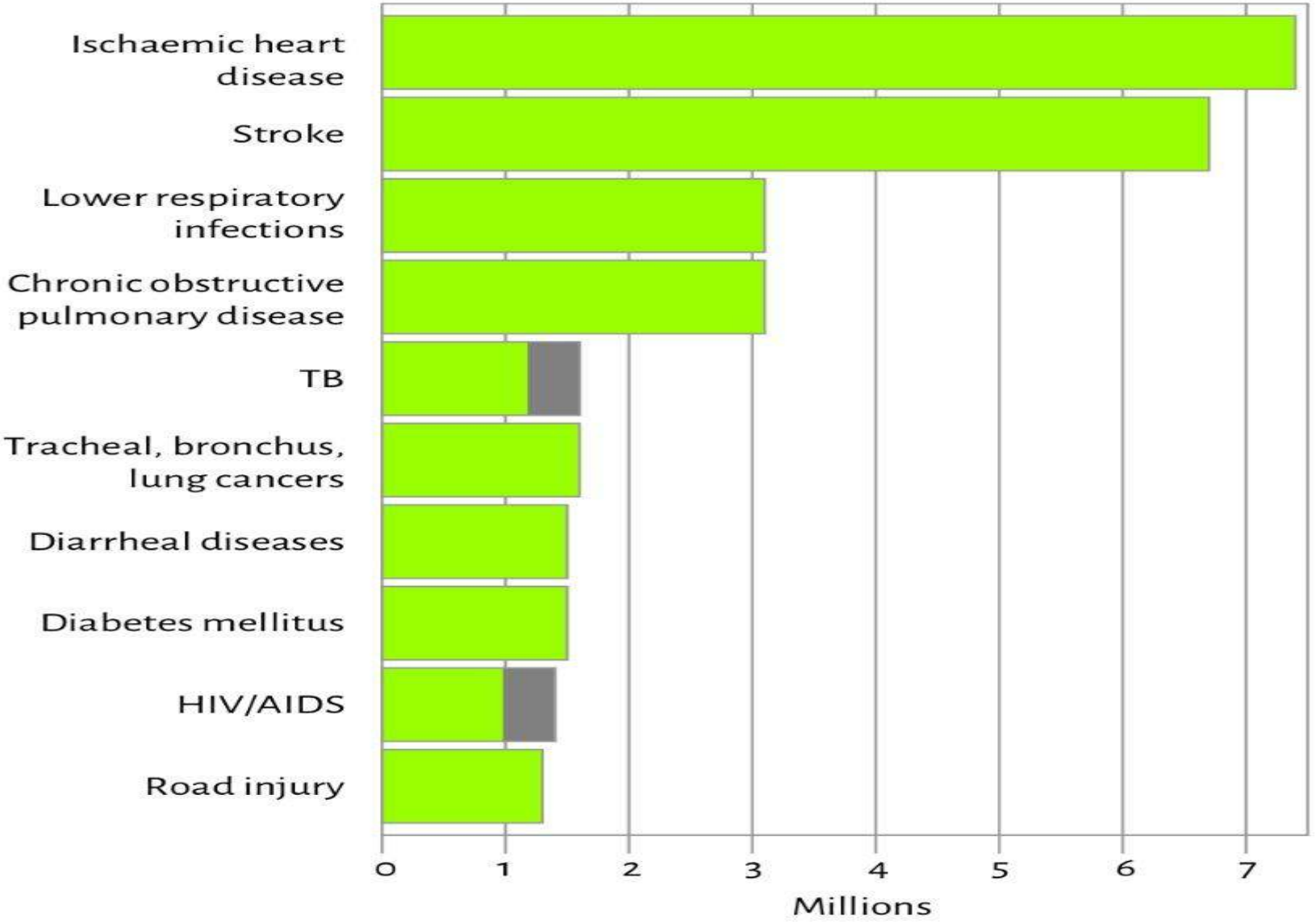
HIV enfeksiyonu ve ekstrapulmoner TB

Dr Özlem Altuntaş Aydın
Bakırköy Dr Sadi Konuk EAH
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

FIGURE 2.16a

Top causes of death worldwide in 2012.[a,b] Deaths from TB among HIV-positive people are shown in grey.[c]



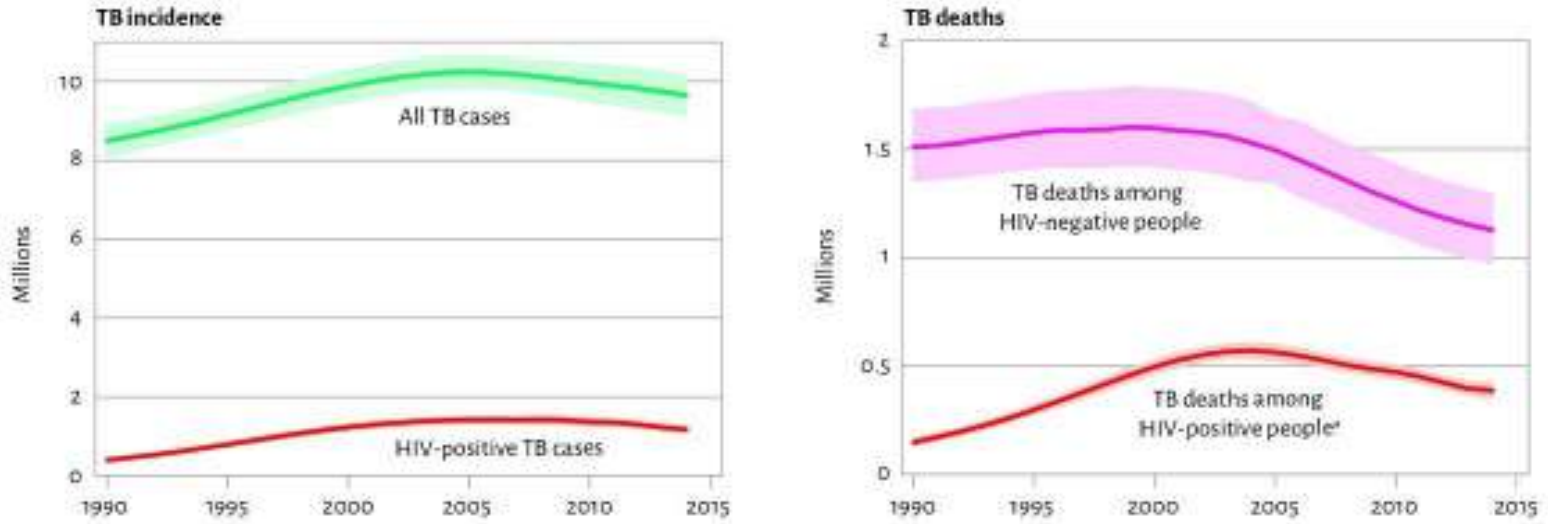
2014 yılında 10 milyon kişi TB

1.5 milyonu ölmüş

ölenlerin 1/3'ü HIV(+)

