

HIV/TB KOENFEKSİYONU TANIDA GELİŞMELER

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

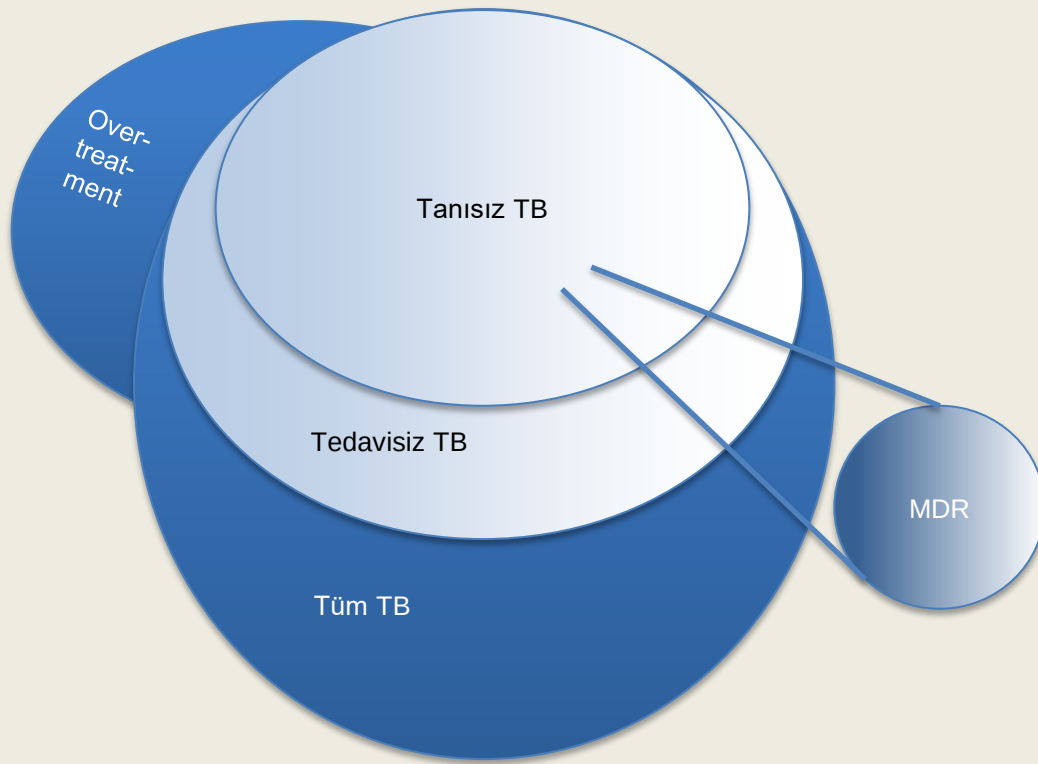


SUNUM PLANI

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

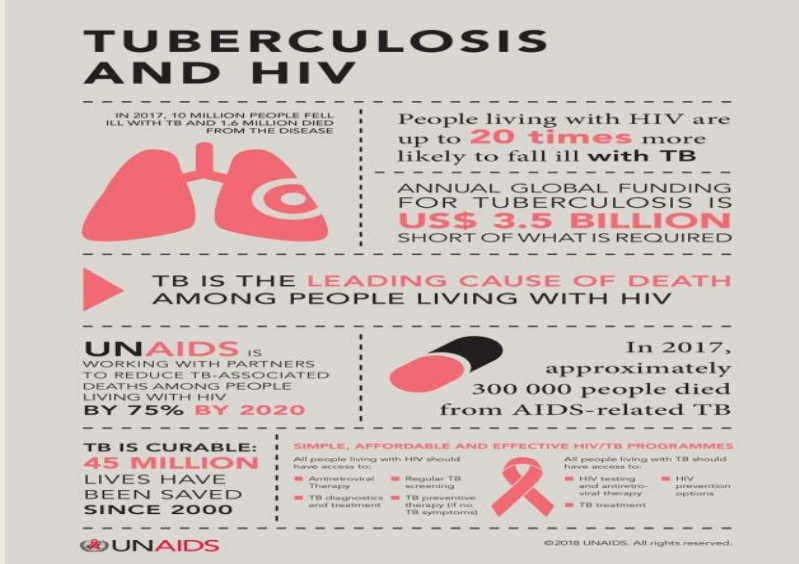
Tüberküloz

Dünyada enfeksiyon hastalıkları arasında en sık mortalite sebebi



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

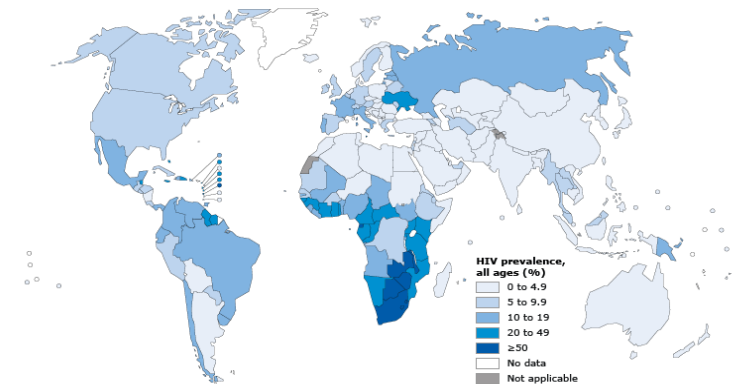
HIV/TB Prevalansı



- ~ 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

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Estimated global HIV prevalence in new and relapsed tuberculosis cases, 2016



Reprinted from: Global Tuberculosis Report 2017. Available at: http://www.who.int/tb/publications/global_report/en/ (Accessed on April 2, 2018). Copyright © 2017 World Health Organization.

