Clinical case - opportunistic infections in HIV disease

Ole Kirk
Centre of Excellence for Health, Immunity and Infections &
Department of Infectious Diseases
Rigshospitalet
University of Copenhagen & University of Southern Denmark
Copenhagen, Denmark

29-09-2024

Fight Infections Foundation

FLS SCIENCE

Conflict of interests

- Honorarium for the case presentation today

- Unrestricted research grant from Gilead
- Honoraria for lectures from Gilead, Merck and Viiv
- Support for travelling and conference participation from Gilead, Merck and Viiv

- No ad boards since 2019, earlier ad boards with Gilead, Janssen, Merck and Viiv

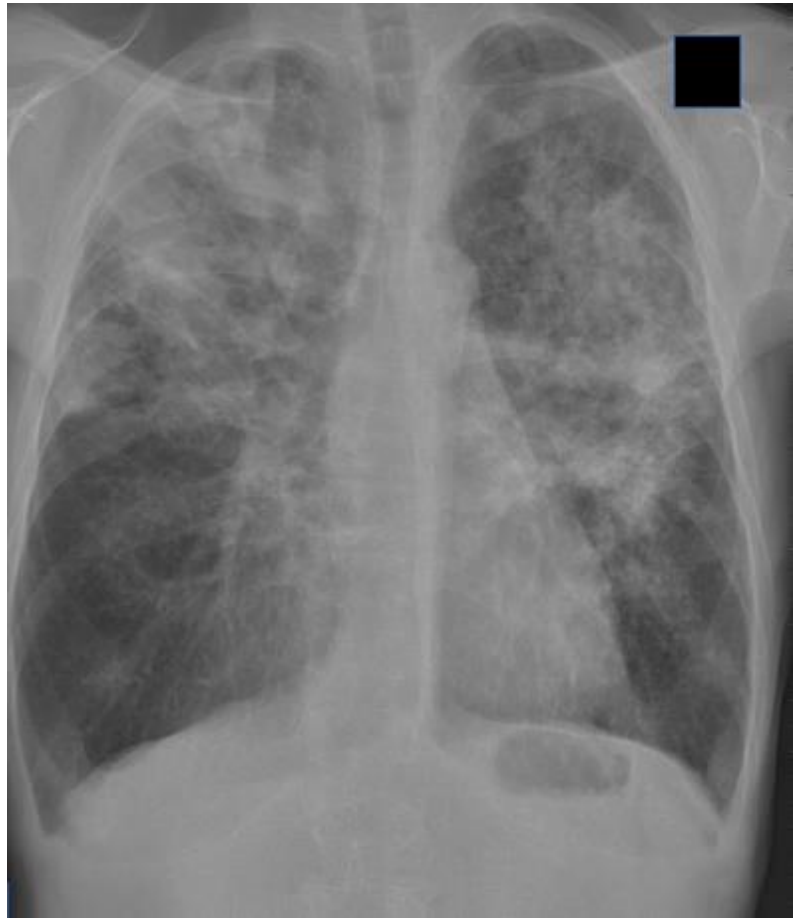
Case

- 35 years old woman from South East Africa presents with persistent dry cough and shortness of breath, slowly worsening over several weeks
- Weight loss of 3 kg
- No fever, but night sweat, but also warm period (Denmark!)

- Biochemistry:
  - anaemia, no leucocytosis, but lymphocytopenia, thrombocytopenia, elevated CRP
  - HIV-test….

Case

- 35 years old woman from South East Africa presents with persistent dry cough and shortness of breath, slowing worsening over several weeks
- Weight loss of 3 kg
- No fever, but night sweat, but also warm period (Denmark!)



- Biochemistry:
  - anaemia, no leucocytosis, lymphocytopenia, thrombocytopenia, elevated CRP
  - HIV-test….
- Chest X-ray

Differential diagnoses?

Differential diagnoses

- COVID-19…..
- *Pneumocystis jirovecii* pneumonia
- Pulmonary tuberculosis
- Bacterial pneumonia
- Atypical pneumonia
- Malignant disease
- Interstitial lung disease

- Other opportunistic infection:
  - Cryptococcal pneumonia
  - Talaromycosis
  - Pulmonary MAC?
  - Candida pneumonia?
  - CMV pneumonitis?

Differential diagnoses

- **COVID-19…..**
- ***Pneumocystis jirovecii* pneumonia**
- **Pulmonary tuberculosis**
- Bacterial pneumonia
- Atypical pneumonia
- **Malignant disease**
- Interstitial lung disease

- Other opportunistic infection:
  - Cryptococcal pneumonia
  - Talaromycosis (Asia)
  - Pulmonary MAC?
  - Candida pneumonia?
  - CMV pneumonitis?

Differential diagnoses

- COVID-19…..
- *Pneumocystis jirovecii*
- Pulmonary tub
- Bacterial pn
- Atypical pneu
- Malignant disea
- Interstitial lung di

Negative PCR for SARS-CoV-2
Negative PCR for *Pneumocystis jirovecii*
Negative culture for bacteria
Negative plasma-cryptococcal antigene
IGRA/Quantiferon indeterminate
Positive PCR for *m. tuberculosis*
(microscopy negative, culture ongoing)
CD4 count 23 cells/mm^3
HIV-1-RNA 364,000 copies/mL

opportunistic infection:
tococcal pneumonia
mycosis
ary MAC?
neumonia?
monitis?

