Annelies Verbon
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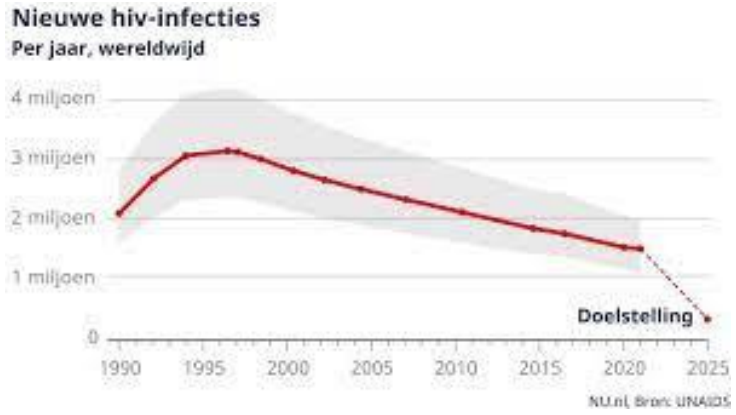
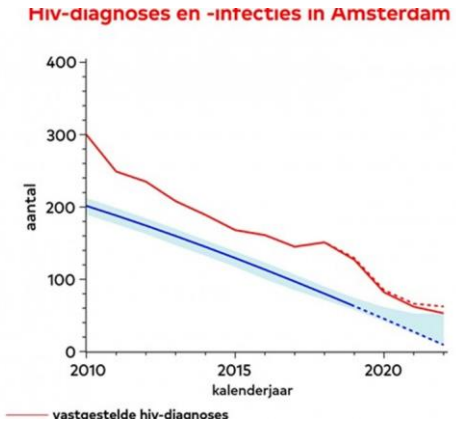
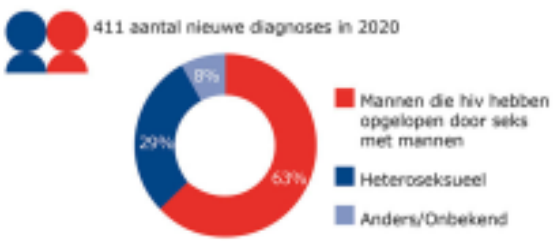
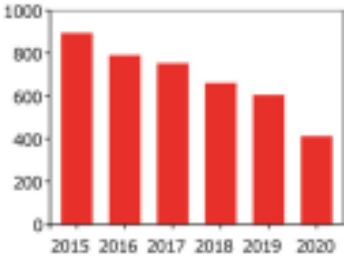
HIV incidentie



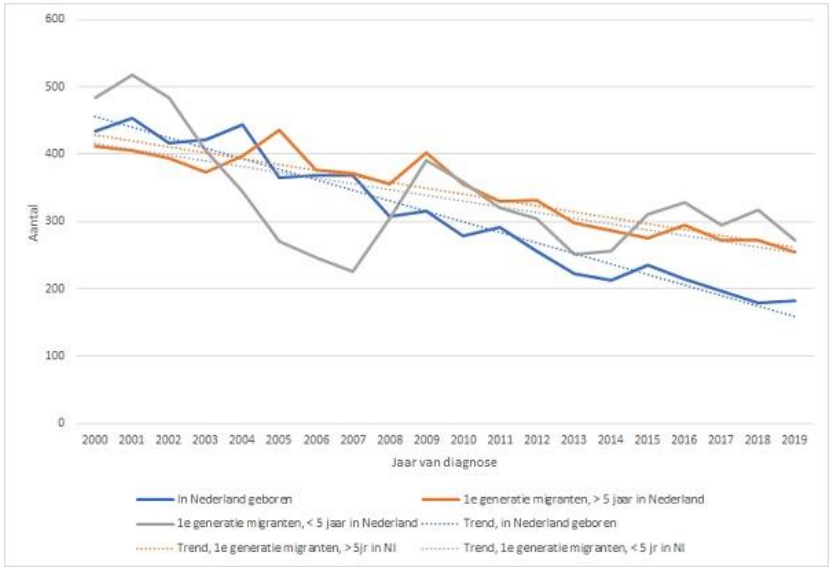




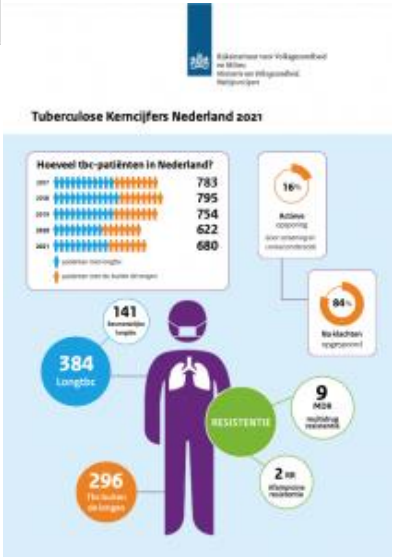


2022: 461 nieuwe HIV diagnoses

Tuberculose incidentie

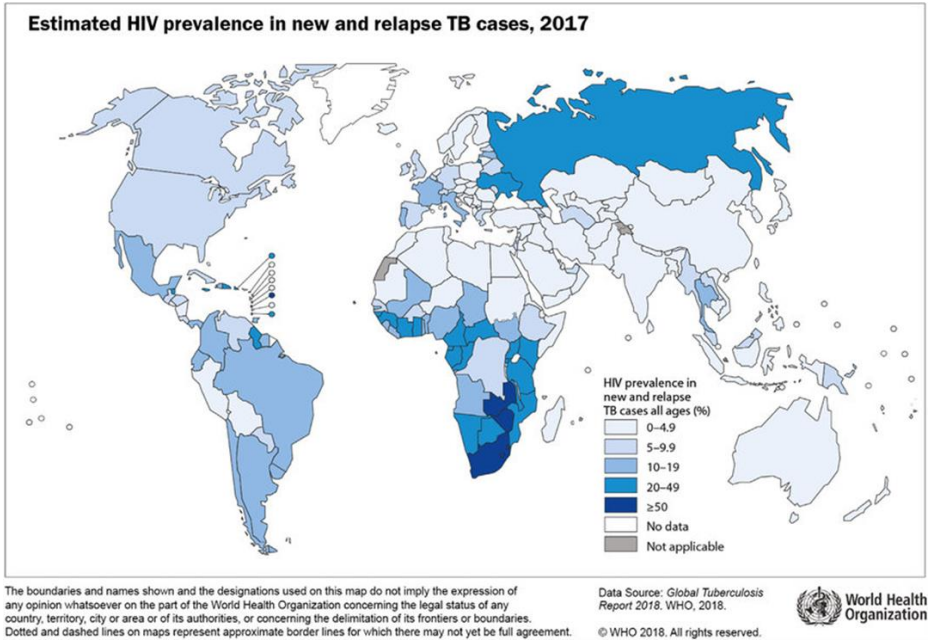


	Tuberculose	HIV
2017	783	753
2018	794	667
2019	753	625
2020	620	447
2021	651	439
2022		461



Tuberculose en HIV

- WORLDWIDE
  - 35 500 000 people infected with HIV
  - 787000 co-infected with TB in 2020
  - 214000 co-infected pat died in 2020
  - 25% of AIDS deaths are TB related

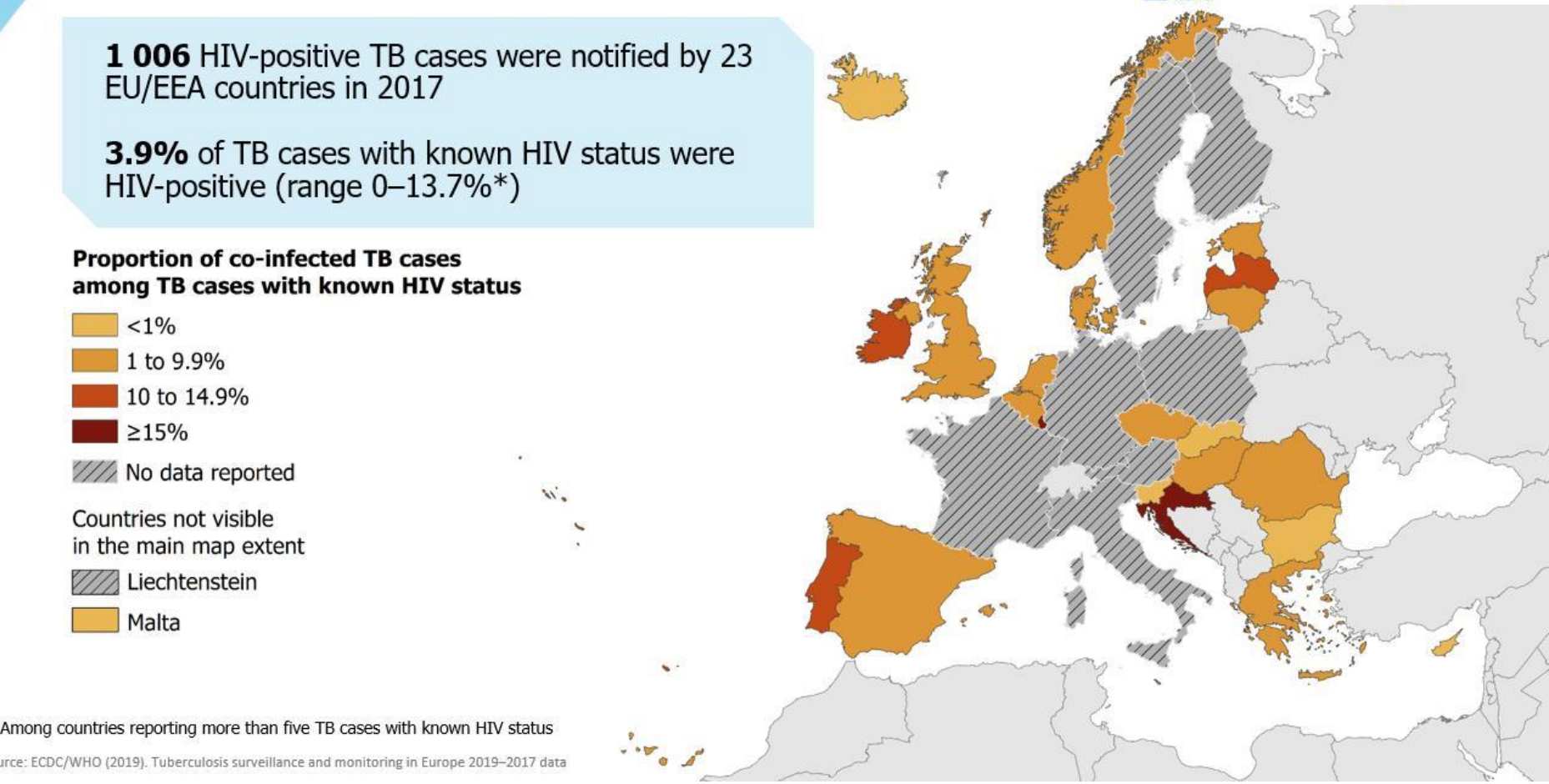


CID 2023;76:e580

TB/HIV co-infection, EU/EEA, 2017

1 006 HIV-positive TB cases were notified by 23 EU/EEA countries in 2017

3.9% of TB cases with known HIV status were HIV-positive (range 0–13.7%*)



* Among countries reporting more than five TB cases with known HIV status

Source: ECDC/WHO (2019). Tuberculosis surveillance and monitoring in Europe 2019–2017 data

Nederland:

2020-2022: 15 pulm en 15 extrapulm TB en HIV

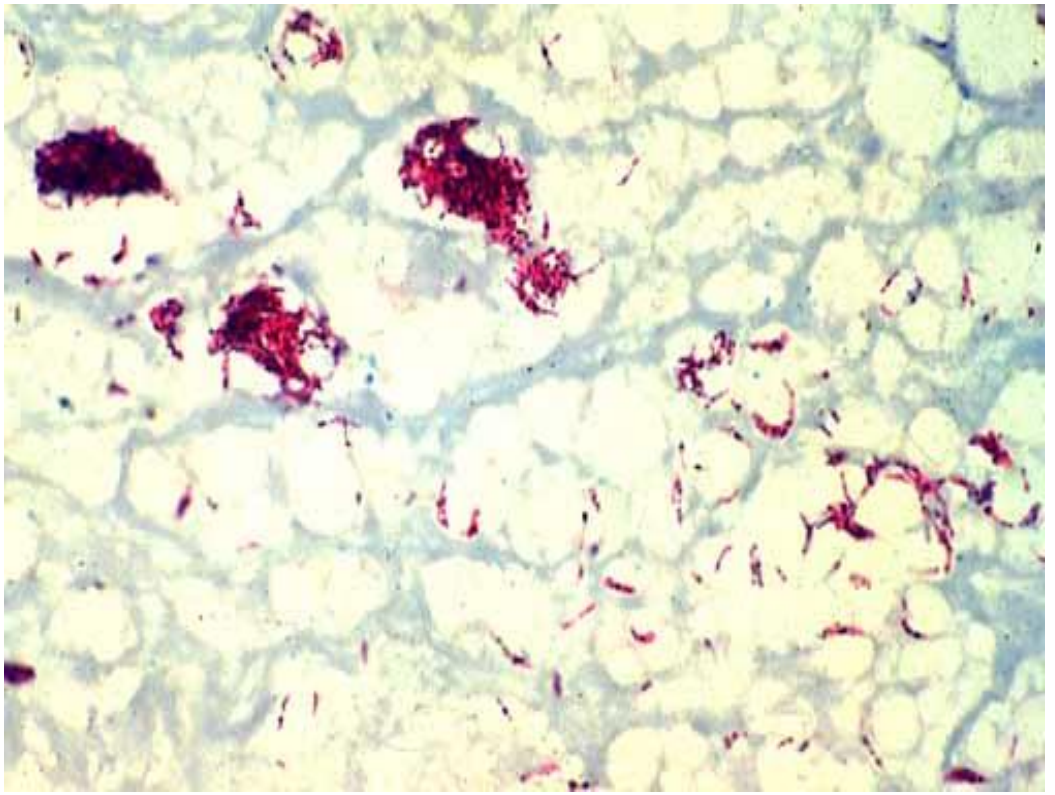
Tabel 3. Aandoeningen of condities met een verhoogde kans op progressie naar tuberculose indien geïnfecteerd met *Mycobacterium tuberculosis* complex

Aandoening of conditie*	Relatief risico#
Pathologisch	
Hiv-infectie	50-170
Jejunale by-pass	27-63
Silicose	30
Chronische nierinsufficiëntie of hemodialyse	10-25
Maligniteit	2,5-16
Diabetes mellitus - insuline afhankelijk	2-3,6
Medicamenteuze immunosuppressie	
Middelen bij orgaantransplantatie	20-74
TNF-α blokkerende geneesmiddelen	1,5-17
Glucocorticosteroïden (≥ 7,5 mg prednison equivalent per dag)	7,0**
Gebruik overige immunosuppressiva ter behandeling van auto-immuunziekten en inflammatoire aandoeningen	2-16
Fysiologisch	
Leeftijd < 5 jaar	2-5

* Tabel ontleend aan Erkens et al.[27] die de tabel ontleende aan verschillende bronnen.
** De gecorrigeerde odds ratio OR bij een dagelijkse dosering van <7,5 mg is 2.3 (95% BI 0,7–7,5).
# Het relatieve risico is de factor waarmee de kans op ziekte hoger is dan de kans op ziekte van gezonde volwassenen.

Patiënt Z

- lymphnode
- bone marrow
- sputum
- urine

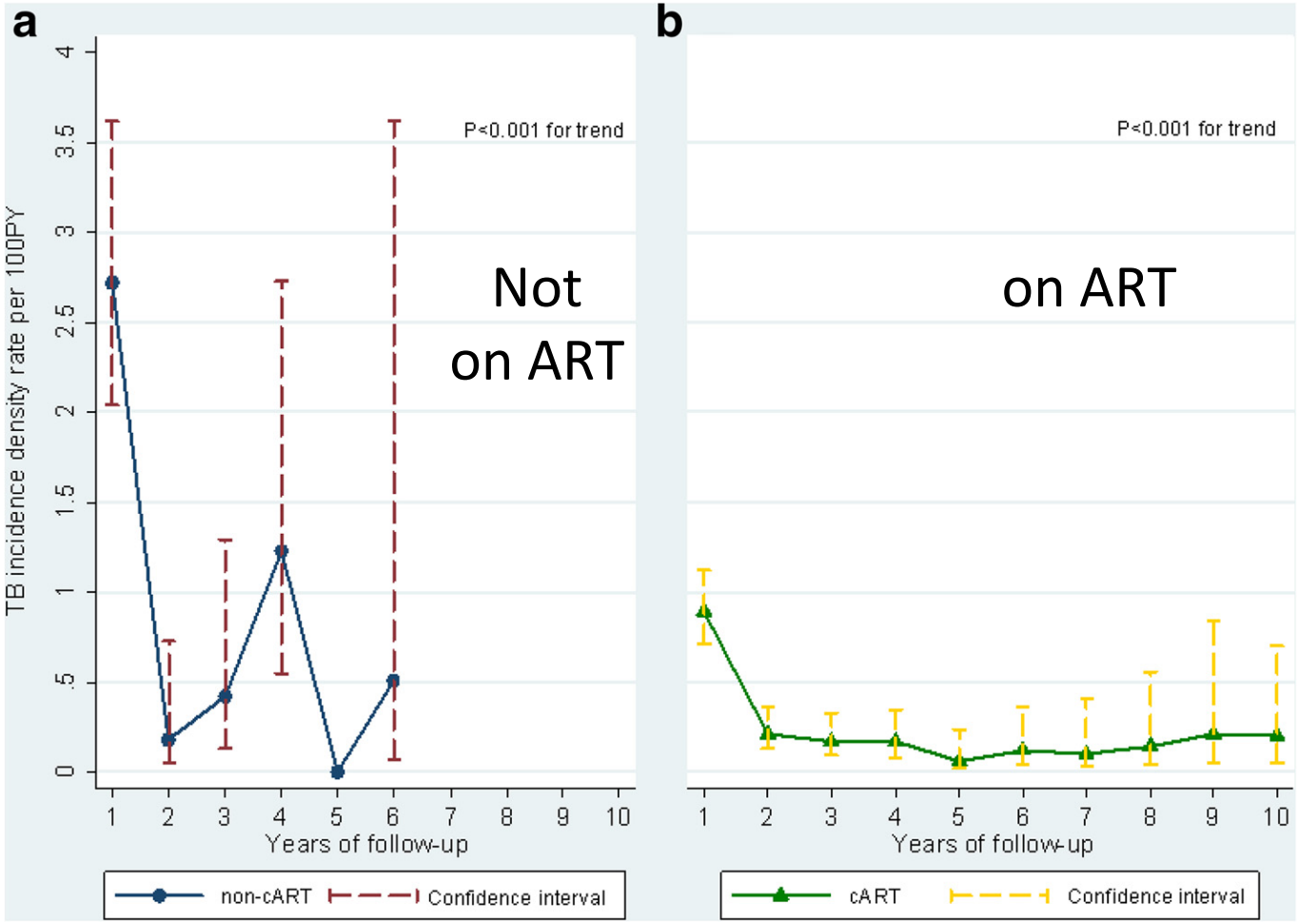


1. Risico factor voor HIV+ patienten met > 3 maanden cART voor TB ?

1. mode of transmission
2. aantoonbaar HIV RNA (>500 copies/ml)
3 etniciteit
4. geen met cART

German cohort (n=11693)

Karo et al, BMC inf Dis 2014



Risk factors for TB after starting cART

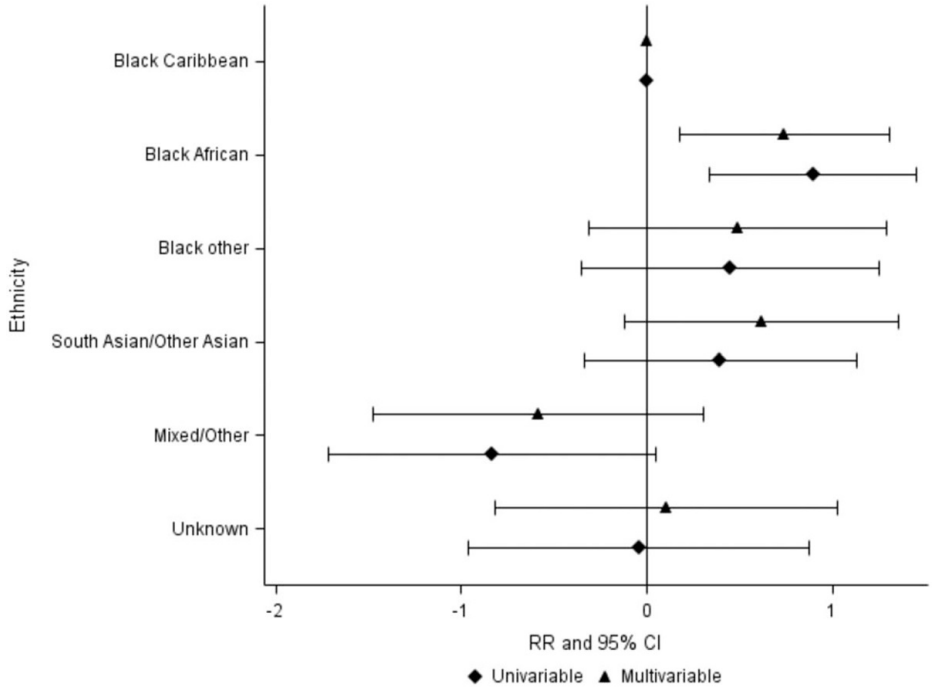
stratified for year of cART inititation

Variable		All years aRR (95% CI)	*P* value	<2004 aRR (95% CI)	*P* value	2004–2007 aRR (95% CI)	*P* value	2008–2011 aRR (95% CI)	*P* value	>2011 aRR (95% CI)	*P* value
Ethnicity	White	1	0.01	1	0.01	1	0.02	1	0.03	1	0.01
	Black	3.13 (2.23–4.38)		3.32 (2.05–5.37)		2.47 (1.29–4.72)		2.84 (1.24–6.50)		5.05 (1.31–19.51)	
	Other/unknown	1.85 (1.20–2.85)		1.82 (0.97–3.45)		1.94 (0.87–4.33)		2.04 (0.72–5.80)		1.55 (0.25–9.48)	
Age	/10 years	0.96 (0.86–1.08)	0.52	1.00 (0.84–1.19)	0.98	0.86 (0.70–1.06)	0.16	0.86 (0.66–1.12)	0.25	1.21 (0.84–1.75)	0.32
HIV viral load (time-updated)	Log copies/ml	1.43 (1.32–1.55)	0.01	1.50 (1.34–1.67)	0.01	1.33 (1.14–1.57)	0.01	1.49 (1.23–1.79)	0.01	1.18 (0.84–1.66)	0.37
$CD4^+$ cell count (time-updated)	/100 cells/μl	0.85 (0.80–0.89)	0.01	0.86 (0.80–0.92)	0.01	0.92 (0.84–1.00)	0.05	0.78 (0.68–0.89)	0.01	0.69 (0.55–0.85)	0.01
Years since cART initiation	/additional year	0.95 (0.92–0.99)	0.01	0.90 (0.87–0.94)	0.01	0.87 (0.82–0.93)	0.01	0.76 (0.67–0.87)	0.01	0.61 (0.42–0.91)	0.01
Year cART initiated	/later year	0.93 (0.91–0.95)	0.01								
Sex/exposure	Sex between men	1	0.01	1	0.27	1	0.01	1	0.01	1	0.08
	Male heterosexual	2.30 (1.57–3.36)		1.52 (0.89–2.59)		2.56 (1.17–5.63)		4.38 (1.61–11.90)		6.30 (1.18–33.82)	
	Female heterosexual	2.40 (1.67–3.46)		1.70 (1.03–2.81)		3.05 (1.46–6.39)		3.86 (1.46–10.25)		3.85 (0.70–21.21)	
	Male other mode	1.81 (1.05–3.11)		1.14 (0.48–2.71)		3.48 (1.31–9.27)		2.10 (0.53–8.26)		3.86 (0.51–29.15)	
	Female other mode	2.44 (1.34–4.47)		1.97 (0.86–4.53)		5.63 (2.1–15.12)		–		–	

Results are from a multivariable Poisson regression model. 95% CI, 95% confidence interval; aRR, adjusted rate ratio for incident tuberculosis; cART, combination antiretroviral treatment.

