TB-HIV Update
ความก้าวหน้าทางวิชาการเรื่องวัณโรคและโรคเอดส์

การประชุมวิชาการสถาบันวิจัยวิทยาศาสตร์สุขภาพ

โรงแรมเชียงใหม่แกรนด์วิว

12 กุมภาพันธ์ 2559

ประเด็นในการนำเสนอ

- เสนอความก้าวหน้าในการจัดการวัณโรคและโรคเอดส์ (TB-HIV)ตามข้อเสนอแนะขององค์การอนามัยโลกเน้นการดำเนินการในสถานบริการ
- เน้นความก้าวหน้าในการลดปัญหา TB ในผู้มีเชื้อเอชไอวี และการเริ่มให้ยาต้านไวรัสโดยเร็ว (the Three I's)
- และ การลดปัญหา HIV ในผู้ป่วย TB และผู้สงสัย
- การนำเสนอเฉพาะผู้ใหญ่และวัยรุ่นเท่านั้น

WHO-recommended collaborative TB/HIV activities

WHO 2012

A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services
A.1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels
A.2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV
A.3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
A.4. Monitor and evaluate collaborative TB/HIV activities
B. Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (the *Three I's for HIV/TB*)
B.1. Intensify TB case-finding and ensure high quality antituberculosis treatment
B.2. Initiate TB prevention with isoniazid preventive therapy and early antiretroviral therapy
B.3. Ensure control of TB infection in health-care facilities and congregate settings
C. Reduce the burden of HIV in patients with presumptive and diagnosed TB
C.1. Provide HIV testing and counselling to patients with presumptive and diagnosed TB
C.2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB
C.3. Provide co-trimoxazole preventive therapy for TB patients living with HIV
C.4. Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
C.5. Provide antiretroviral therapy for TB patients living with HIV

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การลดปัญหา TB ในผู้มีเชื้อ HIV และการเริ่มยาต้านไวรัสโดยเร็ว (the Three I's)

1. การตรวจหาวัณโรค(TB ICF) และการรักษาที่มีคุณภาพ
2. การป้องกันวัณโรคโดยให้ยา INH (INH Preventive Therapy = IPT) และเริ่ม ART โดยเร็ว
3. การป้องกันการกระจายเชื้อวัณโรคในสถานบริการและในที่มีคนอยู่แออัด เช่นในที่คุมขัง บ้านคนชรา

ICF of TB among PLHIV (WHO 2011)

1 Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

Strong recommendation, moderate quality of evidence[1]

2 Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

Strong recommendation, moderate quality of evidence

TB ICF เสนอแนะโดย องค์การอนามัยโลก

ผู้ใหญ่และวัยรุ่นที่มี HIV ต้อง screen TB โดยใช้ clinical algorithm ถ้าไม่มีอย่างน้อยหนึ่งอาการคือไอ (current cough) ไข้ น้ำหนักลด หรือเหงื่อออกกลางคืน โอกาศมี active TB น้อย ควรให้ IPT

ถ้ามีอาการหนึ่งได อาจมี active TB ควรตรวจหา TB และโรคอื่น

- TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least six months of rifampicin treatment regimen *(strong recommendation, high-quality evidence).*