Tuberculosis

TB the leading cause of morbidity and mortality among PWH

Risk of reactivation of latent *M. tuberculosis* infection (LTBI) in untreated HIV infection is 3-16%/year - life-time risk of 5% among HIV-negative with LTBI

Unlike most other OIs, TB can i) transmit from person to person, ii) occur at a wide CD4 spectrum, and iii) ART and TB preventive treatment independently reduce the risk of TB disease

Clinical presentation:

- Pulmonary: can be subclinical. Classical symptoms: cough, fever, night sweats, and weight loss (high sensitivity for diagnosing TB, but low specificity)
- At CD4 counts >200 cells/mm^3, HIV-related TB generally resembles TB among persons without HIV

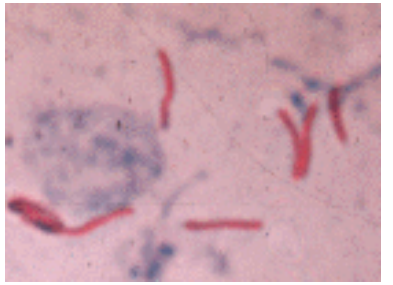
Paraclinical findings:

- At CD4 counts <200 cells/mm^3, infiltrates show no predilection for the upper lobes, cavitation is uncommon

Tuberculosis

Diagnosis:

- LTBI:
  - Tuberculin Skin Test (TST) and interferon gamma release assays (IGRA – high specificity, lower sensitivity)
  - A negative test does not exclude LTBI or TB disease, and a positive test does not in itself mean LTBI therapy is warranted
- TB disease:
  - Microscopy, PCR and culture
  - Sputum smear-negative TB common among PWH, particularly at low CD4 counts and non-cavitary disease
  - The Xpert MTB/RIF (MTB/XDR) assay detects both *M. tuberculosis* and mutations in the *rpoB* gene associated with rifampin resistance
  - Urine Lipoarabinomannan (LAM, *M. tuberculosis* cell wall polysaccharide): low sensitivity - best performance at CD4 counts <100 cells/mm^3 with a sensitivity of 37-56% and specificity of up to 95% [generally not available in Europe]



What to do next?

TB treatment

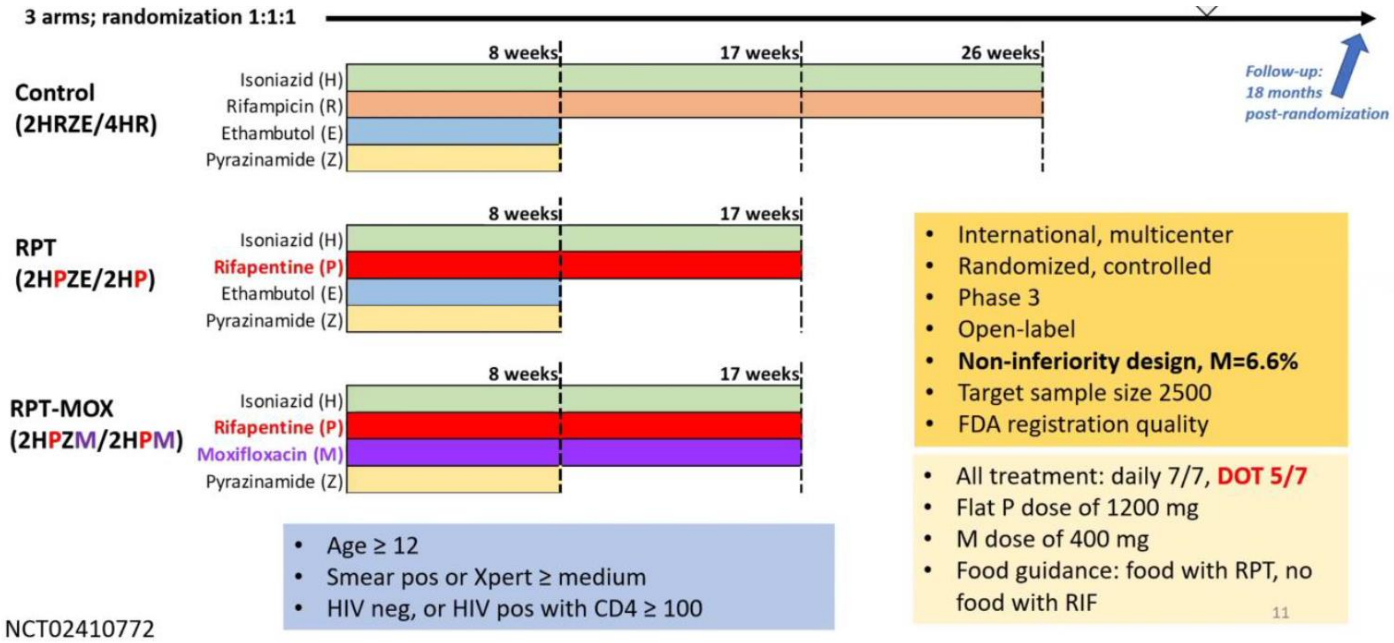
- Guided by drug susceptibility testing (incl. X-pert MTB/RIF)
- Standard therapy for fully susceptible TB:
  - Isoniazid, rifampin, ethambutol, pyrazinamide for 2 months + isoniazid and rifampin for 4 months (2+7/10 months for TB meningitis)
  - Isoniazid, pyrazinamide, moxifloxacin, rifapentine for 2 months + isoniazid, moxifloxacin and rifapentine for additional 2 months
- *Short treatment and monitoring (TRUNCATE):*
  - *Bedaquiline, linezolid, isoniazid, pyrazinamide and ethambutol for 8 weeks*