AIDS34(12):1813-1821, October 1, 2020.

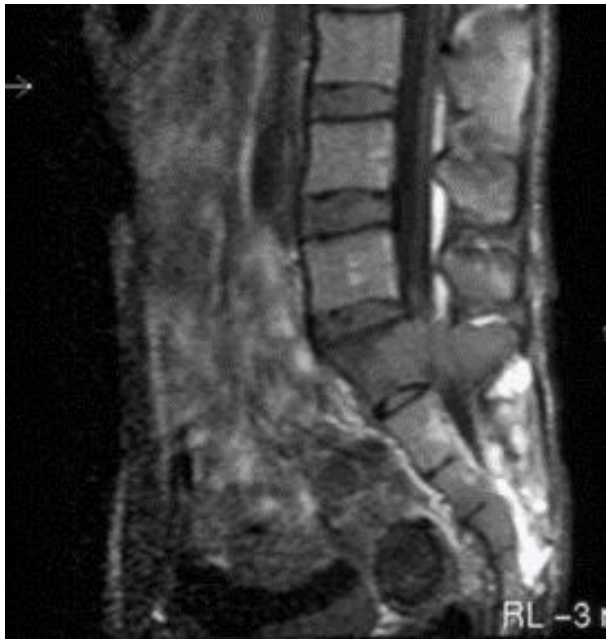
RR for TB after starting cART



AIDS34(12):1813-1821, October 1, 2020.

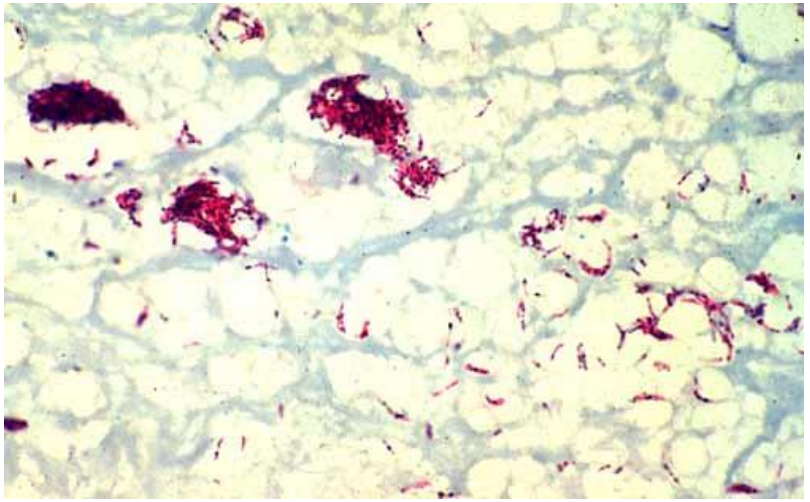
HIV
invloed op kliniek TB

- Mantoux vaak negatief
- Vaker extrapulmonale TB
- Hogere mortaliteit
- Veranderde X-thorax
- Vaker paucibacillair



2. Wat is de beste diagnostiek voor TB in HIV+ patiënten ?

1. Auramine staining
2. Culture
3. PCR
4. Urine POCT

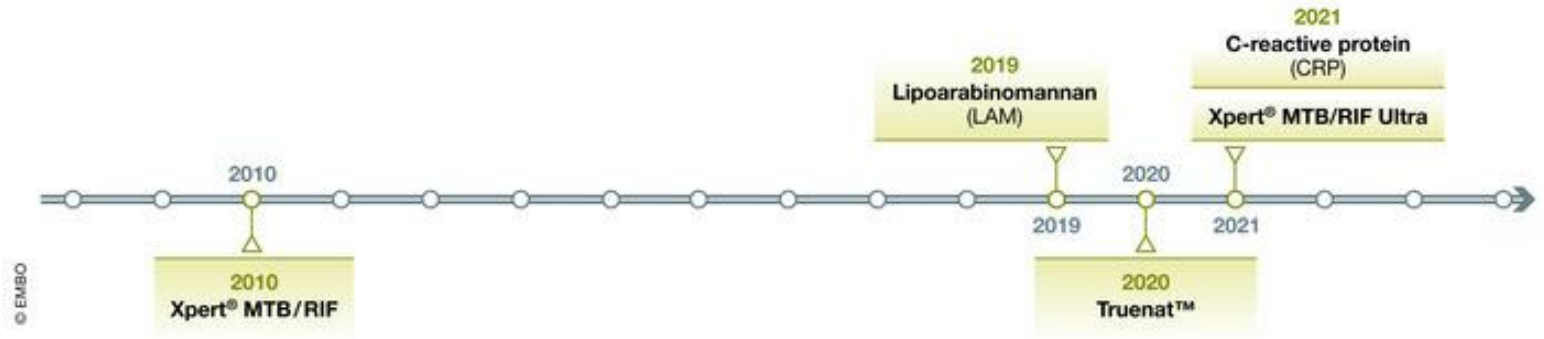


Diagnosis of TB in HIV patients

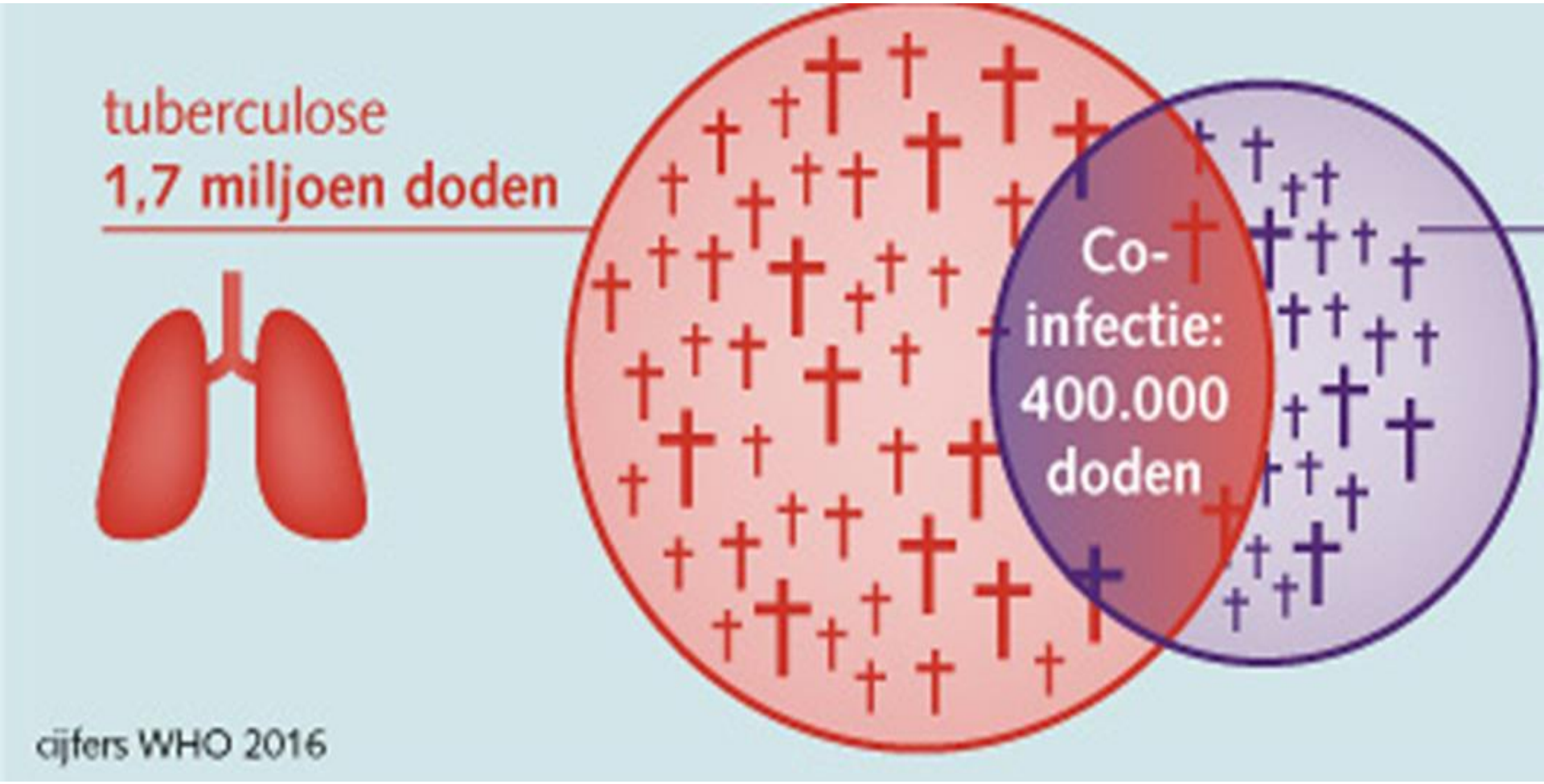
test	WHO year	Time	advantage	limitation
Smear microscopy	ages	Same day	Inexpensive rapid	Lacks sensitivity
Culture (DST)	2007	10-21 days	sensitivity	BSL3 Time needed
Xpert MTB/RIF	2010	Same day	Sensitivity Rif detection	Expensive Dead/live
LAMP	2016	Same day	inexpensive	infrastructure
LPA first-line	2008	1-2 days	Rif/INH resist	Cost-effective
LPA sec-line	2016	1-2 days	Resistance quinol/inject	Cost-effective
LAM urine	2016	Same day	rapid	Sensitivity increasing

Curr Opin HIV aids 2017;12:129
Scand J Immunol 2017;86:76

Tijdlijn nieuwe testen



EMBO mol med 2022;14:e14088


tuberculose
1,7 miljoen doden
Co-infectie: 400.000 doden
cijfers WHO 2016

3. Wat is juist over mortaliteit en HIV/TB co-infectie?

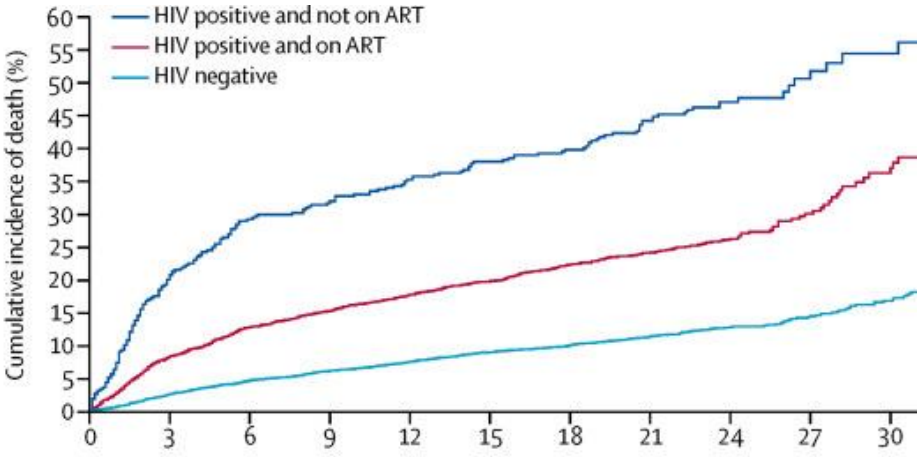
1. Mortaliteit HIV/TB is gelijk aan TB bij gelijke behandeling
2. Mortaliteit HIV/TB is >4x zo hoog als TB bij gelijke behandeling
3. Timing van behandeling is geassocieerd met mortaliteit
4. Weinig over te zeggen nu MDR TB steeds meer voorkomt

Table 3
Factors associated with mortality among Pulmonary TB Patients receiving treatment in Dar es Salaam, Tanzania.