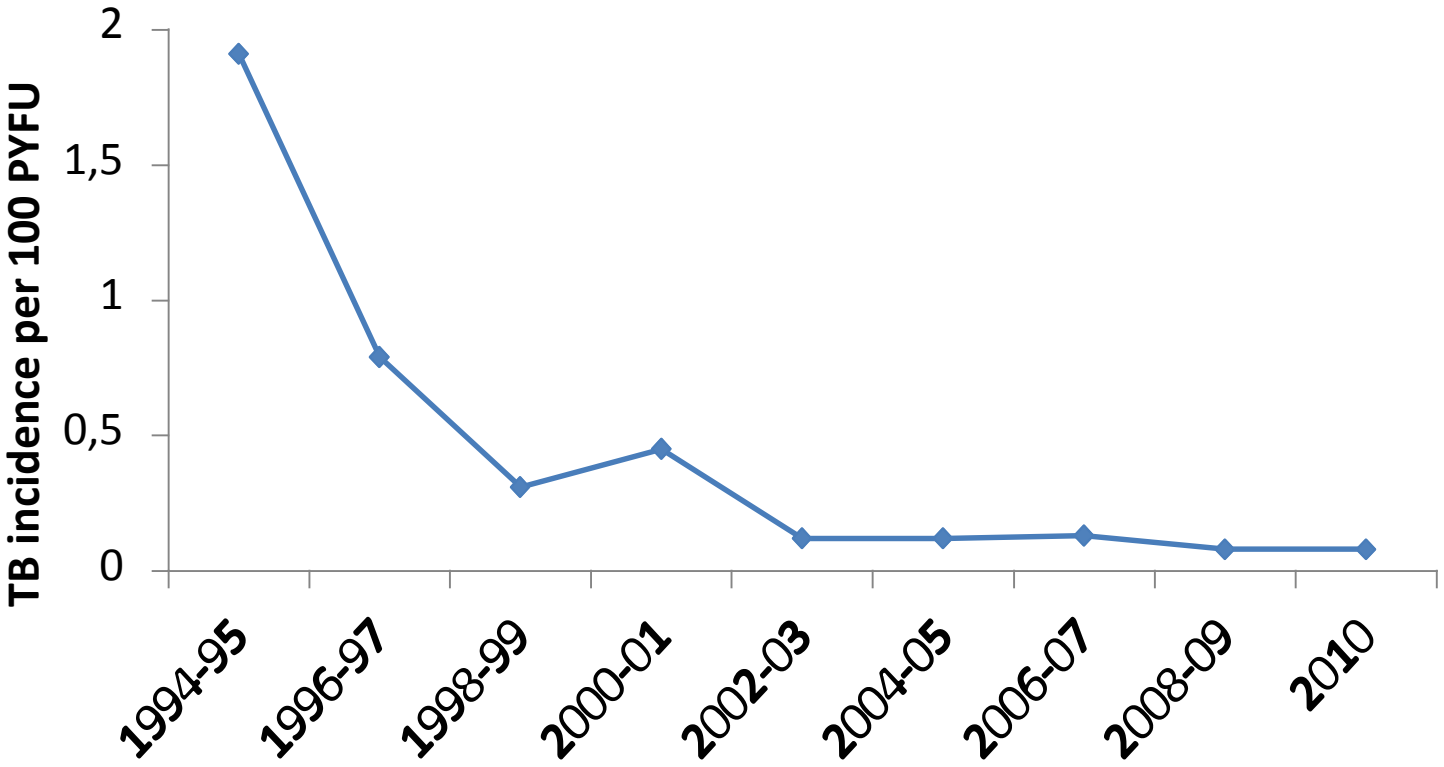
FIGURE 2.3

Estimated absolute numbers of TB cases and deaths (in millions per year), 1990–2014



[a] HIV-associated deaths are classified as HIV deaths according to ICD-10.

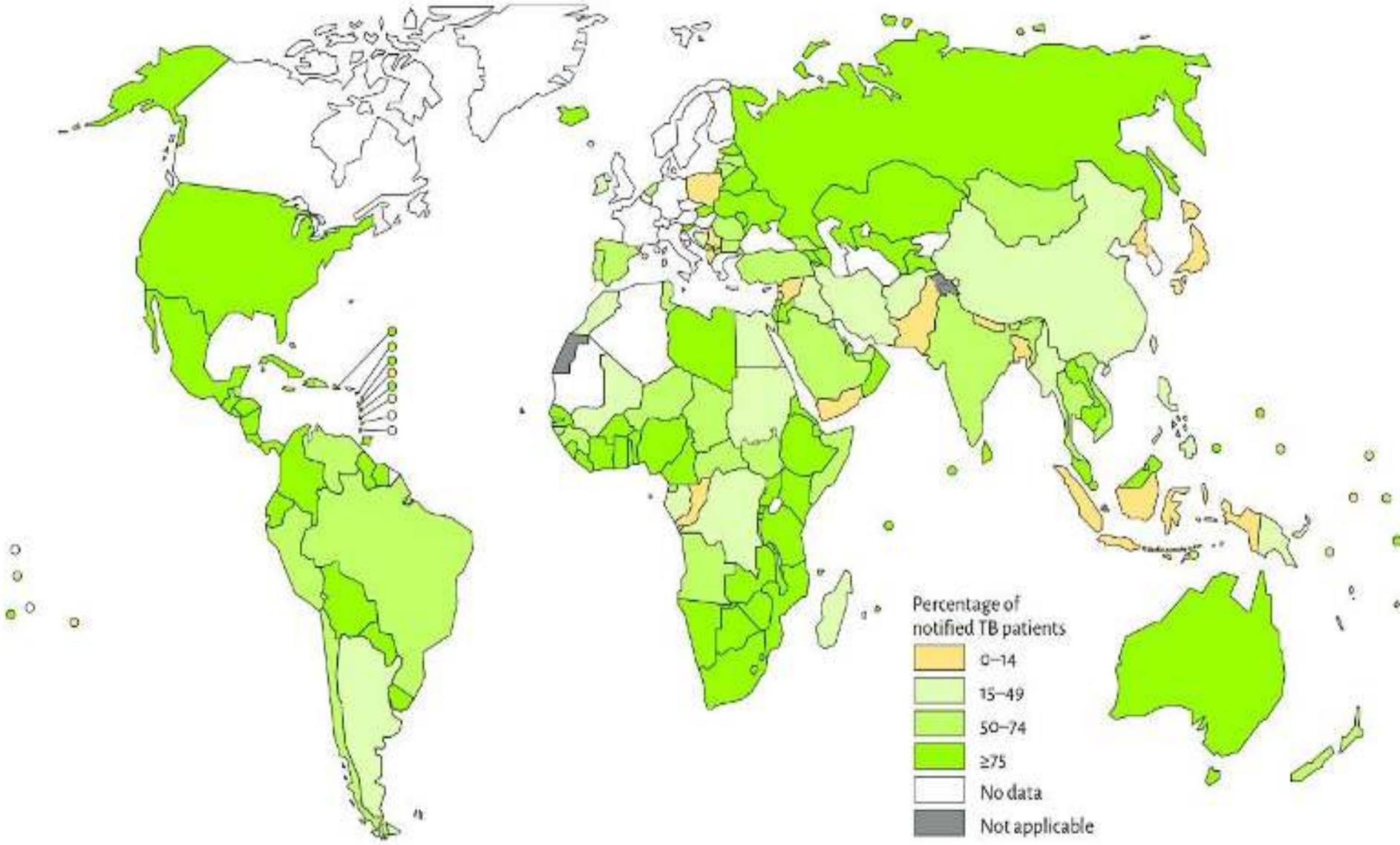
Batı Avrupa'da HAART sonrası HIV(+) hastalarda TB insidansı



Kruk et al – EuroSIDA AIDS 2011

FIGURE 6.2

Percentage of notified TB patients with known HIV status by country, 2014[a]



[a] Data for the Russian Federation are for new TB patients in the civilian sector only.

TABLE A4.8

HIV testing for TB patients, provision of CPT and ART to HIV-positive TB patients, and initiation of IPT for people newly enrolled in HIV care, 2014

	Total TB patients notified	TB patients with known HIV status		HIV-positve TB patients		HIV-positive TB patients on CPT[a]		HIV-positive TB patients on ART[b]		HIV-positive people provided IPT[c]
		(Number)	(%)	(Number)	(%)	(Number)	(%)	(Number)	(%)	
South Africa	318 193	295 136	93	179 756	61	155 017	86	141 755	79	551 787
South Sudan	8 856	5 892	67	752	13	713	95	463	62	
Spain	5 048	3 191	63	233	7.3					
Sri Lanka	9 473	7 418	78	21	0.28	18	86	18	86	9
Sudan	20 392	5 501	27	329	6			147	45	
Suriname	158	154	97	44	29	27	61	32	73	
Swaziland	5 616	5 430	97	3 972	73	3 904	98	3 123	79	1 188
Sweden	670									
Switzerland	473									
Syrian Arab Republic	3 576	0	0	0		0		0		
Tajikistan	6 260	5 656	90	161	2.8	156	97	128	80	280
Thailand	71 618	50 670	71	6 831	13	4 359	64	4 691	69	
The Former Yugoslav Republic of Macedonia	285	171	60	1	0.58	1	100	1	100	1
Timor-Leste	3 778	2 054	54	24	1.2	24	100	24	100	
Togo	2 577	2 511	97	523	21	465	89	396	76	
Tokelau	0									
Tonga	13	13	100	0	0	0		0		
Trinidad and Tobago	293	289	99	71	25	17	24	40	56	
Tunisia	3 173	2 317	73	12	0.52	0	0	12	100	54
Turkey	13 378	9 344	70	45	0.48	13	29	28	62	
Turkmenistan	2 887									
Turks and Caicos Islands	3	1	33	1	100	1	100	1	100	
Tuvalu	15	15	100	0	0	0		0		
US Virgin Islands										
Uganda	46 171	43 883	95	19 612	45	19 211	98	15 877	81	
Ukraine	40 302	39 057	97	7 640	20	3 350	44	4 273	56	16 263

