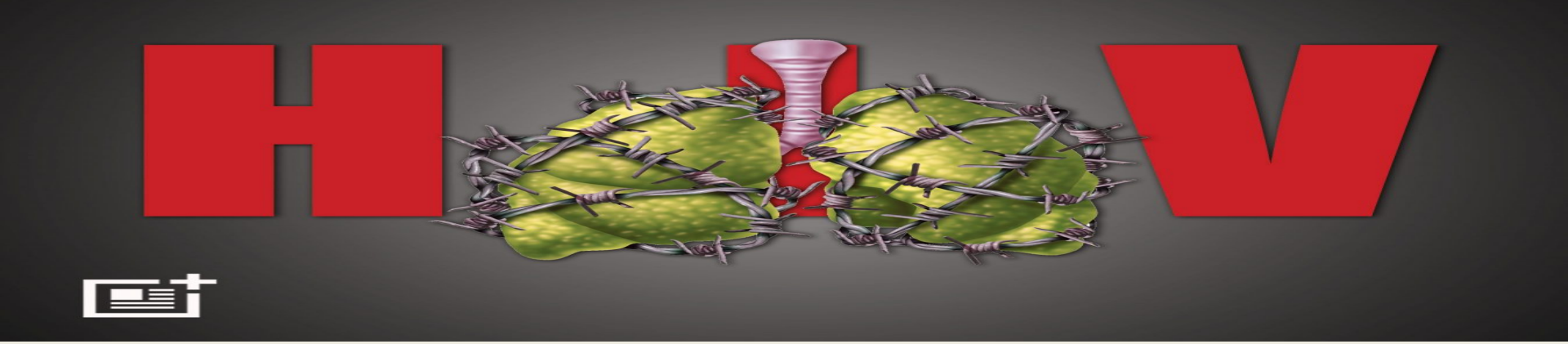


HIV/TB KOENFEKSİYONU
TANIDA GELİŞMELER

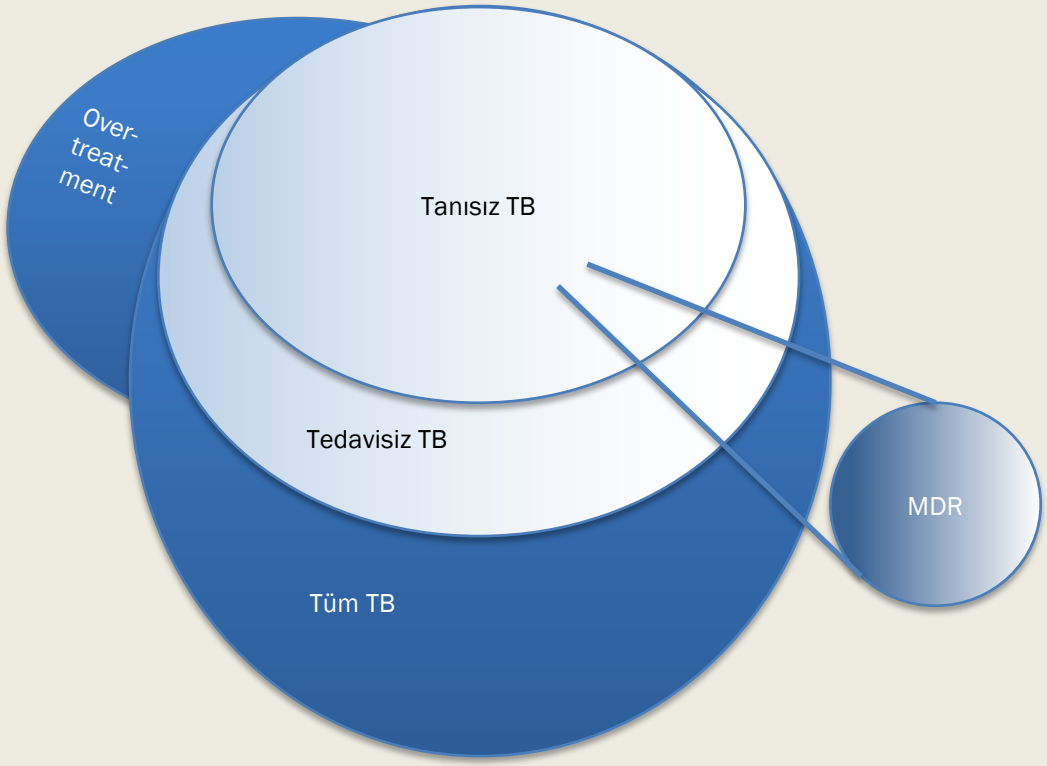
Dr. Hayat Kumbasar Karaosmanoğlu
SBÜ Bakırköy Dr. Sadi Konuk EAH
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

SUNUM PLANI

- Epidemiyoloji
- HIV&TB Etkileşim
- Tanıda güçlükler
- Tanısal testler
- Yeni gelişmeler

Tüberküloz

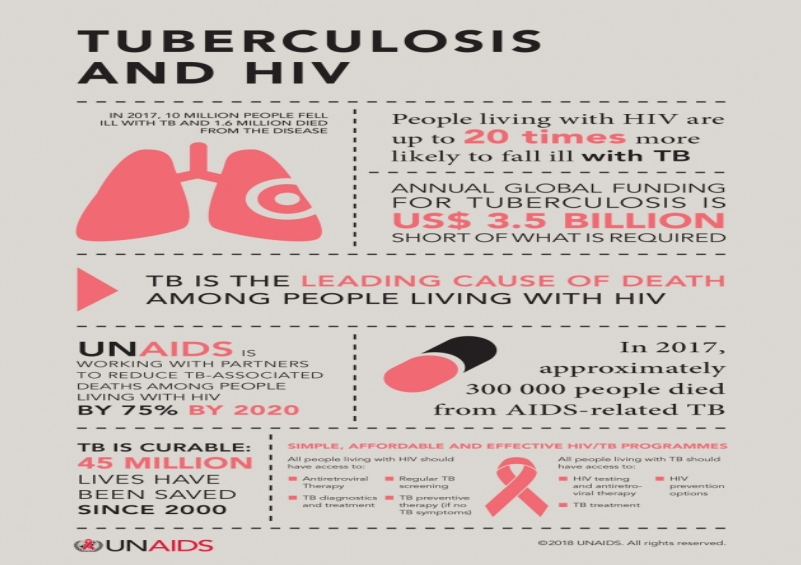
Dünyada enfeksiyon hastalıkları arasında en sık mortalite sebebi

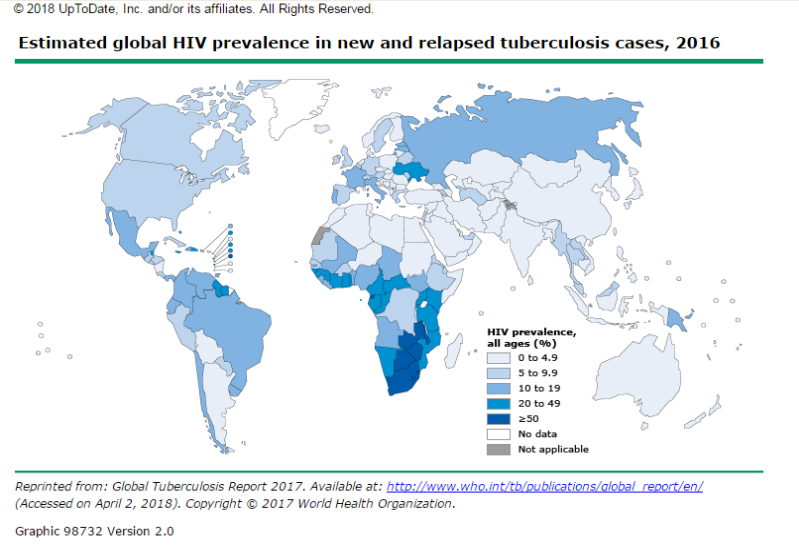


- Yılda 10.4 milyon vaka
- 1.8 milyon ölüm
- >4 milyon tanı almamış ve tedavisiz

WHO Global TB report 2017

HIV/TB Prevalansı

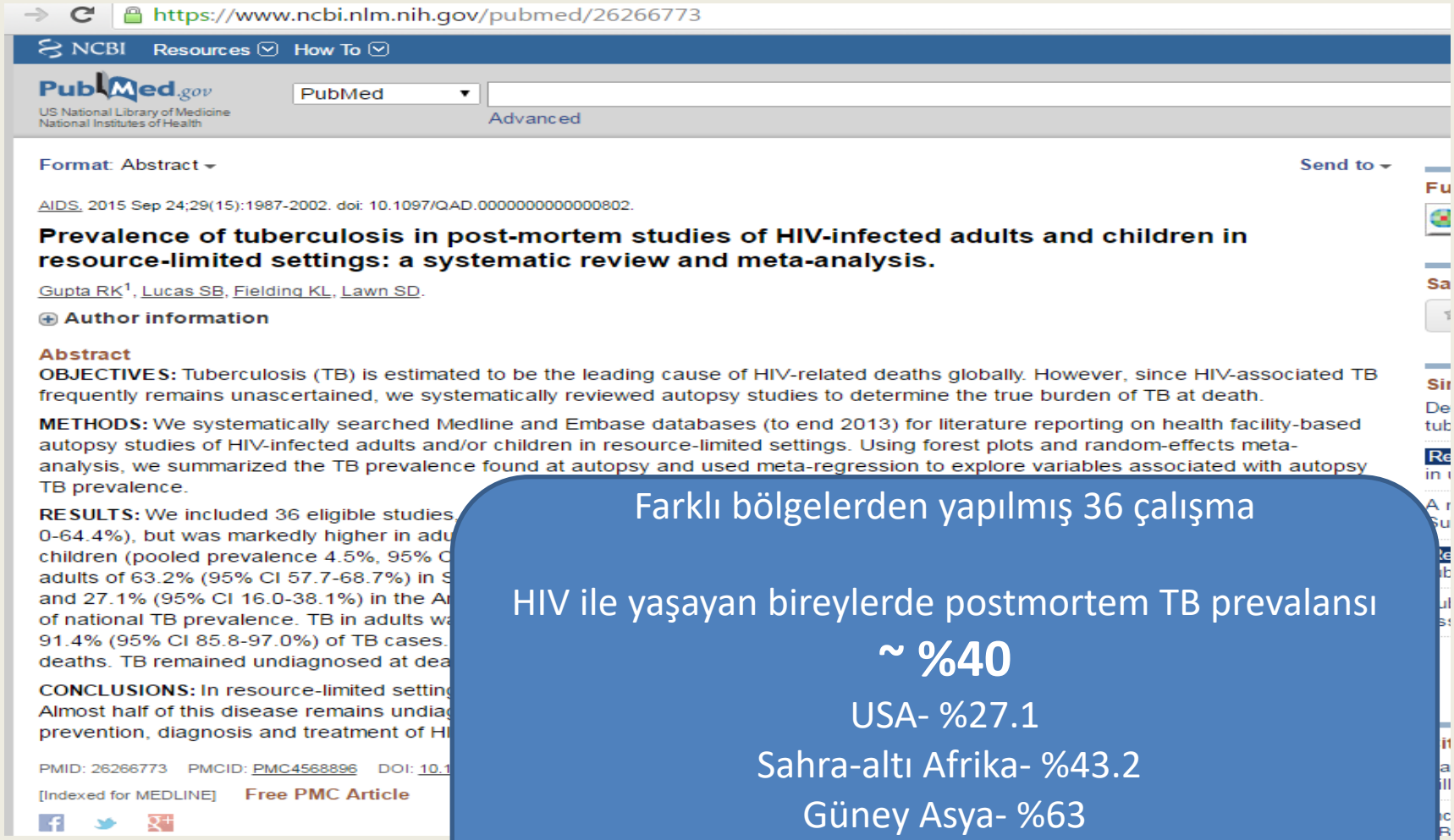




- ~ 1.2 milyon HIV/TB
- Tüm TB olgularının %11'i HIV ile enfekte
- TB'ye bağlı ölen olguların %22'si
- AIDS ilişkili ölümlerin üçte birinde TB

https://www.uptodate.com/contents/epidemiology-of-tuberculosis?search=hiv%20tuberculosis&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=7

Postmortem HIV/TB Prevalansı



https://www.ncbi.nlm.nih.gov/pubmed/26266773

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AIDS. 2015 Sep 24;29(15):1987-2002. doi: 10.1097/QAD.0000000000000802.

Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis.

Gupta RK[1], Lucas SB, Fielding KL, Lawn SD.

Author information

Abstract

OBJECTIVES: Tuberculosis (TB) is estimated to be the leading cause of HIV-related deaths globally. However, since HIV-associated TB frequently remains unascertained, we systematically reviewed autopsy studies to determine the true burden of TB at death.

METHODS: We systematically searched Medline and Embase databases (to end 2013) for literature reporting on health facility-based autopsy studies of HIV-infected adults and/or children in resource-limited settings. Using forest plots and random-effects meta-analysis, we summarized the TB prevalence found at autopsy and used meta-regression to explore variables associated with autopsy TB prevalence.

RESULTS: We included 36 eligible studies
0-64.4%), but was markedly higher in adu
children (pooled prevalence 4.5%, 95% C
adults of 63.2% (95% CI 57.7-68.7%) in S
and 27.1% (95% CI 16.0-38.1%) in the Ar
of national TB prevalence. TB in adults wa
91.4% (95% CI 85.8-97.0%) of TB cases.
deaths. TB remained undiagnosed at dea

CONCLUSIONS: In resource-limited setting
Almost half of this disease remains undiag
prevention, diagnosis and treatment of HI

PMID: 26266773 PMCID: PMC4568896 DOI: 10.1

[Indexed for MEDLINE] Free PMC Article

Farklı bölgelerden yapılmış 36 çalışma

HIV ile yaşayan bireylerde postmortem TB prevalansı

~ %40

USA- %27.1

Sahra-altı Afrika- %43.2

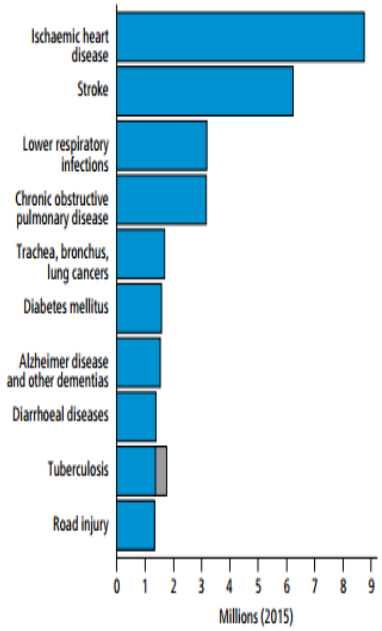
Güney Asya- %63

Yaklaşık yarısı tanı alamadan ex

WHO Global Tüberküloz Raporu 2017

FIG. 3.11

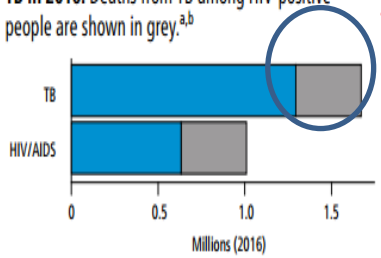
Top causes of death worldwide in 2015.[a,b,c] Deaths from TB among HIV-positive people are shown in grey.



[a] This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD (accessed 28 August 2017).
[b] For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_bounds_1990-2016. For TB, the estimates for 2016 are those published in this report.
[c] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International classification of diseases.

FIG. 3.12

Estimated number of deaths from HIV/AIDS and TB in 2016. Deaths from TB among HIV-positive people are shown in grey.[a,b]

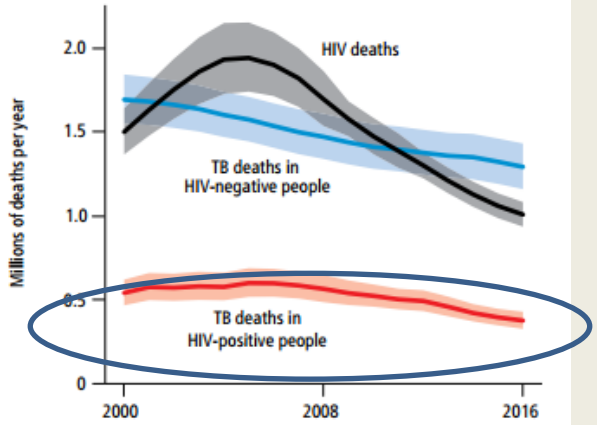


400.000 HIV ile enfekte

[a] For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_bounds_1990-2016. For TB, the estimates for 2016 are those published in this report.
[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International classification of diseases.

FIG. 3.13

Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2016.[a,b]
Shaded areas represent uncertainty intervals.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2016 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2017/HIV_estimates_with_uncertainty_bounds_1990-2016. For TB, the estimates for 2016 are those published in this report.
[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International classification of diseases. Deaths from TB among HIV-positive people accounted for 37% of deaths classified as caused by HIV/AIDS in 2016.

WHO Global TB report 2017

HIV&TB ETKİLEŞİM

- HIV enfekte bireylerde TB gelişme riski 26-31 kat fazla
- Reaktivasyon riski HIV enfekte bireylerde yıllık %3-16
  (HIV enfekte olmayanlarda yaşam boyu ~%5)
- HIV infeksiyonunun her evresinde TB ortaya çıkabilir
- İmmünsüpresyonun derecesine bağlı olarak aktif TB riski artar
- TB riski HIV enfeksiyonunun ilk yılında 2 kat fazla
- Yaygın tüberküloz insidansı ise immün yetmezliğin ileri evresinde daha yüksek
- Tedavisiz TB HIV enfekte bireylerde daha progresif ve fatal
- Ekstrapulmoner tüberküloz oranı HIV enfekte bireylerde daha fazla (özellikle geç prezente olanlarda)

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/325/tb

HIV-enfekte bireylerde TB neden sorun?

- Hızlı ilerler
- Tedavi edilmezse daha fatal
- Dissemine olma riski fazla
- Tedavi sonrası rekürrens fazla
- Direnç gelişirse tedavi çok zor
- **Tanısı güç!**

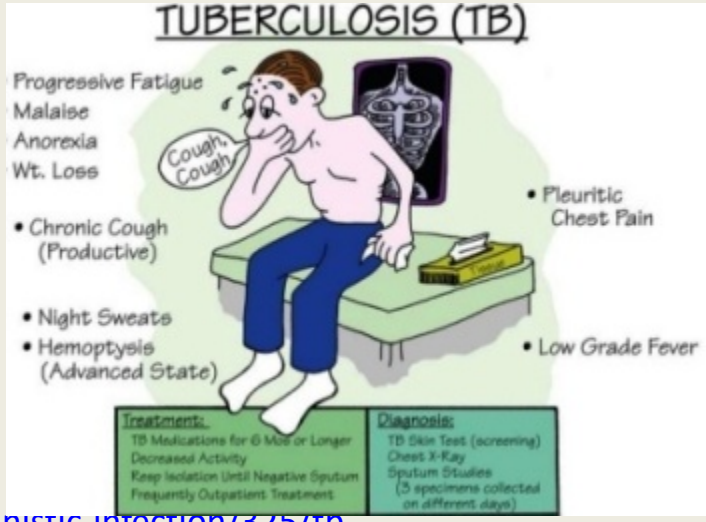
Tanı neden güç?

- ✓ **Klinik farklı**
- ✓ **Radyolojik bulgular farklı**
- ✓ **Histopatolojik bulgular farklı**
- ✓ **Laboratuvar bulguları farklı**

- HIV ile ilişkili pek çok hastalık ayırıcı tanıyı güçleştiriyor
- İmmünsupresyon derecesi tanıyı güçleştiriyor
- EP tüberküloz oranı fazla

KLİNİK

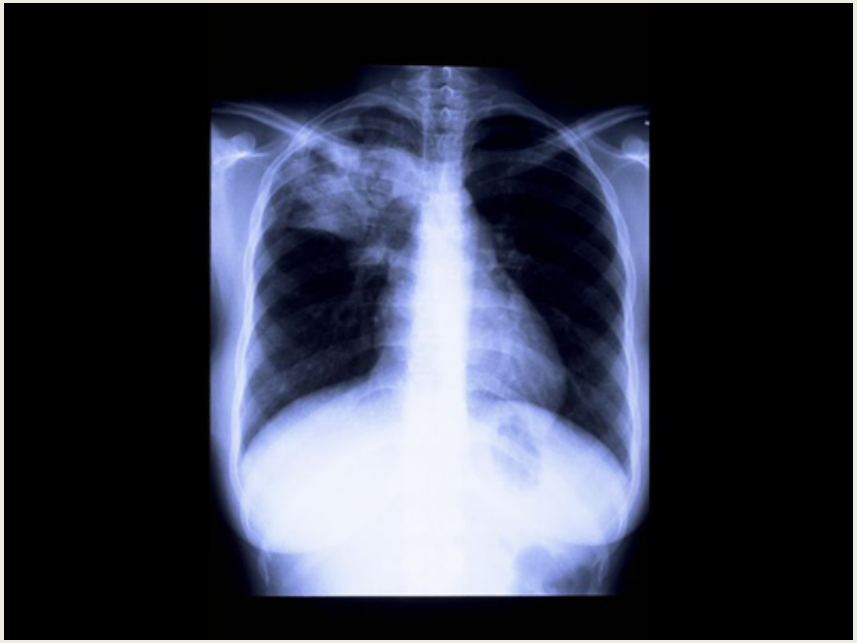
- CD4 sayısı >200 klinik HIV enfekte olmayanlarla benzer
- Klasik semptom varlığının duyarlılığı ve özgüllüğü düşük
- İleri evre HIV enfeksiyonunda hiç semptom olmayabilir
- Semptomların süresi daha kısa
- Ekstrapulmoner tutulum %40-80
- EP tutulumda en sık lenfadenit



https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/325/tb

RADYOLOJİ

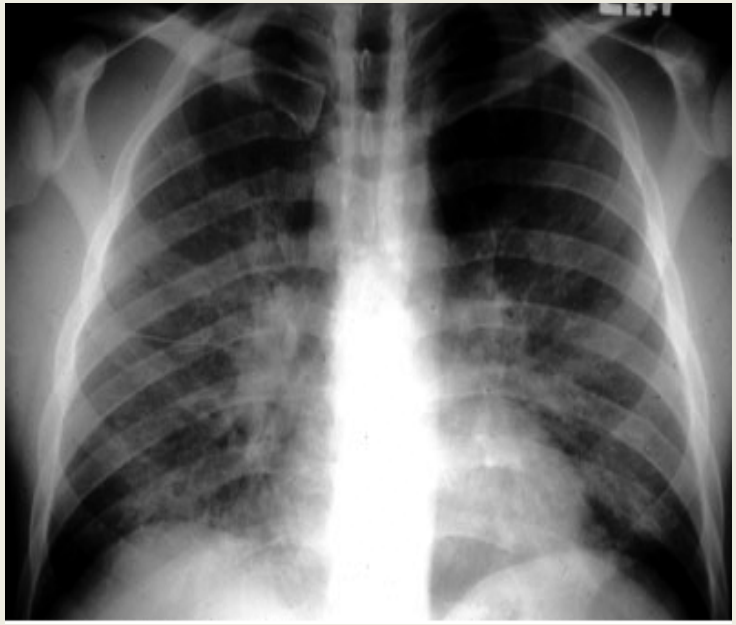
Tipik görünüm; üst lob apikal segmentte opasite+ kavitasyon



Geç evre HIV enfekte olgularda;

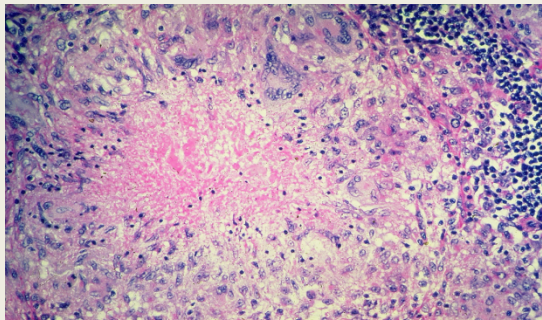
Radyolojik görünüm hiç olmayabilir veya

Mediastinal Lap'lar, alt loblarda infiltrasyonlar, kavitasyon yokluğu, miliyer görünüm….