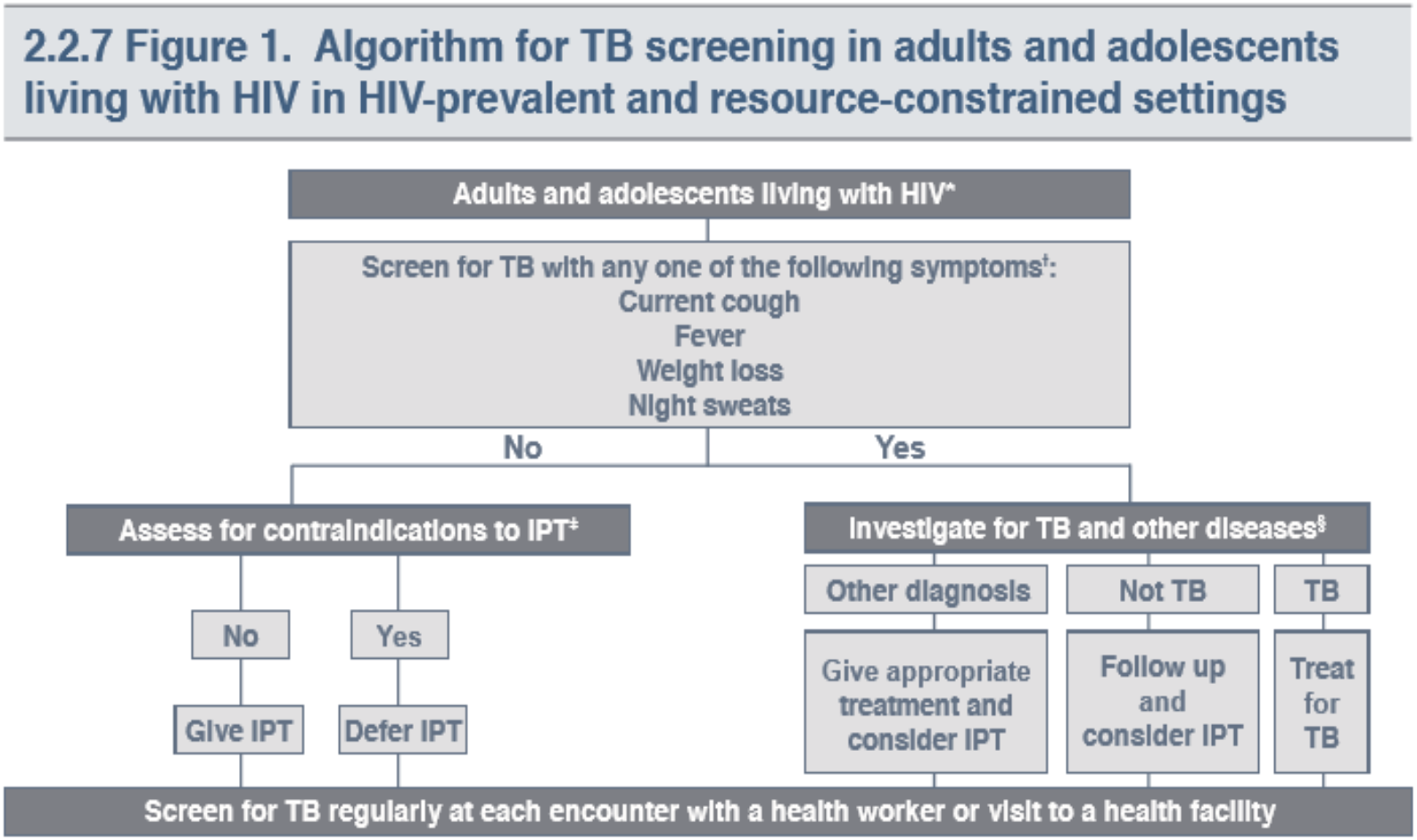
  The optimal dosing frequency is daily during the intensive and continuation phases *(strong recommendation, high-quality evidence) (2).*

- Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having HIV-associated TB or multidrug-resistant TB *(strong recommendation) (21).*

WHO 2013

ผู้ปวยวัณโรคที่มี HIV หรือผู้ป่วยวัณโรคในพื้นที่ HIV สูง ควรได้รับยาสูตรที่มี rifampicin อย่างน้อย 6 เดือน ควรได้ขนาดยาที่เหมาะสมและได้ทุกวัน ตลอดการรักษา (daily dosage)
ควรใช้ Xpert MTB/RIF ในการวินิจฉัยตั้งแต่ต้น ในผู้มีเชื้อ HIV ที่สงสัยมี TB, MDR TB