Dorman NEJM 2021; Paton *NEJM* 2023; Pettit *CID* 2023

Rifapentine With and Without Moxifloxacin for Pulmonary Tuberculosis in People With Human Immunodeficiency Virus (S31/A5349)

April C. Pettit,[1,a] Patrick P. J. Phillips,[2,a] Ekaterina Kurbatova,[3] Andrew Vernon,[3] Payam Nahid,[2] Rodney Dawson,[4] Kelly E. Dooley,[5] Ian Sanne,[6] Ziyaad Waja,[7] Lerato Mohapi,[7] Anthony T. Podany,[8] Wadzanai Samaneka,[9] Rada M. Savic,[2] John L. Johnson,[10,11] Grace Muzanyi,[11] Umesh G. Lalloo,[12] Kia Bryant,[3] Erin Sizemore,[3] Nigel Scott,[3] Susan E. Dorman,[13] Richard E. Chaisson,[5] and Susan Swindells[14]; for the Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 study team

- Open-label phase 3 noninferiority trial
- PWH with CD4 ≥100 cells/µl
- Primary endpoint: TB-disease-free survival 12 mo after randomization
- ART: efavirenz based



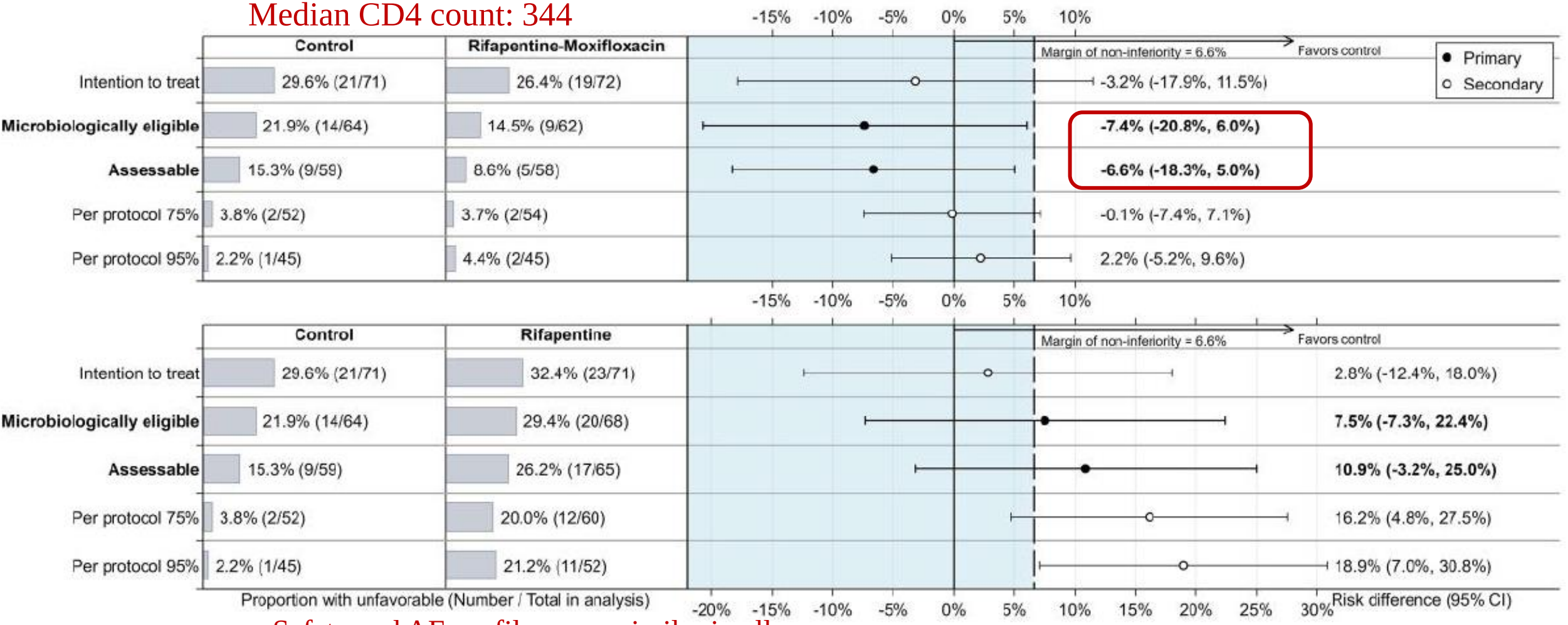
CID 2023:76 (1 February)

Figure 2. Unadjusted differences in unfavorable outcomes in each analysis population among PWH. Figure 2 shows the results of the primary efficacy results in all 4 analysis populations (top, rifapentine–moxifloxacin regimen vs control regimen; bottom, rifapentine regimen vs control regimen). The noninferiority margin of 6.6% is designated by the dashed vertical line.