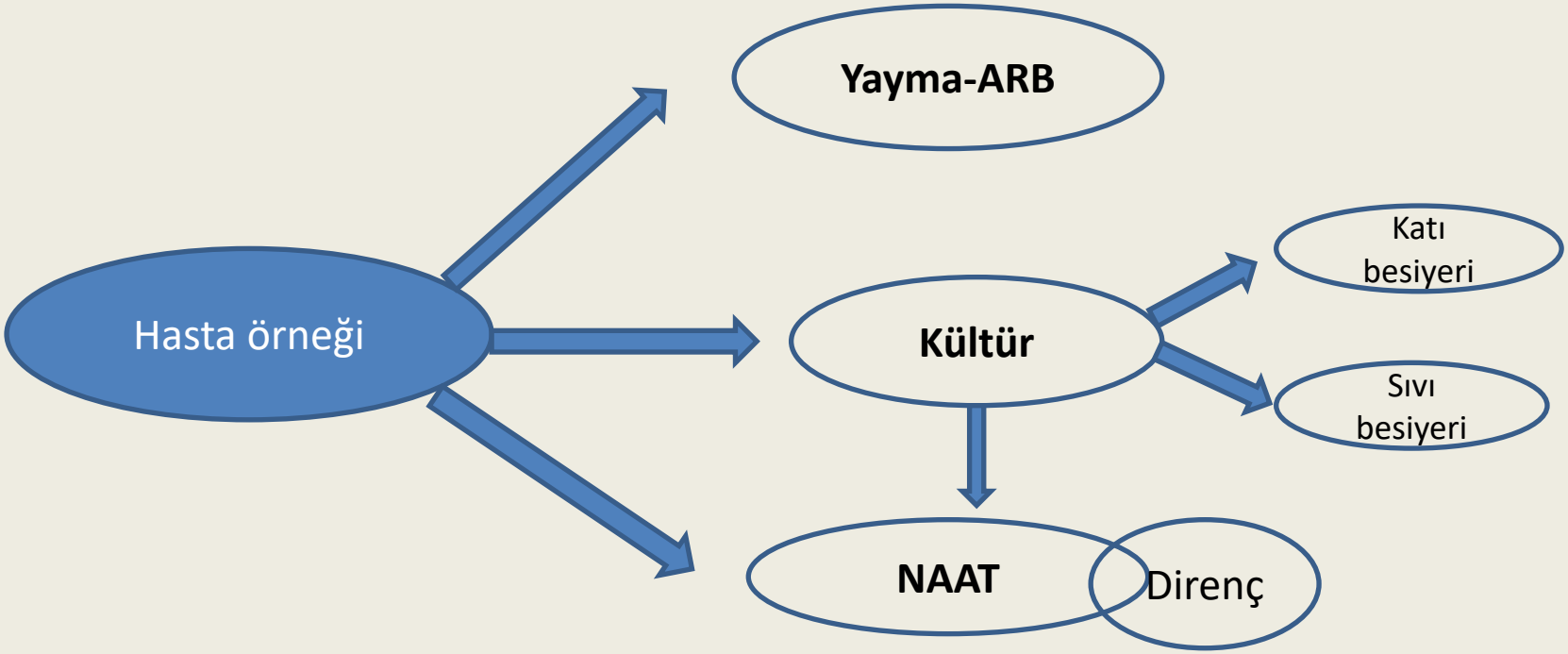


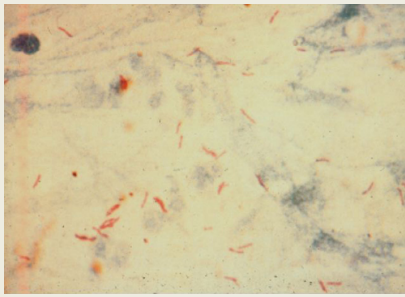
HİSTOPATOLOJİK İNCELEME

- Özellikle ekstrapulmoner ve dissemine TB'de elverişli
- Nodal tutulum HIV /TB koenfeksiyonunda sık-ince iğne aspirasyonu
- Histopatolojik bulgular immünsupresyonun derecesiyle doğrudan ilişkili
- Erken evrelerde tipik granülomlar
- İmmunsupresyon ilerledikçe granülom ya hiç görülmez ya da zayıf forme olmuştur



LABORATUVAR





LABORATUVAR

Konvansiyonel Yöntemler

Mikroskobik inceleme; Balgamda ARB bakı

- Özellikle ileri evre HIV enfeksiyonunda ARB negatifliği sık (kavitasyon yok)
- Hızlı ve ucuz olması avantajı
- Pulmoner TB için elverişli
- Yüksek HIV prevalansı olan bölgelerde ARB duyarlılığı %20-30, özgüllüğü >%90
- Düşük bakteri yükü, disseminasyon ve EPTB daha sık olduğundan duyarlılık düşük
- LED mikroskop %10 artmış duyarlılık, kısa zaman

Bruchfeld J. et al.Trans. R. Soc. Trop. Med. Hyg. 2000;94:677–680

Mikobakteri kültürü

- Altın standart
- Duyarlılığı ve özgüllüğü yüksek
- HIV enfekte olanlarda da benzer
- Zaman alıcı
- Doku biyopsi materyalleri de gönderilmeli

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/325/tb

Tanıda sorunlarımız

- Klinik, radyolojik ve patolojik bulgular atipik
- Balgamda ARB duyarlılığı çok düşük
- Kültür zaman alıcı

- Zaman önemli
- Klasik tanı yöntemleri elverişsiz

O zaman neye ihtiyacımız var??

Tanıda ihtiyacımız olan;

1-Mikroskobi yerine konabilecek hızlı ve duyarlı moleküler testler

- **NAATs**

2-Tüm TB formlarında kullanılabilen balgam-bazlı olmayan hızlı test

- **LAM**

3- Hızlı ilaç duyarlılığı testleri

- **NAATs, LPA**

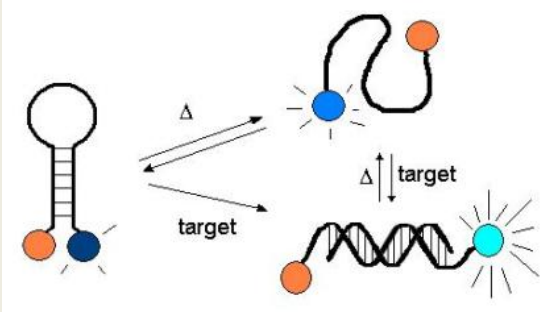
NÜKLEİK ASİD AMPLİFİKASYON TESTLERİ (NAATs)

- Hızlı tanı imkanı (24-48 sa)
- Direnç profilini belirleme
- Yayma+ olgularda duyarlılık çok yüksek TB dışı mikobakterileri hızla dışlama ve erken tedavi kararı
- Duyarlılığı yaymadan yüksek,
- Yayma- kültür+ olgularda duyarlılık %50-90
- CDC Önerisi: En az bir örnek NAATs için gönderilmeli

https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/325/tb

NAAT: GeneXpert (Cepheid)

- **Aynı anda TB ve RIF direnci saptama**
- **2 saatten kısa süre**
- **Yüksek duyarlılık (%70-80), yüksek özgüllük (%99)**
- Kapalı otomatize sistem
- Eğitimli personele ihtiyaç duymaz
- Düşük biyogüvenlik düzeyi (periferik lab'lar için uygunluk)
- Hem pulmoner hem EPTB
- Aynı cihazda HIV ve HCV viral yük



WHO 2011

5. Policy recommendations

The GRADE process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of TB and rifampicin resistance and resulted in the following main recommendations:

1. Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. (Strong recommendation)
2. Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. (Conditional recommendation ac

WHO 2013

World Health Organization

THE USE OF THE XPERT MTB/RIF ASSAY FOR THE DETECTION OF PULMONARY AND EXTRAPULMONARY TUBERCULOSIS AND RIFAMPICIN RESISTANCE IN ADULTS AND CHILDREN

EPTB tanısında Xpert

EXPERT GROUP MEETING REPORT
October 2013

Pre-publication copy

http://www.stoptb.org/wg/gli/assets/documents/Xpert%20Meeting%20Report%2024102013%20%20Pre%20publication%20FINAL.pdf

Xpert Ultra

THE LANCET
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Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study

Prof Susan E Dorman, MD † • Samuel G Schumacher, PhD † • Prof David Alland, MD • Pamela Nabeta, MD
Derek T Armstrong, MHS • Bonnie King, MHS • et al. Show all authors • Show footnotes

Open Access • Published: November 30, 2017 • DOI: https://doi.org/10.1016/S1473-3099(17)30691-6

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PlumX Metrics

Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study

Susan E Dorman, Samuel G Schumacher*, David Alland, Pamela Nabeta, Derek T Armstrong, Bonnie King, Sandra L Hall, Soumitesh Chakravorty, Daniela M Cirillo, Nestani Tukvadze, Nino Bablishvili, Wendy Stevens, Lesley Scott, Camilla Rodrigues, Mubin I Kazi, Moses Joloba, Lydia Nakiyingi, Mark P Nicol, Yonas Ghebrekristos, Irene Anyango, Wilfred Murithi, Reynaldo Dietze, Renata Lyrio Peres, Alena Skrahina, Vera Auchynka, Kamal Kishore Chopra, Mahmud Hanif, Xin Liu, Xing Yuan, Catharina C Boehme, Jerrold J Ellner, Claudia M Denkinger, on behalf of the study team†*

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This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on February 21, 2018.

See Comment page 8

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Summary

Background The Xpert MTB/RIF assay is an automated molecular test that has improved the detection of tuberculosis and rifampicin resistance, but its sensitivity is inadequate in patients with paucibacillary disease or HIV. Xpert MTB/RIF Ultra (Xpert Ultra) was developed to overcome this limitation. We compared the diagnostic performance of Xpert Ultra with that of Xpert for detection of tuberculosis and rifampicin resistance.

Methods In this prospective, multicentre, diagnostic accuracy study, we recruited adults with pulmonary tuberculosis symptoms presenting at primary health-care centres and hospitals in eight countries (South Africa, Uganda, Kenya, India, China, Georgia, Belarus, and Brazil). Participants were allocated to the case detection group if no drugs had been taken for tuberculosis in the past 6 months or to the multidrug-resistance risk group if drugs for tuberculosis had been taken in the past 6 months, but drug resistance was suspected. Demographic information, medical history, chest imaging results, and HIV test results were recorded at enrolment, and each participant gave at least three sputum specimen on 2 separate days. Xpert and Xpert Ultra diagnostic performance in the same sputum specimen was compared with culture tests and drug susceptibility testing as reference standards. The primary objectives were to estimate and compare the sensitivity of Xpert Ultra test with that of Xpert for detection of smear-negative tuberculosis and rifampicin resistance and to estimate and compare Xpert Ultra and Xpert specificities for detection of rifampicin resistance. Study participants in the case detection group were included in all analyses, whereas participants in the multidrug-resistance risk group were only included in analyses of rifampicin-resistance detection.