Algorithm ในการ screen TB ในผู้ใหญ่และวัยรุ่นที่มี HIV ในที่ทรัพยากรจำกัด (WHO 2013)



Confirmed MTB survey cases: Symptoms and CXR screening results

Screening method	Smear positive MTB survey cases, n=58		Bacteriologically confirmed MTB survey cases, n=142	
	Total number of survey cases	Percentage of *all survey cases*	Total number of survey cases	Percentage of *all survey cases*
Symptom positive only	1	2%	5	4%
CXR positive only	30	52%	95	67%
Symptom and CXR positive	27	47%	42	30%

- What proportion of MTB survey cases were smear negative? => 84/142 = 59%
- What proportion of MTB survey cases were detected by CXR? => 95/142 = 67%
- What proportion of MTB survey cases were detected by symptoms? => 5/142 = 4%
- What proportion of MTB survey cases would have been detected by the current screening strategy in your country? => 42/142 = 30%

BTB, Thailand, 2012-2013

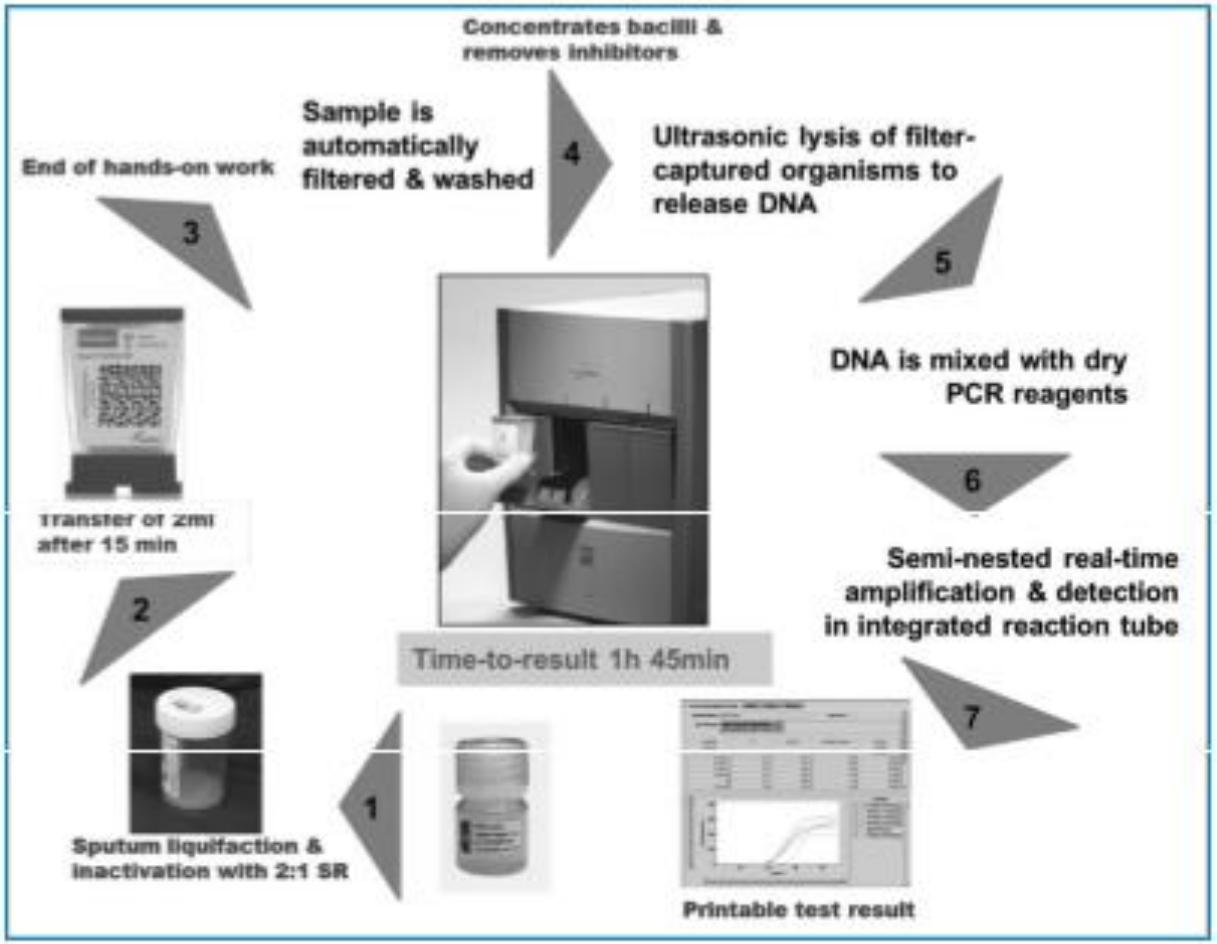
Why perform XpertMTB/RIF ?