N=194

Median CD4 count: 344

Suboptimal rifampicin exposure in the control arm?



Safety and AE profiles were similar in all groups

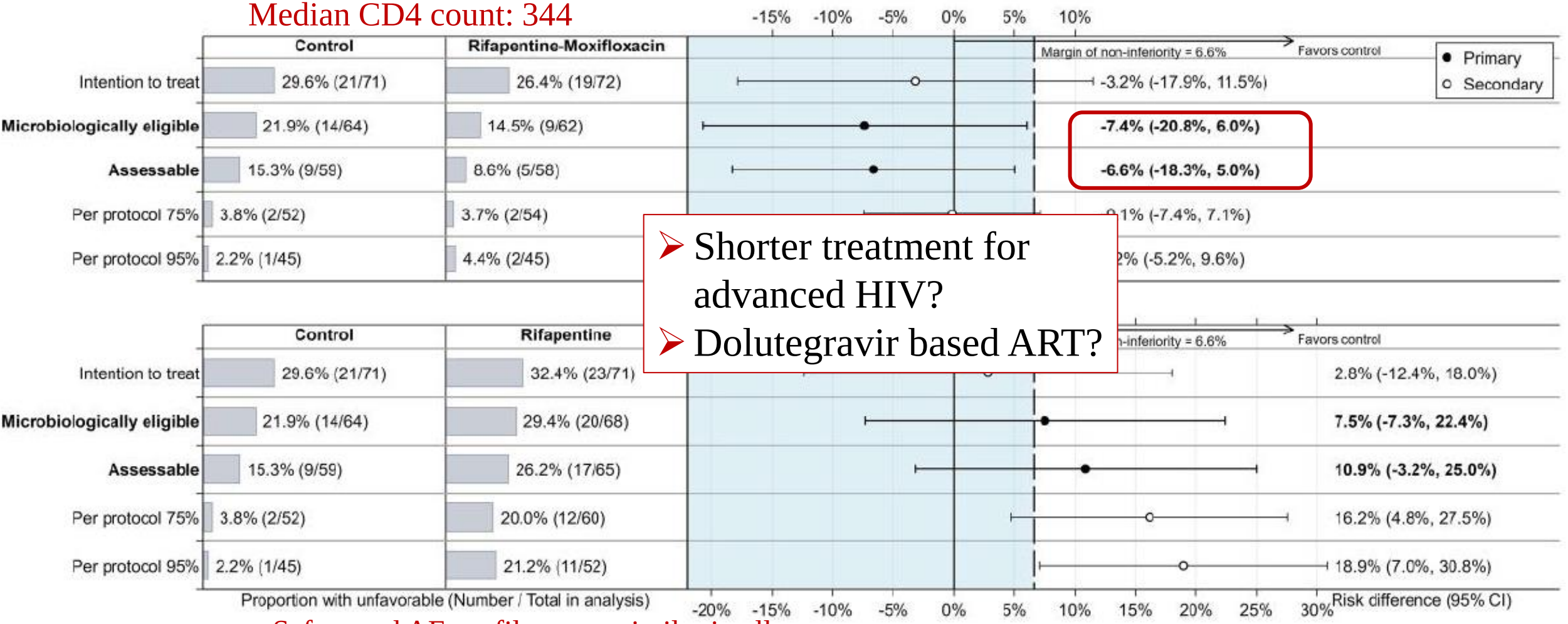
Pettit *CID* 2023

Figure 2. Unadjusted differences in unfavorable outcomes in each analysis population among PWH. Figure 2 shows the results of the primary efficacy results in all 4 analysis populations (top, rifapentine–moxifloxacin regimen vs control regimen; bottom, rifapentine regimen vs control regimen). The noninferiority margin of 6.6% is designated by the dashed vertical line.

N=194

Median CD4 count: 344

Suboptimal rifampicin exposure in the control arm?