	Unadjusted					Adjusted			
	No of deaths	HR	95% CI		P	HR	95% CI		P
HIV infection and ART use					**<0.001**				**<0.001**
HIV uninfected	17/1182	1.00				1.00			
HIV infected; ART >90 days prior to anti-TB therapy	5/49	7.00	2.58	18.96		8.26	2.89	23.64	
HIV infected; ART 90 days prior to anti-TB and within 14 days of anti-TB therapy initiation	4/39	7.55	2.54	22.44		10.00	3.28	30.54	
HIV infected; ART >14 days post anti-TB therapy initiation	7/141	3.43	1.42	8.26		3.55	1.44	8.73	
HIV infected; No ART at any time during anti-TB therapy	25/285	6.34	3.42	11.74		6.46	3.41	12.24	
Isoniazid or rifampicin resistance					**0.01**				**0.02**
No	21/851	1.00				1.00			
Yes	3/29	4.50	1.34	15.10		4.24	1.24	14.48	
Age (years)					**0.08**				**0.60**
15-29	16/682	1.00				1.00			
30-50	36/868	1.76	0.98	3.17		1.11	0.60	2.06	
>50	6/146	1.74	0.68	4.45		1.29	0.49	3.40	
Sex					**0.95**				**0.20**
Male	39/1138	1.00				1.00			
Female	19/558	0.98	0.57	1.70		1.46	0.82	2.62	
Monthly income (USD)					**0.07**				**0.03**
≥ 100	21/746	1.00				1.00			
<100	28/588	1.70	0.97	3.00		1.91	1.07	3.39	
Illicit substance use					**0.09**				**0.09**
Never	48/1542	1.00				1.00			
Current or past	6/98	2.06	0.88	4.82		2.14	0.90	5.12	

Int J Infect Dis 2017;56:39

Mortaliteit MDR-TB patienten

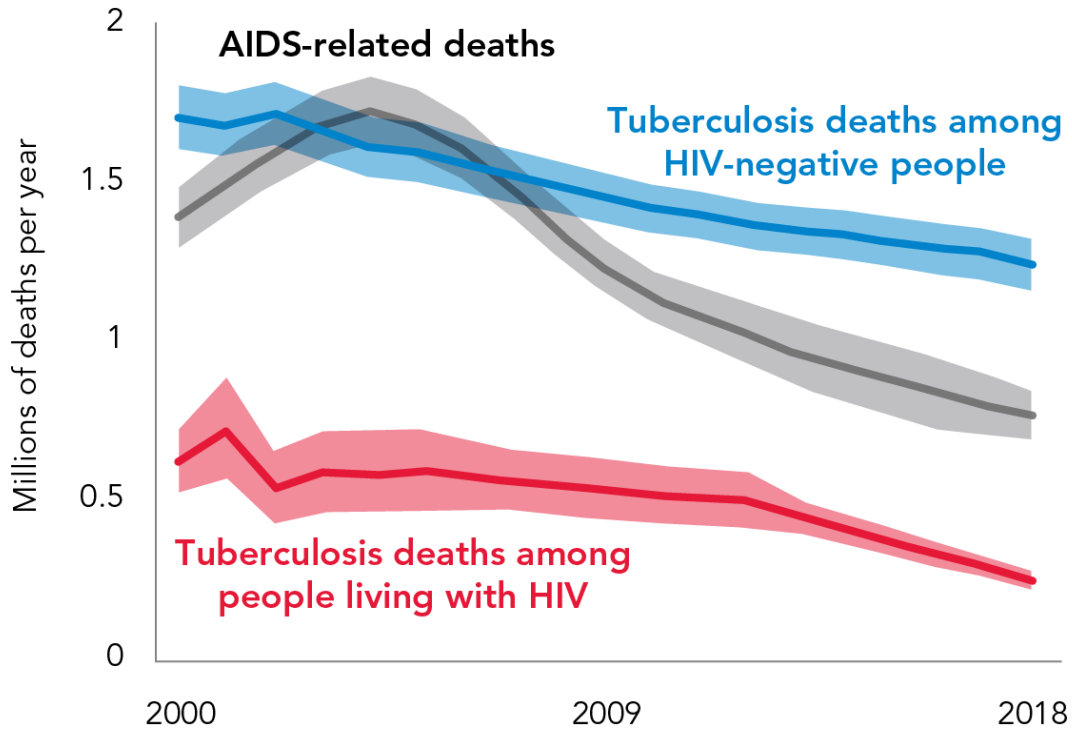


Number at risk											
HIV negative	5584	5425	5291	5166	5013	4753	4345	2764	1696	578	311
HIV positive and on ART	2445	2218	2098	2022	1942	1859	1672	1093	536	143	66
HIV positive and not on ART	403	314	277	266	250	236	215	164	95	33	17

Lancet 2020;396:402

Global trends in the estimated number of deaths caused by TB and AIDS, 2000–2018

Shaded areas represent uncertainty intervals



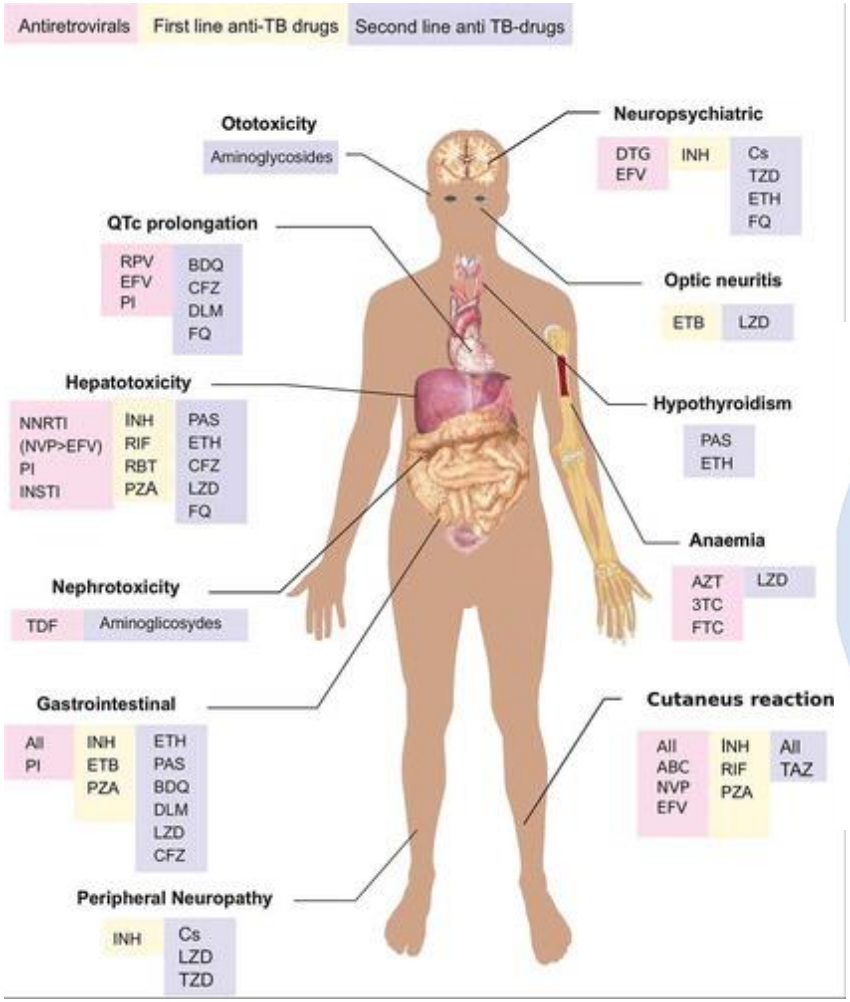
For AIDS, the latest estimates of the number of deaths in 2018 that have been published by UNAIDS are available at http://www.unaids.org/en/. For TB, the estimates for 2018 are those published in the Global Tuberculosis Report 2019. Deaths from TB among people living with HIV are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

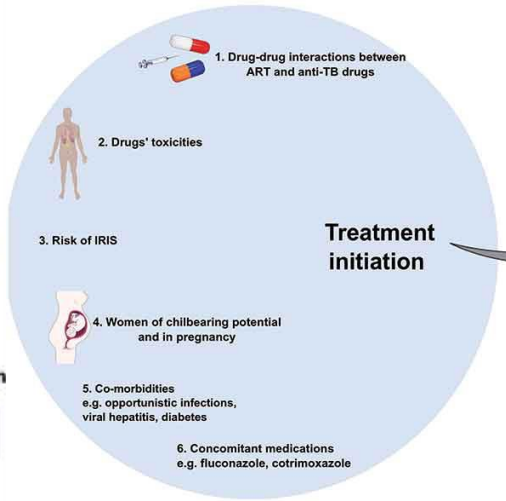
Source: Global tuberculosis report 2019. Geneva: World Health Organization, 2019.

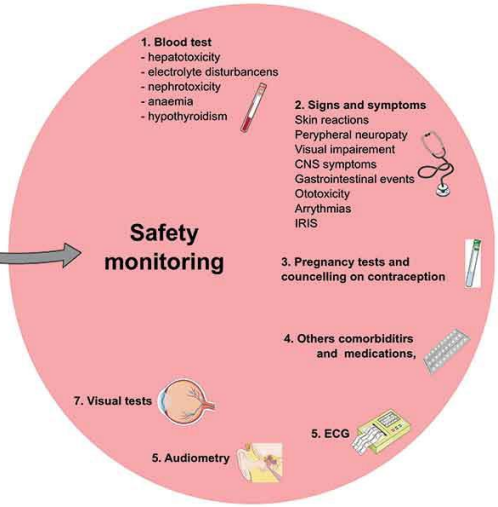
4. Welke behandeling start u?

1. INH/rifampicine/ethambutol/pyrazinamide
2. INH/rifabutine/ethambutol/pyrazinamide
3. INH/moxifloxacine/ethambutol
4. nog geen TB-statica, eerst switch naar triumeq