Graphic 98732 Version 2.0

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 RK¹, 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. TB prevalence was higher in adults (pooled prevalence 63.2%, 95% CI 57.7-68.7%) than in children (pooled prevalence 4.5%, 95% CI 1.0-10.0%). TB prevalence was higher in adults (pooled prevalence 63.2%, 95% CI 57.7-68.7%) than in children (pooled prevalence 4.5%, 95% CI 1.0-10.0%). TB prevalence was higher in adults (pooled prevalence 63.2%, 95% CI 57.7-68.7%) than in children (pooled prevalence 4.5%, 95% CI 1.0-10.0%).

CONCLUSIONS: In resource-limited settings, TB remains a leading cause of death. Almost half of this disease remains undiagnosed at death. Prevention, diagnosis and treatment of HIV and TB are essential to reduce the burden of TB.

PMID: 26266773 PMCID: [PMC4568896](#) DOI: [10.1097/QAD.0000000000000802](#)

[Indexed for MEDLINE] [Free PMC Article](#)

f t

Farklı bölgelerden yapılmış 36 çalışma

HIV ile yaşayan bireylerde postmortem TB prevalansı

~ %40

USA- %27.1

Sahra-altı Afrika- %43.2

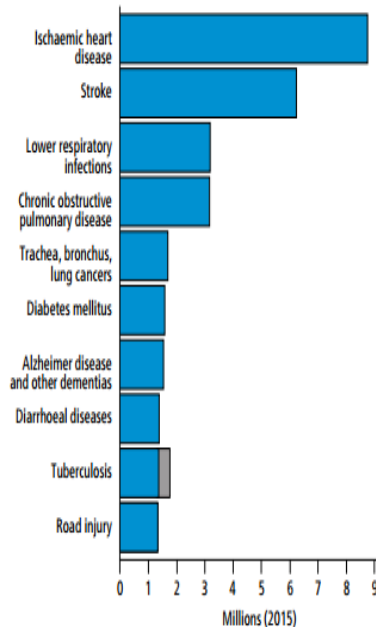
Güney Asya- %63

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.



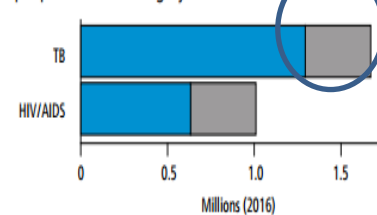
^a This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at <http://apps.who.int/gho/data/node.main.GHECOD> (accessed 28 August 2017).

^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}



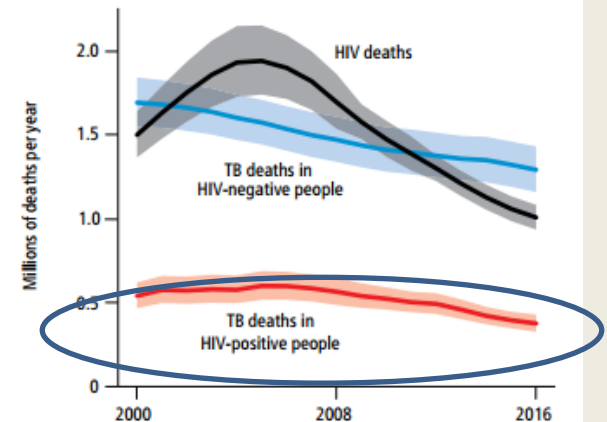
400.000
HIV ile
enfekte

^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.

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 enfeksiyonunun 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)

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!**



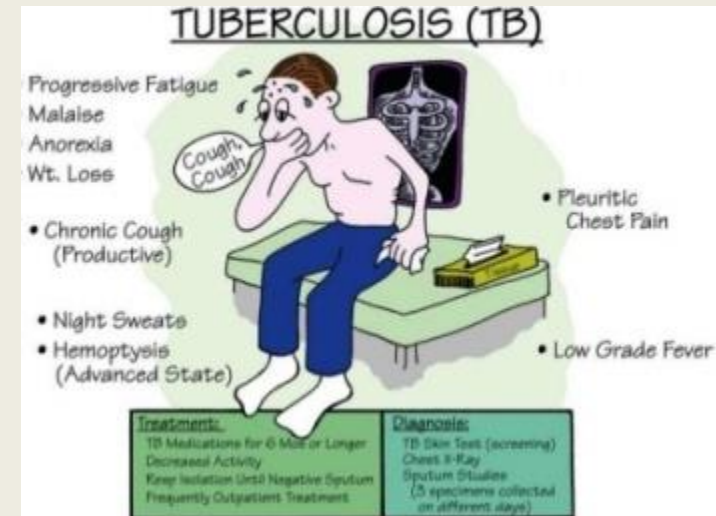
Tanı neden güç?

