other**
  - Hemoglobin <10
  - TST positive
  - Hospitalized at enrollment
  - Not on ART
  - CXR (?)

*All significant at level of p <0.01

Validation of proposed algorithms using ID-TB/HIV study data

Algorithm	Sens	Spec
Day (cough, NS, wt. loss)	86	34
Mohammed (any 2 of cough, NS, fever, measured wt. loss >2.5%)	74	61
Any one of above (Mohammed)	91	33
Kimerling – 2002 (cough >3 wks, hemoptysis, wt. loss, fever, NS, weakness	82	45
Kimerling – 2007 (hemoptysis, wt. loss, fever)	82	47
Shah (cough or fever)	89	43

Table. Approaches for Detecting Tuberculosis in Patients with HIV Infection

Diagnostic Approach	Early HIV Disease WHO Stage 1-2 CD4 >250	Late HIV Disease WHO Stage 3-4 CD4 <250
Symptom Review • Have you had cough > 2weeks? • Have you lost >2 kg recently? • Do you have fevers? • Do you have night sweats? • Do you have chest pain?	All patients (Symptom screen positive if answer is yes for cough or yes for 2 or more of remaining questions)	All patients (Symptom screen positive if answer is yes for cough or yes for 2 or more of remaining questions)
Sputum Smear	If symptom screen +	All patients
Sputum Culture	If available and symptom screen +	All patients if available
Chest x-ray	Not required	Optional if available, especially for symptom screen +
Tuberculin skin test or Inteferon-gamma release assay	Not required	Not required

Evaluation of algorithm from IPT consensus statement

- **CD4 <250:**
  - 382 total patients, 38 (10%) with TB
  - 35 (92%) of TB had positive sx screen
  - Sx screen 92% sensitive, 51% specific
- **CD4 >250:**
  - 541 total patients, 27 (5%) with TB
  - 14 (52%) of TB had positive sx screen
  - Sx screen 52% sensitive, 64% specific

Sensitivity and specificity of algorithms, stratified by CD4 count

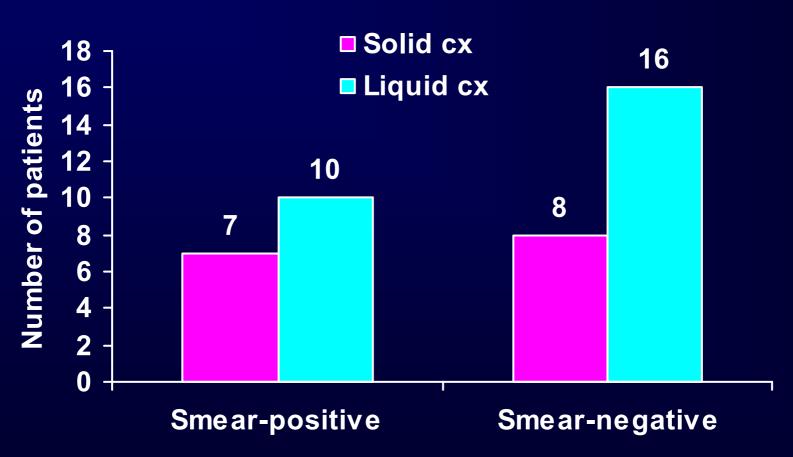| Algorithm	CD4 < 250		CD4 >250	
	Sensitivity	Specificity	Sensitivity	Specificity
Day	97	31	70	39
Mohammed	92	51	48	67
Kimerling	92	35	67	54
Shah	95	37	81	47
Pre-IPT	92	51	52	64
Cough/fever /wt. loss	97	27	81	37

Added yield of non-sputum specimen collection

- 66 with any culture positive for TB
  - 51 had positive sputum culture on solid media
  - 12 of the remaining 15 had positive sputum culture on liquid media
  - 2 had no liquid culture of sputum performed, but had positive blood culture
  - 1 had negative liquid culture of sputum but positive stool culture on liquid media