Safety of TB and HIV drugs

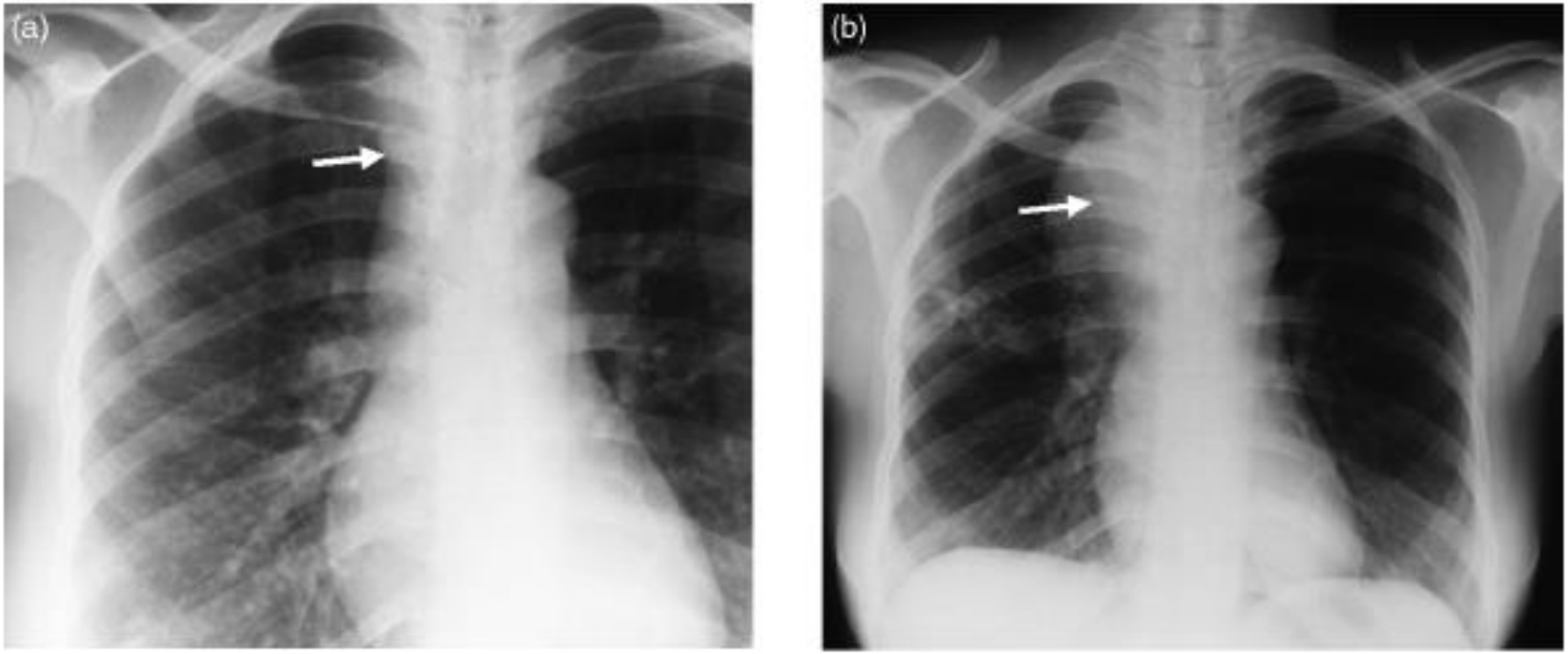






Exp Opinion Drug Safety 2020;19:23-41

stridor na 2 maanden HAART en TB-statica



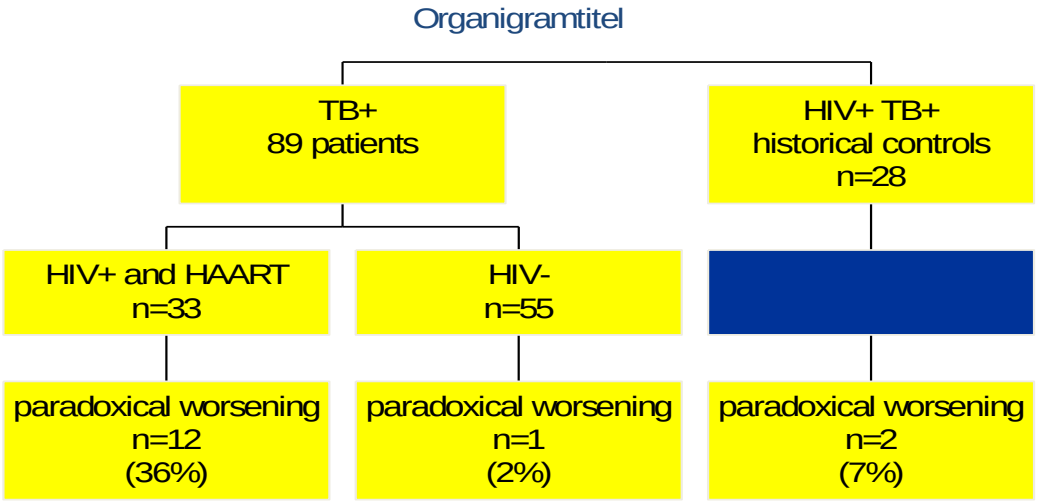
Clin Radiol 2004;59:505

5. Wat is uw volgende stap?

1. RIVM bellen waar resistentie *M.tub* blijft
2. toevoegen moxifloxacine
3. start prednison
4. bespreek therapietrouw nogmaals goed

IRIS TB en HIV

- Phenomenon occurring in TB after start antituberculous therapy
- immunosuppressive effect of uncontrolled infection
- HAART increases paradoxical worsening at least 5x
- Defer HAART (2-8 wks)
- Role for prednisone use?



Narita et al., AJRCCM 26;1008

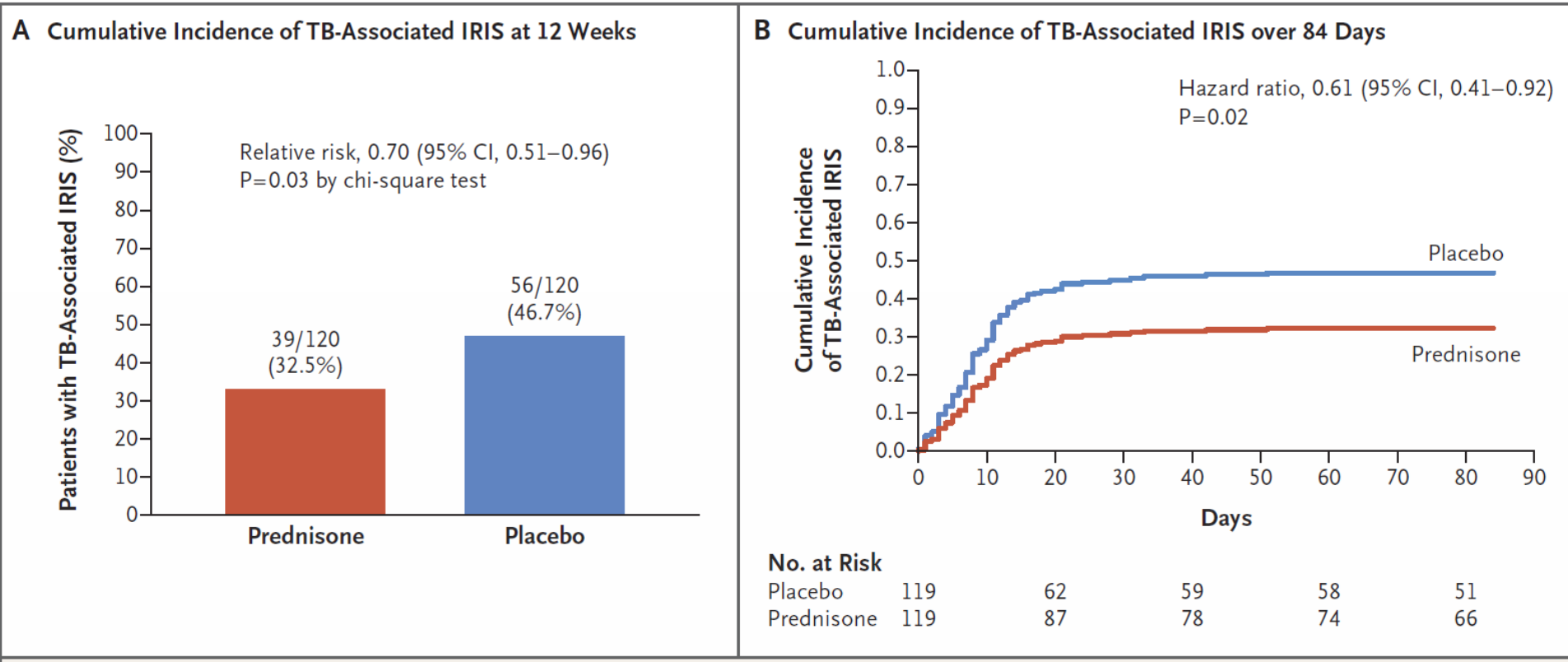


Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).

NEJM 2018;379:1915

Behandeling IRIS in Nederland richtlijn

- Bij optreden van een IRIS dienen ART en tuberculostatica in principe te worden gecontinueerd. Therapie van eerste keus bij IRIS is corticosteroïden; start, dosering en duur dienen individueel bepaald te worden, afhankelijk van klinische verschijnselen en eventuele contra-indicaties. De gebruikelijke startdosering corticosteroïden is 1.5 mg/kg prednison per dag. Bij patiënten met een hoog risico op IRIS (CD4
- Bij patiënten met een hoog risico op IRIS (CD4 <100/mm^3, uitgebreide of extrapulmonale tuberculose en hoge HIV-RNA load) kan preventieve behandeling met 30-50 mg prednison worden overwogen.
- Bij ernstige IRIS, of bij twijfel over de diagnose van IRIS of over indicatiestelling, dosering, duur en effect van profylactische of therapeutische corticosteroïden wordt geadviseerd te overleggen met landelijke expertisecentra.

6. Patiënt met onbehandelde HIV en TB: wanneer start u cART?

1. gelijktijdig met TB-statica
2. na intensieve fase TB-statica
3. 2 weken na start TB-statica
4. timing afhankelijk van CD4 aantal

When to start ART?

The NEW ENGLAND JOURNAL of MEDICINE

Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew Gray, M.Sc. (Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S. (Epi.), Gonasagrie Nair, M.B., Ch.B., Sheila Bamber, M.B., Ch.B., Aarthi Singh, M.B., Ch.B., Munira Khan, M.B., Ch.B., Jacqueline Pienaar, M.Sc., Wafaa El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

Diane V. Havlir, M.D., Michelle A. Kendall, M.S., Prudence Ive, M.D., Johnstone Kumwenda, M.B., B.S., Susan Swindells, M.B., B.S., Sarojini S. Qasba, M.D., Anne F. Luetkemeyer, M.D., Evelyn Hogg, B.A., James F. Rooney, M.D., Xingye Wu, M.S., Mina C. Hosseinipour, M.D., Umesh Lalloo, M.B., Ch.B., Valdilea G. Veloso, M.D., Fatuma F. Some, M.B., Ch.B., N. Kumarasamy, M.D., Nesri Padayatchi, M.D., Breno R. Santos, M.D., Stewart Reid, M.D., James Hakim, M.B., Ch.B., Lerato Mohapi, M.D., Peter Mugyenyi, M.D., Jorge Sanchez, M.D., Javier R. Lama, M.D., Jean W. Pape, M.D., Alejandro Sanchez, M.D., Aida Asmelash, M.D., Evans Moko, M.B., Ch.B., Fred Sawe, M.B., Ch.B., Janet Andersen, Sc.D., and Ian Sanne, M.D., for the AIDS Clinical Trials Group Study A5221*

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew L. Gray, M.Sc.(Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S.(Epi.), Santhanalakshmi Gengiah, M.A.(Res.Psych.), Anushka Naidoo, M.Med.Sci.(Pharm.), Niraksha Jithoo, M.B., Ch.B., Gonasagrie Nair, M.B., Ch.B., M.P.H., Wafaa M. El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

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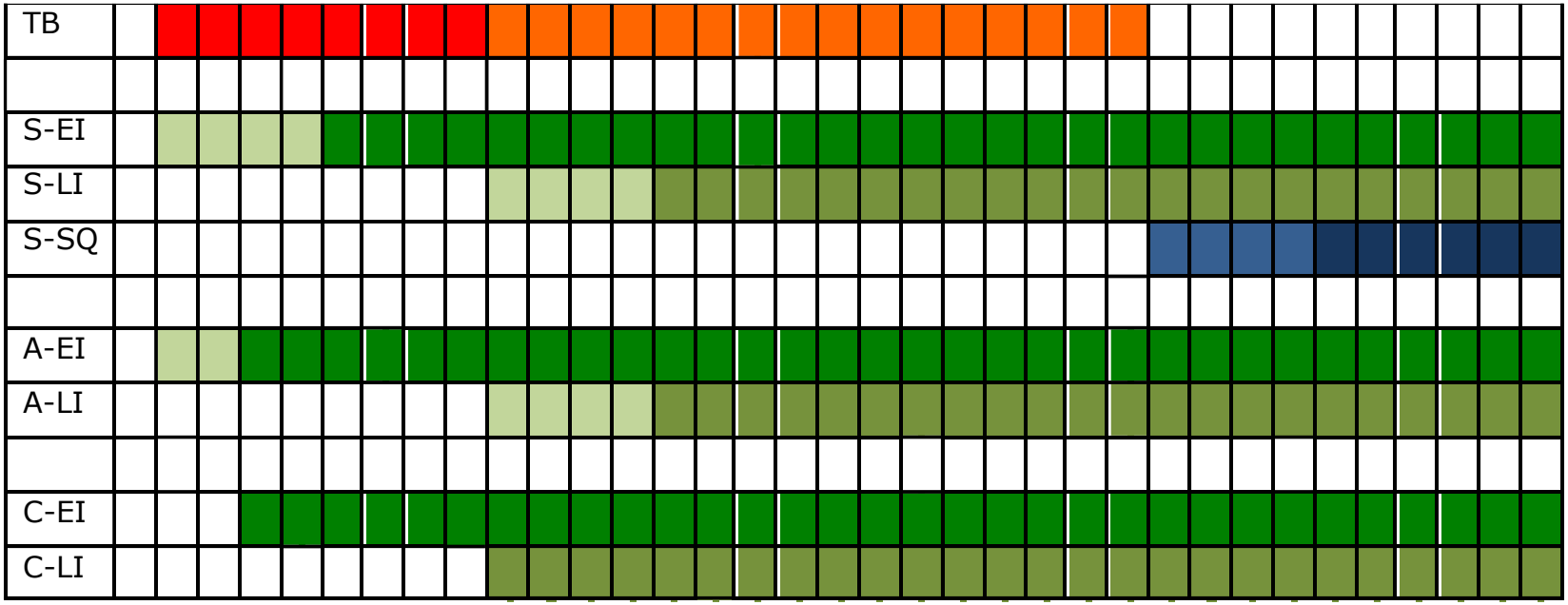
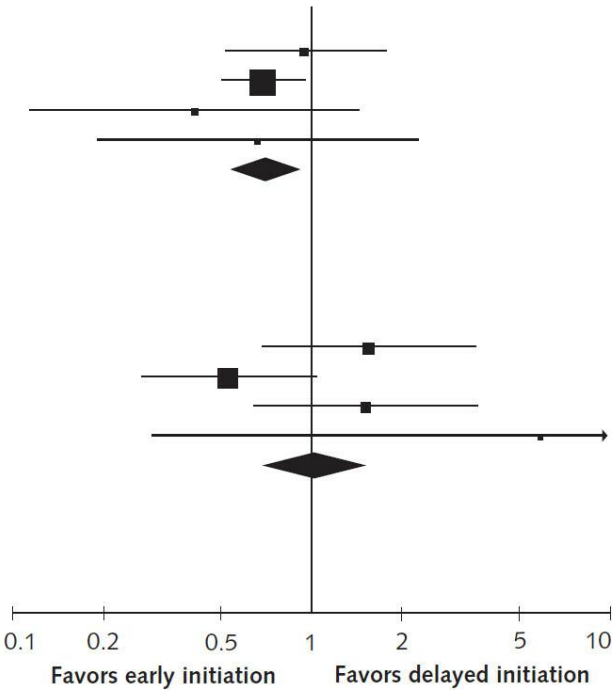
Trial designs