- Laboratory infrastructure similar to that for microscopy is required
- Can be de-centralized for testing at lower levels of the laboratory network
- Suitable for the diagnosis of TB and rifampicin resistance in AFB smear-negative and smear-positive individuals
- New WHO policy recommendations issued for use in adults children and extrapulmonary TB

7.1.3 Testing capacity

Figure 2. GeneXpert instruments with 1, 2, 4 and 16 modules

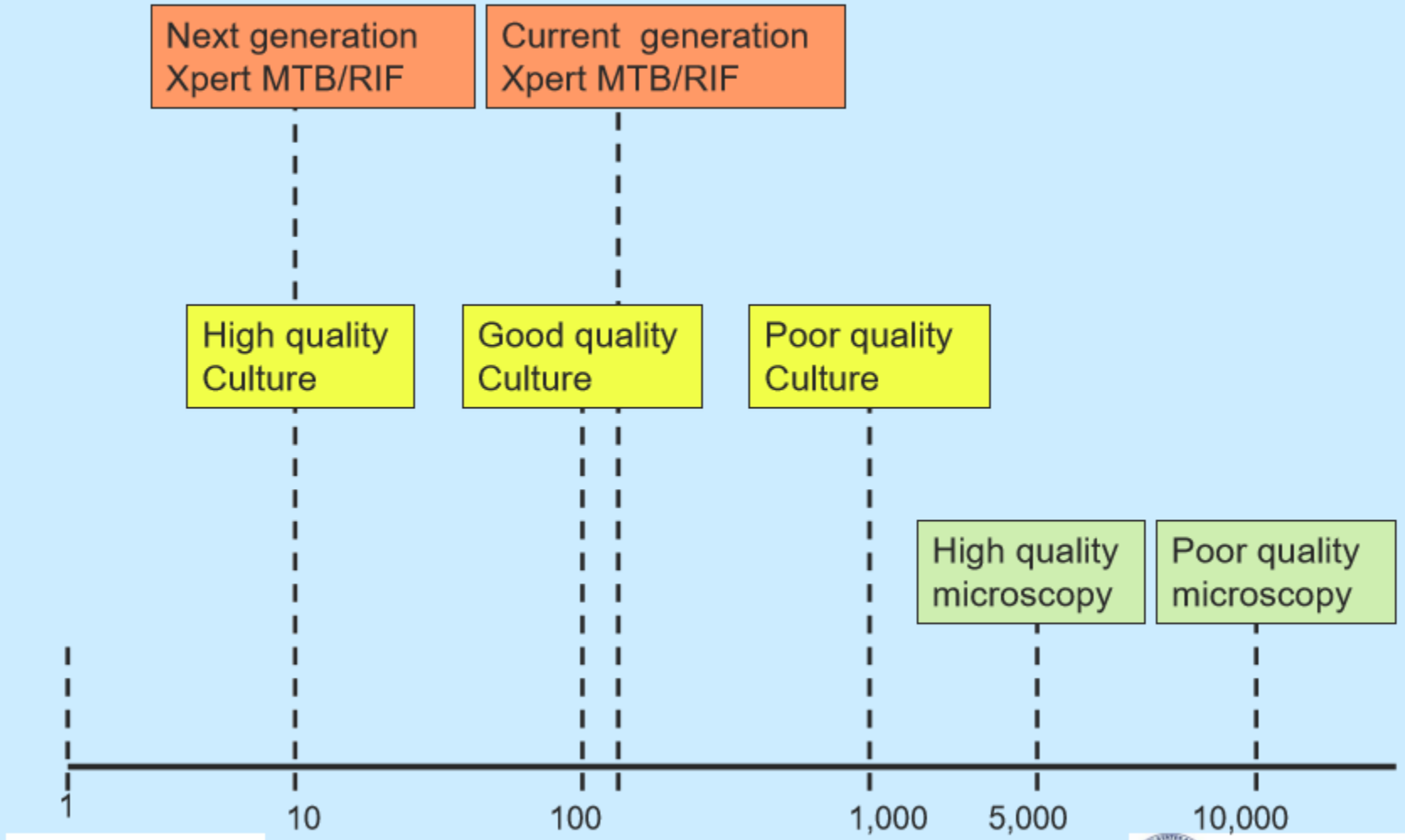
Figure 1. Steps in using the Xpert MTB/RIF assay[a]