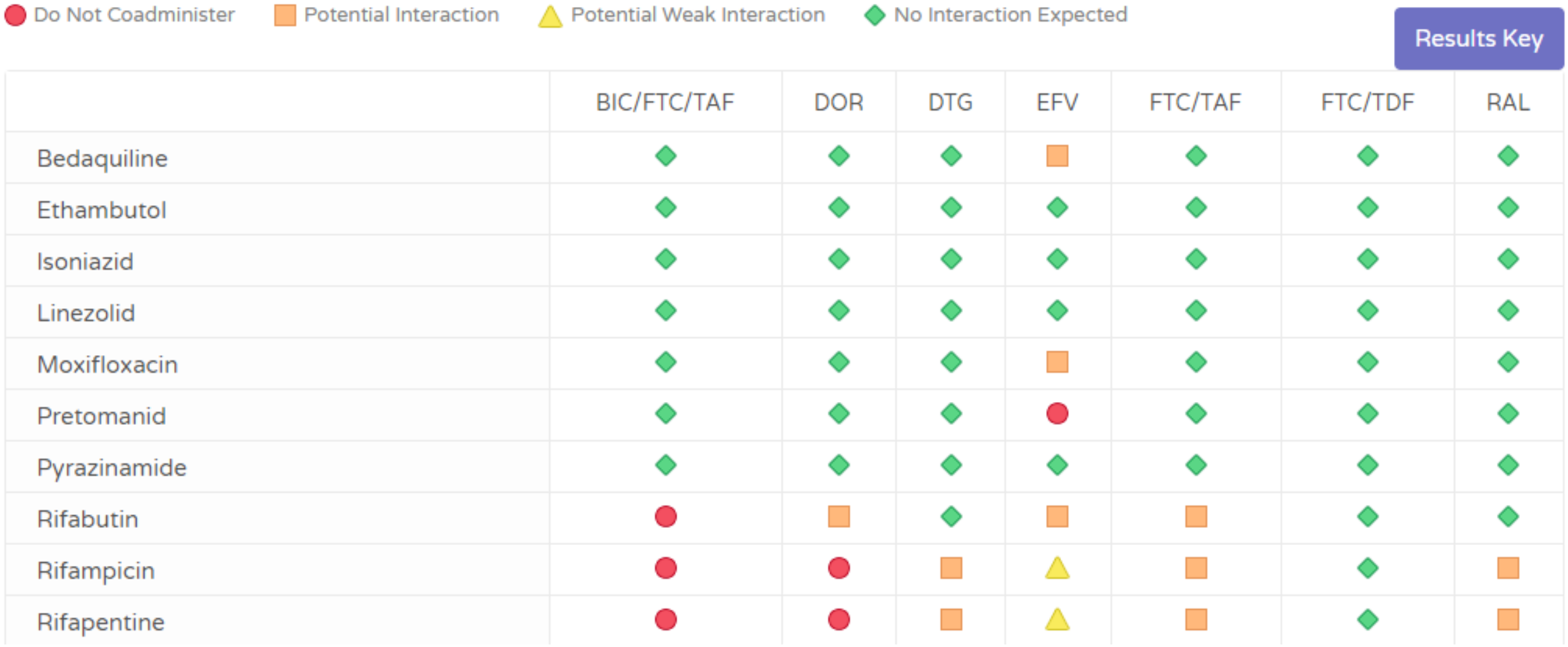


- Shorter treatment for advanced HIV?
- Dolutegravir based ART?

Safety and AE profiles were similar in all groups

Pettit *CID* 2023

HIV treatment



	BIC/FTC/TAF	DOR	DTG	EFV	FTC/TAF	FTC/TDF	RAL
Bedaquiline	◆	◆	◆	■	◆	◆	◆
Ethambutol	◆	◆	◆	◆	◆	◆	◆
Isoniazid	◆	◆	◆	◆	◆	◆	◆
Linezolid	◆	◆	◆	◆	◆	◆	◆
Moxifloxacin	◆	◆	◆	■	◆	◆	◆
Pretomanid	◆	◆	◆	●	◆	◆	◆
Pyrazinamide	◆	◆	◆	◆	◆	◆	◆
Rifabutin	●	■	◆	■	■	◆	◆
Rifampicin	●	●	■	▲	■	◆	■
Rifapentine	●	●	■	▲	■	◆	■

www.hiv-druginteractions.com

HIV treatment

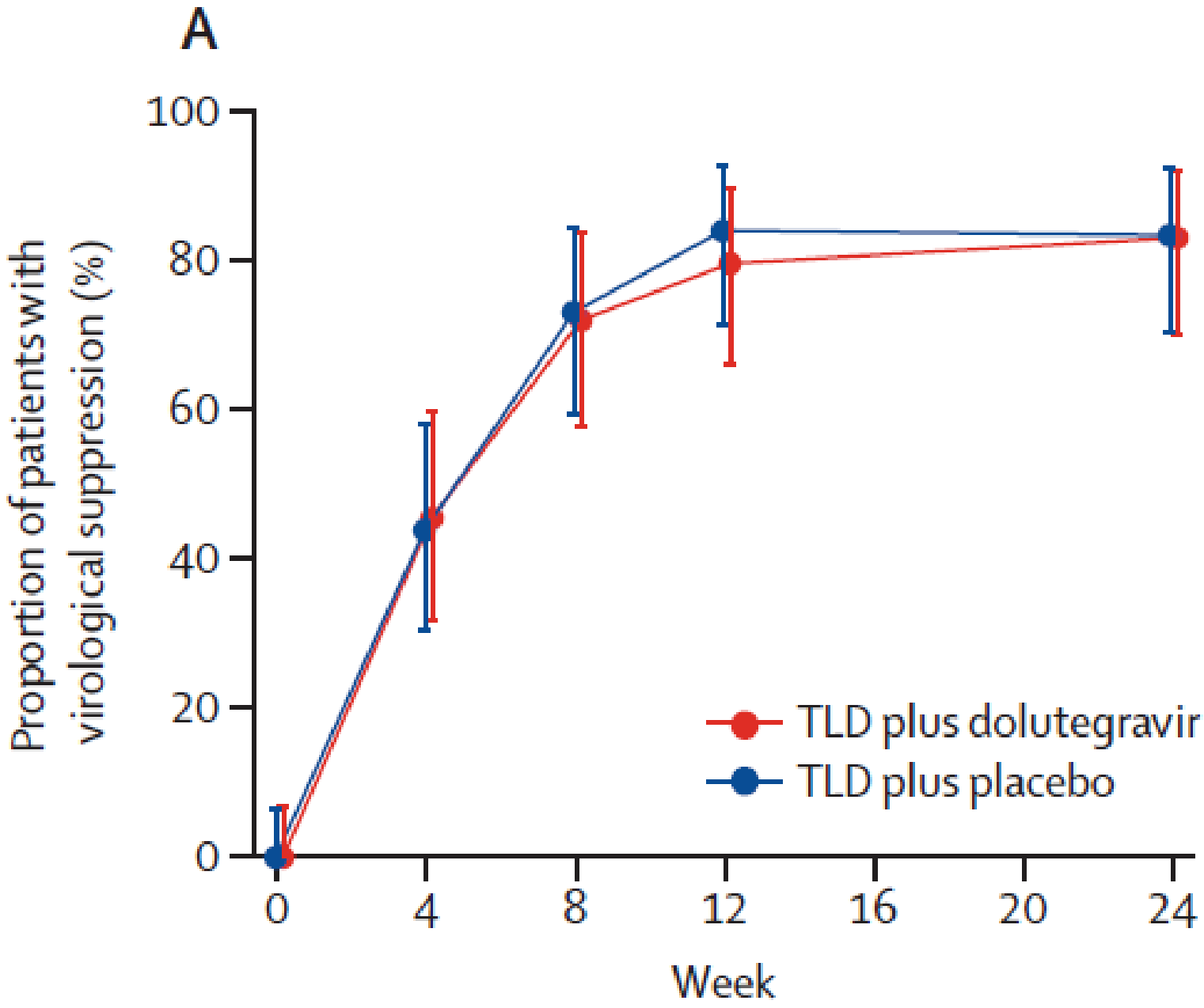
Suggested regimen:

- Dolutegravir 50 mg x 2 (interaction between rifampin and DTG)
- Tenofovir-TDF + lamivudine/emtricitabine x 1

Do not use:

Tenofovir-TAF (interaction between rifampin and TAF)

HIV treatment



No resistance mutations

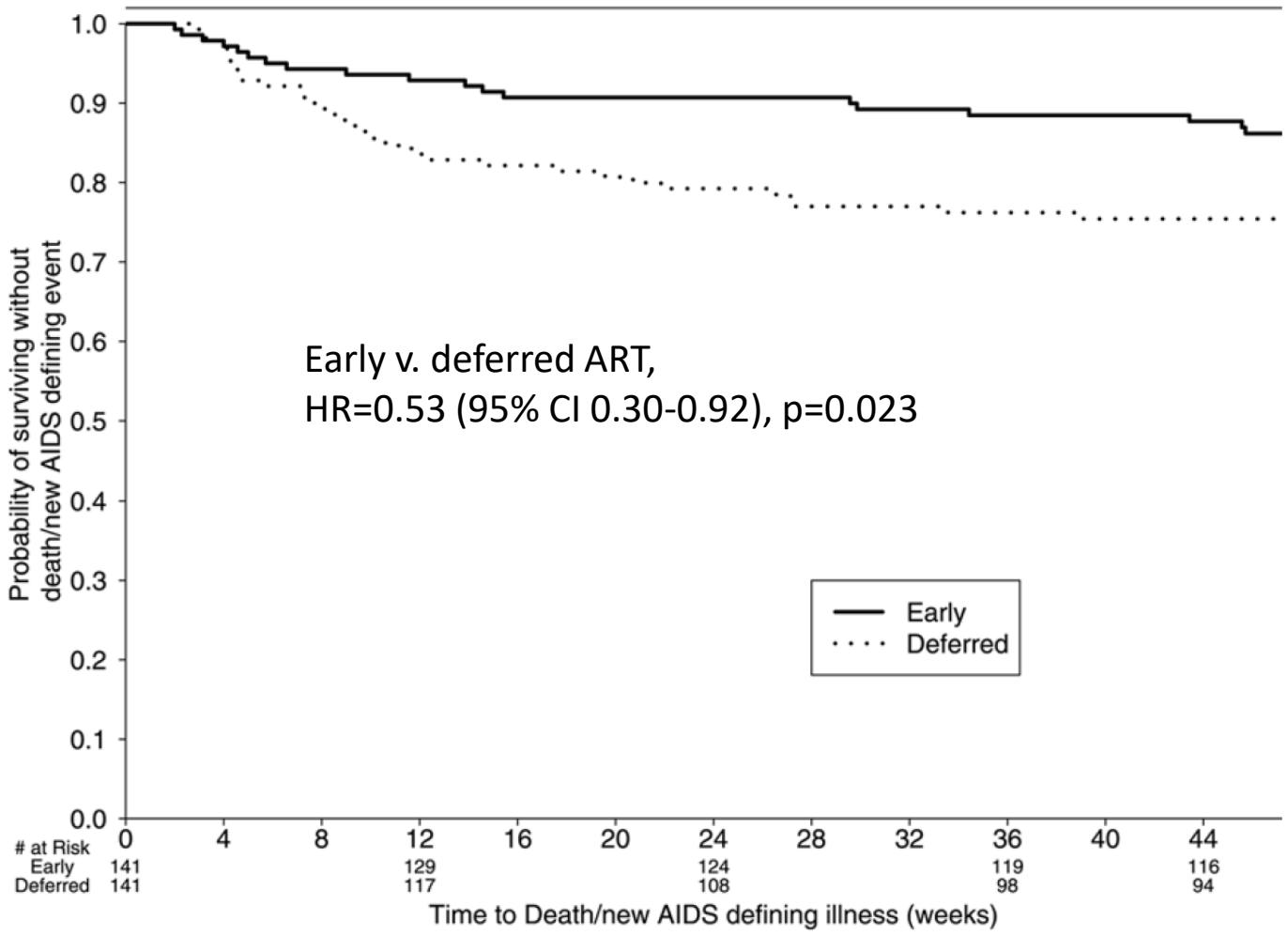
Coadministration decreased dolutegravir AUC, Cmax and Ctrough by 54%, 43% and 72%, respectively by induction of UGT1A1 and CYP3A.

