hiv & aids treatment in practice

Think TB in people with HIV: start routinely screening for TB now

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This article forms part 1 of a special double edition of HIV & AIDS Treatment in Practice on intensified TB case finding in people with HIV, kindly supported by the World Health Organization Stop TB Department.

Intensified case finding

"Intensified TB case finding" (ICF) is an activity, recommended by the World Health Organization (WHO), intended to detect possible TB cases as early as possible among people living with HIV – usually by using a simple questionnaire for the signs and symptoms of TB. ICF does not mean making a TB diagnosis, but it is the first step towards making a diagnosis. Ultimately for ICF to make a difference, people suspected of having TB should receive a thorough diagnostic evaluation, with timely results, and begin appropriate treatment, either to cure active TB or prevent it.

TB control programmes generally rely on passive TB case finding – where the onus is on the individual with TB to come in for diagnosis and care.

There isn't time for that in people with HIV, who are at much greater risk of getting TB (often aggressive cases including hard-to-diagnose smear-negative or extrapulmonary disease) and, if not treated soon enough, dying from it. And wherever there is a high burden of TB/HIV coinfection, these effects have been amplified – leading to the breakdown of TB control, with the number of new cases of TB growing dramatically in the last 15 years.

People who learn that they are HIV-positive and begin ART can reduce their risk of TB by about two-thirds. But according to data from South Africa, three years after starting ART, the TB incidence is still 4.5-fold higher than the reported rate for the general population (Lawn).

In another South African study, the absolute number of smear-positive TB cases among people with HIV (4441 cases per 100,000 people) was dramatically higher than among people without HIV, but a markedly lower proportion of TB cases among people with HIV are being diagnosed and reported by health services (Wood).

That delay costs lives. Based on data from Southeast Asia,"the case fatality rate for HIV-infected TB patients is extremely high, between 25 and 50% during the six months of TB treatment. But about half of these deaths occur within the first two months of TB treatment, [meaning that treatment probably comes too late to save their lives]. Earlier diagnosis should decrease this case fatality," Dr Kevin Cain of the US Centers for Disease Control (CDC) reported at the 38th Union World Conference on Lung Health (the UWCLH) in Cape Town last November.

Lack of TB screening, diagnosis and treatment may also put more people with HIV and unrecognised TB at risk of serious immune reconstitution inflammatory reactions (IRIS) when they are put on ART, and could be a factor in high early mortality on ART.

“We suspect in Malawi that a proportion of these patients have TB but the TB is not diagnosed at the time of their ART assessment. The patients start on ART and then die in the first few months of ART as a result of undiagnosed and untreated TB,” Dr Anthony Harries told HATIP (see his recent paper on the subject in *J Infect Developing Countries 2007; 1: 118-122*).

Clearly, a more aggressive approach to case finding and diagnosis is needed to protect people with HIV from TB. This should perhaps start with increasing the uptake of HIV testing and counselling, so that people with HIV know whether they are at greater risk. But people with HIV also have a right to prompt TB screening and diagnosis.

WHO recommends intensified case finding (ICF)

In 2004, WHO’s *Policy on Collaborative TB/HIV Activities* recommended that people living with HIV, their household contacts, groups at high risk for HIV and those in congregate settings should be regularly screened for TB whenever they come into contact with the health services.

Studies have shown that early detection, diagnosis and treatment of TB can interrupt disease transmission by infectious cases, in general (Harries, de Cock) and within healthcare settings (Burgess). It prevents mortality (Nachega), and presents an opportunity to provide isoniazid preventive therapy to people without active TB (Burgess) (see HATIP #96).

Furthermore, earlier in the decade, ProTest, a WHO-coordinated initiative using HIV counseling and testing as an entry point to a range of HIV/TB and STI prevention and care interventions at sites in Zambia, Malawi and South Africa, demonstrated that ICF could be introduced at little additional cost in existing health services. Since that time, studies have piloted ICF in general health services, ART clinics, prevention of mother to child transmission (PMTCT) sites, HIV support groups, home based care delivery, and congregate settings.