Findings Between Feb 18, and Dec 24, 2016, we enrolled 2368 participants for sputum sampling. 248 participants were excluded from the analysis, and 1753 participants were distributed to the case detection group (n=1439) and the multidrug-resistance risk group (n=314). Sensitivities of Xpert Ultra and Xpert were 63% and 46%, respectively, for the 137 participants with smear-negative and culture-positive sputum (difference of 17%, 95% CI 10 to 24); 90% and 77%, respectively, for the 115 HIV-positive participants with culture-positive sputum (13%, 6·4 to 21); and 88% and 83%, respectively, across all 462 participants with culture-positive sputum (5·4%, 3·3 to 8·0). Specificities of Xpert Ultra and Xpert for case detection were 96% and 98% (–2·7%, –3·9 to –1·7) overall, and 93% and 98% for patients with a history of tuberculosis. Xpert Ultra and Xpert performed similarly in detecting rifampicin resistance.

Interpretation For tuberculosis case detection, sensitivity of Xpert Ultra was superior to that of Xpert in patients with paucibacillary disease and in patients with HIV. However, this increase in sensitivity came at the expense of a decrease in specificity.

- Çok merkezli, prospektif çalışma (8 Afrika ülkesi)
- 2016 yılı içerisinde çalışma kapsamına alınan 1753 olgu (314'ü MDR risk grubu),
- Solunum örnekleri
- Pulmoner tüberkülozda **Xpert ve Xpert Ultra duyarlılık karşılaştırması**

	Tuberculosis detection*					Detection of rifampicin resistance†	
	Sensitivity: all culture-positive (95% CI; n/N)	Sensitivity: smear-negative (95% CI; n/N)	Sensitivity: HIV-negative (95% CI; n/N)‡	Sensitivity: HIV-positive (95% CI; n/N)‡	Specificity (95% CI; n/N)	Sensitivity (95% CI; n/N)	Specificity (95% CI; n/N)
Xpert	83% (79 to 86; 383/462)	46% (37 to 55; 63/137)§	90% (84 to 94; 143/159)	77% (68 to 84; 88/155)	98% (97 to 99; 960/977)	95% (91 to 98; 167/175)	98% (96 to 99; 369/376)
Xpert Ultra	88% (85 to 91; 408/462)	63% (54 to 71; 86/137)§	91% (86 to 95; 145/159)	90% (83 to 95; 103/115)	96% (94 to 97; 934/977)	95% (91 to 98; 166/175)	98% (97 to 99; 370/376)
Difference (Xpert Ultra minus Xpert)	5·4% (3·3 to 8·0; 25/162)	17% (10 to 24; 23/137)	1·3% (−1·8 to 4·9; 2/159)	13% (6·4 to 21; 15/115)	−2·7% (−3·9 to −1·7; 36/977)	−0·6% (−3·2 to 1·6; 1/175)	0·3% (−0·7 to 1·5; 1/376)
Non-inferiority margin	Not predefined	−7%	Not predefined	Not predefined	Not predefined	−3%	−3%

Results are based on initial testing of the first sample with Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) assays. Uninterpretable results (contaminated cultures or non-determinate Xpert or Ultra results) were excluded from the analysis. Culture contamination averaged 4·3–7·8%, depending on sample and culture type. Non-determinate results (invalid, error, no result) are reported in the main text. Sensitivities of Xpert and Xpert Ultra for detection of smear-positive tuberculosis (n=323) were 99% (95% CI 97–100) and 99% (97–100). *Accuracy for tuberculosis detection was estimated in study participants in the case detection group. Patients with unknown HIV-infection status are excluded from analyses stratified by HIV status but included in all other analyses. †Accuracy for detection of rifampicin resistance was estimated in all study participants with available drug susceptibility test results and valid rifampicin resistance results for both Xpert and Xpert Ultra. ‡Data on HIV-infection status were not available for 188 culture-positive and 336 culture-negative study participants. Sensitivity of Xpert and Xpert Ultra in study participants with missing HIV status was 81% and 85%, respectively. Note that the estimate for pooled sensitivity of Xpert Ultra irrespective of HIV status does not fall between the estimates for HIV-infected and HIV-uninfected individuals. §Accuracy estimates are based on the reference standard as defined in the Methods section (using four cultures to define tuberculosis); using a less stringent reference standard with only one liquid and one solid culture (both from sputum sample 2), which is similar to the reference standard used in 21 of 22 studies included in the most recent Cochrane systematic review of the Xpert assay,* resulted in Xpert sensitivity for smear-negative tuberculosis of 73% (Cochrane review pooled estimate 67%) and Xpert Ultra sensitivity of 84% (appendix p 5).

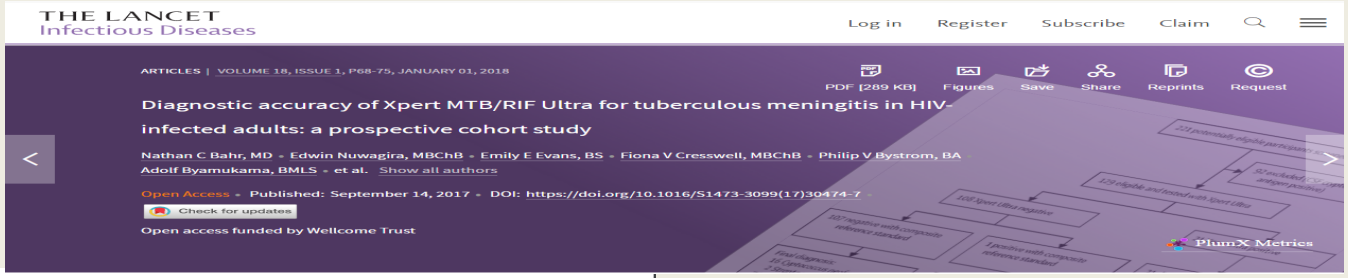
Table 2: Comparative accuracy for detection of tuberculosis and rifampicin resistance

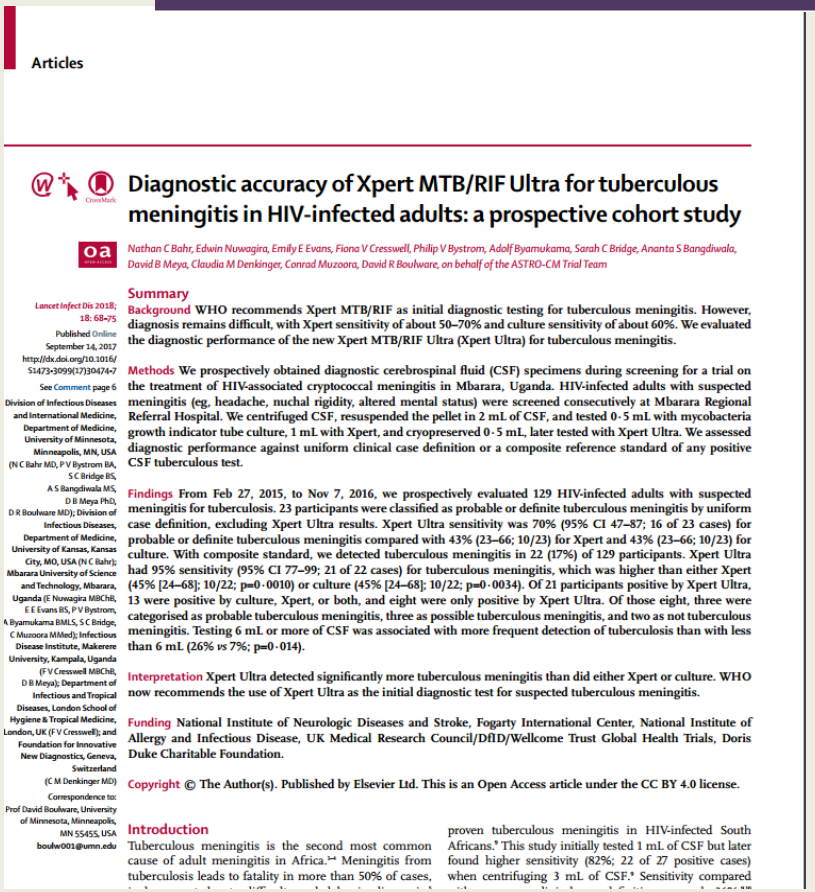
	Sensitivity		Specificity		
	All culture-positive (95% CI; n/N)	Smear-negative, culture-positive (95% CI; n/N)	All culture-negative	No history of tuberculosis	Any history of tuberculosis
Xpert	83% (79–86; 383/462)	46% (37–55; 63/137)			
Xpert Ultra	88% (85–91; 408/462)	63% (54–71; 86/137)			
Xpert Ultra, no trace*	86% (82–89; 395/462)	54% (45–63; 74/137)			
Xpert Ultra, conditional trace†	88% (85–91; 406/462)	61% (53–70; 84/137)			
Xpert Ultra, trace-repeat‡	87% (84–90; 404/462)	61% (52–69; 83/137)			

Sensitivity varied little by history of tuberculosis and did not vary systematicall
tuberculosis-positive based on a trace-positive Xpert Ultra result (n=32) were
trace-positive Xpert Ultra result were reclassified as tuberculosis-negative only
on a trace-positive Xpert Ultra result had Xpert Ultra testing on a subsequent
the participant was reclassified as tuberculosis-negative; if the subsequent Xpe
was not reclassified and remained tuberculosis-positive (14 out of 32 participa
on sample 2 and were not reclassified; and four were were non-determinate by

Table 3: Test sensitivity and specificity depending on tuberculosis history and different approaches to the interpretation of semiquantitative trace-positive results for *Mycobacterium tuberculosis* detection by Xpert MTB/RIF Ultra (Xpert Ultra)

Kültür pozitif HIV-enfekte olgularda Xpert Ultra ile TB saptamada duyarlılık %90





Articles

Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study

Nathan C Bahr, Edwin Nuwagira, Emily E Evans, Fiona V Cresswell, Philip V Bystrom, Adolf Byamukama, Sarah C Bridge, Ananta S Bangdiwala, David B Meya, Claudia M Denkinger, Conrad Muzoora, David R Boulware, on behalf of the ASTRO-CM Trial Team

Lancet Infect Dis 2018; 18: 68–75
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See Comment page 6

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Correspondence to: Prof David Boulware, University of Minnesota, Minneapolis, MN 55455, USA
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Summary

Background WHO recommends Xpert MTB/RIF as initial diagnostic testing for tuberculous meningitis. However, diagnosis remains difficult, with Xpert sensitivity of about 50–70% and culture sensitivity of about 60%. We evaluated the diagnostic performance of the new Xpert MTB/RIF Ultra (Xpert Ultra) for tuberculous meningitis.

Methods We prospectively obtained diagnostic cerebrospinal fluid (CSF) specimens during screening for a trial on the treatment of HIV-associated cryptococcal meningitis in Mbarara, Uganda. HIV-infected adults with suspected meningitis (eg, headache, nuchal rigidity, altered mental status) were screened consecutively at Mbarara Regional Referral Hospital. We centrifuged CSF, resuspended the pellet in 2 mL of CSF, and tested 0·5 mL with mycobacteria growth indicator tube culture, 1 mL with Xpert, and cryopreserved 0·5 mL, later tested with Xpert Ultra. We assessed diagnostic performance against uniform clinical case definition or a composite reference standard of any positive CSF tuberculous test.