- ✓ 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 tutulumunda en sık lenfadenit

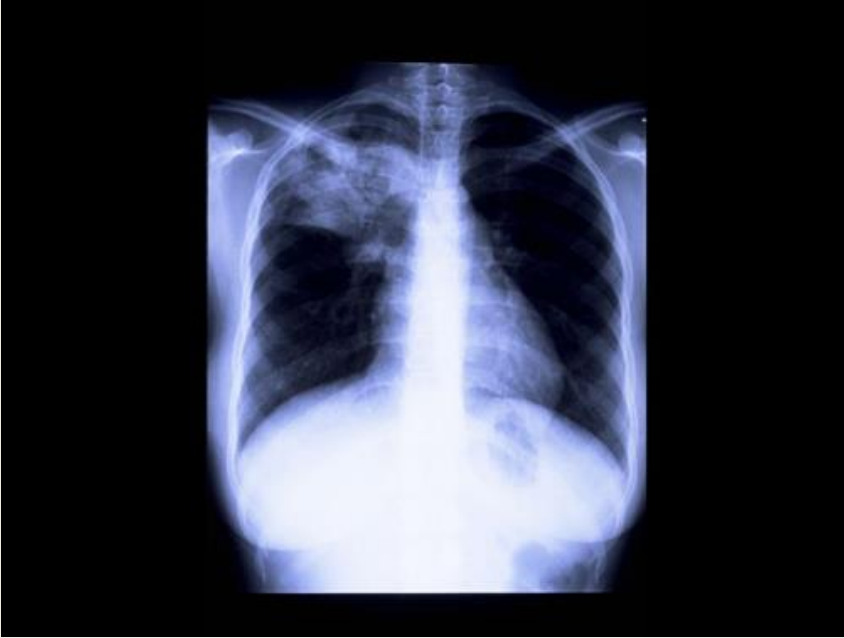


RADYOLOJİ

Tipik görünüm; üst lob apikal segmentte opasite+ kavitasyon

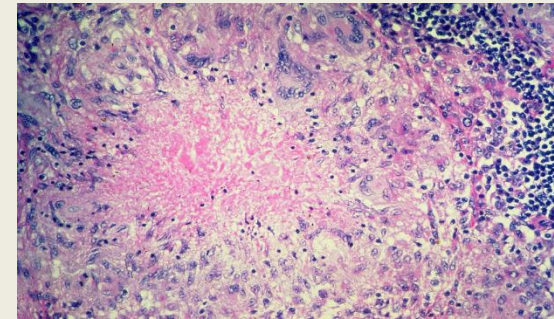
**Geç evre HIV enfekte olgularda;
Radyolojik görünüm hiç olmayabilir
veya**