As a result of this, 115 countries have policies recommending ICF – but only 44 reported on performance of the activity to WHO in 2006, according to Dr Haileyesus Getahun of WHO’s STOP TB Department at a satellite symposium of the Conference on Retroviruses and Opportunistic Infections (CROI) this February.

Worse yet, no country reported implementing it widely. Globally, only 314,394 people with HIV (0.96%) were screened for TB. This fell well short of the target to screen 11 million people with HIV for TB in 2006, as set out by the Global Plan to Stop TB 2006-2015.

Of the high burden countries, South Africa screened the most, over 100,000, but that represented only 1.83% of the country's total HIV-infected population.

And no other high burden country comes anywhere close to screening as many people living with HIV for TB. For instance, India screened 1.07% of the HIV-infected population (a little over 20,000 people) with Rwanda, Nigeria, Ethiopia and Mozambique trailing behind.

Why isn't ICF being more widely implemented?

Experts and clinicians working with people with HIV have suggested several reasons to HATIP why ICF is not being adopted as widely as it should be.

- There is no internationally recommended standardised TB screening tool (existing tools are insensitive or their use in people with HIV hasn't been well tested).
- Failure of countries to develop ICF implementation plans.
- Fear that increasing detection and treatment of new cases could lead to more poor treatment outcomes and the development of resistance in settings where TB programmes are currently weak.
- Fears that it could increase the burden on already over-worked staff and health systems (extra work/little training).
- Obtaining the diagnosis
- Low incorporation of TB interventions by HIV stakeholders including policy makers and service providers.
- Case in point: although cough is clearly an important symptom in people with TB, there is a debate about the role of chronic cough (cough for more than two or three weeks).
- Lack of rapid, simple and accurate TB diagnostic tool
- Lack of clarity about how best to use existing tools/weak laboratory infrastructure and systems
- Problems with referrals to diagnostic sites/specimen transport/delivery of results

These issues are reviewed in more detail in this article and in the accompnaying edition of HATIP, *Intensified case finding: developing an action plan.*

Agreeing on the optimal screening tool

Although WHO strongly recommended screening for TB "using, at a minimum, a simple set of questions," the policy didn't really spell out what exactly those questions should be. A companion document, *A guide to monitoring and evaluation for collaborative TB/HIV activities* suggested that healthcare workers could do the following:

Ask the patient with HIV whether he or she is currently taking TB treatment, if not, use a simple checklist asking whether they have any of the key symptoms of TB disease such as:

- cough
- fever
- night sweats
- recent [unintentional] weight loss
- lymphadenopathy, etc

Any positive response indicates that the person could have TB, and should be given a diagnostic evaluation for TB (or referred to the TB service for diagnosis).

But a number of experts in the field have complained the guidance is too vague and that lack of an evidenced-based and internationally recommended standardised screening tool for TB in people with HIV could be slowing the uptake of ICF.

"I think that the absence of guidelines is a major factor," Dr Jay Varma of the CDC in Bangkok, Thailand told HATIP. "Internationally-accepted guidelines lead to advocacy and training in the various WHO regions, then changes in national policies, and then finally implementation, monitoring and evaluation in individual countries. The absence of guidelines creates a vacuum in which various implementers adopt their own ICF strategies, but no one analyses the data in a uniform way."

In a presentation at the UWCLH, Dr. Joseph Odhiambo of the CDC/KEMRI confirmed that in Kenya "different providers use their own guidelines and tools in various pilot initiatives;" and he referred to a symptoms screening algorithm used by International Center for AIDS Care and Treatment Programmes (ICAP) supported sites in the central part of Kenya (see a comparison of some tools, including ICAP's in the pdf annex attached to this email).

From July to September 2007, ICAP-supported HIV care clinics in Kenya screened 46% (1325) of their clients using this questionnaire for TB. Only 115 or 4% screened positive as TB suspects but 92% of these, or 106 patients, were diagnosed with active TB.

The screening criteria in the ICAP tool seem to have a high positive predictive value for TB (the cases it detects are likely to really have TB). But the ICAP clinics did not perform bacteriologic assessments (smear microscopy and culture) in all of the screened patients, so it is impossible to say how sensitive the tool is (whether it's likely to detect every single person who had TB).