Findings From Feb 27, 2015, to Nov 7, 2016, we prospectively evaluated 129 HIV-infected adults with suspected meningitis for tuberculosis. 23 participants were classified as probable or definite tuberculous meningitis by uniform case definition, excluding Xpert Ultra results. Xpert Ultra sensitivity was 70% (95% CI 47–87; 16 of 23 cases) for probable or definite tuberculous meningitis compared with 43% (23–66; 10/23) for Xpert and 43% (23–66; 10/23) for culture. With composite standard, we detected tuberculous meningitis in 22 (17%) of 129 participants. Xpert Ultra had 95% sensitivity (95% CI 77–99; 21 of 22 cases) for tuberculous meningitis, which was higher than either Xpert (45% [24–68]; 10/22; p=0·0010) or culture (45% [24–68]; 10/22; p=0·0034). Of 21 participants positive by Xpert Ultra, 13 were positive by culture, Xpert, or both, and eight were only positive by Xpert Ultra. Of those eight, three were categorised as probable tuberculous meningitis, three as possible tuberculous meningitis, and two as not tuberculous meningitis. Testing 6 mL or more of CSF was associated with more frequent detection of tuberculosis than with less than 6 mL (26% *vs* 7%; p=0·014).

Interpretation Xpert Ultra detected significantly more tuberculous meningitis than did either Xpert or culture. WHO now recommends the use of Xpert Ultra as the initial diagnostic test for suspected tuberculous meningitis.

Funding National Institute of Neurologic Diseases and Stroke, Fogarty International Center, National Institute of Allergy and Infectious Disease, UK Medical Research Council/DfID/Wellcome Trust Global Health Trials, Doris Duke Charitable Foundation.

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Introduction

Tuberculous meningitis is the second most common cause of adult meningitis in Africa.[1–4] Meningitis from tuberculosis leads to fatality in more than 50% of cases, proven tuberculous meningitis in HIV-infected South Africans.[3] This study initially tested 1 mL of CSF but later found higher sensitivity (82%; 22 of 27 positive cases) when centrifuging 3 mL of CSF.[3] Sensitivity compared

- Prospektif,
- 2015-2016 yılları arasında TB menenjit şüphesi olan 129 HIV-enfekte olgu
- Xpert Ultra yüksek duyarlılık **(%95)**
- Xpert ve MGIT ile duyarlılık %45
- Xpert Ultra TB menenjit tanısında anlamlı derecede daha duyarlı

Tuberculosis (TB)

Tuberculosis
The End TB Strategy
Areas of work
TB publications
TB data
News, events and features
About us

Next-generation Xpert® MTB/RIF Ultra assay recommended by WHO

24 MARCH 2017 - The World Health Organization (WHO) today recommended the use in all settings of a next-generation Xpert® MTB/RIF assay (called Xpert® MTB/RIF Ultra) as a replacement for the current Xpert MTB/RIF® cartridge.

The Ultra cartridge, that has been developed by Cepheid (Sunnyvale, USA), showed significantly better performance (increased sensitivity) compared to the current Xpert® MTB/RIF cartridge for the detection of Mycobacterium tuberculosis in specimens with low numbers of bacilli, especially in smear-negative, culture-positive specimens (such as those from persons with HIV co-infection), in paediatric specimens and in extra-pulmonary specimens (notably cerebrospinal fluid). The accuracy in detection of rifampicin resistance was also better although not enough data were available to conclusively confirm this.

The recommendation on the Ultra cartridge is based on a recent WHO Expert Group evaluation of data from a study coordinated by FIND, in collaboration with the Tuberculosis Clinical Diagnostics Research Consortium (CDRC). The study compared the Ultra assay with the current Xpert® MTB/RIF assay for diagnostic accuracy and non-inferiority across 10 study sites in eight countries. 1,520 patients with signs and symptoms of TB were enrolled in these countries for a direct comparison of the performance of Ultra against Xpert MTB/RIF on the same specimen.

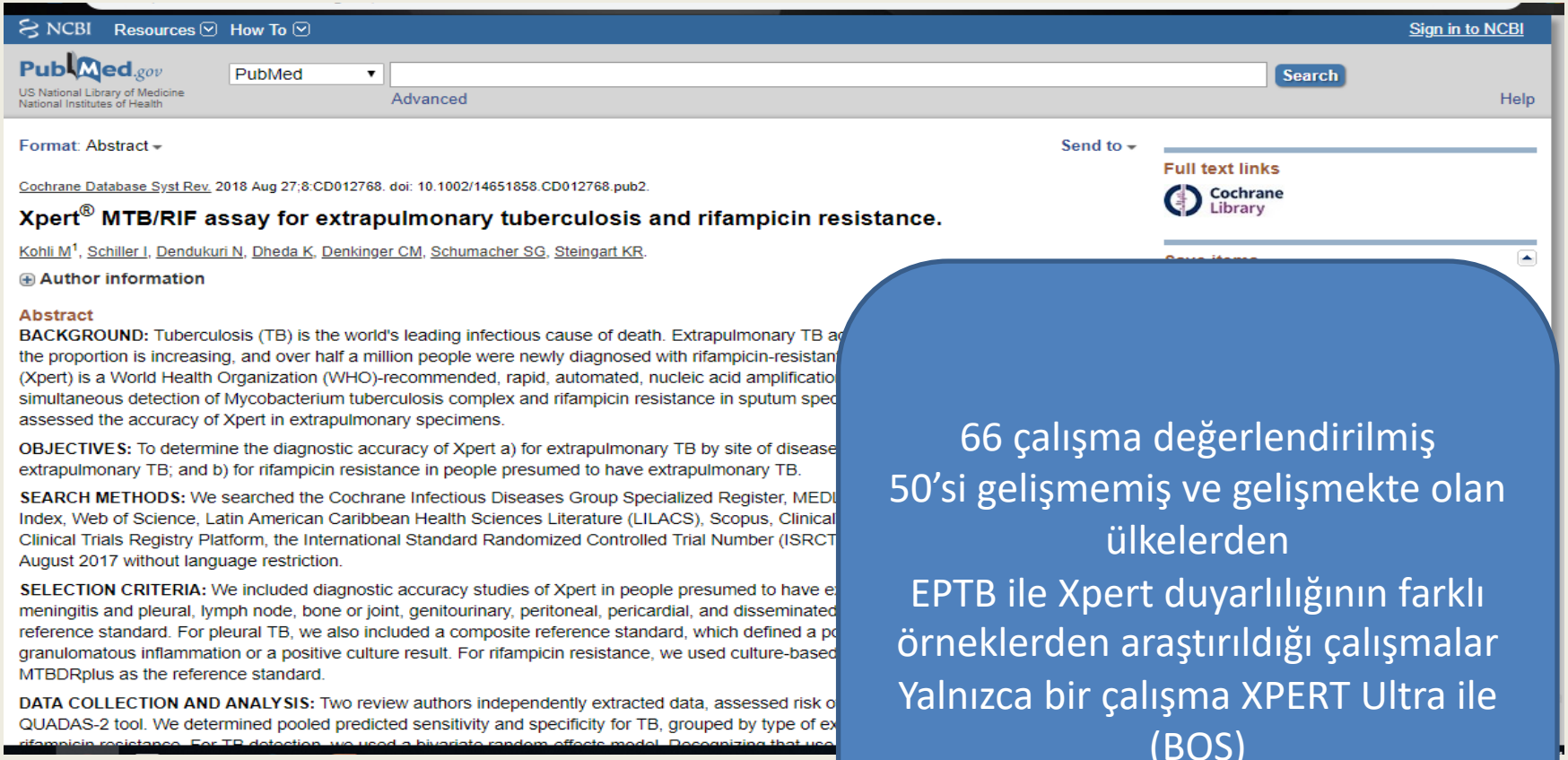
"Innovations in technology and the strong science behind it have brought significant breakthroughs in TB diagnosis over the last 10 years" said Dr Mario Raviglione, Director of the WHO Global TB Programme. "Achieving the targets in the WHO End TB Strategy necessitates urgent scale-up of these innovations at all levels and in all settings for early and rapid diagnosis of TB and rifampicin resistance in all persons with signs or symptoms of TB."

About the Ultra cartridge

Download:

- WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF
- Frequently Asked Questions pdf, 271kb
- FIND Website

EPTB tanısında Xpert MTB/RIF



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Cochrane Database Syst Rev. 2018 Aug 27;8:CD012768. doi: 10.1002/14651858.CD012768.pub2.

Xpert® MTB/RIF assay for extrapulmonary tuberculosis and rifampicin resistance.

Kohli M[1], Schiller I, Dendukuri N, Dheda K, Denkinger CM, Schumacher SG, Steingart KR.

Author information

Abstract

BACKGROUND: Tuberculosis (TB) is the world's leading infectious cause of death. Extrapulmonary TB a
the proportion is increasing, and over half a million people were newly diagnosed with rifampicin-resistan
(Xpert) is a World Health Organization (WHO)-recommended, rapid, automated, nucleic acid amplificatio
simultaneous detection of Mycobacterium tuberculosis complex and rifampicin resistance in sputum spec
assessed the accuracy of Xpert in extrapulmonary specimens.

OBJECTIVES: To determine the diagnostic accuracy of Xpert a) for extrapulmonary TB by site of disease
extrapulmonary TB; and b) for rifampicin resistance in people presumed to have extrapulmonary TB.

SEARCH METHODS: We searched the Cochrane Infectious Diseases Group Specialized Register, MEDL
Index, Web of Science, Latin American Caribbean Health Sciences Literature (LILACS), Scopus, Clinical
Clinical Trials Registry Platform, the International Standard Randomized Controlled Trial Number (ISRCT
August 2017 without language restriction.

SELECTION CRITERIA: We included diagnostic accuracy studies of Xpert in people presumed to have e
meningitis and pleural, lymph node, bone or joint, genitourinary, peritoneal, pericardial, and disseminated
reference standard. For pleural TB, we also included a composite reference standard, which defined a p
granulomatous inflammation or a positive culture result. For rifampicin resistance, we used culture-based
MTBDRplus as the reference standard.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data, assessed risk o
QUADAS-2 tool. We determined pooled predicted sensitivity and specificity for TB, grouped by type of ex
rifampicin resistance. For TB detection, we used a bivariate random effects model. Recognizing that use

66 çalışma değerlendirilmiş
50'si gelişmemiş ve gelişmekte olan ülkelerden
EPTB ile Xpert duyarlılığının farklı örneklerden araştırıldığı çalışmalar
Yalnızca bir çalışma XPERT Ultra ile (BOS)

Table 3. Accuracy of Xpert® MTB/RIF for detection of extrapulmonary TB and rifampicin resistance — Open in table viewer

Form of extrapulmonary TB, type of specimen	Number of studies (specimens)	Number of specimens with culture-confirmed TB (%)	Pooled sensitivity (95% credible interval)	Pooled specificity (95% credible interval)	Predicted sensitivity (95% credible interval)	Predicted specificity (95% credible interval)
TB meningitis, cerebrospinal fluid	29 (3774)	433 (11.5)	71.1% (60.9 to 80.4)	98.0% (97.0 to 98.8)	71.1% (27.8 to 94.8)	98.0% (88.1 to 99.7)
Pleural TB, fluid[a]	27 (4006)	607 (15.2)	50.9% (39.7 to 62.8)	99.2% (98.2 to 99.7)	50.9% (12.3 to 88.8)	99.2% (81.6 to 100)
Pleural TB, tissue	3 (207)	71 (34.3)	30.5% (3.5 to 77.)	97.4% (92.1 to 99.3)	30.9% (0.2 to 98.2)	97.4% (87
Lymph node, aspirate	17 (1710)	671 (39.2)	87.6% (81.7 to 92.0)	86.0% (78.4 to 91.5)	87.7% (58.1 to 97.4)	86.0% (46
Lymph node, tissue	10 (484)	147 (30.4)	84.4% (74.7 to 91.0)	78.9% (52.6 to 91.5)	78.9% (52.6 to 91.5)	78.9% (9.
Genitourinary TB, urine	13 (1199)	73 (6.1)	82.7% (69.6 to 91.1)	98.7% (94.8 to 99.7)	82.7% (54.3 to 95.1)	98.8% (45
Bone or joint TB, fluid	5 (385)	58 (15.1)	97.2% (89.5 to 99.6)	90.2% (55.6 to 98.5)	97.3% (83.9 to 99.7)	90.5% (6.
Bone or joint TB, tissue	7 (618)	179 (29.0)	91.8% (82.5 to 96.8)	82.0% (56.6 to 94.9)	91.8% (70.1 to 98.4)	82.0% (10.4
Peritoneal TB, fluid	16 (712)	115 (16.2)	59.2% (45.2 to 73.5)	97.9% (96.2 to 99.1)	59.1% (23.3 to 88.8)	97.9% (93.4 to 99.6)

DISCUSSION

Summary of main results

This systematic review summarizes the current literature and includes 66 unique studies on the accuracy of Xpert for extrapulmonary tuberculosis (TB) and rifampicin resistance. Seventy-six per cent of these studies were conducted in low- and middle-income countries. Major findings from our review include the following.