a Figure used with permission from the Foundation for Innovative New Diagnostics (FIND).

8 Rapid implementation of the Xpert MTB/RIF diagnostic test. Technical and operational 'how-to': practical considerations. Geneva; World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf).

Limit of Detection and Diagnostic Technology



TB CARE I

USAID FROM THE AMERICAN PEOPLE

Key selected existing recommendations

Isoniazid preventive therapy (IPT) *(2)*

- Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT
  (strong recommendation, moderate-quality evidence).
- **Duration of IPT**
  - Adults and adolescents who are living with HIV, have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women
    (strong recommendation, high-quality evidence).
  - Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also those on ART, those who have previously been treated for TB and pregnant women
    (conditional recommendation, moderate-quality evidence).
- A TST is not a requirement for initiating IPT in people living with HIV
  (strong recommendation, moderate-quality evidence).
  People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals
  (strong recommendation, high-quality evidence).
- Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT
  (strong recommendation, moderate-quality evidence).

WHO's Recommendation on IPT 36 months for adults and adolescents with HIV

WHO 2015 update

In resource-constrained settings with high TB incidence and transmission, adults and adolescents living with HIV, who have an unknown or positive tuberculin skin test (TST) status and among whom active TB disease has been safely ruled out, should receive at least 36 months of isoniazid preventive therapy (IPT). IPT should be given to such individuals regardless of whether or not they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment, and pregnancy.

(Conditional recommendation, low quality of evidence).

Remarks: *People living with HIV in high TB incidence and transmission settings, regardless of their TST status, benefit more from IPT of 36 months or longer, compared to six-month IPT, with greater protective benefit in those with a positive TST. There is a significant additional benefit from longer-term IPT for those receiving ART. TST is encouraged whenever feasible, but it is not a pre-requisite for IPT. If TST is performed, those with a negative TST should not receive 36 months of IPT. Settings with high TB incidence and transmission should be defined by national authorities, taking into consideration the local epidemiology and transmission of both TB and HIV.*

WHO 2013

Box 8.1. Summary of recommendations for key actions for infection control *(3)*

Administrative (facility-level infection control committee and protocols)

- A triage system to identify people suspected of having TB
- Separate people with suspected or confirmed TB
- Cough etiquette and respiratory hygiene
- Rapid diagnosis with Xpert MTB/RIF (with prompt treatment of active TB)
  (strong recommendation, low-quality evidence).