Dr Odhiambo said that participants at a stakeholder's meeting, held in Kenya last May, lacked confidence in the screening tools being used and felt that if "intensified case finding was suboptimal, introducing IPT could promote development of resistant TB strains. This is perhaps one of the reasons for lack of enthusiasm for wide scale IPT," (although many IPT supporters would contest this, see HATIP #96)

So in Kenya, Dr Odhiambo and colleagues are testing an enhanced screening tool with eleven signs and symptoms. The goal is to see which symptoms are most commonly associated with TB in people with HIV, and what would be the best screening strategies for TB in that population. Other researchers, including Dr Varma, Dr Cain and Dr Michael Kimerling of the University of Alabama Birmingham, (who is also the Director of the Gorgas TB Initiative in Cambodia) have already been performing similar work in South-east Asia.

There is already a large body of data that provides some useful insight into what sort of signs and symptoms should be considered, but most studies did not use bacteriological (smear microscopy and culture) diagnosis of TB as the reference standard, Dr Cain told HATIP.

The new studies are intended "to develop an algorithm based on all patients, meaning that we wanted to make no assumptions about the importance of cough or other symptoms prior to screening individuals," said Dr. Cain. "We wanted to use a sensitive combination of microbiological tests as our gold standard."

The poor sensitivity of chronic cough for TB in people with HIV

Chronic cough (usually cough for 3 weeks), which is used as the entry point to further diagnostic evaluations in many algorithms, has already been demonstrated to be an insensitive symptom for TB in people with HIV according to results from Dr Kimerling's studies in Cambodia (Chheng), and preliminary results of a large multicentre study, the Improving Diagnosis of TB in HIV-infected Persons in Southeast Asia Study (ID-TB/HIV) being led by Dr Varma and Dr Cain in Thailand, Cambodia and Vietnam. These results were presented at the UWCLH.

Some have found the suggestion that chronic cough should no longer be the single "gatekeeper" symptom when screening highly controversial.

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But the studies in Southeast Asia are not the first to make the observation that chronic cough is sometimes absent in people with TB in high burden settings.

A study in South Africa demonstrated that primary care nurses using the Practical Approach to Lung Health in South Africa (PALSA), an integrated respiratory symptom algorithm for several conditions, were better able to detect TB suspects, leading to a higher number of TB diagnoses, than expert doctors — who had the added advantage of using chest-x-rays —in the same group of patients (English).

“In our study, restricting screening to those with a cough for 2 weeks or longer would have resulted in failure to detect one-fifth of the confirmed cases. In high TB prevalence settings, TB should be suspected in all patients with cough, even when of a shorter duration than 2 weeks,” the authors wrote.

One problem with using chronic cough, or any symptom of a specific duration, is that, by definition, it is likely to miss people in the earlier stages of illness. In addition, there is also the subset of people with TB/HIV who seem to progress rapidly from typical pulmonary TB into atypical smear negative TB or extrapulmonary TB. These people don’t always continue coughing.

And yet, cough for two to three weeks remains the entry point to the WHO’s clinical algorithm for diagnosis of smear negative TB.

And even when cough is present in people with more advanced disease, it may not be the first symptom that they think to complain about.

“There are a lot of patients that will come and not report any cough but they do have two or three of the other symptoms,” said Annatjie Peters, a TB programme consultant in South Africa who trains home-based care volunteers to screen for cough, fever, night sweats, weight loss and fatigue. “Eventually we do get sputums from them and if you question them further, they will tell you that they actually have a chronic cough but it’s not a problem for them. That’s why it’s so important to concentrate on all the signs and symptoms and not only on the cough.”

“Any” cough picked up more TB (71% sensitive) than cough of more than 2 or 3 weeks, but cough lasting more than 3 weeks only detected TB with 24% sensitivity in the first 900 out of a planned 2050 people in the ID-TB/HIV study, according to data Dr Cain reported at the TB/HIV satellite meeting at CROI.

This is remarkably similar to the experience in Zambia, according to Dr Helen Ayles, who spoke about her findings at a Médecins Sans Frontières Symposium on TB diagnosis held just before the UWCLH last year. Dr Ayles described a door-to-door prevalence survey of 8000

individuals. “In the survey, everyone was asked to give us a sputum sample, regardless of whether they had any symptoms, and their HIV status was recorded.”