- Xpert sensitivity for TB in extrapulmonary specimens varied across different types of specimens (from 31% in pleural

uid was
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2% for
3% for
oled sensi-
ence and speci-
ficity was similar or lower in settings with lower TB prevalence (Table 4).

Xpert duyarlılığı hasta örneklerine göre %31 ile %97 arasında değişiyor
Özgüllüğü çok yüksek

İlaç duyarlılık testleri

- Fenotipik direnç testi altın standart (sıvı kültür)

- Daha hızlı sonuç için;

✓ **LPA**

✓ **Xpert XDR**

✓ **Yeni kuşak sekanslama teknikleri (NGS)**

Line probe assays (LPAs)

- MTB saptamada elverişli
- 1. kuşak LPA – RIF ve INH direnci **(MDR-TB)**
- 2. kuşak LPA- enjektabl ajanlar ve florokinolon direnci
- RIF direnci;
  duyarlılık %97-100
  özgüllük %98-100

•LPAs hızlı tedavi kararında önemli bir teknik:

- INH direnci
- MDR-TB için uygun tedavi

2008'DEN BU YANA WHO HIZLI DİRENÇ TESTİ İÇİN ÖNERİYOR

Dezavantajları;

- Pahalı
- Yüksek biyogüvenlik düzeyi
- Eğitimli personel
- Xpert kadar hızlı değil

Xpert XDR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis

Y.L. Xie, S. Chakravorty, D.T. Armstrong, S.L. Hall, L.E. Via, T. Song, X. Yuan, X. Mo, H. Zhu, P. Xu, Q. Gao, M. Lee, J. Lee, L.E. Smith, R.Y. Chen, J.S. Joh, Y.S. Cho, X. Liu, X. Ruan, L. Liang, N. Dharan, S.-N. Cho, C.E. Barry III, J.J. Ellner, S.E. Dorman, and D. Alland

Table 3. Sensitivity and Specificity of the Investigational Assay, with DNA Sequencing as the Reference Standard, in the Main Analysis Population for Drug-Susceptibility Testing.*

Drug	Investigational-Assay Result + DNA Sequencing Result†				Sensitivity		Specificity	
	M+M	M+NM	NM+M	NM+NM				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid‡	151	0	3	149	151/154	98.1 (94.4–99.6)	149/149	100.0 (97.6–100.0)
Fluoroquinolones§	91	0	4	208	91/95	95.8 (89.6–98.8)	208/208	100.0 (98.2–100.0)
Kanamycin¶	38	1	3	256	38/41	92.7 (80.1–98.5)	256/257	99.6 (97.9–100.0)
Amikacin¶	30	0	1	267	30/31	96.8 (83.3–99.9)	267/267	100.0 (98.6–100.0)

gyrB	**Fluoroquinolones**	Codons 538-540		
rrs	**Amikacin, kanamycin**	1401, 1402		
		1484	X	
eis	**Kanamycin**	Promoter -10		
		Promotor -37		X

Hasta Başı Testleri (POC)

- Diğer tekniklerin; pahalı olması, ekipman, mekan, eğitimli personel ve zaman gerektirmesi nedeniyle ihtiyaç…

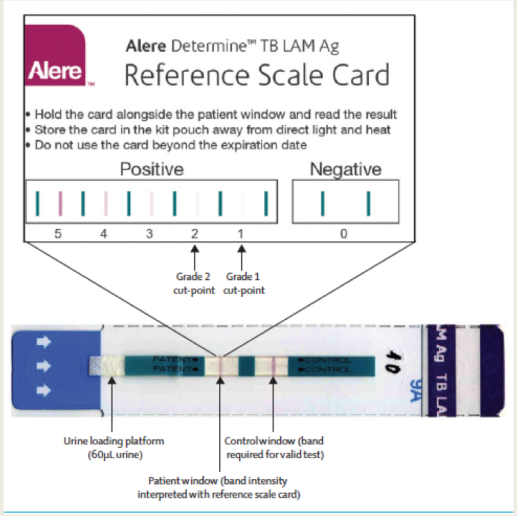
HIV-enfekte olgular için onaylı test

İdrarda LAM testi

LAM TEST

- İdrarda antijen saptama
- LAM ; MTB'nin hücre duvarında bulunan bir Ag
- Yalnızca aktif TB hastalığı olanlarda saptanır

  Pulmoner ve ekstrapulmoner TB
- Basit, kart test (gebelik testi benzeri)
- 20-25 dakikada sonuç
- Duyarlılığı düşük
- 2015 WHO Onayı; Yalnızca CD4<100/mm^3 veya ağır hasta olan HIV-enfekte olgularda



WHO's policy recommendations

Policy Recommendations for the use of the lateral flow urine lipoarabinomannan (LF-LAM) assay

1. **Except as specifically described below for persons with HIV infection with low CD4 counts or who are seriously ill**[2], LF-LAM **should not be used** for the diagnosis of TB **(strong recommendation, low quality of evidence)**.
2. LF-LAM **may be used** to assist in the diagnosis of TB **in HIV positive** adult *in-patients* with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill[2] regardless of CD4 count or with unknown CD4 count **(conditional recommendation; low quality of evidence)**.

Remarks

a. This recommendation also applies to HIV positive adult *out-patients* with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/µL, or HIV positive patients who are seriously ill[2] regardless of CD4 count or with unknown CD4 count, based on the generalisation of data from in-patients.

b. This recommendation also applies to HIV positive children with signs and symptoms of TB (pulmonary and/or extrapulmonary) based on the generalisation of data from adults while acknowledging very limited data and concern regarding low specificity of the LF-LAM assay in children.

Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial

Jonny G Peter, Lynn S Zijenah*, Duncan Chanda*, Petra Clowes*, Maia Lesosky, Phindile Gina, Nirja Mehta, Greg Calligaro, Carl J Lombard, Gerard Kadzirange, Tsitsi Bandason, Abidan Chansa, Namakando Liusha, Chacha Mangu, Bariki Mtafya, Henry Msila, Andrea Rachow, Michael Hoelscher, Peter Mwaba, Grant Theron, Keertan Dheda*

Açık uçlu, çok merkezli, randomize kontrollü çalışma
Olguların tamamı HIV+ ve hospitalize
2 kol: **2 arms: LAM +rutin TB tanı testleri *ve* rutin TB tanı testleri**

	Overall (n=2528)	LAM (n=1257)	No LAM (n=1271)
Age (years)	37 (30–44)	37 (30–44)	37 (30–44)
Sex			
Male	1228 (49%)	628 (50%)	600 (47%)
Female	1300 (51%)	629 (50%)	671 (53%)
Previous tuberculosis	682 (27%)	339 (27%)	343 (27%)
Days between admission and study enrolment	1 (1–2)	1 (1–2)	1 (1–2)
HIV status			
CD4 cell count (cells per µL)	84 (26–208)	81 (26–198)	87 (28–217)
WHO clinical stage			
Stage 1	59 (2%)	28 (2%)	31 (2%)
Stage 2	671 (27%)	337 (27%)	334 (26%)
Stage 3	1331 (53%)	675 (54%)	656 (52%)
Stage 4	438 (17%)	204 (16%)	234 (18%)
ART at randomisation	1224 (48%)	604 (48%)	620 (49%)
Co-trimoxazole prophylaxis at randomisation	1130 (45%)	552 (44%)	578 (45%)
ART initiated by 8-week follow-up if alive and no ART at study entry	615/848† (73%)	312/435 (72%)	303/413 (73%)
Tuberculosis symptoms			
Cough	2350 (93%)	1166 (93%)	1184 (93%)
Weight loss	2180 (86%)	1084 (86%)	1096 (86%)
Night sweats	1894 (75%)	927 (74%)	967 (76%)
Fever	1896 (75%)	950 (76%)	946 (74%)
Clinical severity markers			
Body-mass index (kg/m²)‡	18·8 (16·6–21·4)	18·8 (16·7–21·4)	18·7 (16·5–21·4)
Weight (kg)‡	51·0 (45·0–59·0)	52·0 (45·5–59·9)	51·0 (45·0–59·0)
Urea concentration (mmol/L)§	4·9 (3·2–8·8)	4·8 (3·2–8·7)	4·9 (3·2–9·3)
Respiratory rate (breaths per min)	22 (20–26)	22 (20–26)	22 (20–26)
Heart rate (beats per min)	100 (88–115)	100 (87–114)	100 (88–116)
Systolic blood pressure (mm Hg)	110 (100–120)	110 (100–120)	110 (100–120)
Haemoglobin (g/L)§	92 (71–112)	93 (72–113)	90 (71–111)

	Sensitivity (n/N [%, 95% CI])	Specificity (n/N [%, 95% CI])	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Overall	156/342 (45·6% [40·4–50·9])	736/830 (88·7% [86·3–90·7])	4·03 (3·89–4·18)	0·61 (0·61–0·62)
CD4 cell count subgroups†				
>200 cells per μL	7/49 (14·3% [7·1–26·7])	197/211 (93·4% [89·2–96·0])	2·15 (0·35–13·3)	0·92 (0·88–0·96)
≤200 cells per μL	136/267 (50·9% [45·0–56·9])	495/569 (87·0% [84·0–89·5])	3·92 (3·76–4·08)	0·56 (0·56–0·57)
>100 cells per μL	20/103 (19·4% [12·9–28·0])	349/379 (92·1% [88·9–94·4])	2·45 (1·53–3·93)	0·88 (0·85–0·90)
≤100 cells per μL	123/213 (57·7% [51·0–64·2])	343/401 (85·5% [81·8–88·6])	3·99 (3·82–4·18)	0·49 (0·48–0·51)
>50 cells per μL	50/170 (29·4% [23·1–36·7])	459/500 (91·8% [89·1–93·9])	3·59 (3·11–4·13)	0·77 (0·76–0·78)
≤50 cells per μL	93/146 (63·7% [55·6–71·1])	233/280 (83·2% [78·4–87·1])	3·80 (3·60–4·00)	0·44 (0·42–0·45)