HIV/TB neden önemli ?

bağışıklığın baskılanması

MTB direnç sorunu

ART-TB
ilaç etkileşimi

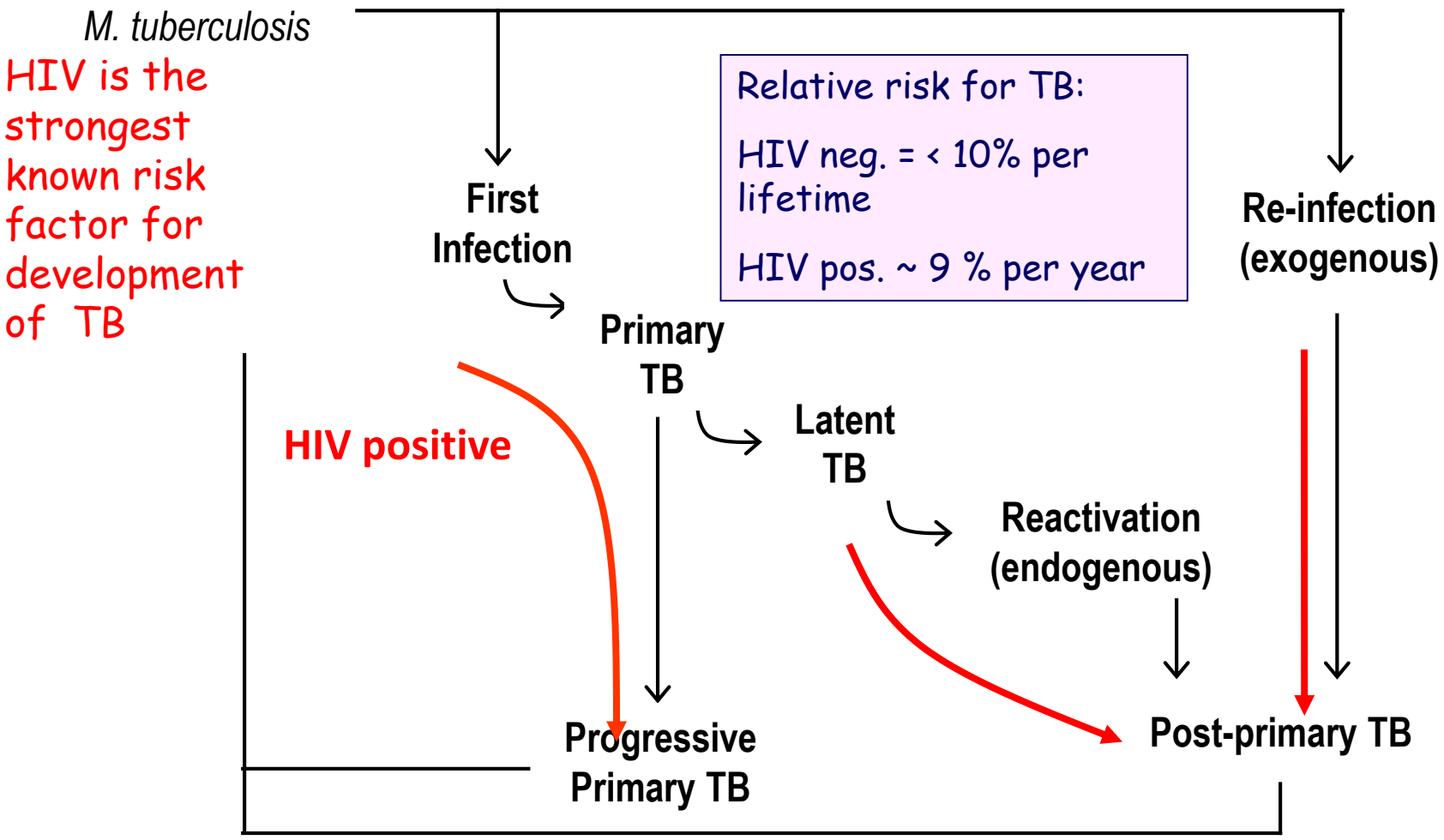
ilaç toksisitesi

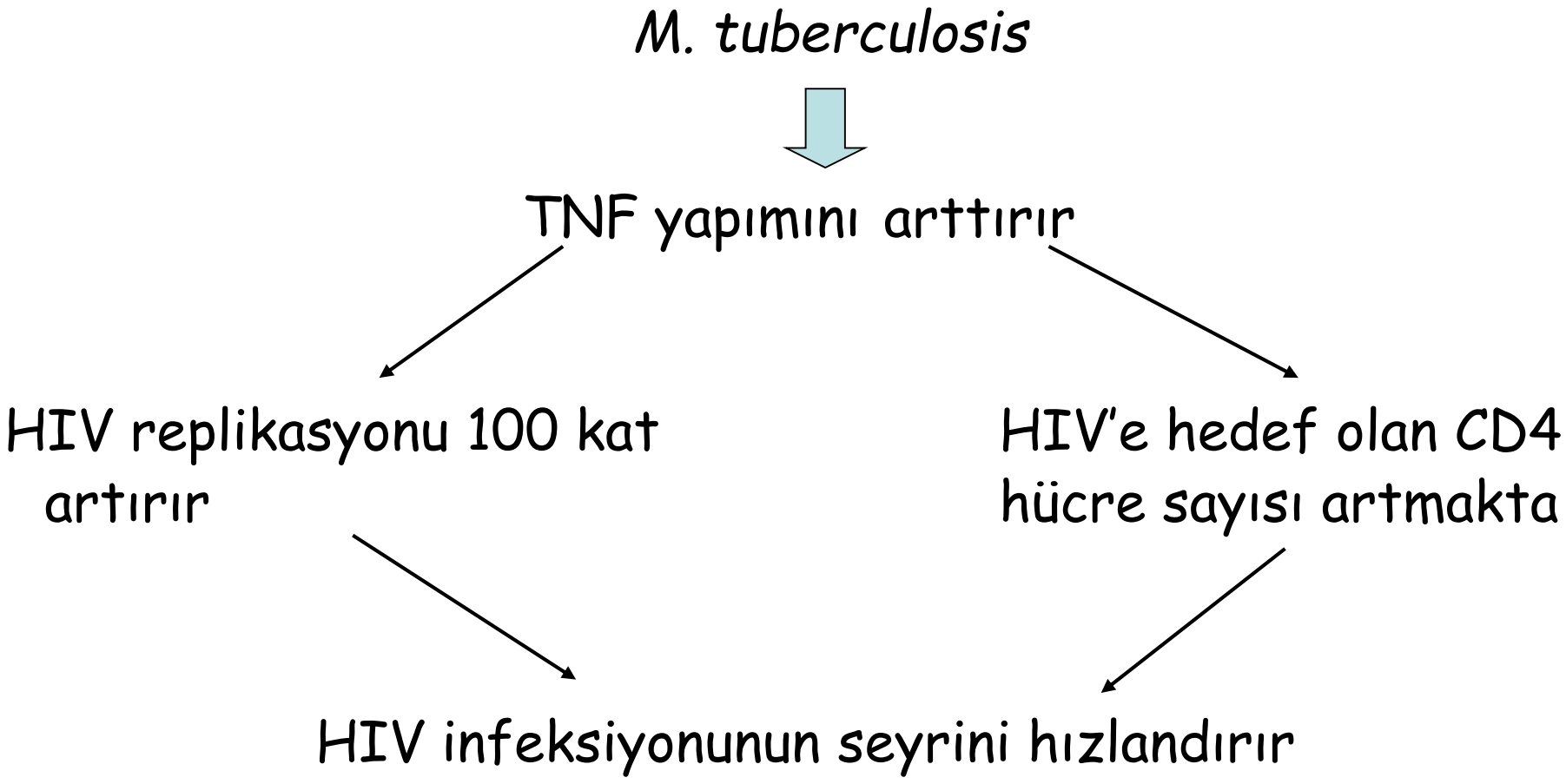
artan ilaç sayısı

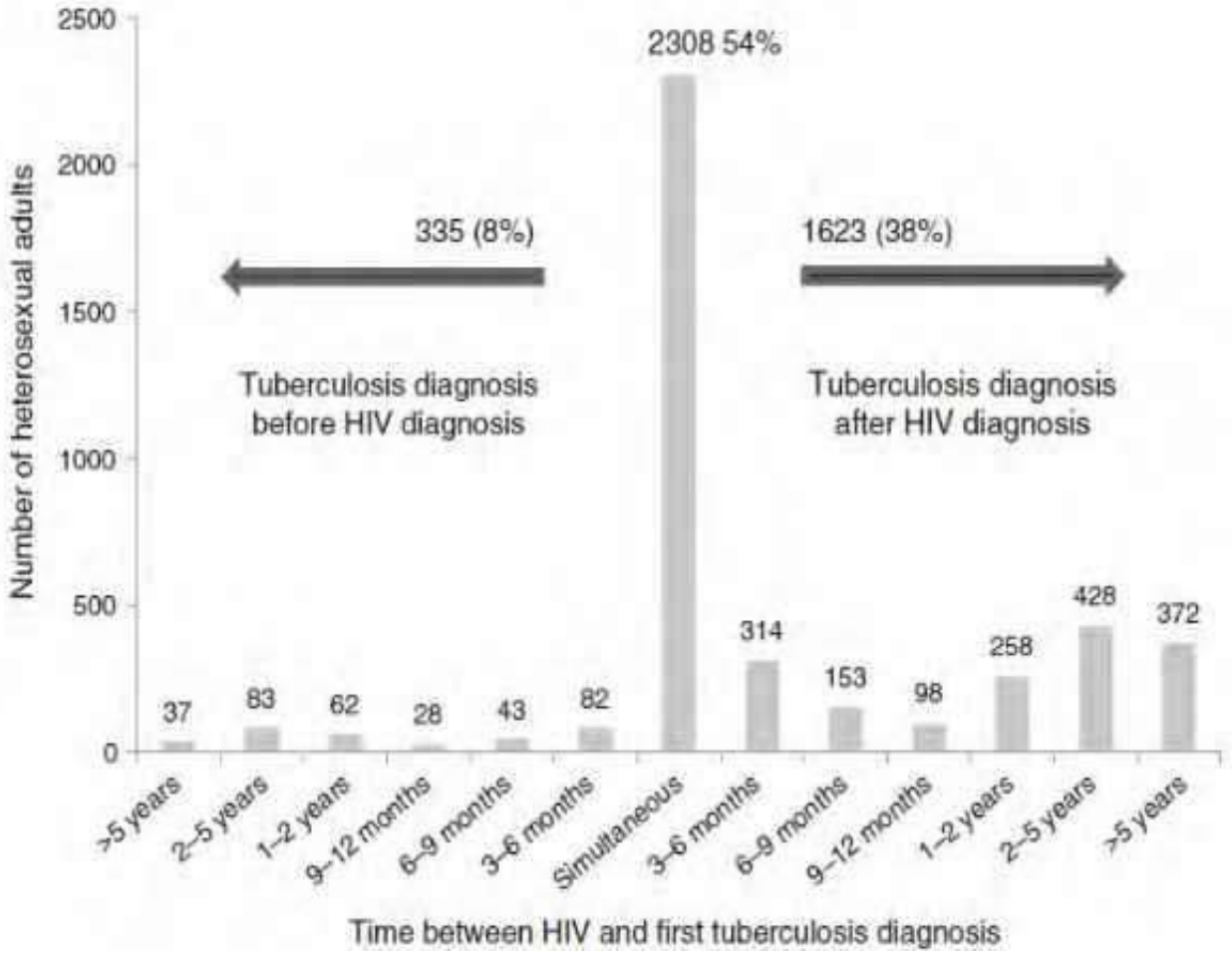
tedaviye uyumda azalma

Mortalite
HIV+TB %11
TB %3.4

HIV&TB - Bulaş ve patogenez



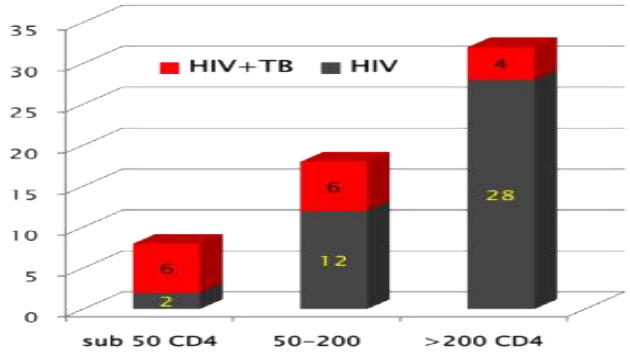

M. tuberculosis
TNF yapımını arttırır
HIV replikasyonu 100 kat artırır
HIV'e hedef olan CD4 hücre sayısı artmakta
HIV infeksiyonunun seyrini hızlandırır



Rice B et al. AIDS 2013

TB herhangi bir CD4 sayısında ortaya çıkabilir

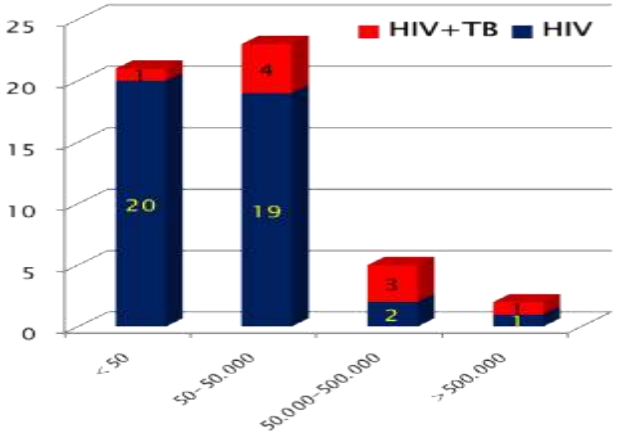
CD4 sayısına göre



Risk faktörleri

- Düşük CD4 hücre sayısı
- Geç tanı
- Düşük vücut kitle indeksi
- Anemi
- Yüksek viral yük

HIV RNA düzeyine göre



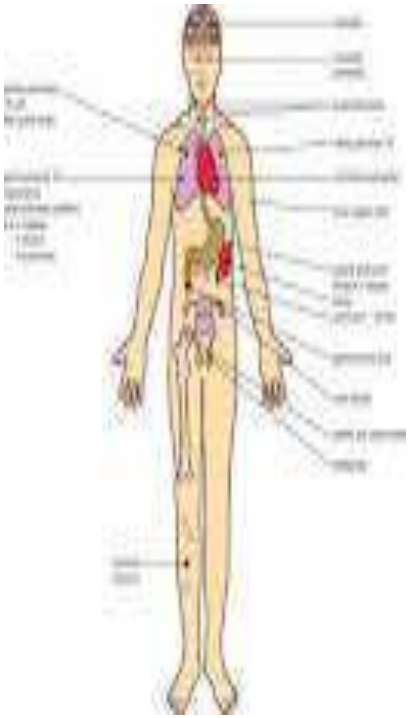
Pulmoner TB yarısından fazlasında CD4 > 200/mm3

İmmünyetmezliğin ilerlemesi ile mikobakterilerin hematojen ve lenfatik yayılımları ile

- Miliyer TB
- Lokalize ektrapulmoner TB daha sık

Ekstrapulmoner TB çoğunlukla CD4<200/mm3

En sık servikal lenf nodları (sert, ağrısız)
Menenjit
Perikardit
Osteoartrit
Ürogenital
Cilt
Adrenal gland-Addison's
Pratikte her organ……



Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for ≥1 month) or chronic weakness and documented fever for ≥1 month

Table 2. WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Clinical Stage	Clinical Conditions or Symptoms
Primary HIV infection	• Asymptomatic • Acute retroviral syndrome
Clinical Stage 1	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical Stage 2	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrheic dermatitis • Fungal nail infections
Clinical Stage 3	• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) • Persistent oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/μL) • Chronic thrombocytopenia (platelets <50,000 cells/μL)
Clinical Stage 4	• HIV wasting syndrome, as defined by the CDC (see Table 1, above) • *Pneumocystis* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) • Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma

Tani

Site	Practical approach to diagnosis
Peripheral lymph t (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest radiograph and lumbar puncture (to test for meningitis)
Tuberculous meningitis	Lumbar puncture (and imaging where available)
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound (3) and ascitic tap
Osteoarticular	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