“In the HIV-positive population, 70% of them were coughing. So if we’d only started with cough as an entry point, we wouldn’t have picked everybody up. But 95% had at least one symptom if you include fever, weight loss, shortness of breath,” she said.

The continued importance of cough for infection control – and general patient care

However, screening for cough in any form remains important because it is a critical activity for infection control, since the people who are coughing are most likely to be infectious. Individuals who are coughing should be triaged for rapid assessment for their sake and to prevent onward transmission within the healthcare setting.

Another issue, addressed in more detail below, is that in primary healthcare and other facility settings, illness is managed by syndrome. “Any” cough can be related to a number of other conditions that also need to be considered for patient management (*see Checklists may be too simple*).

Towards better screening algorithms

Dr Cain has also used the preliminary data from ID-TB/HIV to analyse the performance of some of the algorithms proposed by other trials that have used the bacteriological diagnosis as a reference standard. For instance, in one of the studies in Cambodia, Dr Kimerling found that fever, rapid weight loss noticeable to the patient within the previous month and haemoptysis (coughing up blood) would be 100% sensitive for TB, but in the ID-TB/HIV study, it would be 82% sensitive.

So far in the ID-TB/HIV study, a simple screen for any one of cough, fever, weight loss has been the most sensitive symptom combination (91%).

Algorithms perform somewhat differently depending upon the CD4 cell count. For instance, the three-symptom screen mentioned above is 97% sensitive below 250 CD4 cells, and 81% sensitive above 250 CD4 cells, and a similar pattern was seen when other algorithms were assessed in the same way. ID-TB/HIV has confirmed that a host of other symptoms, signs and test results are significantly associated with TB (see box), so a large number of possible screening algorithms can be modeled with the data.

It is important to remember that these data are still preliminary and, thus far, only derived from Southeast Asia. The study that Dr Odhiambo and colleagues have planned in Kenya should expand the evidence base, as would pooling available data from other similar studies using the same reference standard.

Furthermore, Dr Getahun of WHO said that " it is imperative to replicate the type of study that Dr Varma and his group are conducting in South East Asia (ID-TB/HIV) in sub-Saharan Africa, the region most affected by the dual TB and HIV epidemic and get the results as a matter of urgency. It will help us to further address the questions we have around TB diagnosis in PLHIV and understand the situation more".

It's not clear yet whether there will be a one-size-fits-all algorithm that will work equally well in every setting. For instance, the sensitivity of self-reported symptoms could vary by population for cultural reasons.

"The interpretation of cough, like many symptoms, is likely culturally influenced," Dr Kimerling told HATIP. "We know from other research that patients reach some sort of threshold in interpretation of their symptoms/signs before seeking care, and the level of care they seek is influenced by other factors, traditions, access issues, costs, etc."

In Cambodia, "there are different types of cough and for each type of cough there is one specific health-seeking behavior," said Dr Mukadi Ya Diul of Family Health International at the UWCLH. "If it's a cold cough, then they have to go to the traditional healer. If it's a warm cough then they have to take this type of medicine. And so on and so on. This is really delaying access to treatment."

Which raises another issue: Could these symptoms be so non-specific that healthcare workers won't want to refer patients for TB diagnosis on that basis?

"So many of our patients have fevers, have weight loss, many have cough – many for reasons other than TB," said Dr Ayles. Both Dr Harries and Dr Kimerling stressed to HATIP that weight loss and fever are very common symptoms of AIDS.

Another danger is that the quest for a perfect screening tool could postpone the use of a good one.

People may conclude that ICF implementation should wait until these studies define the optimal algorithm – but delay would put thousands of lives at risk. Implementation of a less than perfect algorithm would be progress over what is currently happening, and so far the data suggest that using any one of cough, fever and weight loss could detect up to 80% of the cases.

“Implementation should occur now,” Dr Varma told HATIP, “concurrent with research on developing better tools.”

“People are dying unnecessarily with readily diagnosable TB disease,” said Dr Kimerling. “It is the health system that is failing them, not their willingness to get screened.”