Health workers and carers

- Surveillance and information
- Package of care for HIV-positive workers (ART and isoniazid preventive therapy)
- Protective equipment (particulate respirator masks that meet or exceed N95 standards)
- Relocation for health care workers living with HIV to a lower-risk area
  (strong recommendation, high-quality evidence).

Environmental

- Ventilation (mechanical)
- Ventilation (natural)
- Upper-room ultraviolet germicidal irradiation
  (strong recommendation, low-quality evidence).

Personal

- Spend as much time as possible outside
- Cough etiquette
- Sleep alone while smear-positive
- Avoid congregate settings and public transport while smear-positive
  (strong recommendation, low-quality evidence).

C. Reduce the burden of HIV in patients with presumptive and diagnosed TB
C.1. Provide HIV testing and counselling to patients with presumptive and diagnosed TB
C.2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB
C.3. Provide co-trimoxazole preventive therapy for TB patients living with HIV
C.4. Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
C.5. Provide antiretroviral therapy for TB patients living with HIV

การลดปัญหา HIV ในผู้ป่วยและผู้สงสัยเป็นวัณโรค

1. ตรวจ HIV และให้บริการปรึกษาแก่ผู้ป่วยและผู้สงสัยเป็นวัณโรค
2. ให้บริการป้องกันการติดเชื้อ HIV
3. ให้ CPT แก่ผู้ป่วยวัณโรคที่มี HIV
4. ให้บริการป้องกัน รักษา และดูแลแก่ผู้ป่วยวัณโรคที่มี HIV
5. ให้ ART แก่ผู้ป่วยวัณโรคที่มี HIVโดยเร็ว

WHO 2013

Key selected existing recommendations

Timing of ART for adults and children with TB

- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of the CD4 count *(strong recommendation, low-quality evidence) (4).*
- Antituberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment *(strong recommendation, moderate-quality evidence).* The HIV-positive TB patients with profound immunosuppression (such as CD4 counts less than 50 cells/mm^3) should receive ART immediately within the first two weeks of initiating TB treatment *(2).*
- ART should be started in any child with active TB disease as soon as possible and within eight weeks following the initiation of antituberculosis treatment irrespective of the CD4 count and clinical stage
  (strong recommendation, low-quality evidence) (5).
- Efavirenz should be used as the preferred NNRTI in patients starting ART while on antituberculosis treatment *(strong recommendation, high-quality evidence) (2).*

CPT

WHO 2014 supplement

The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children		
Recommendation	**Strength**	**Quality of the evidence**
Adults (including pregnant women)[c]		
Co-trimoxazole prophylaxis is recommended for severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or for a CD4 count ≤350 cells/mm³.	Strong	Moderate
• In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.	Strong	Moderate

Recommendation	Strength	Quality of the evidence
Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV infection who are clinically stable on antiretroviral therapy, with evidence of immune recovery and viral suppression.	Conditional	Low
• In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.	Conditional	Moderate

HIV and TB coinfection		
Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.	Strong	High

ขอบคุณ

เชิญถามและอภิปราย

Reference สำหรับ Xpert, Pulmonary TB

Using Xpert MTB/RIF to diagnose pulmonary TB and rifampicin resistance in adults

WHO 2013

Twenty seven unique studies involving 9558 participants were included in the review. The reference standards for detecting pulmonary TB were solid culture or liquid culture. The reference standard for detecting rifampicin resistance was phenotypic culture-based drug-susceptibility testing (DST).

When used as an initial diagnostic test replacing smear microscopy, Xpert MTB/RIF achieved an overall pooled sensitivity of 88% (95% credible interval [CrI], 84–92%)[4] and a pooled specificity of 99% (95% CrI, 98– 99%) (22 studies, 9008 participants).

When used as an add-on test following a negative smear-microscopy result, Xpert MTB/RIF yielded a pooled sensitivity of 68% (95% CrI, 61–74%) and a pooled specificity of 99% (95% CrI, 98–99%) (23 studies, 7151 participants).