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

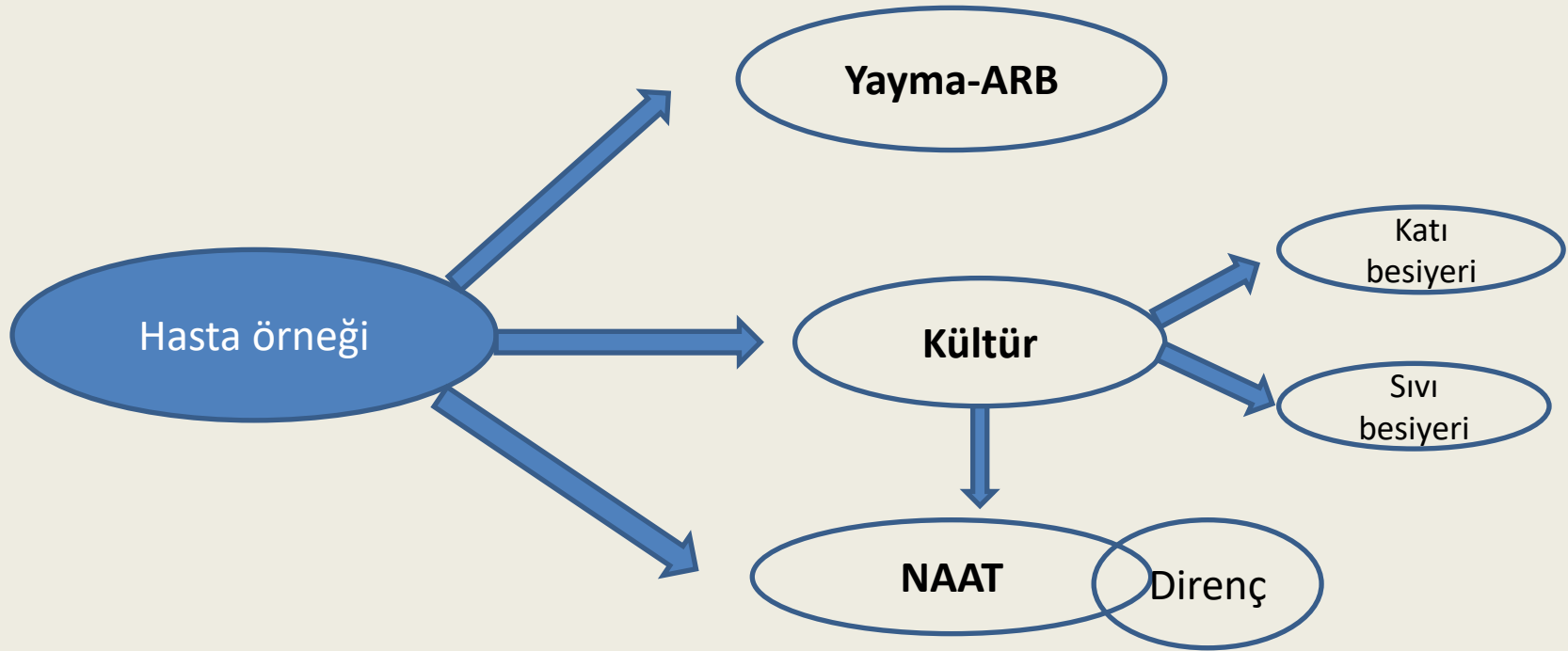


HİSTOPATOLOJİK İNCELEME

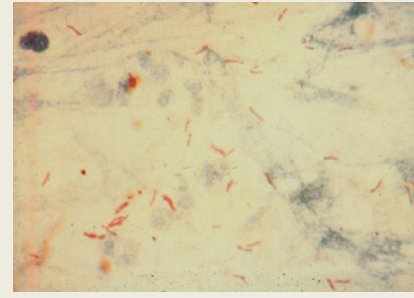
- Özellikle ekstrapulmoner ve dissemine TB'de elverişli
- Nodal tutulum HIV /TB koenfeksiyonunda sık-ince iğne aspirasyonu
- Histopatolojik bulgular immünsupresyonun derecesiyle doğrudan ilişkili
- Erken evrelerde tipik granülomlar
- İmmünsupresyon ilerledikçe granülom ya hiç görülmez ya da zayıf forme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



LABORATUVAR



LABORATUVAR



Konvansiyonel Yöntemler

Mikroskopik 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

Mikobakteri kültürü

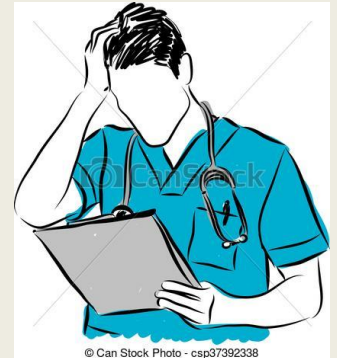
- Altın standart
- Duyarlılığı ve özgüllüğü yüksek
- HIV enfekte olanlarda da benzer
- **Zaman alıcı**
- Doku biyopsi materyalleri de gönderilmeli



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-Mikroskopi 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**

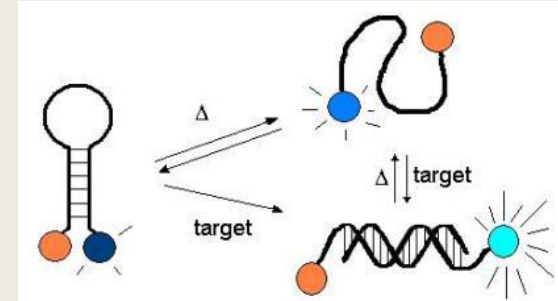


NÜKLEİK ASİD AMPLİFİKASYON TESTLERİ (NAATs)

- 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

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 acknowledging major resource implications)

WHO 2013



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

Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy studyProf 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](https://doi.org/10.1016/S1473-3099(17)30691-6)[Check for updates](#)

Open access funded by Bill & Melinda Gates Foundation

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 Babilashvili, Wendy Stevens, Lesley Scott, Camilla Rodrigues, Mubini Kazi, Moses Jobaba, Lydia Nakyingi, Mark P Nicol, Yonas Ghebrelastos, Irene Anyango, Wilfred Murithi, Reynaldo Dietze, Renata Lyrio Peres, Alena Skrahina, Vera Auchynika, Kamal Kishore Chopra, Mahmud Hanif, Xin Liu, Xing Yuan, Catharina C Boehme, Jerrold J Ellner, Claudia M Denkiner, on behalf of the study team†

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

Lancet Infect Dis 2018;
18: 76-84
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This online publication has been corrected. The corrected version first appeared at [thelancet.com/infection](http://www.thelancet.com/infection) on February 21, 2018.

See Comment page 8
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	Tuberculosis detection*				Specificity (95% CI; n/N)	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)‡		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% (84 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).