Lancet 2016; 387: 1187–97

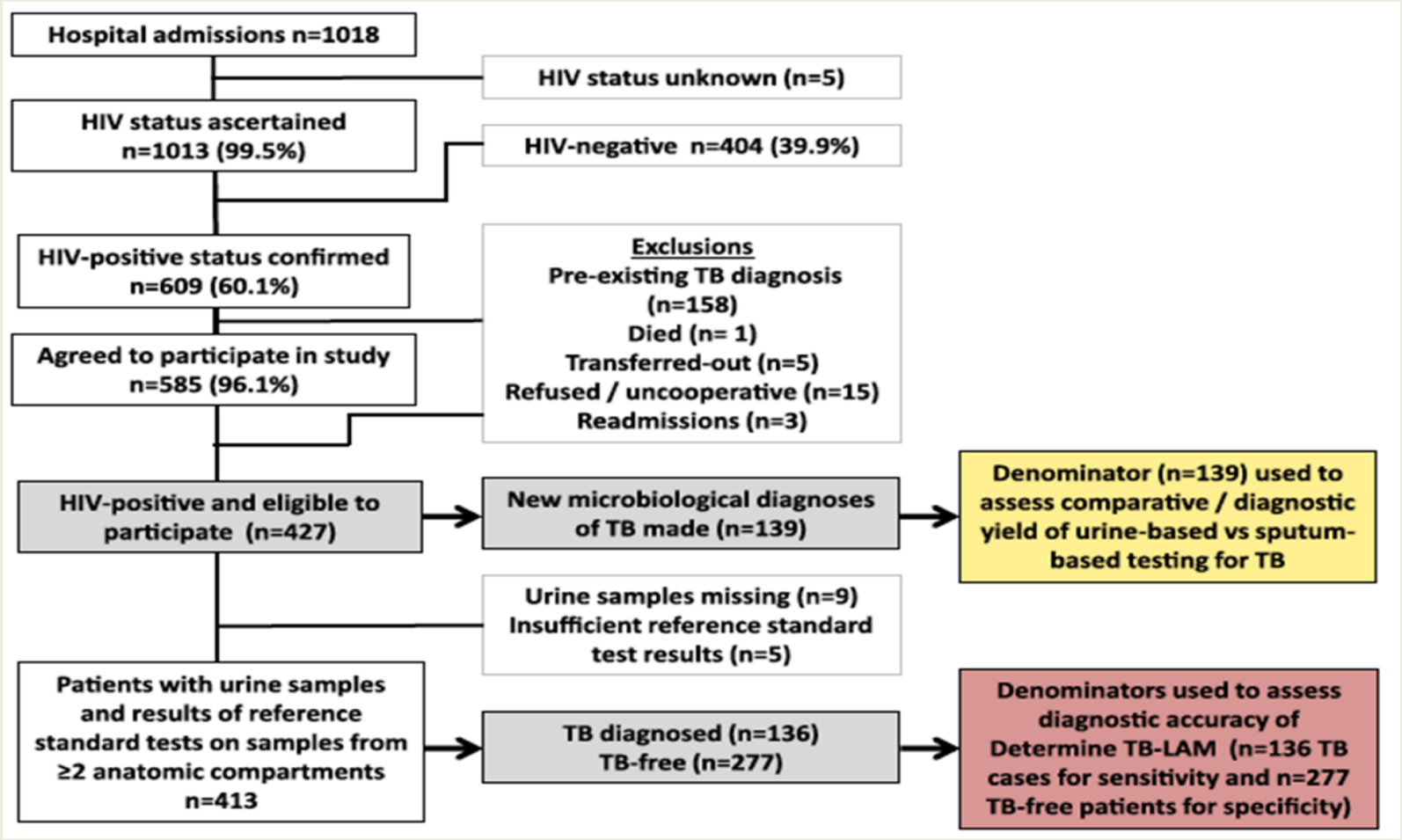
Lawn *et al. BMC Medicine* (2017) 15:67
DOI 10.1186/s12916-017-0822-8

BMC Medicine

RESEARCH ARTICLE Open Access

Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort

Stephen D. Lawn[1,2,3*], Andrew D. Kerkhoff[4], Rosie Burton[3,5,6], Charlotte Schutz[3,5,7], Andrew Boulle[8], Monica Vogt[2], Ankur Gupta-Wright[1], Mark P. Nicol[9,10] and Graeme Meintjes[3,5,6,7*]



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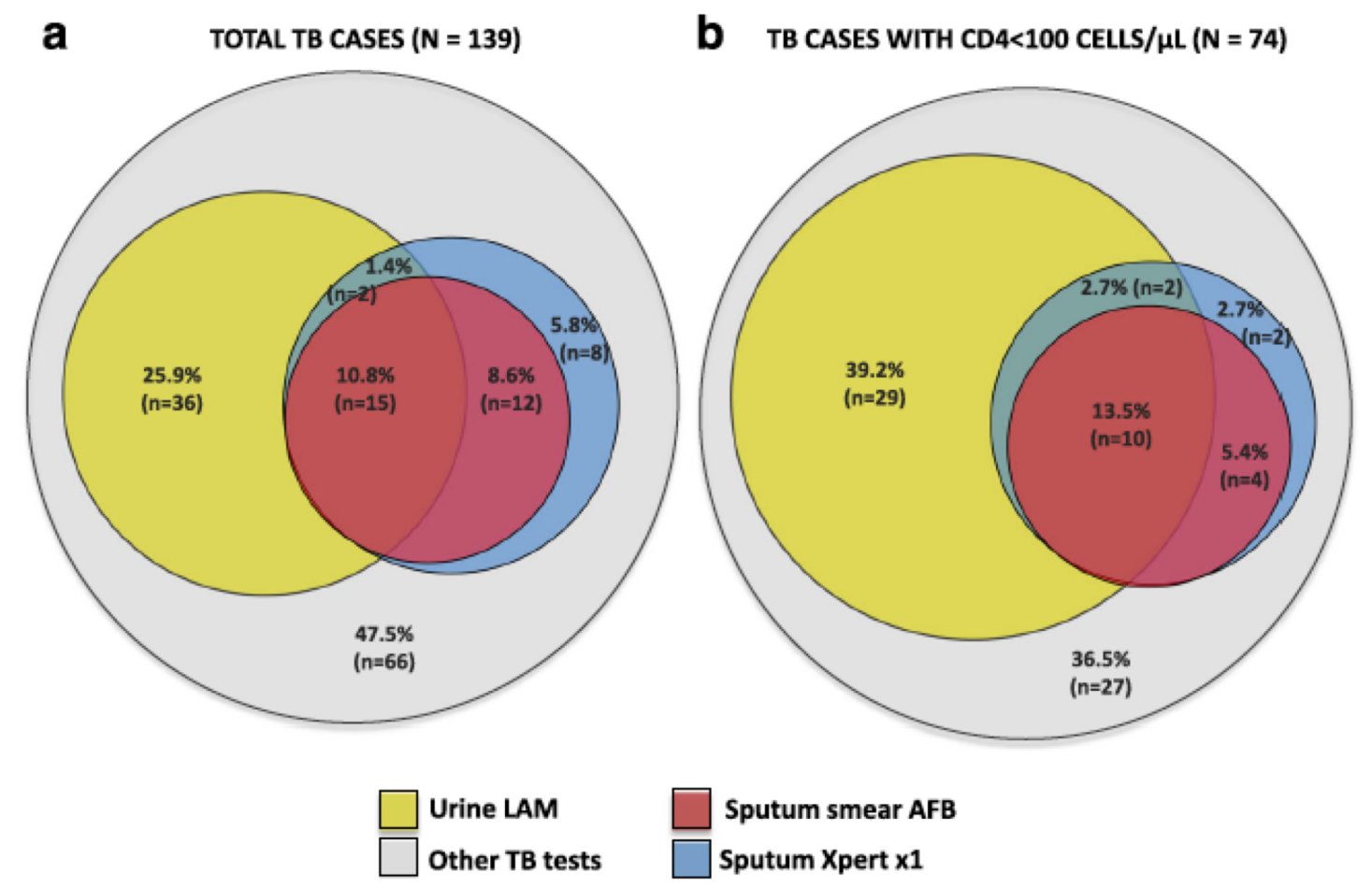

a
TOTAL TB CASES (N = 139)
25.9% (n=36)
1.4% (n=2)
10.8% (n=15)
8.6% (n=12)
5.8% (n=8)
47.5% (n=66)
b
TB CASES WITH CD4<100 CELLS/µL (N = 74)
39.2% (n=29)
2.7% (n=2)
13.5% (n=10)
2.7% (n=2)
5.4% (n=4)
36.5% (n=27)
Urine LAM
Other TB tests
Sputum smear AFB
Sputum Xpert x1

	%	CD4 <100/mm³ %
Balgam mikroskopisi	19.4	18.9
Balgam Xpert	26.6	24,3
İdrar LAM	38.1	55,4
Balgam Xpert + İdrar LAM	52.2 (p< 0.01)	63,5

Özgüllük: %98.9

Stephen D. Lawn.et al BMC Med. 2017; 15: 67

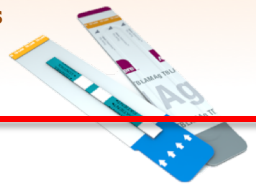
LAM-Hızlı Antijen Testi

- Aktif TB tanısı ve dışlanması için bağımsız bir tanısal test olarak yararlı görünmemektedir
- Yüksek HIV prevalansı durumunda yayma mikroskobu ve/veya kültür ile birlikte tanıyı arttırabilir
- **CD4 < 100 hücre/ml HIV (+) hastalarda TB'nin tanısında özel bir değere sahip olabilir**

Non-sputum based tests for diagnosis or triage

2017

Determine TB LAM Ag (urine) for HIV co-infected with low CD4 counts
(Alere)



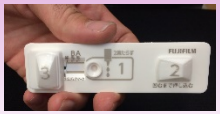
Negative recommendation for Serological assays by the WHO

2018

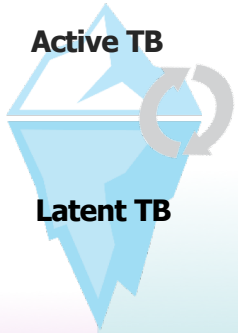
Pediatric TB Disposable Squeeze Bottle for Stool Processing prior Xpert
(FIND, Elma Fdn & partners)

2019

Next-generation LAM POC assays (urine, blood)
- Fujifilm/FIND
- and others



2020-2025



Incipient TB tests (blood)
- QIA-Predict (Qiagen)
- QIA-TB Signature (Qiagen)
- mRNA Signatures (Stanford, Zak et al.)
- T-cell Immune Profiling (BD)
- RTT TB (Lophius)
- Incipient TB Assay (Abbott)

Source: http://lnbd.technion.ac.il

Breath Tests and Skin Patches
- breathtec/Technion
- RBS
- eNose

Blood host marker POC tests
- TransDot signature (ScreenTB consortium)
- SomaLogic signature (SomaLogic, FIND)
- and others