Altın standart **kültür**

- LJ medium, BACTEC, MGIT
- Üreme özelliklerine göre MTB, tüberküloz dışı mikobakteri (NTM) ayrımı
- 1. basamak tüberküloz ilaçlarına duyarlılık testleri yapılmalı

- 2. basamak duyarlılık (kinolonlar, aminoglikozidler, kapreomisin, etionamid) referans laboratuvarlarında yapılmalı

PCR kültürden daha kısa sürede sonuçlanır

ARB incelemesinden daha sensitif ve spesifik

Ancak yanlış negatif olarak sonuçlanabilir

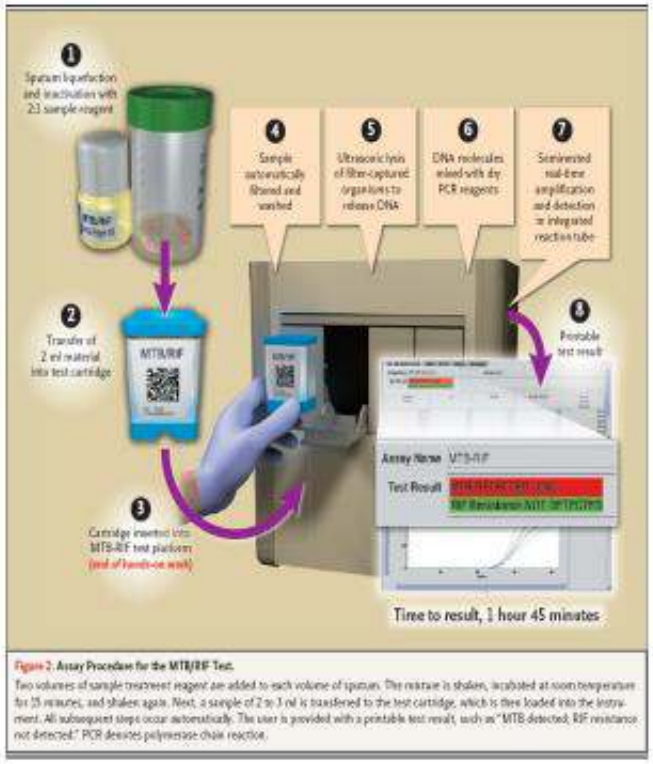
Genotipik testler ilaç direnç mutasyonlarını göstererek direncin erken saptanmasını sağlar

Rifampisin ve izoniazid için genotipik direnci saptayan ticari testler

Xpert MTB/Rif

Balgam

Diğer materyaller



2 saatte tanı

Duyarlılık

ARB (+) PTB - 1 örnek = 98%

ARB (-) PTB - 1 örnek = 72%; 3 örnek = 90%

EPTB – farklı örnekler= 81% (25% - 97%)

Boehme et al, N Engl J Med 2010; 363: 1005-15: Lawn and Zumla, Exp Rev Anti-Infect Ther 2012

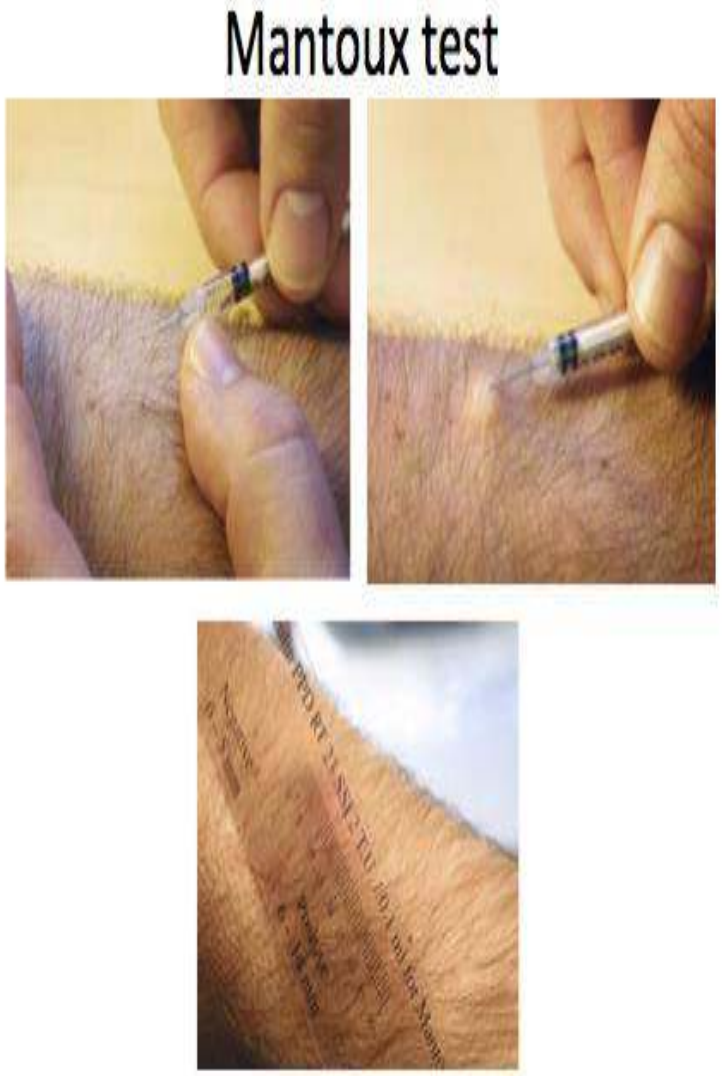
LTBI

Klinik ve radyolojik olarak TB bulgusu olamayan bireylerde TST≥5 mm olması

Tüberkülin Deri Testi (TDT)

•Antijen: PPD

-*MTBC'e* ait çok sayıda antijenin karışımı
-*M. bovis* BCG ve pek çok TDM için de ortaktır



Dezavantajlar

ppd

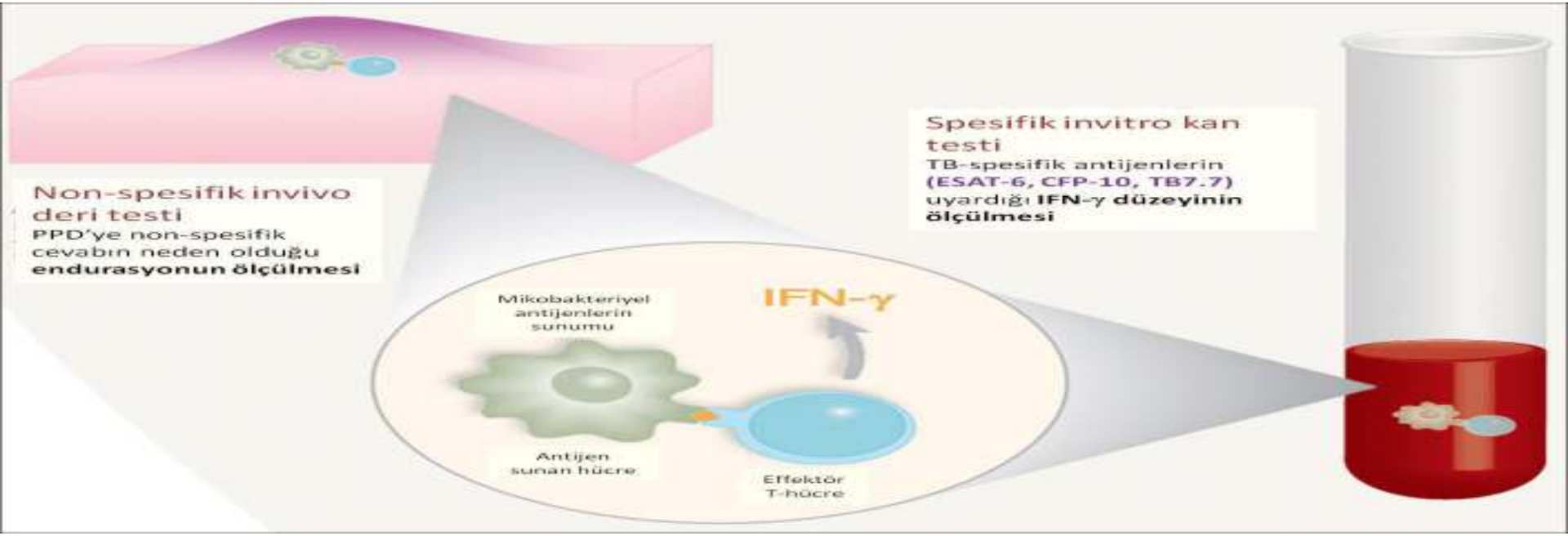
Yanlış pozitiflik (BCG, TDM)
Yanlış negatiflik (anerji, düşük CD4)