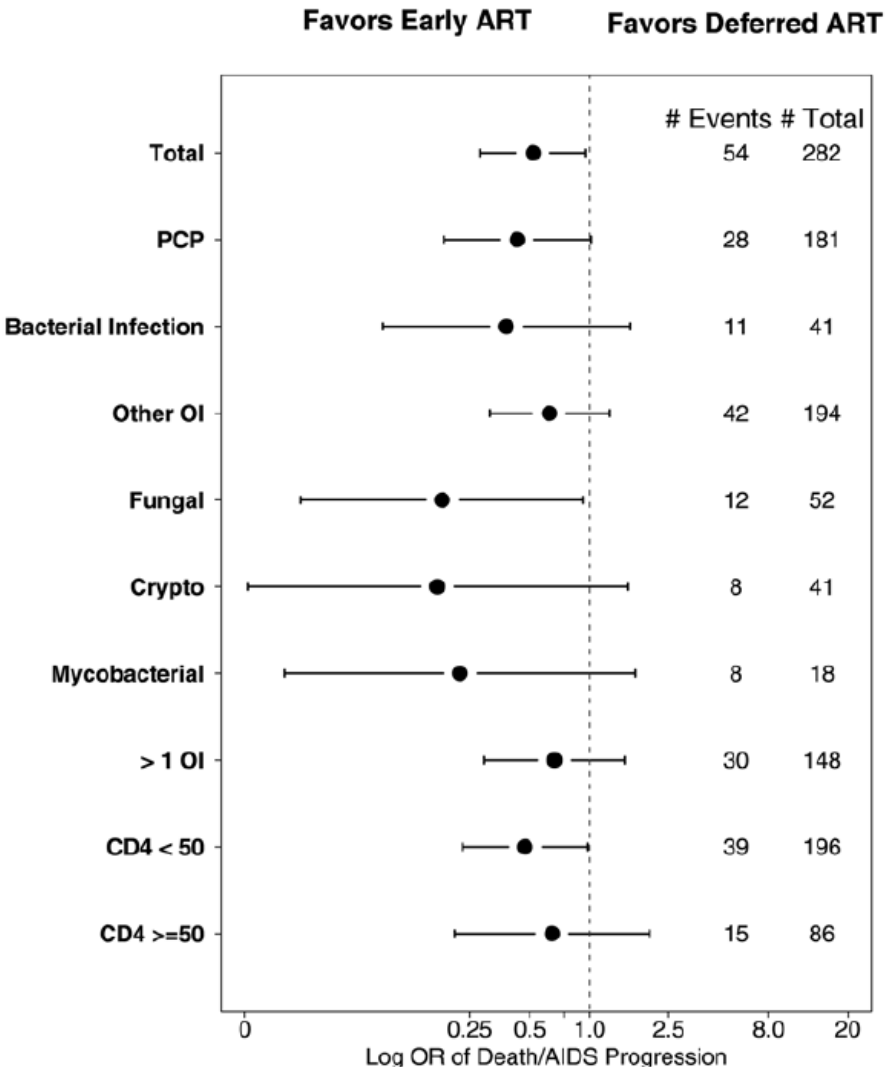
Griesel, Lancet HIV 2023

When to start ART?

- Start ART ASAP if CD4 count <200 cells/mm^3
- Start ART before TB treatment
- Start ART after 8 weeks of TB treatment
- Start ART within the first 2 weeks of TB treatment

When to start ART in PWH with OIs?