For smear-positive culture-positive TB, the pooled sensitivity of Xpert MTB/RIF was 98% (95% CrI, 97–99%) (23 studies, 1952 participants); for smear-negative culture-positive TB, the pooled sensitivity was 68% (95% CrI, 61–74%) (23 studies, 7151 participants).

For people living with HIV, the pooled sensitivity of Xpert MTB/RIF was 79% (95% CrI, 70–86%) (7 studies, 1789 participants); for people without HIV infection, the pooled sensitivity was 86% (95% CrI, 76–92%) (7 studies, 1470 participants).

When used to detect rifampicin resistance, Xpert MTB/RIF achieved a pooled sensitivity of 95% (95% CrI, 90–97%) (17 studies, 555/2624 total specimens) and a pooled specificity of 98% (95% CrI, 97–99%) (24 studies, 2414 specimens, including true negatives and false positives).

Reference สำหรับ Xpert, Extrapulmonary TB, WHO 2013

Table 1. Meta-analysis of the sensitivity and specificity of Xpert MTB/RIF in diagnosing extrapulmonary TB and rifampicin resistance in adults and children compared against culture as a reference standard as well as against a composite reference standard, by type of extrapulmonary specimen

Specimen type	Comparison (No. of studies, No. of samples)	Median (%) pooled sensitivity (pooled 95% CrI)	Median (%) pooled specificity (pooled 95% CrI)
Lymph node tissue and aspirate	Xpert MTB/RIF compared against culture (14 studies, 849 samples)	84.9 (72–92)	92.5 (80–97)
	Xpert MTB/RIF compared against a composite reference standard (5 studies, 1 unpublished)	83.7 (74–90)	99.2 (88–100)
Cerebrospinal fluid	Xpert MTB/RIF compared against culture (16 studies, 709 samples)	79.5 (62–90)	98.6 (96–100)
	Xpert MTB/RIF compared against a composite reference standard (6 studies, 512 samples)	55.5 (51–81)	98.8 (95–100)
Pleural fluid	Xpert MTB/RIF compared against culture (17 studies, 1385 samples)	43.7 (25–65)	98.1 (95–99)
	Xpert MTB/RIF compared against a composite reference standard (7 studies, 698 samples)	17 (8–34)	99.9 (94–100)
Gastric lavage and aspirate	Xpert MTB/RIF compared against culture (12 studies, 1258 samples)	83.8 (66–93)	98.1 (92–100)
Other tissue samples	Xpert MTB/RIF compared against culture (12 studies, 699 samples)	81.2 (68–90)	98.1 (87–100)

CrI, credible interval; the CrI is the Bayesian equivalent of the confidence interval.

The data for additional sample types (such as, ascitic fluid, pericardial fluid, urine, blood and stool) were limited and therefore not considered in the analysis.

WHO 2013

WHO's policy recommendations

Box 1. Using Xpert MTB/RIF to diagnose pulmonary TB and rifampicin resistance in adults and children

These recommendations should be read in conjunction with the remarks in section 5.1.

- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).
- Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected of having TB (conditional recommendation acknowledging resource implications, high-quality evidence).
- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children suspected of having TB (conditional recommendation acknowledging resource implications, very low-quality evidence).
- Xpert MTB/RIF may be used as a follow-on test to microscopy in adults suspected of having TB but not at risk of MDR-TB or HIV-associated TB, especially when further testing of smear-negative specimens is necessary (conditional recommendation acknowledging resource implications, high-quality evidence).

WHO 2013

Box 2. Using Xpert MTB/RIF to diagnose extrapulmonary TB and rifampicin resistance in adults and children

These recommendations should be read in conjunction with the remarks in section 5.2.

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test for CSF specimens from patients suspected of having TB meningitis (strong recommendation given the urgency for rapid diagnosis, very low-quality evidence).

- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture or histopathology) for testing specific nonrespiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB (conditional recommendation, very low-quality evidence).