Uygulamada, değerelendirmede hatalar
Hastaneye iki kez gelmek zorunda

IGRAs

TDT'ne alternatif olarak geliştirilmiş T-hücre temelli yöntemler

M. tuberculosis antijenlerine karşı in vitro IFN-γ salınımının saptanmasına (IGRA) dayalıdır



CD4<200/mm^3 de IGRA'larda da yalancı negatif ve belirsiz sonuçlarda artış olabilmektedir

Pahalı

HIV-enfekte hastalarda MTB tanısında spesifikliği

ppd %56-95
IGRAs %92-97

testler arası fark az

T-SPOT-TB ~ % 70 > QFT-GIT ~ % 60

J Acquir Immune Defic Syndr 2011; 56:230

- TST ve IGRAs (+) » TB riski artmıştır

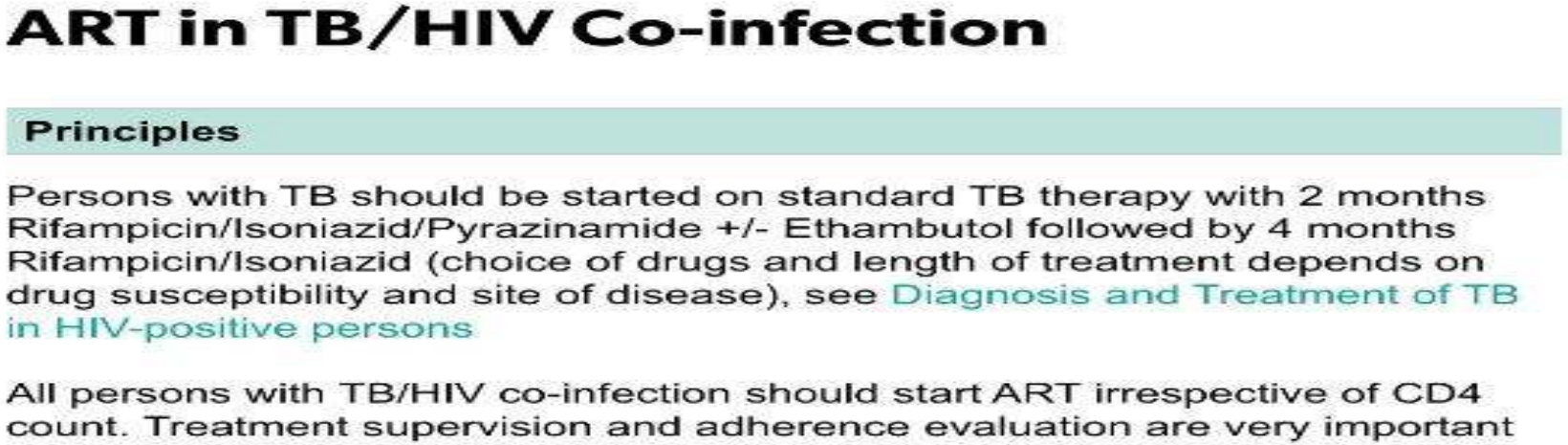
- Hem TST hem de FDA onaylı IGRAs HIV-enfekte olgularda TB taraması için uygun testlerdir

- İki testin birlikte kullanılması önerilmez

MMWR Recomm Rep 25 June 2010

Tedavi

TB tedavisi ve tedavinin etkinliği HIV negatif olgulardaki ile benzerdir



ART in TB/HIV Co-infection

Principles

Persons with TB should be started on standard TB therapy with 2 months Rifampicin/Isoniazid/Pyrazinamide +/- Ethambutol followed by 4 months Rifampicin/Isoniazid (choice of drugs and length of treatment depends on drug susceptibility and site of disease), see Diagnosis and Treatment of TB in HIV-positive persons

All persons with TB/HIV co-infection should start ART irrespective of CD4 count. Treatment supervision and adherence evaluation are very important

TB tedavisinin başlangıç döneminde intermitan tedavi önerilmemektedir, devam fazında 3-5gün/hf olabilir **(AII)**

Diagnosis and Treatment of TB in HIV-positive Persons

Treatment of TB in HIV-positive persons

For standard treatment of TB in HIV-positive persons, including appropriate choice of ARVs, see below table and ART in TB/HIV Co-infection

Disease	Drug	Dose	Comments
Susceptible *Mycobacterium tuberculosis*			
Initial Phase	**Rifampicin** **+ Isoniazid** **+ Pyrizinamide** **+ Ethambutol**	Weight based	**Initial phase** (Rifampicin+Isoniazid+Pyrizinamide+Ethambutol) for 2 months, then **Continuation phase** (Rifampicin+Isoniazid) according to TB type
Alternative	**Rifabutin** **+ Isoniazid** **+ Pyrizinamide** **+ Ethambutol**	Weight based	**Initial phase** (Rifabutin+Isoniazid+Pyrizinamide+Ethambutol) for 2 months, then **Continuation phase** (Rifabutin + Isoniazid) according to TB type
Continuation phase	**Rifampicin/Rifabutin** **+ Isoniazid** according to TB type		Total duration of therapy: 1. Pulmonary drug susceptible TB: 6 months 2. Pulmonary TB & positive culture at 8 weeks of TB treatment: 9 months 3. Extrapulmonary TB with CNS involvement or disseminated TB: 9-12 months 4. Extrapulmonary TB with bone/joint involvement : 9 months 5. Extrapulmonary TB in other sites: 6-9 months

tedavi süresi

- duyarlı TB
- Ekstrapulmoner TB (SSS tutulumu +): **9 - 12 ay**
- Ekstrapulmoner TB (kemik eklem tutulumu): **6 - 9 ay**
- Ekstrapulmoner TB (diğer bölgeler): **6 ay**
- MDR TB olgularında tedavi süresi daha uzun

- SSS ve perikard tutulumunda kortikosteroid kullanımı hayatta kalma şansını arttırır **(AI)**

- SSS tutulumunda deksametazon (12hf)
- Perikard TB prednizon/prednizolon (6hf)

TB tedavisi ve ART başlama zamanı

Erken başlanan ART

- ilaç-ilaç etkileşimi
- Artmış toksisite
- IRIS
- İlaç sayısında artış (uyumda azalma)

Geç başlanan ART

- HIV enfeksiyonunun ilerlemesi

CD4 sayısı	ART başlama zamanı
<50/mm^3	<2 hf **(AI)**
>50/mm^3 Ciddi hastalık olmadığında Ciddi hastalık varlığında	 > 2-4 hf, < 8-12 wks **(AI)** 2-4 hf içinde **(AI)**

TB tedavisi süresince ART güvenle verilebilir ve ART HIV-ilişkili hastalıkları ve mortaliteyi azaltır

Blanc FX, et al. N Engl J Med 2011;365(16):1471-81

Suggested timing of ART initiation in TB/HIV co-infection according to CD4 count

< 50 cells/μL* : As soon as TB treatment is tolerated and wherever possible within 2 weeks

≥ 50 cells/μL** :Can be deferred until between 8 and 12 weeks of TB treatment, especially when there are difficulties with drug-drug interactions, adherence and toxicities