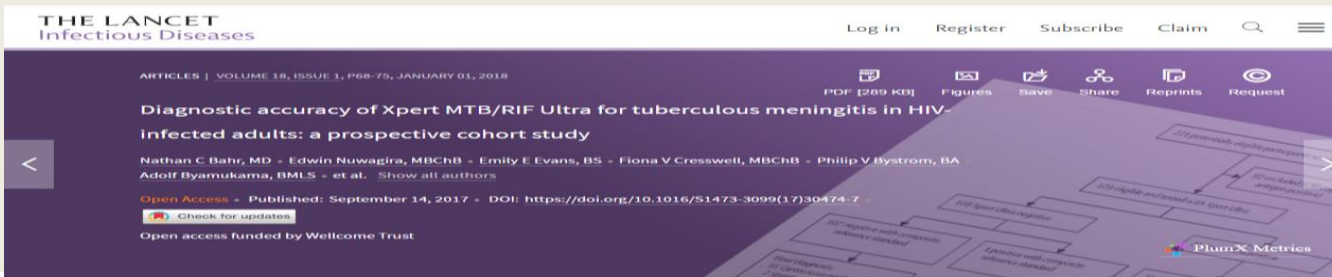
Table 2: Comparative accuracy for detection of tuberculosis and rifampicin resistance

	Sensitivity		Specificity		
	All culture-positive (95% CI; n/N)	Smear-negative, culture-positive (95% CI; n/N)	All culture-negative (95% CI; n/N)	No history of tuberculosis (95% CI; n/N)	Any history of tuberculosis (95% CI; n/N)
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 systematically. Tuberculosis-positive based on a trace-positive Xpert Ultra result (n=32) were reclassified as tuberculosis-negative only on a trace-positive Xpert Ultra result had Xpert Ultra testing on a subsequent sample. The participant was reclassified as tuberculosis-negative; if the subsequent Xpert Ultra was not reclassified and remained tuberculosis-positive (14 out of 32 participants on sample 2 and were not reclassified; and four were non-determinate by Xpert Ultra).

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 Denkiniger, Conrad Muzoora, David R Bouware, on behalf of the ASTRO-CM Trial Team

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.⁵ 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.⁶ Sensitivity compared

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See Comment page 6

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- 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



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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~~ spinal 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 M¹, 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 and the proportion is increasing, and over half a million people were newly diagnosed with rifampicin-resistant TB in 2017. Xpert (Xpert) is a World Health Organization (WHO)-recommended, rapid, automated, nucleic acid amplification assay for the simultaneous detection of Mycobacterium tuberculosis complex and rifampicin resistance in sputum specimens. We assessed the accuracy of Xpert in extrapulmonary specimens.

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

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

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

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

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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 77.0)	97.4% (92.1 to 99.3)	30.9% (0.2 to 98.2)	97.4% (87.1 to 99.7)
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% (46.1 to 99.7)
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% (9.1 to 99.7)
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% (45.1 to 99.7)
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% (6.1 to 99.7)
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 to 99.7)
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

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

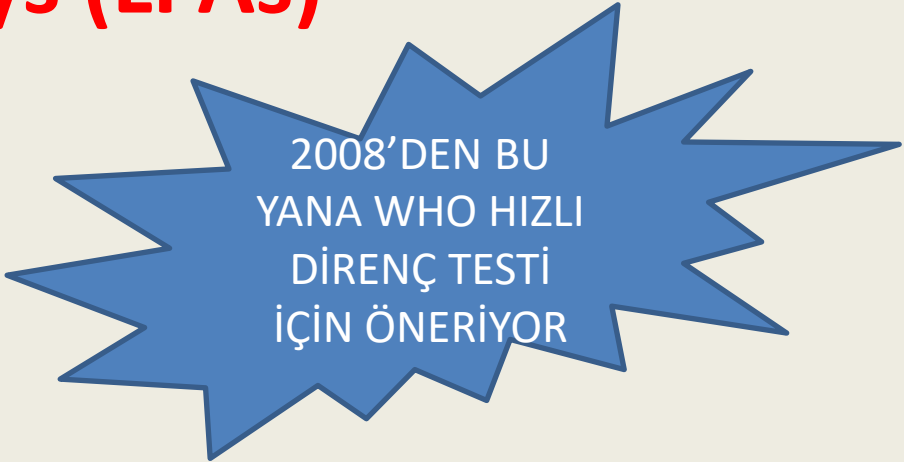
fluid was reference specificity were re 51% and ificity 2% for 3% for pooled sensi- nce and speci- ficity was similar or lower in settings with lower TB prevalence (Table 4).

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
 - özellik %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

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./total no.	% (95% CI)	no./total no.	% (95% CI)
	no. of specimens							
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)

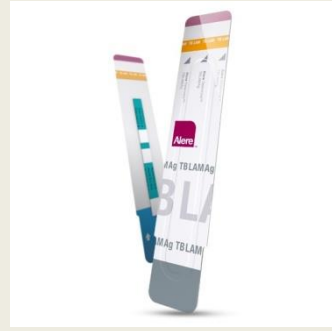
<i>gyrB</i>	Fluoroquinolones	Codons 538-540	✓	✓
<i>rrs</i>	Amikacin, kanamycin	1401, 1402	✓	✓
		1484	✗	✓
<i>eis</i>	Kanamycin	Promoter -10	✓	✓
		Promotor -37	✓	✗

Hasta Başı Testleri (POC)

- Diğer tekniklerin; pahalı olması, ekipman, mekan, eğitilmiş personel ve zaman gerektirmesi nedeniyle ihtiyaç...