All cause mortality with early vs late start of ART in TB co-infected patients

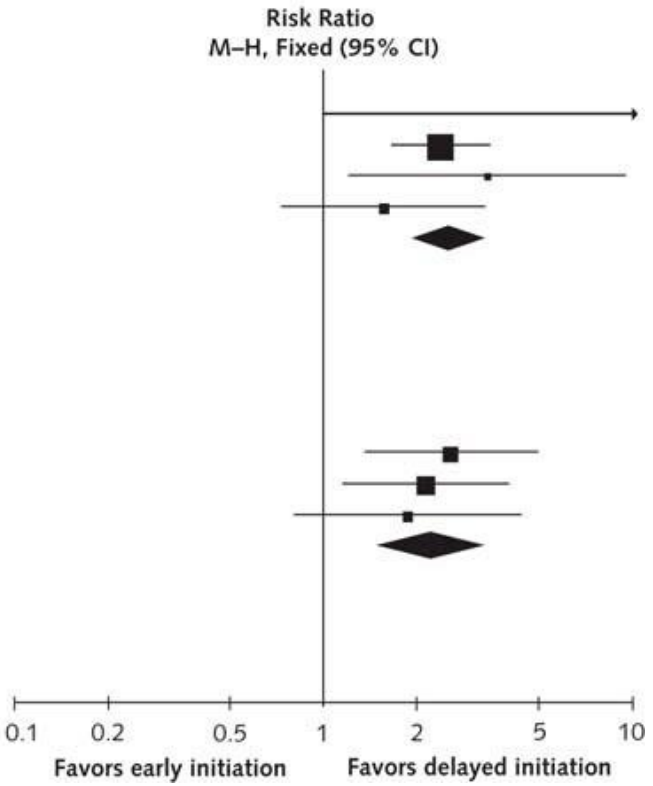
Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
CD4⁺ T-cell counts <0.050 × 10^9 cells/L				
Amogne et al, 2015 (27)	27/111	10/39	15.2	0.95 (0.51–1.78)
Blanc et al, 2011 (25 [CAMELIA])	48/237	70/238	71.8	0.69 (0.50–0.95)
Abdool Karim et al, 2011 (24 [SAPiT])	3/37	7/35	7.4	0.41 (0.11–1.45)
Manosuthi et al, 2012 (28 [TIME])	4/46	5/38	5.6	0.66 (0.19–2.29)
Subtotal	431	350	100.0	0.71 (0.54–0.93)
Total events	82	92		
Heterogeneity: $X^2 = 1.62$ ($P = 0.66$); $I^2 = 0\%$				
Test for overall effect: $Z = 2.52$ ($P = 0.01$)				
CD4⁺ T-cell counts >0.050 × 10^9 cells/L				
Amogne et al, 2015 (27)	20/212	7/116	23.9	1.56 (0.68–3.59)
Blanc et al, 2011 (25 [CAMELIA])	11/95	20/91	53.9	0.53 (0.27–1.04)
Abdool Karim et al, 2011 (24 [SAPiT])	12/177	8/180	20.9	1.53 (0.64–3.64)
Manosuthi et al, 2012 (28 [TIME])	2/33	0/39	1.2	5.88 (0.29–118.36)
Subtotal	517	426	100.0	1.05 (0.68–1.61)
Total events	45	35		
Heterogeneity: $X^2 = 6.84$ ($P = 0.08$); $I^2 = 56\%$				
Test for overall effect: $Z = 0.22$ ($P = 0.83$)				
Test for subgroup differences: $X^2 = 2.36$ ($P = 0.12$); $I^2 = 57.7\%$				



Annal Int Med 2015;163:32

TB IRIS with early vs late start of ART in TB co-infected patients

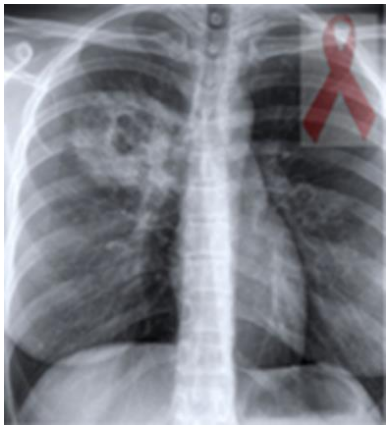
Study, Year (Reference)	Events/Total, *n/N* Early ART	Delayed ART	Weight, %	Risk Ratio M–H, Fixed (95% CI)
CD4⁺ T-cell counts <0.050 × 10^9 cells/L				
Amogne et al, 2015 (27)	22/111	0/39	1.5	16.07 (1.00–258.82)
Blanc et al, 2011 (25 [CAMELIA])	81/237	34/234	71.5	2.35 (1.65–3.36)
Abdool Karim et al, 2011 (24 [SAPiT])	14/37	4/35	8.6	3.31 (1.21–9.10)
Manosuthi et al, 2012 (28 [TIME])	15/46	8/38	18.3	1.55 (0.74–3.26)
Subtotal	431	346	100.0	2.50 (1.84–3.40)
Total events	132	46		
Heterogeneity: $X^2 = 3.72$ ($P = 0.29$); $I^2 = 19\%$				
Test for overall effect: $Z = 5.83$ ($P = 0.001$)				
CD4⁺ T-cell counts >0.050 × 10^9 cells/L				
Amogne et al, 2015 (27)	0/212	0/116	–	Not estimable
Blanc et al, 2011 (25 [CAMELIA])	29/95	11/91	35.6	2.53 (1.34–4.75)
Abdool Karim et al, 2011 (24 [SAPiT])	29/177	14/180	44.0	2.11 (1.15–3.85)
Manosuthi et al, 2012 (28 [TIME])	11/33	7/39	20.3	1.86 (0.81–4.24)
Subtotal	517	426	100.0	2.21 (1.50–3.24)
Total events	69	32		
Heterogeneity: $X^2 = 0.36$ ($P = 0.83$); $I^2 = 0\%$				
Test for overall effect: $Z = 4.01$ ($P = 0.001$)				
Test for subgroup differences: $X^2 = 0.25$ ($P = 0.62$); $I^2 = 0\%$				



Annal Int Med 2015;163:32

Keuze van ART tijdens de TBC-behandeling (richtlijn)

- Eerste keus ART bij gebruik van rifampicine: dolutegravir (of raltegravir als alternatieve integraseremmer) gecombineerd met 2 nucleoside/nucleotide analogen (lamivudine, abacavir, tenofovir); tenofovir alafenamide (TAF).

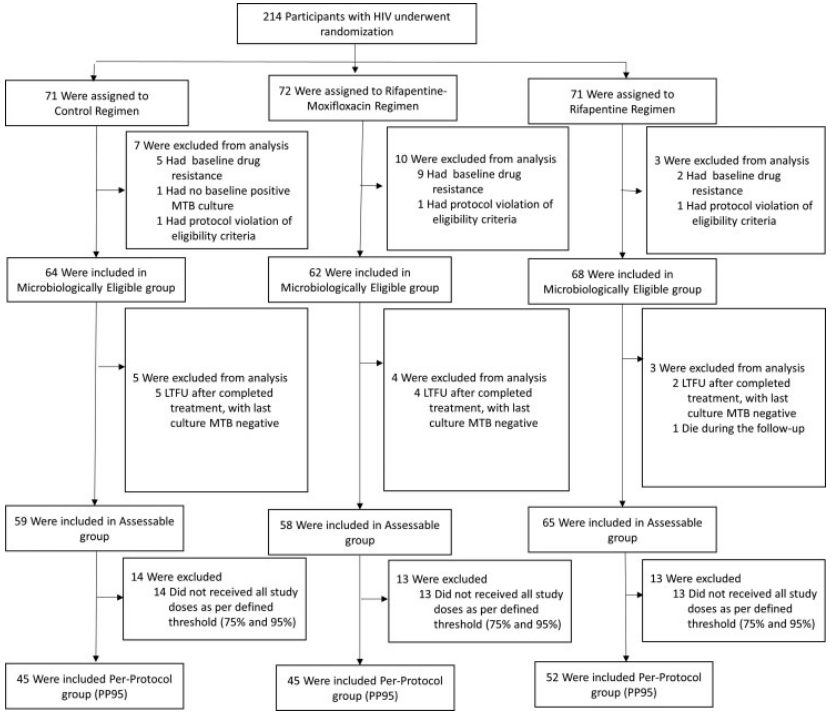


- Dosering bij gebruik van rifampicine nan niet nucleoside analogon:
  - dolutegravir2 maal daags 50 mg;
  - raltegravir: 2 maal 800 mg.
  - alternatieve keuze ART efavirenz in een standaarddosering

- Monitoring van HIV-behandeling
  - éénmalig een dalspiegel dolutegravir/raltegravir/efavirenz, ten minste 1 week na start van rifampicine. Plasma Hiv-RNA dient bij aanvang en ten minste éénmalig tijdens de tbc-behandeling te worden gecontroleerd.

Keuze van de TBC-behandeling (richtlijn)

- Eerste keus: 2HRZE/4HR
  - 3 maanden langer bij cavernes of sputum+ na 2 maanden
- 4 maanden rifapentin, moxifloxacine, INH en pyrazinamide, niet inferieur
- Monitoring van TB-behandeling
  - Spiegels na 2 weken.