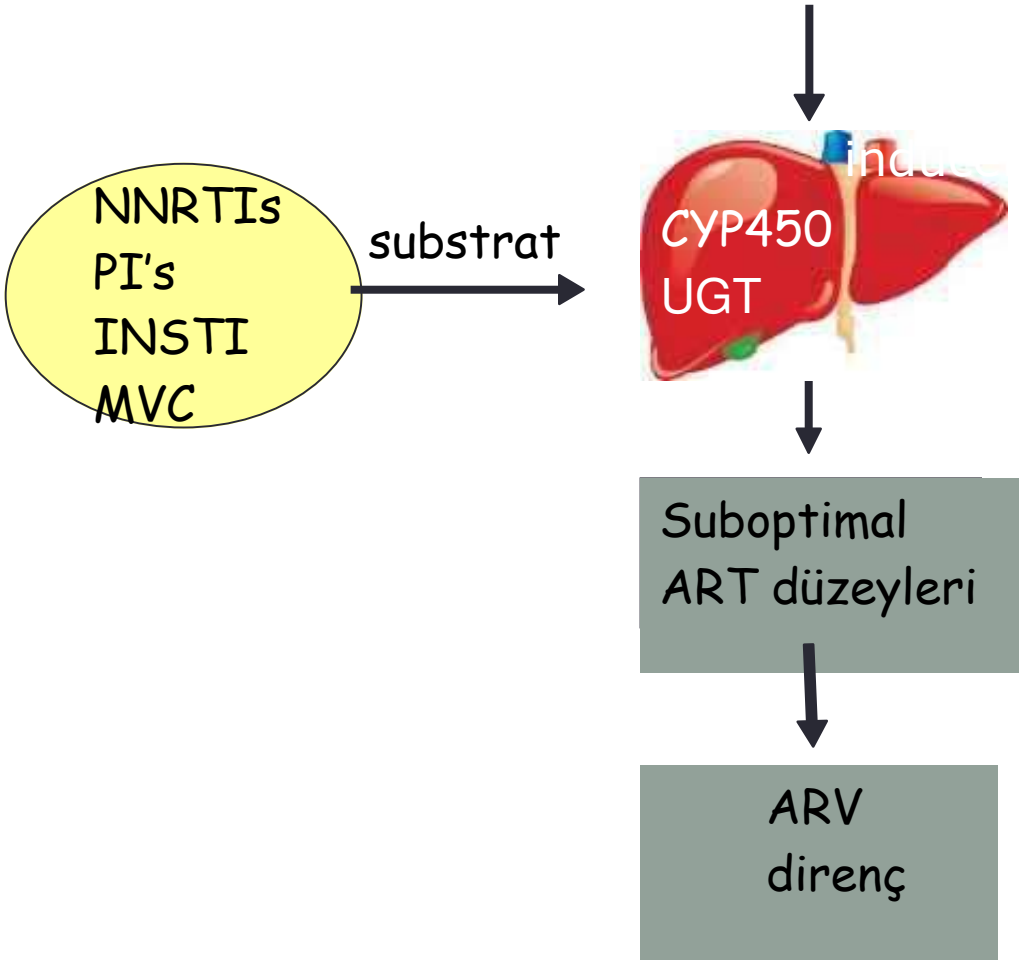
Although a RCT showed that early ART (within 2 weeks) did not reduce mortality in TB meningitis, recommendations on ART initiations should be based on the CD4 count in HIV-positive persons with TB co-infection.

* Be aware of IRIS reaction in persons starting ART at low CD4 count levels and with early initiation of ART. Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response.

** Although the data suggests a cut-off of 50 cells/μL, because of the daily variability in CD4 count, a cut-off of 100 cells/μL may be more appropriate.

İlaç etkileşimleri

Rifamisin



ARV drug class	Specific ARVs	Drug-drug interactions and recommended adjustment of dose of either or both drugs
NRTIs		Rifampicin: standard dose of all drugs
		Rifabutin: standard dose of all drugs
PI/r and PI/c		Rifampicin: not recommended
PI/r	Monitor liver enzymes and, whenever possible, perform TDM for PI	Rifabutin: dose as 150 mg qd[(i)]. PI/r at standard dose
PI/c		Rifabutin: not recommended. If needed recommended dose of rifabutin: 150 mg qd[(ii)]
NNRTIs	EFV	Rifampicin: No dose change required. EFV: standard dose ARV TDM recommended after 2 weeks
		Rifabutin: 450 mg qd. EFV: standard dose
	NVP	Neither rifampicin nor rifabutin recommended
	RPV	Rifampicin: not recommended
		Rifabutin: standard dose. RPV dose should be increased (use with caution)
	ETV	Rifampicin: not recommended
		Rifabutin: standard dose of both drugs (few data – use with caution)
INSTI	EVG/c	Rifampicin: not recommended
		Rifabutin: 150 mg qd. EVG: standard dose. Use with caution.
	RAL	Rifampicin: standard dose. RAL 400 or 800 mg bid and perform TDM for RAL
		Rifabutin: standard dose of both drugs
	DTG	Rifampicin: standard dose. DTG 50 mg bid (use only in absence of INSTI resistance)
		Rifabutin: standard dose of both drugs
Other ART	MVC	Rifampicin: MVC 600 mg bid
		Rifabutin: Standard dose of MVC (300 mg bid in absence of a PI, 150 mg bid in

Recommended 1st line ARV combination with anti-TB medicines

TDF/FTC + RAL or TDF/FTC/EFV (see table for dose adjustment with rifamycins).

Alternatives

Where combinations are not recommended or to be used with caution or because of resistance/intolerance, specialist HIV treatment advice should be sought.

- TDF/FTC + PI/r, using rifabutin instead of rifampicin (see table for dose adjustment of rifabutin). Use with caution.
- TDF/FTC + DTG bid*** with rifampin.

In countries where neither DTG nor rifabutin are available, following combinations could also represent a short-term alternative until anti-TB treatment has been completed.

- Rifampin plus fixed-dose combination of ABC/3TC/ZDV bid + TDF qd (if HIV-VL < 100,000 copies/mL).
- Rifampin plus double dose LPV/r or with RTV super boosted (400 mg bid) + LPV.
- For other regimens based on 2NRTIs plus NVP, RPV, ETV or MVC, consultation with an HIV specialist is recommended.

*** Only pharmacokinetic and not clinical data are available, use with caution.

Advers etkiler

- Tüberküloz ilaçlarına spesifik reaksiyon olduğuna dair kanıt olmadan ilk basamak ilaçlar (öz. INH, RIF) kesilmemelidir

- AST artışı (%20)

  Çoğunda kendiliğinden geriler

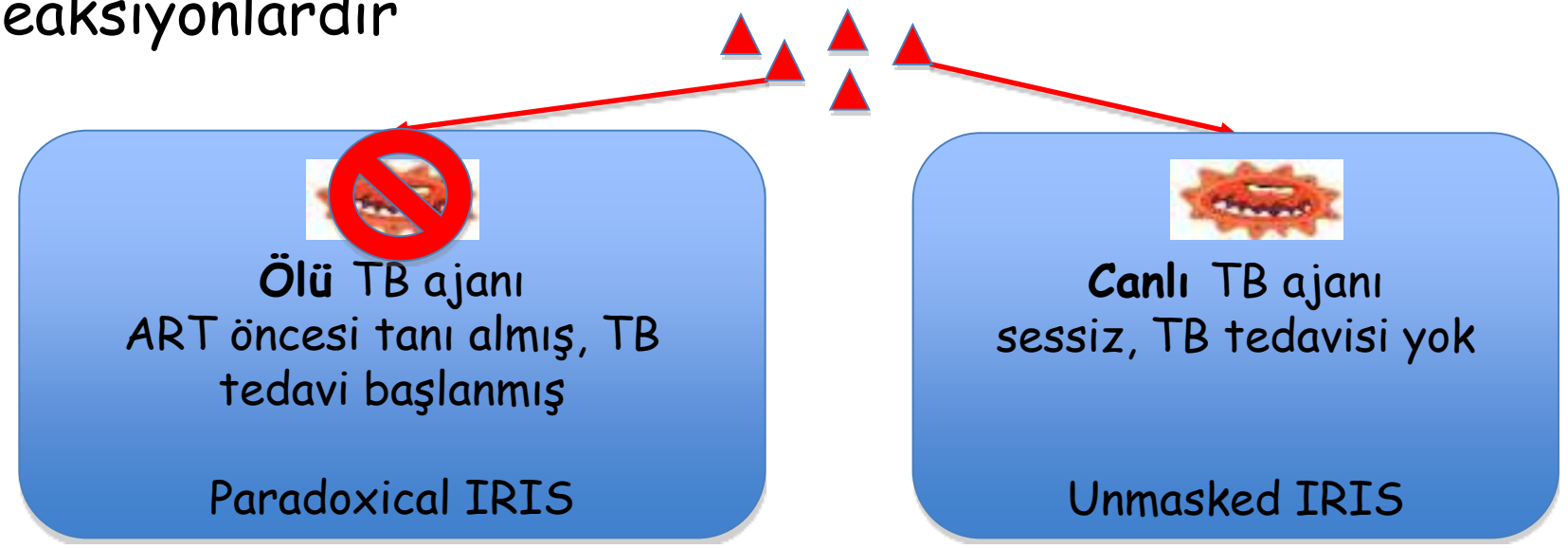
  >X3 semptomatik, >X5 asemptomatik, Bil ve/veya ALP artışı var ise hepatotoksik olb ilaçlar kesilir