Impact of liquid media on diagnosis of TB
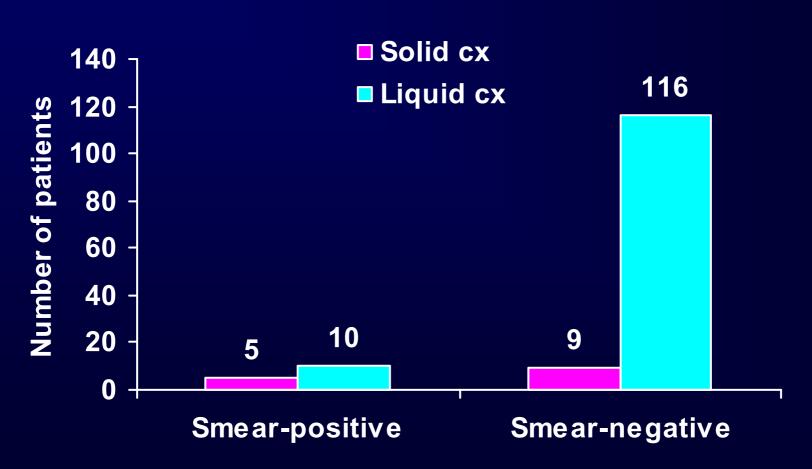Limited to Thailand, N=571

High burden of NTM

Country	Total with culture results	≥ 1 culture positive for NTM	≥ 2 cultures positive for NTM
Thailand*	561	127 (22)	37 (7)
Cambodia	360	1 (0)	0
TOTAL	921	128 (14)	37 (4)

*Thailand uses liquid culture

Impact of liquid media on identification of NTM

Limited to Thailand, N=571

Details of NTM isolated

- 38/127 (30%) patients with NTM on culture had at least
  - 2 positive cultures
  - Pulmonary symptoms or an abnormal CXR
  - OR ≥ 1 culture positive from normally sterile site
- 11 identified with HPLC as of now
  - 5 chelonae / abscessus
  - 2 kansasii
  - 2 fortuitum / peregrinum
  - 1 MAC
  - 1 gordonae

Conclusions from study

- **Chronic cough alone insensitive predictor of TB**
- **Simple symptom-based algorithms with sensitivity >80-90% feasible**
- **At CD4 <250, symptom screening may be able to rule out TB**
- **At CD4 >250, symptom screening may not be able to rule out TB**

Conclusions from study

- At any CD4 count, diagnosing TB requires sputum culture, ideally liquid culture, as smear microscopy misses too many cases
- NTM are commonly isolated, particularly with liquid media
  - Identification is essential
  - Many likely disease-causing NTM identified

Research questions remain

- Are findings from settings outside of Asia similar?

- What is the appropriate frequency of screening?

- Once implemented, how well will these algorithms perform?

- What impact will evidence-based algorithms have on TB incidence and mortality?

Recommendations

- For WHO smear-negative algorithm: cough>2 or 3 weeks should not be used alone as entry point because it does not capture enough TB suspects
- For IPT consensus statement: current algorithm may need revision, as it may perform too many cultures in CD4 <250 and too few in CD4 >250
- More evidence needed
  – Conduct similar studies in sub-Saharan Africa
  – Convene an expert working group that will perform meta-analysis of existing data and develop interim TB screening guidelines

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Extra slides

Sensitivity of combinations of liquid culture in Thailand

Combination	Number of TB patients identified (%) (N=27)
1 liquid sputum cx	19 (73)
2 liquid sputum cx	23 (85)
3 liquid sputum cx	25 (93)
1 liquid sputum + blood	21 (78)
1 liquid sputum + liquid urine	20 (74)
1 liquid sputum + liquid stool	20 (74)

TST result sensitive marker of TB disease

Criteria	Cx+ TB (N=26) n (%)	No TB (N=516) n (%)	Sensitivity	Specificity
TST >5mm	17 (65)	109 (21)	65	79
TST >10mm	17 (65)	99 (19)	65	81
TST >15mm	16 (62)	78 (15)	62	85

Limited only to data from Thailand

Positive cultures by specimen type

Specimen	Total number of cultures	Culture-positive for TB
Sputum #1	945	49 (5)
Sputum #2	934	45 (5)
Sputum #3	936	46 (5)
Urine	940	8 (1)
Blood	942	6 (1)
Stool	931	18 (2)
Lymph node	47	6 (13)

Contamination rate by specimen type, solid media

Specimen	Total number of cultures	Contaminated
Sputum	2816	100 (4)
Urine	940	28 (3)
Blood	943	19 (2)
Stool	941	147 (16)

Contamination rate by specimen type, liquid media

Specimen	Total number of cultures	Contaminated
Sputum	1,672	136 (8)
Urine	567	9 (2)
Stool	563	107 (19)

Smear result vs. culture

	Culture positive TB	Culture positive NTM	Culture negative	TOTAL
Smear positive	7	5	0	12
Smear negative	21	79	373	473
TOTAL	28	84	373	485