Source: http://precision-bio.com/en/images/sub/sub2_1_3.jpg

TB antigen POC assays (blood)
- Arizona State Univ.
- Tufts Univ.
- and others

cfDNA in blood or urine
- Standford Univ.
- Cornell Univ.
- Karius
- and others

Source: https://www.whatisepigenetics.com

Slide from Claudia Denkinger, FIND

Geliştirilmekte olan yeni tanısal teknikler ve Biyomarkerler

	Platform (sample type)	Sensitivity	Specificity	Diagnosis
Host gene expression				
Neutrophil-driven type 1 interferon, interferon-γ (393 genes), and type 1 interferon-α or interferon-β (86 genes)[31] gene signatures	Illumina microarray, RT-qPCR validation (blood)	61·7%*, 94·1%†, 92%	93·7%*, 96·6%†, 83%	Tuberculosis, LTBI, healthy controls
FCGR1B, *CD64* (*FCGR1A*), *LTF*, *GBP5*, and *GZMA*[32]	Agilent microarray (blood)	94%	97%	Tuberculosis, LTBI
Gene signature (44 genes)[33]	Illumina microarray (blood)	100%	96%	Tuberculosis, LTBI, other disease
GZMA, *GBP5*, and *CD64* (*FCGR1A*)[30]	RT-qPCR (blood)	93%	95%	Tuberculosis, asthma, non-tuberculous pneumonia
CD64 (*FCGR1A*)[34]	MLPA technique	88%	75%	Tuberculosis
Gene signature (144 genes)[35]	Illumina microarray (blood)	>80%	>90%	Tuberculosis, lung cancer, pneumonia, healthy controls
Gene signature (51 genes)[36]	Illumina microarray (blood)	82·9%	83·6%	Tuberculosis, other lung disease
Gene signature (16 genes)[30]	Illumina RNA sequencing (blood)	66·1%*, 53·7%†	80·6%*, 82·8%†	Tuberculosis progression
Host protein markers				
CRP[37]	POC fluorescent scanner	89%	72%	Tuberculosis and in participants who were HIV-positive
CRP, transthyretin, interferon γ, CFH, ApoA1, IP10, SAA[38]	Multiplex cytokine platform (serum)	93·8%	73·3%	Tuberculosis, pulmonary disease
SYWC, kallistatin, CC9, gelsolin, testican-2, aldolase-C[39]	SOMAscan aptamer proteomics (serum)	90%	80%	Tuberculosis
Metabolomic markers				
Ketone bodies, lactate, pyruvate metabolites[40]	NMR spectroscopy (plasma)	NR	NR	Tuberculosis, healthy controls, diabetes, pneumonia
IDO-1, phospholipase, adenosine metabolites[41]	GCMS (serum)	NR	NR	Tuberculosis, LTBI, healthy controls
Fatty acids, mycolic acids, carbohydrates[42]	GCTOFMS (sputum)	NR	NR	Tuberculosis, pulmonary disease
Glycolipids, resolvins, glutamate, choline metabolites[43]	LCMS (plasma)	NR	NR	Tuberculosis, tuberculosis household contacts
Ceramide, cholesterol sulphate, eicosatetraenoic acid, 4α-formyl-4β-methyl-5α-cholesta-8-en-3β-ol[44]	UHPLC–ESIQTOFMS (plasma)	>70%	>80%	Tuberculosis, pneumonia

Lancet Infect Dis 2018; 18: e199–210 P

TBHIV

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Lancet Infect Dis. 2017 Dec;17(12):1285-1292. doi: 10.1016/S1473-3099(17)30488-7. Epub 2017 Aug 25.

Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study.

Yoon C[1], Semitala FC[2], Atuhumuza E[3], Katende J[4], Mwebe S[3], Asege L[3], Armstrong DT[5], Andama AO[6], Dowdy DW[7], Davis JL[8], Huang L[9], Kamya M[2], Cattamanchi A[10].

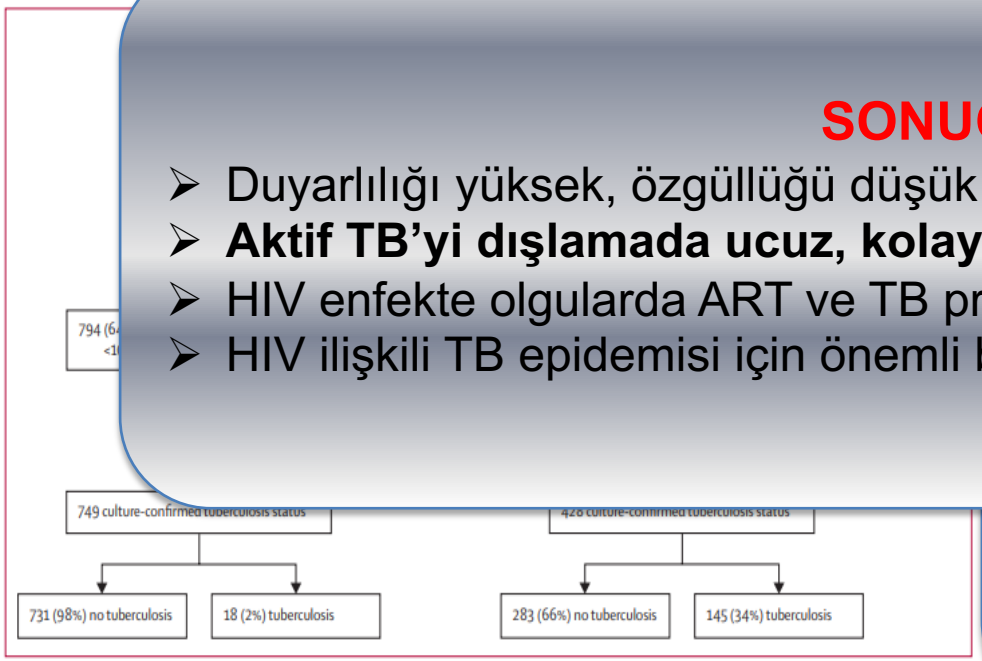

Figure 1: **Patient flow diagram**
ART=antiretroviral therapy. *All enrolled participants underwent point-of-care C-reactive protein testing and submitted two spot sputum samples for liquid culture. Tuberculosis defined as at least one sputum culture positive for *Mycobacterium tuberculosis*. No tuberculosis defined as any sputum cultures negative for *M tuberculosis*.

SONUÇ

- Duyarlılığı yüksek, özgüllüğü düşük
- **Aktif TB'yi dışlamada ucuz, kolay bir teknik**
- HIV enfekte olgularda ART ve TB proflaksisini hızlı planlama imkanı
- HIV ilişkili TB epidemisi için önemli bir halk sağlığı stratejisi olabilir

ve

TB

POC CRP duyarlılığı %94
Özgüllük düşük- CD4<200 mm/^{3}

HIV ilişkili TB'de tanısal yöntemler- Bakteri saptama ve direnç Özet

Test	WHO Onayı	Süre	Avantajlar	Dezavantajlar
Yayma mikroskobi Klasik LED	 2010	 Aynı gün Aynı gün	 Ucuz, hızlı eknik Daha duyarlı	Düşük duyarlılık
Mikrobiyal kültür ve duyarlılık testi	2007	10-21 gün	Sıvı besiyerleri daha duyarlı	Yüksek biyogüvenlik düzeyi Uzun süre
NAATs -Xpert MTB-RIF -LAMP -LPA . 1. Kuşak . 2. Kuşak	 2010 2016 2008 2016	 Aynı gün Aynı gün 1-2 gün 1-2 gün	 Yüksek duyarlılık, RIF direnci Ucuz RIF ve INH direnci Enjektabl ajanlar ve kinolon direnci	 Pahalı Alt yapı gereksinimi Maliyet etkinlik? Kaynak sorunu
Hızlı Antijen testi LAM	 2016	 Yarım saat	 Kısa sürede tanı	Düşük duyarlılık CD4 <100/mm3 te etkili

British HIV Association guidelines for the management of TB/HIV co-infection in adults 2017

2 Recommendations

Diagnosis of active pulmonary TB

- We recommend performing microscopy for acid-fast bacilli (AFB) on respiratory samples (sputum, induced sputum or bronchoalveolar lavage [BAL]), followed by molecular testing, e.g. Xpert MTB/RIF, for rapid identification of MTB, in conjunction with culture and drug-sensitivity testing. (GRADE 1B)
- We recommend the use of molecular tests in pulmonary smear-negative samples, always in conjunction with culture and drug-sensitivity testing. (GRADE 1B)
- When individuals present with symptoms suggestive of tuberculosis, we recommend asking for any known TB contact among family members, colleagues and friends. (GPP)

Diagnosis of active extra-pulmonary TB

- We recommend sending CSF samples for TB molecular tests and conventional microscopy and culture for the diagnosis of TB meningitis. (GRADE 1C)
- We recommend performing microscopy and obtaining cultures for mycobacteria on respiratory samples (induced sputum/BAL) in individuals with suspected pleural TB, even in the absence of obvious lung parenchymal involvement. (GRADE 1B)
- We recommend obtaining material for microscopy and culture, as well as histology in combination with molecular biological techniques, for diagnosis of extra-pulmonary TB. (GPP)

Diagnosis of multidrug-resistant TB infection

- We recommend the routine use of molecular techniques, in addition to phenotypic drug susceptibilities, in order to achieve rapid detection of at least rifampicin resistance in patients' samples. (GRADE 1C)
- We recommend that individuals with positive molecular tests for rifampicin resistance should be assumed to have MDR/XDRTB and managed in conjunction with a designated MDR centre. (GPP)

DHHS Fırsatçı Enfeksiyonlar Kılavuzu

Nucleic-acid amplification testing: Standard mycobacterial cultures for TB may take weeks to months to grow, but rapid diagnosis is needed in patients with HIV infection given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB (some assays also provide rapid detection of drug resistance—see below). NAA tests have at least two uses among patients with suspected HIV-related TB. First, these assays are highly predictive of TB among specimens that are AFB smear-positive. Non-tuberculous mycobacterial infections are relatively common among patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation among patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, being positive in 50 to 80% of smear-negative, culture-positive specimens[85,86] and up to 90% when three NAA tests are performed. Therefore, use of an NAA test is recommended on at least one specimen from all patients with suspected pulmonary TB.[87] NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than in sputum specimens.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations
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MTB/RIF
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Lipoarabinomannan (LAM): LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of TB patients. LAM can be detected using an ELISA or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity but has the advantages of being available as a true point of ca
HIV-infected pa
specificity of u
prognoses,[98] w
strategies sucl

Immune-based
unusual circun
evidence of pri
However, these
interpreted as
up to 11 to 30%

Drug susceptib
all patients sus
increased risk
medications.[10
isoniazid and r
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markedly incre

Phenotypic drug-susceptibility testing: Conventional DST is widely used, and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turn-around time of conventional broth or agar-based culture followed by DST may be as long as 6 weeks,[103] due to the slow growth of *M. tuberculosis*. During this time, patients with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow for ongoing transmission, further clinical deterioration, and death, particularly in HIV-infected individuals.[102]

NAA testing for drug resistance: Genotypic testing to identify mutations that confer drug resistance allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications.[104] Commercial NAA tests such as Xpert MTB/RIF identify resistance mutations associated with rifampin and commercially available line probe assays identify genotypic resistance for rifampin and isoniazid.[92,105] Next generation commercial line probe assays such as GenoType MTBDR*sl* identify genotypic resistance to other TB medications, but results should be confirmed with standard culture-based DST.[106] Several assays can be performed on cultured isolates or directly on sputum specimens.

Sonuç olarak;

- ✓ HIV ile yaşayan bireylerde aktif TB riski yüksek, daha progresif ve fatal
- ✓ HIV, TB tanısını güçleştiriyor, klasik tanı yöntemleri çoğunlukla elverişsiz
- ✓ HIV ile ilişkili TB tanısında ilk seçenek : **Xpert-Ultra** (yüksek duyarlılık, kısa süre, eş zamanlı RIF direnci)
- ✓ **LAM testi**; CD4 <100/mm^3 olan olgular için ucuz, kolay ve hızlı bir yöntem olarak önemli bir seçenek
- ✓ Özellikle, HIV prevalansı yüksek bölgelerde LAM testi HIV/TB koenfeksiyonuna bağlı mortalite oranını azaltabilir
- ✓ İlaç duyarlılık testleri içinde sıvı kültür altın standart ama süre uzun, **LPA** testlerinin kullanımı yaygınlaştırılmalı
- ✓ Halen duyarlılığı çok yüksek, hızlı sonuç verebilecek, daha ucuz yeni yöntemlere ihtiyaç var