  RIF---1hf---INH---1hf---PZA

- Döküntü
  - Hafif (antihistaminik- TB tedavisine devam)
  - Ciddi (tüm TB ilaçları döküntü gerileyene kadar stop, sonra 2-3 gün aralıklarla birer birer başlanır-önce RIF)

HIV-(TB) IRIS

İmmün sistemin restore olmasıyla *M. tuberculosis* antijenlerinin olduğu yerlerde görülen inflamatuar reaksiyonlardır



ART den 1-4 hf sonra başlar

ART ilk hf da ortaya çıkar

TB-IRIS klinik bulguları

Ateş

Lenf bezlerinde büyüme

SSS (menenjit, abse)

Serozit: plevral efüzyon, ascites, perikardial efüzyon

Cilt ve ciltaltı tutulumu

Gastrointestinal ve intra-abdominal abseler

Nadiren: akut renal yetmezlik, epididimo-orşit, hiperkalsemi, göz tutulumu

TB-IRIS risk faktörleri

- CD4<100/mm^3 ART başlamak
- Yüksek VL >10^5 kopya/ml
- Dissemine veya **ekstrapulmoner TB**
- TB tedavisi ile ART arasındaki sürenin az olması (TB tedavisinin ilk 2 ayında)
- CD4 ün hızlı yükselip, VL hızlı düşmesi

TB-IRIS tedavisi

- TB tedavisine devam edilmeli (MDR-TB veya ilaç etkileşimi gibi bir neden olmadığı sürece)
- ART devam edilmeli (TB menenjitte KİBAS veya hava yolunu tıkayıcı abse gibi komplikasyonlar olmadığı sürece)
- ART'ye ara verildiyse tekrar steroid altında başlanır
- Lokalize abselerde insizyon ve direnaj
- Çoğu olguda kendini sınırlayan bir durum, tedaviye devam etmekle veya ağır seyirli olmayan olgularda NSAİ kullanımıyla geriler

Discussion - Diagnosis and Management of TB-IRIS - Resource-Limited Settings - Global HIV Web Study
http://depts.washington.edu/ghivaids/reslimited/case3/discussion.html

Kortikosteroid - IRIS

- SSS tutulumu, dispne gibi hayatı tehdit edici durumlarda kortikosteroidlerin kullanılması önerilmektedir

- Steriod dozu ve süresi hastaya göre değerlendirilmelidir
  - 1.5 mg/kg/gün 2 hf, takiben 2 hf daha 0.75 mg/kg/gün
  - Bazı olgularda (yüksek TB yükü veya ciddi klinik bulgular) tedavi süresi daha uzun

- Steroid tedavisine cevap dikkatle değerlendirilmeli
  (klinik iyileşme yoksa ayırıcı tanılar gözden geçirilip steroid tedavisi sonlandırılır)

HIV - TB kontrolü ve korunma

- **3 I**

-Intensive case finding and treatment

-Isoniazid preventive therapy

-Infection control

- Workplace/administrative, environmental, respiratory protection

- **ART**

(PLOSMed 2012;9:e1001270)


STOP
TB

- RIF ± diğer ajanlara dirençle ilgili belirgin endişe varsa başlangıç rejimine

Moksifloksasin/levofloksasin+aminoglikozid/kapreomisin eklenir **(BIII)**

Tüm olgularda DGT önerilir

Dirençli olguların tedavisi

INH direçli

İlk 2 ay INH yerine levofloksasin/moksifloksasin **(BII)**

İdame fazında RIF+EMB **(CIII)**

Tedavi süresi 9 ay **(BII)**

RIF ± diğer anti TB

2., 3. basamak ilaçlar (direnç testine göre)

Tedavi süresi 12-24 ay


HIV POSITIVE
REVENT TB

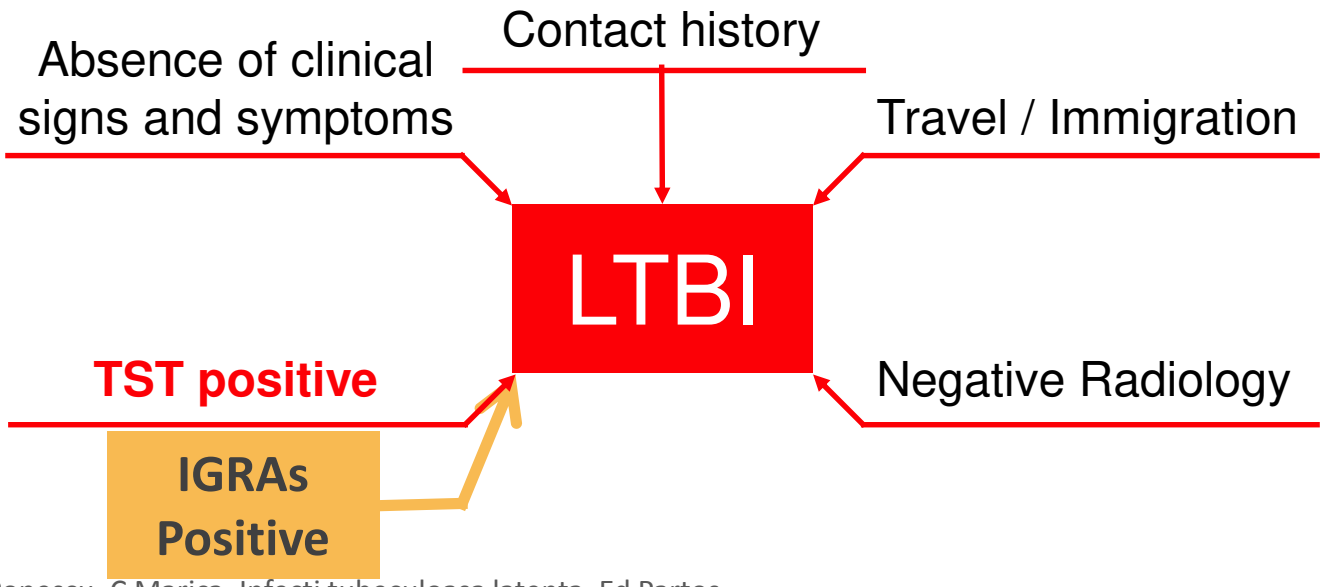
TABLE A4.3

TB case notifications, 2014

	New and relapse[b]	New cases[a]			Relapses			Previously treated, excluding relapse
		Pulmonary		Extra-pulmonary	Pulmonary		Extra-pulmonary	
		Bacteriologically confirmed	Clinically diagnosed		Bacteriologically confirmed	Clinically diagnosed		
South Sudan	8 335	3 565	2 887	1 624	259			521
Spain	4 818	2 843	673	1 302	0	0	0	230
Sri Lanka	9 305	4 345	1 962	2 710	288	0	0	168
Sudan	19 266	6 106	7 934	4 571	655			1 126
Suriname	149	100	16	26	4	2	1	9
Swaziland	5 583	2 540	1 606	765	322		350	33
Sweden	635	313	44	270	4	0	4	35
Switzerland	423	272	30	121				50
Syrian Arab Republic	3 481	1 161	441	1 796	55	6	22	95
Tajikistan	5 807	2 432	1 162	1 423	540	139	111	453
Thailand	67 722	34 394	21 115	10 244	1 969	0	0	3 896
The Former Yugoslav Republic of Macedonia	284	167	31	64	19	0	3	1
Timor-Leste	3 657	1 838	1 222	519	78			121
Togo	2 525	1 899	177	339	110	0	0	52
Tokelau	0	0	0	0	0	0	0	0
Tonga	13	8	5	0	0	0	0	0
Trinidad and Tobago	251	128	88	25	5	5	0	42
Tunisia	3 134	1 052	214	1 834	34			39
Turkey	13 108	5 799	1 897	4 557	568	119	168	270
Turkmenistan	2 570	1 944		415	173		38	317
Turks and Caicos Islands	1	0	0	0	1	0	0	2
Tuvalu	15	8	6	0	1			0
US Virgin Islands								
Uganda	44 187	26 079	11 854	4 180	1 499	468	107	1 984
Ukraine	31 701	14 242	9 296	2 596	4 566	800	201	8 601

Latent Tuberculosis infection (LTBI)

- Potential to develop into active disease at any time
- Identification and treatment of LTBI can reduce the risk of development of disease



A Socaci, GG Popescu, C Marica. Infecti tubeculoasa latenta, Ed Partos, Timișoara 2014