CID 2023;76:e580

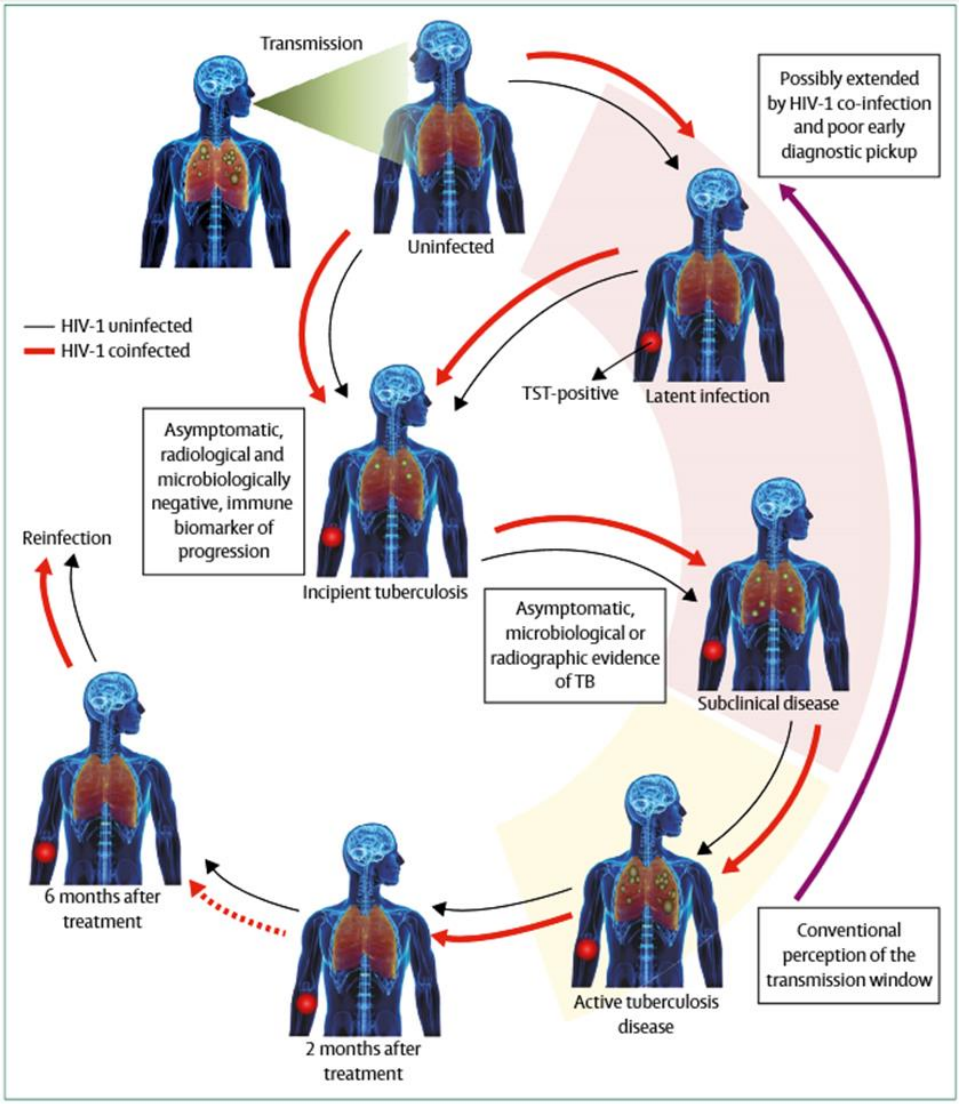
Tuberculosis and HIV

There is a problem !

- HIV- and TB infection:
  5-10% disease (lifetime)

- HIV+ and TB infection:
  5-8% disease (annually)
  >30% disease (lifetime)

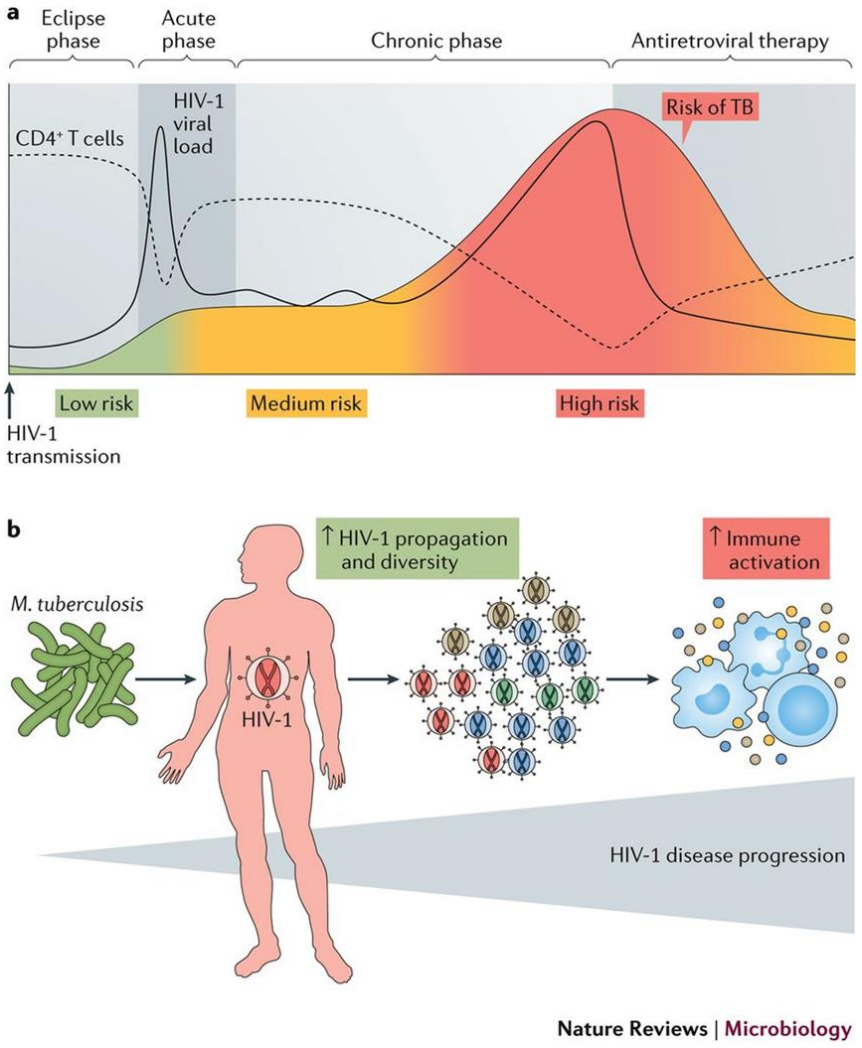
Transmissie TB en HIV



Lancet 2018; dec. 13; Peters et al.

Prevention

- TB patients
  - Test for HIV
  - Treat HIV
- HIV patients
  - Test for latent TB
  - Preventive therapy



Scenario's: antwoord ja =1 of nee=2

1. Liberische man, 36 jaar, 3 maanden in Nederland, CD4: 360x10E6/L
Testen op latente TB?

2. Liberische man, 36 jaar, 3 maanden in Nederland, CD4: 90x10E6/L
Testen op latente TB?

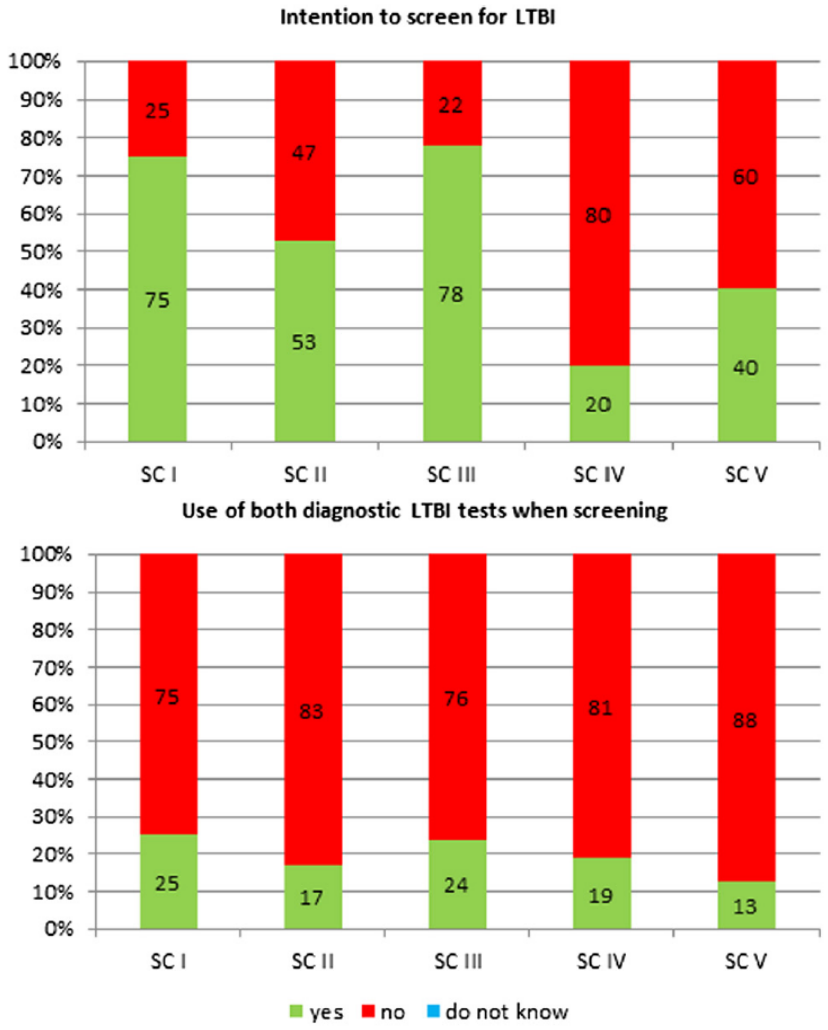
3. Nederlandse MSM, 26 jaar, CD4: 20x10E6/L
Testen op latente TB

Vraag 7,8,9

Results

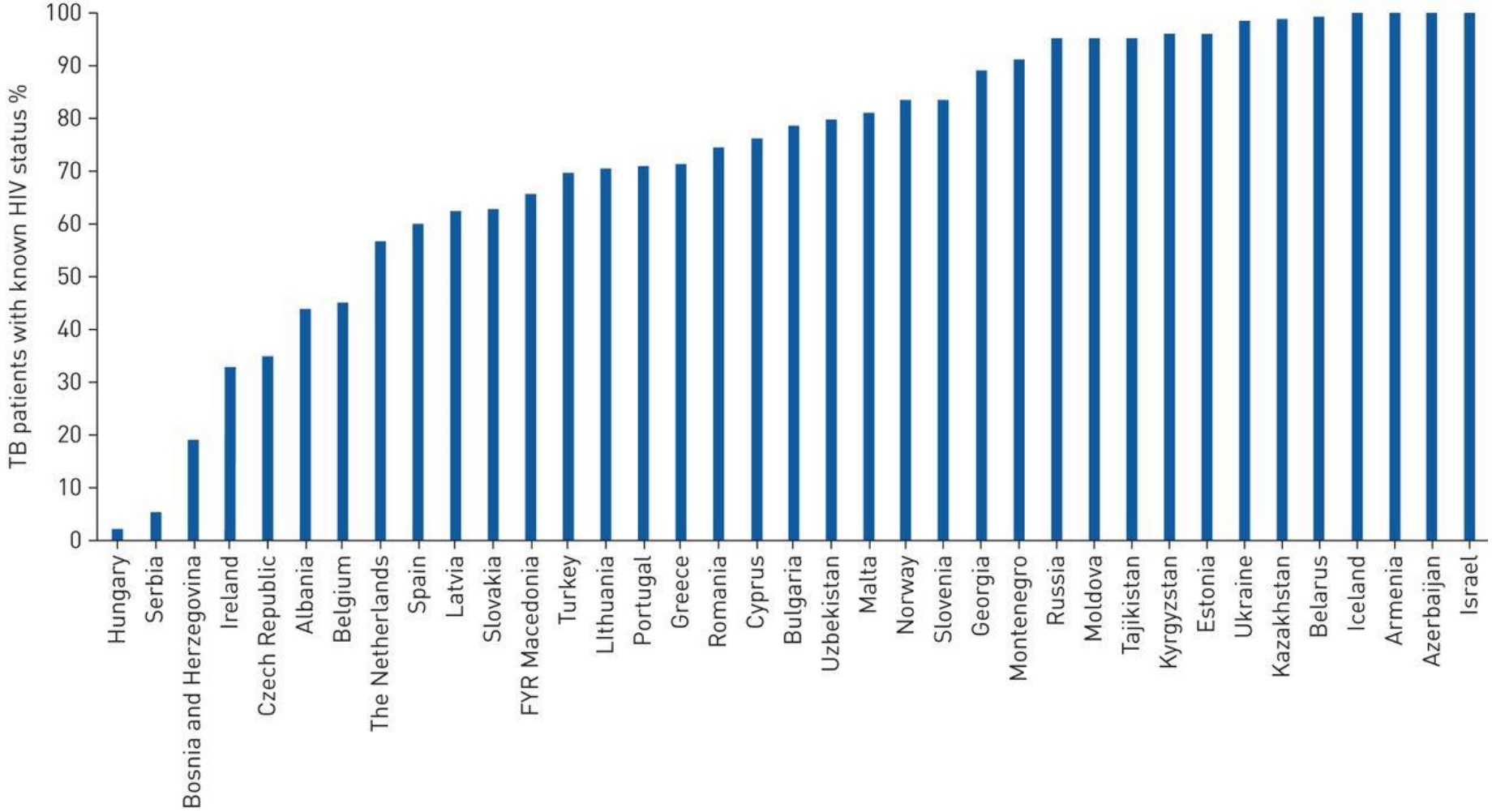
Table 1 Description of screening (SC) and treatment (TC) scenarios