“I certainly agree that intensified TB screening for people living with HIV needs to be rapidly scaled up now,” Dr Cain told HATIP. “Data from published and ongoing studies could be used to produce interim guidelines to facilitate this. We should not delay implementing intensified case finding. It can save lives now.”

“The absence of the perfect screening algorithm is not an excuse to forego TB screening,” Dr Diane Havlir, Chair of the HIV/TB Working group of the Stop TB Partnership told HATIP. “ART programmes can and must adopt an aggressive approach to TB prevention and treatment.”

Symptoms, signs and test results associated with TB in ID-TB/HIV

Symptoms	Signs
Loss of appetite	Temp > 37.5 (or 38)
Cough	Body mass index < 18.5
Weight loss	Lymphadenopathy
Difficulty breathing	
Fatigue	
Fever	Other
Shaking chills	Haemoglobin <10
Night sweats	Tuberculin skin test positive
Chest pain	Hospitalized at enrollment
Abdominal pain	Not on ART
Nausea / vomiting	Chest X-Ray (?)

References (in order of appearance)

Lawn SD et al. Burden of tuberculosis in an antiretroviral treatment programmeme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006; 20:1605–12.

Wood R et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med 2007; 175:87–93.

Wood R. The case for integrating tuberculosis and HIV treatment services in South Africa. JID; 196:S497–9, 2007.

Cain K et al. Developing a clinical algorithm to diagnose TB in HIV-infected persons in SE Asia. 38th World Union Lung Health Conference, Cape Town, Symposium on intensified case finding, 2007.

Cain K, McCarthy K, Varma J. Developing a clinical algorithm to diagnose TB in HIV-infected persons in Southeast Asia.

Interim policy on collaborative TB/HIV activities. Stop TB Department and Department of HIV/AIDS, World Health Organization, Geneva, 2004.

Harries AD, Maher D, Nunn P. Practical and affordable measures for protection of health care workers from tuberculosis in low-income countries. Bulletin of the World Health Organization, 75:477–489, 1997.

De Cock K, Chalsson R. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. International Journal of Tuberculosis and Lung Disease, 3:457–467, 1999.

Burgess A et al. Integration of tuberculosis screening at an HIV voluntary counselling and testing center in Haiti. AIDS, 2001, 15:1875–1879.

Nachega J et al. Tuberculosis active case finding in a mother-to-child HIV transmission prevention programmeme in Soweto, South Africa. AIDS, 2003, 17:1398–1400.

Report on the “lessons learnt” workshop on the six ProTEST pilot projects in Malawi, South Africa and Zambia. 3–6 February 2003, Durban, South Africa. Geneva, World Health Organization.

Getahun H. Global implementation of TB screening and Isoniazid preventive therapy among people living with HIV. Satellite on TB/HIV, CROI Boston, 2008.

A guide to monitoring and evaluation for collaborative TB/HIV activities. Stop TB Department and Department of HIV/AIDS. World Health Organization, Geneva, 2004.

Odhiambo J. Implementing intensified TB case finding guidelines at country level: the Kenya example. 38th World Union Lung Health Conference, Cape Town, Symposium on intensified case finding, 2007.

Kimmerling ME et al. Active TB case finding within a continuum of care package: linking TB and HIV services through voluntary counselling and

testing centres in Battambang province, Cambodia. 38th World Lung Health Conference, Cape Town, symposium on intensified case finding, 2007.

Chheng P et al. Pulmonary tuberculosis among patients visiting a voluntary confidential counseling and testing center, Cambodia. Int J Tuberc Lung Dis 12(3):S54–S62, 2008.

English RG et al. Diagnostic accuracy of an integrated respiratory guideline in identifying patients with respiratory symptoms requiring screening for pulmonary tuberculosis: a cross-sectional study. BMC Pulmonary Medicine 6:22, 2006.

Ayles H. Diagnosing TB in HIV-positive individuals. TB: dying for a test, Cape Town, 2007.

Peters A. Preliminary findings: screening for TB among PLWHA by home based Care Workers South Africa, 2007. 38th World Lung Health Conference, Cape Town, symposium on intensified case finding, 2007.

Cain K, Varma J. Intensified TB case finding among HIV-infected persons in resource-limited settings. Satellite on TB/HIV, CROI Boston, 2008.