HIV-enfekte olgular için onaylı test
İdrarda LAM testi

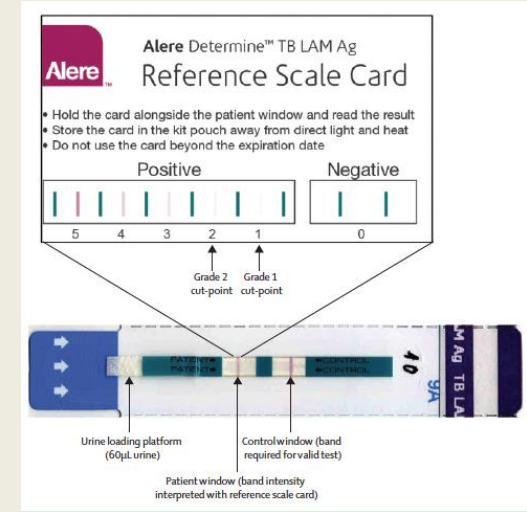
LAM TEST



- 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 ill², 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/ μ L, or HIV positive patients who are seriously ill² 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/ μ L, or HIV positive patients who are seriously ill² 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 μ L)	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/m^2)‡	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 subgroup†				
>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)

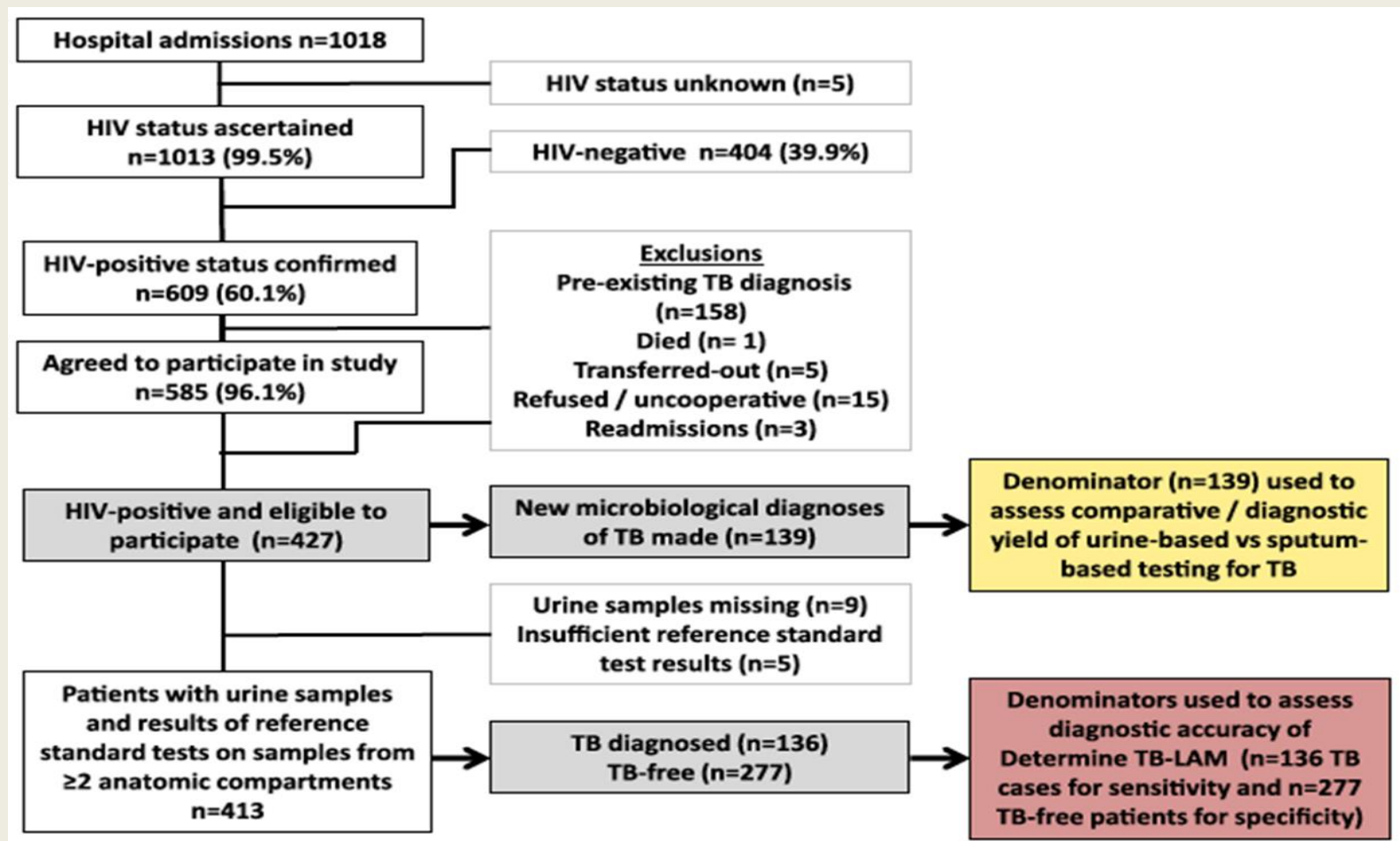
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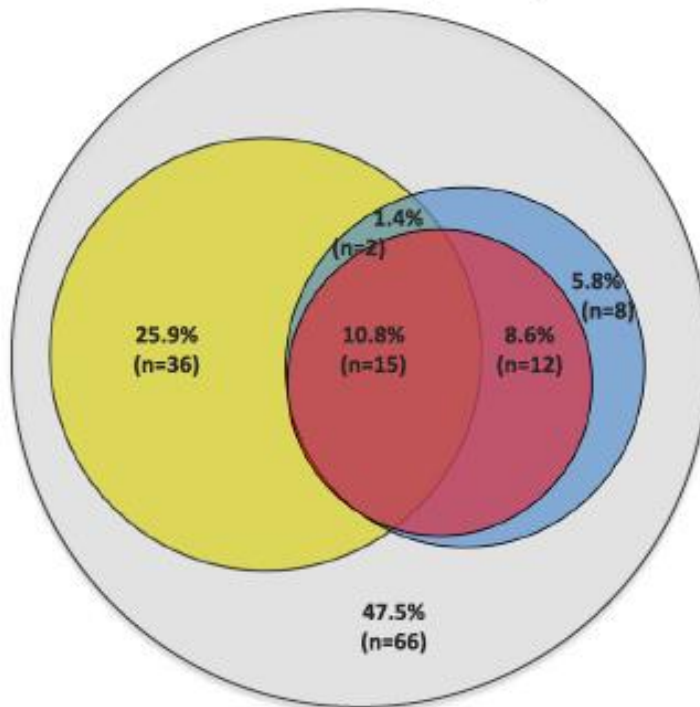


Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort

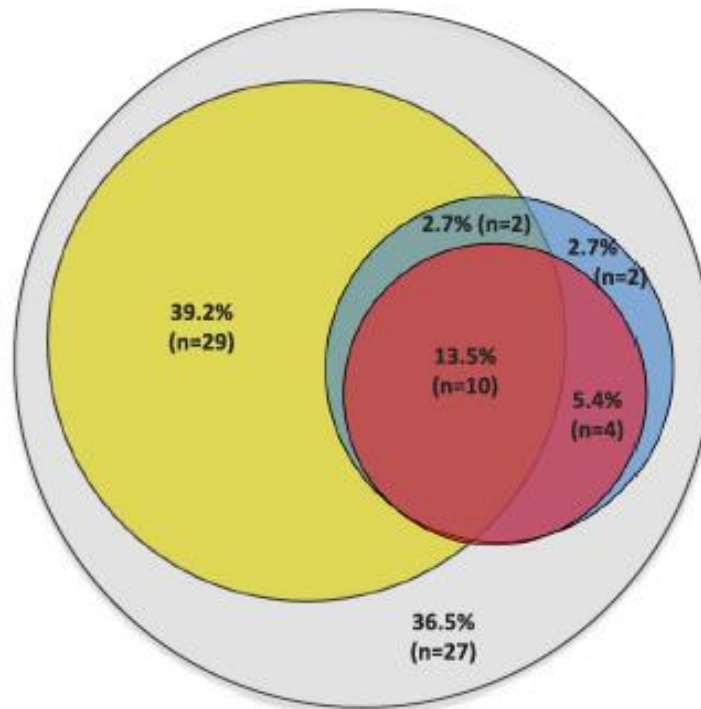
Stephen D. Lawn^{1,2,3*}, Andrew D. Kerkhoff⁴, Rosie Burton^{3,5,6}, Charlotte Schutz^{3,5,7}, Andrew Boulle⁸, Monica Vogt², Ankur Gupta-Wright¹, Mark P. Nicol^{9,10} and Graeme Meintjes^{3,5,6,7*}



a TOTAL TB CASES (N = 139)



b TB CASES WITH CD4<100 CELLS/ μ L (N = 74)