Screening scenario	
SC I	Liberian man, 36 years, 3 months in The Netherlands, CD4 count 360/mm^3
SC II	Liberian man, 36 years, 3 months in The Netherlands, CD4 count 90/mm^3
SC III	Dutch woman, 42 years, intravenous drug use, CD4 count 450/mm^3
SC IV	Dutch homosexual man, 26 years, CD4 count 20/mm^3
SC V	Dutch heterosexual woman, 32 years, CD4 count 200/mm^3



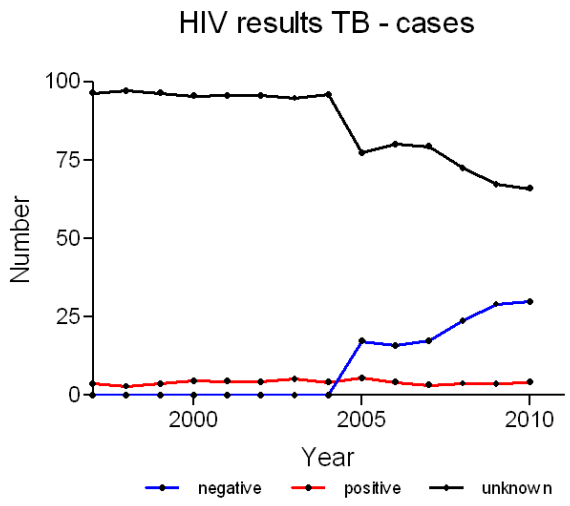
Evenblij *et al. BMC Public Health* (2016) 16:915
DOI 10.1186/s12889-016-3539-2

TB patients with know HIV status



Eur Respir J 2017;50:1701758

HIV testing in TB: Netherlands



Vanaf 1-1-2018 in SHM

1906 patienten IGRA

184 positief

71 behandeling latente TB

-22 INH rifamp	3m
-39 INH	6-9m
-3 rifamp	4m
-8 non-standard	

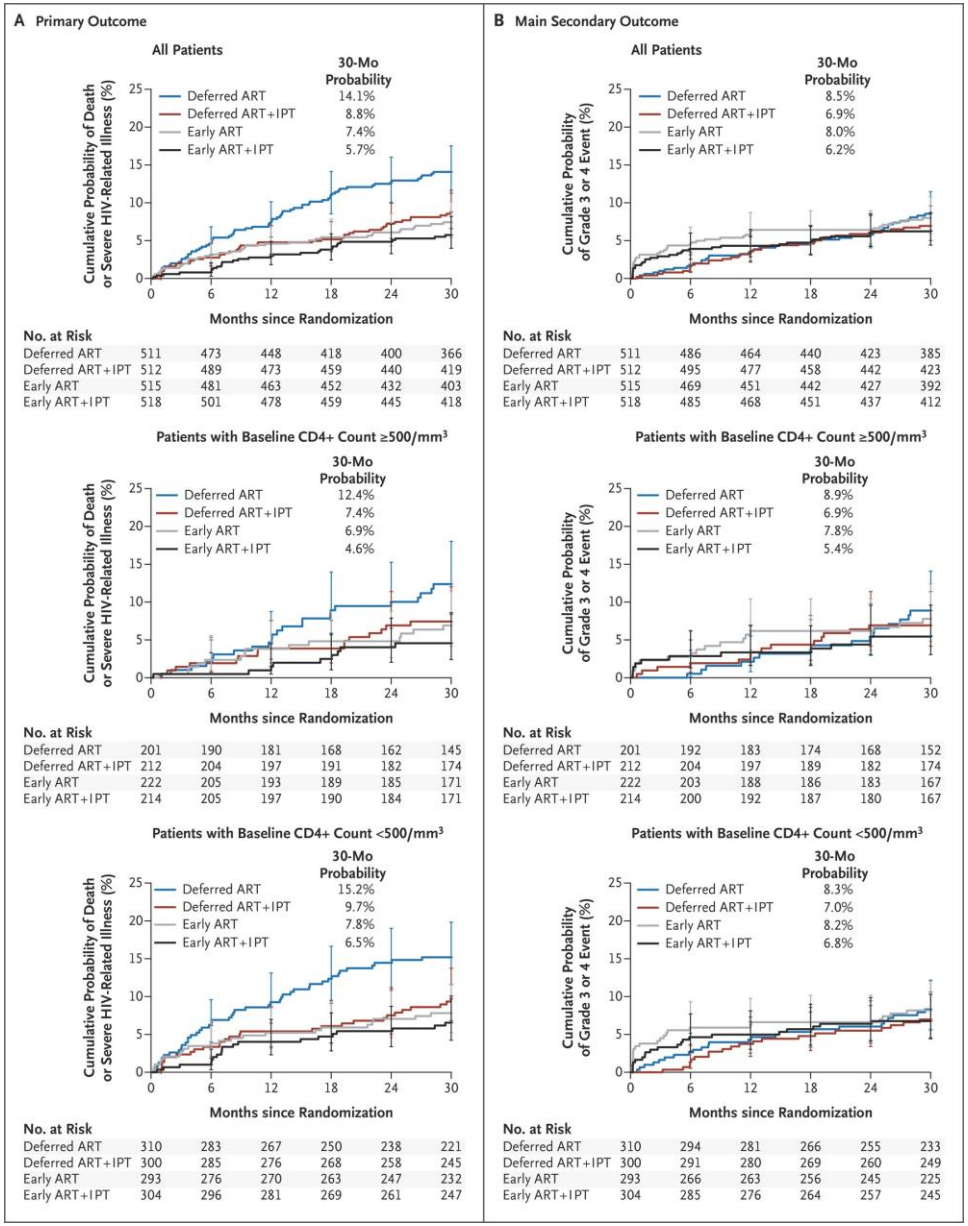
SHM rapport 2023

Behandelt u HIV-patient met positieve Mantoux en/of IGRA

1=ja

2=nee

Nederlandse richtlijnen adviseren sinds 2004 om alle HIV+ patiënten met latente TB te behandelen



Shorter duration preventive therapy?

- 1 month rifapentine plus INH
  versus
- 6 or 9 months daily INH

- Same risk active TB
- Less hepatotoxicity
- Better adherence

- Regimes geven!!

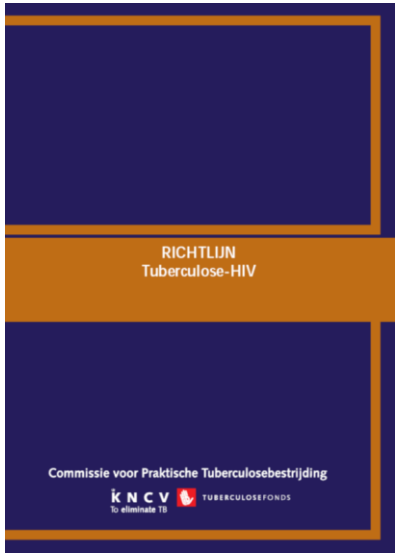
Int J Tuberc Lung Dis 2018;22:1422

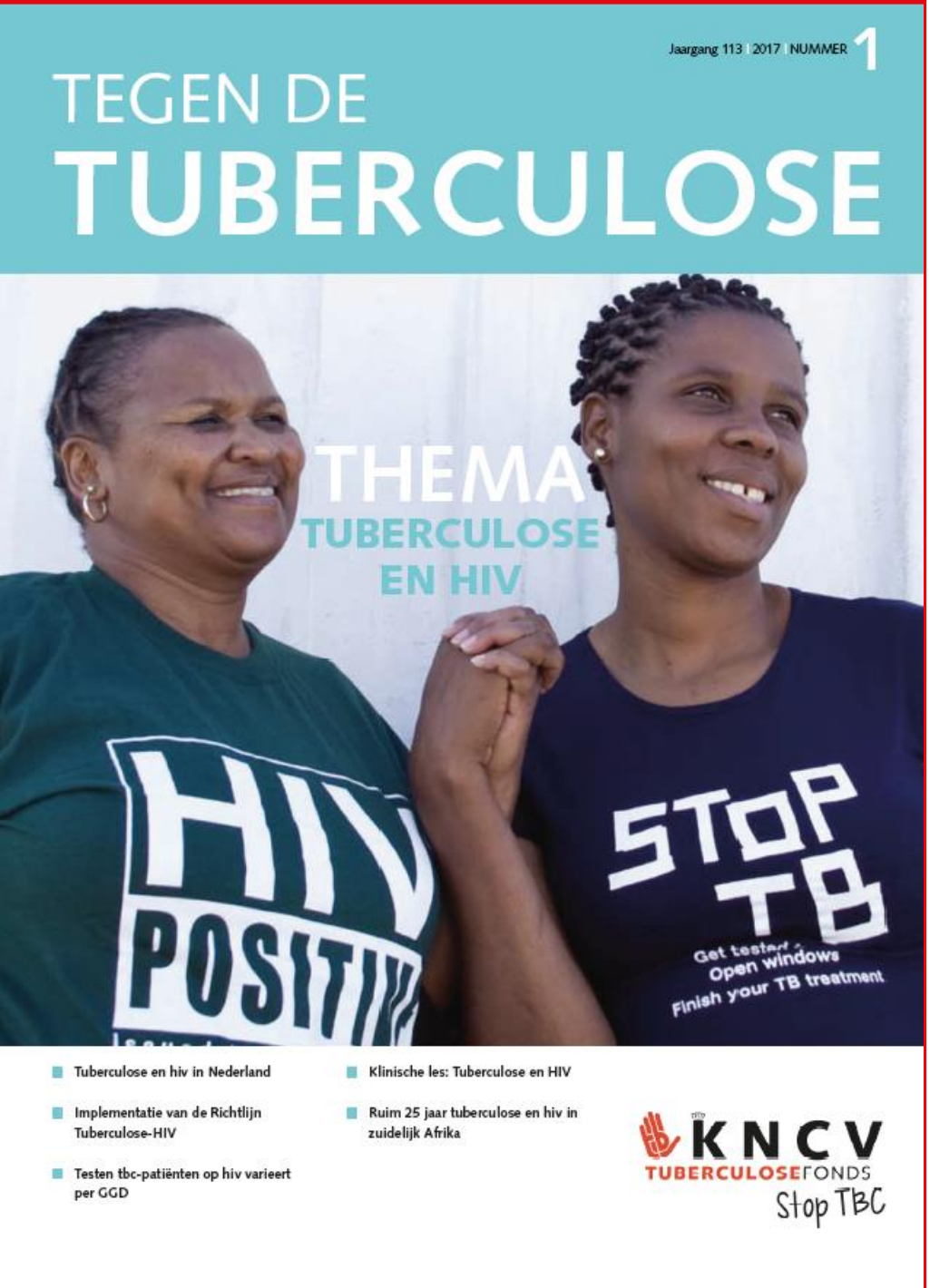
Conclusion

- Low TB risk in high-resource / low TB endemic settings
- But: still much higher than in general population
- Strongly associated with country of origin, CD4 (and VL)

- Poor screening tests for LTBI, especially if CD4 is low
- But: pos. test clearly associated with much higher risk of TB
- And: prophylactic treatment prevents TB

- Behandeling volgens richtlijn, let op
  - Tijdstip start ART
  - Drug-drug interacties
  - TB-IRIS





Thank you for listening!