Urine LAM
 Other TB tests
 Sputum smear AFB
 Sputum Xpert x1

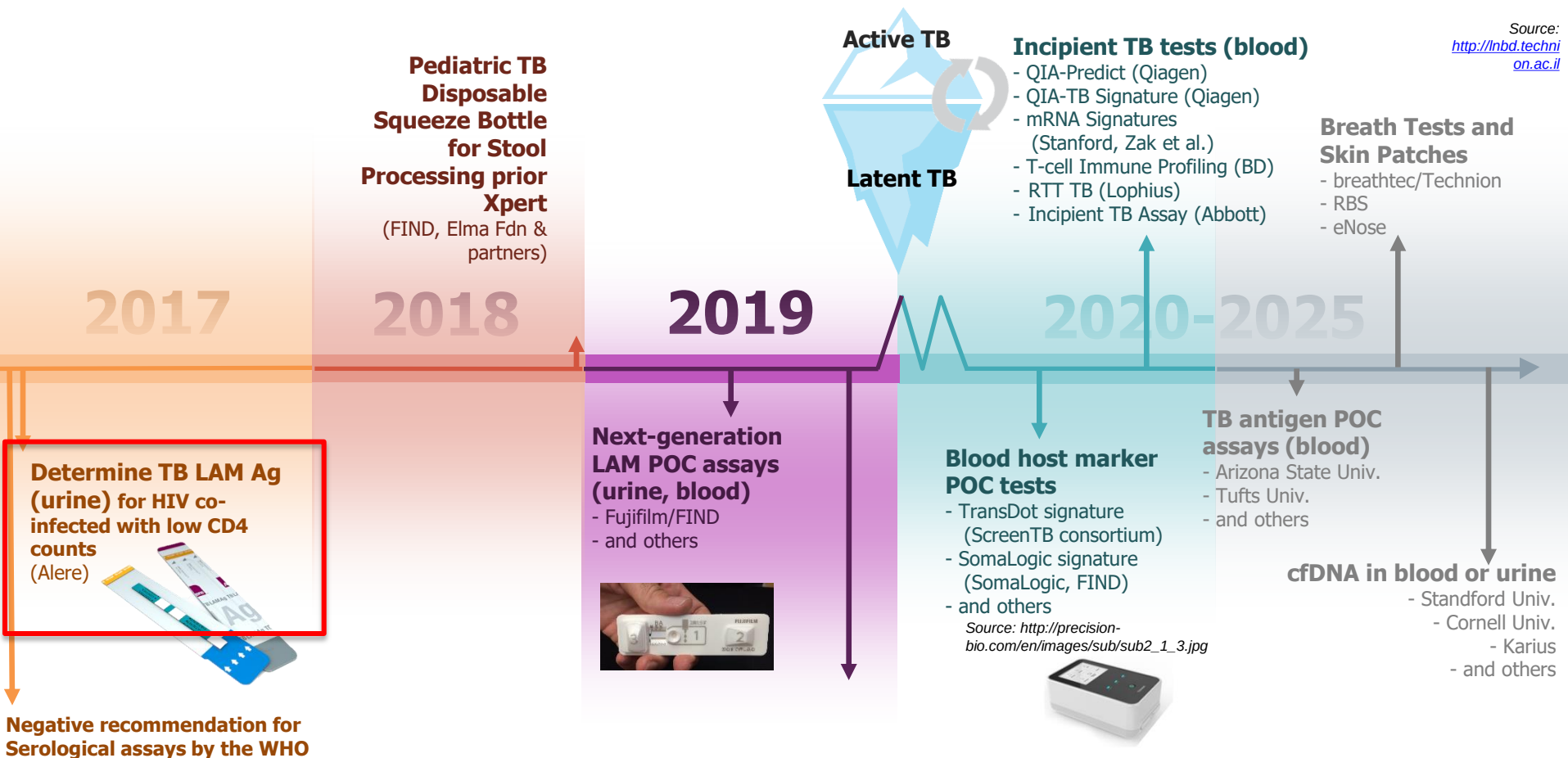
	%	CD4 <100/mm ³ %
Balgam mikroskopisi	19.4	18.9
Balgam Xpert	26.6	24,3
İdrar LAM	38.1	55,4
Balgam Xpert + İdrar LAM	52.2 (p< 0.01)	63,5

Özgüllük: %98.9

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



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) ^{3a} 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, 4 α -formyl-4 β -methyl-5 α -cholesta-8-en-3 β -ol ⁴⁴	UHPLC-ESI/TOFMS (plasma)	>70%	>80%	Tuberculosis, pneumonia

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

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SONUÇ

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

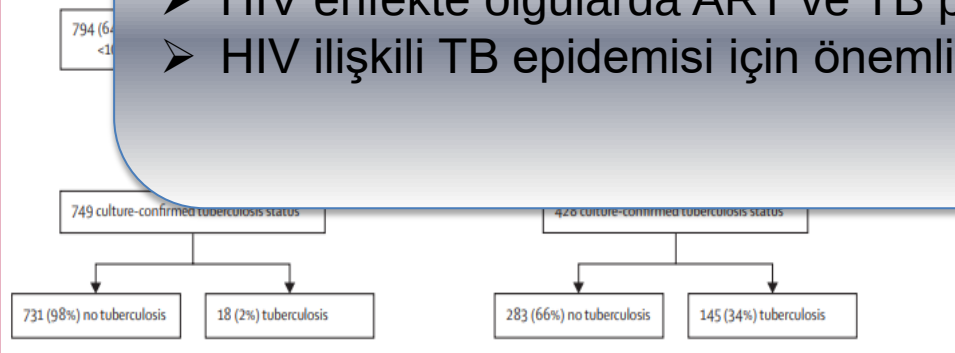


Figure 1: Patient flow diagram

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*.

POC CRP duyarlılığı %94
Özgüllük düşük- CD4<200 mm³

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

Test	WHO Onayı	Süre	Avantajlar	Dezavantajlar
Yayma mikroskopi 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	2010	Aynı gün	Yüksek duyarlılık, RIF direnci	Pahalı
-LAMP	2016	Aynı gün	Ucuz	Alt yapı gereksinimi
-LPA . 1. Kuşak . 2. Kuşak	2008 2016	1-2 gün 1-2 gün	RIF ve INH direnci Enjektabl ajanlar ve kinolon direnci	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

BHIVA guidelines for the management of TB/HIV co-infection in adults

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

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 care.

Phenotypic drug-susceptibility testing: Conventional DST is widely used, and has been the first-line drugs. The disadvantage of this technique, however, is that the combined turn-around time for conventional broth or agar-based culture followed by DST may be as long as 6 weeks, and the slow growth of *M. tuberculosis*. During this time patients with drug-resistant TB may

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

Drug susceptibility
all patients susceptible to
increased risk of
medications.¹⁰
isoniazid and rifampin
resistance to a
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 MTBDRs/ 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 $<100/\text{mm}^3$ 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