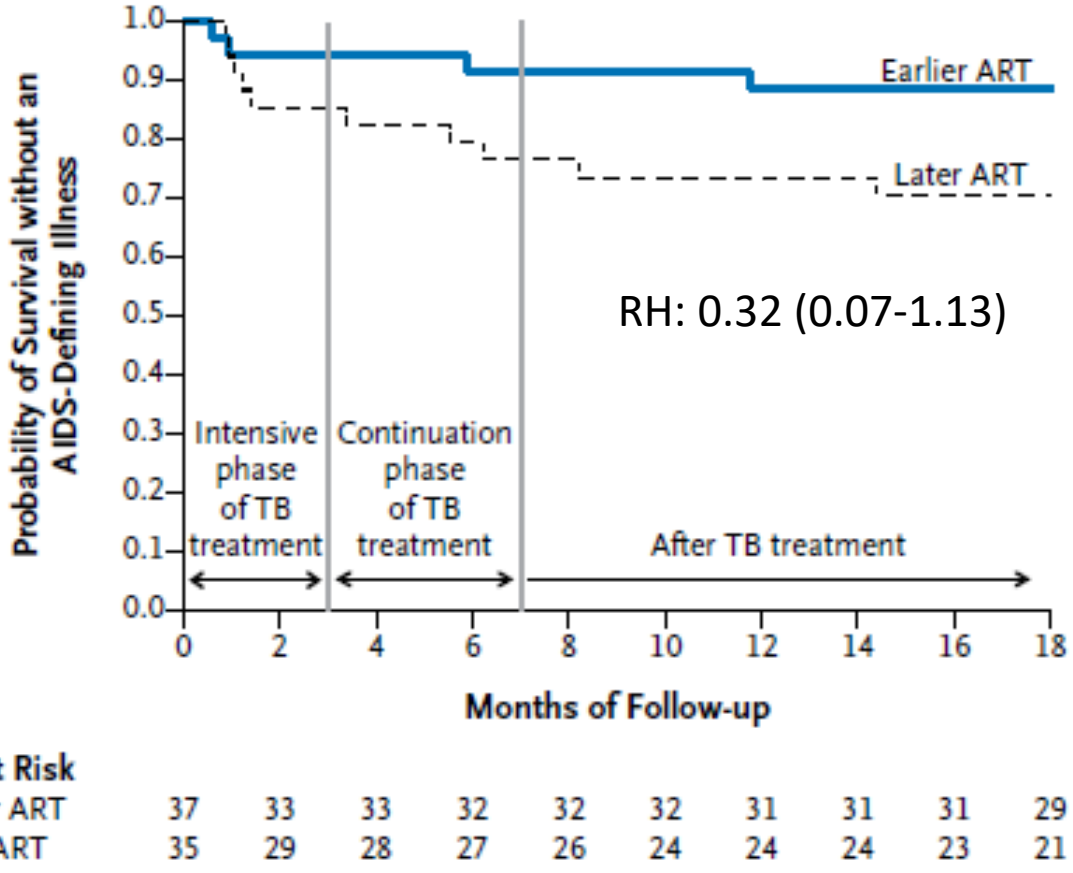


Early ART: within 2 weeks
Deferred ART: after 'acute' OI treatment

Zolopa, *PLoS ONE* 2009

TB and ART

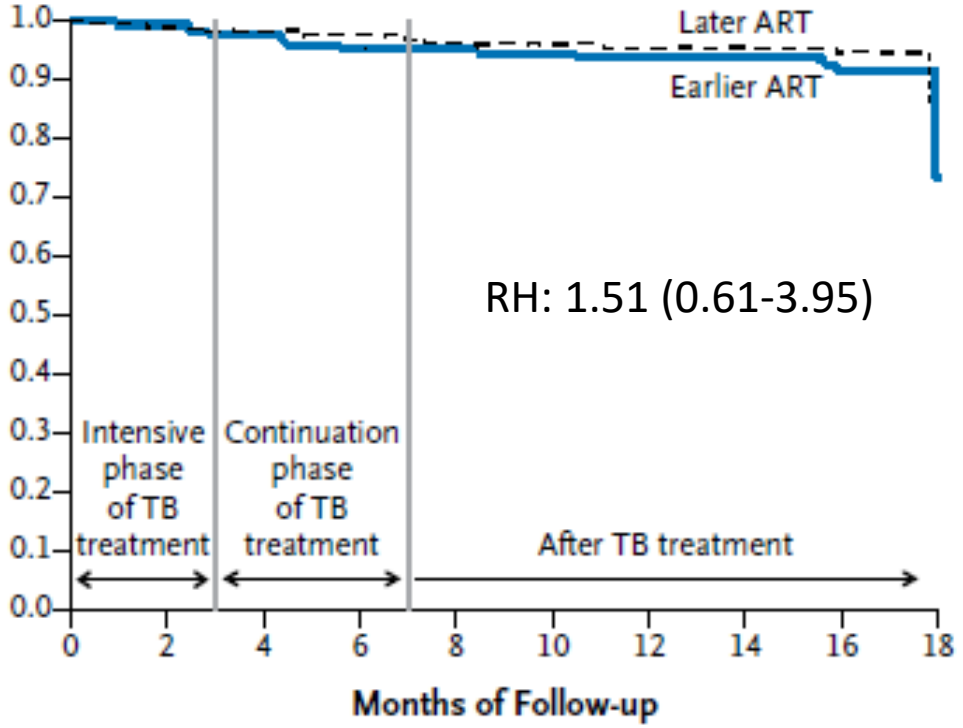
CD4 <50 cells/mm³



RH: 0.32 (0.07-1.13)

No. at Risk										
Earlier ART	37	33	33	32	32	32	31	31	31	29
Later ART	35	29	28	27	26	24	24	24	23	21

CD4 ≥50 cells/mm³



RH: 1.51 (0.61-3.95)

	177	166	159	149	145	140	137	133	125	121
	180	164	153	148	138	134	129	126	124	119

Abdool Karim, *NEJM* 2011; Havlir, *NEJM* 2011; Blanc, *NEJM* 2011; Török, *CID* 2011;

TB meningitis and ART

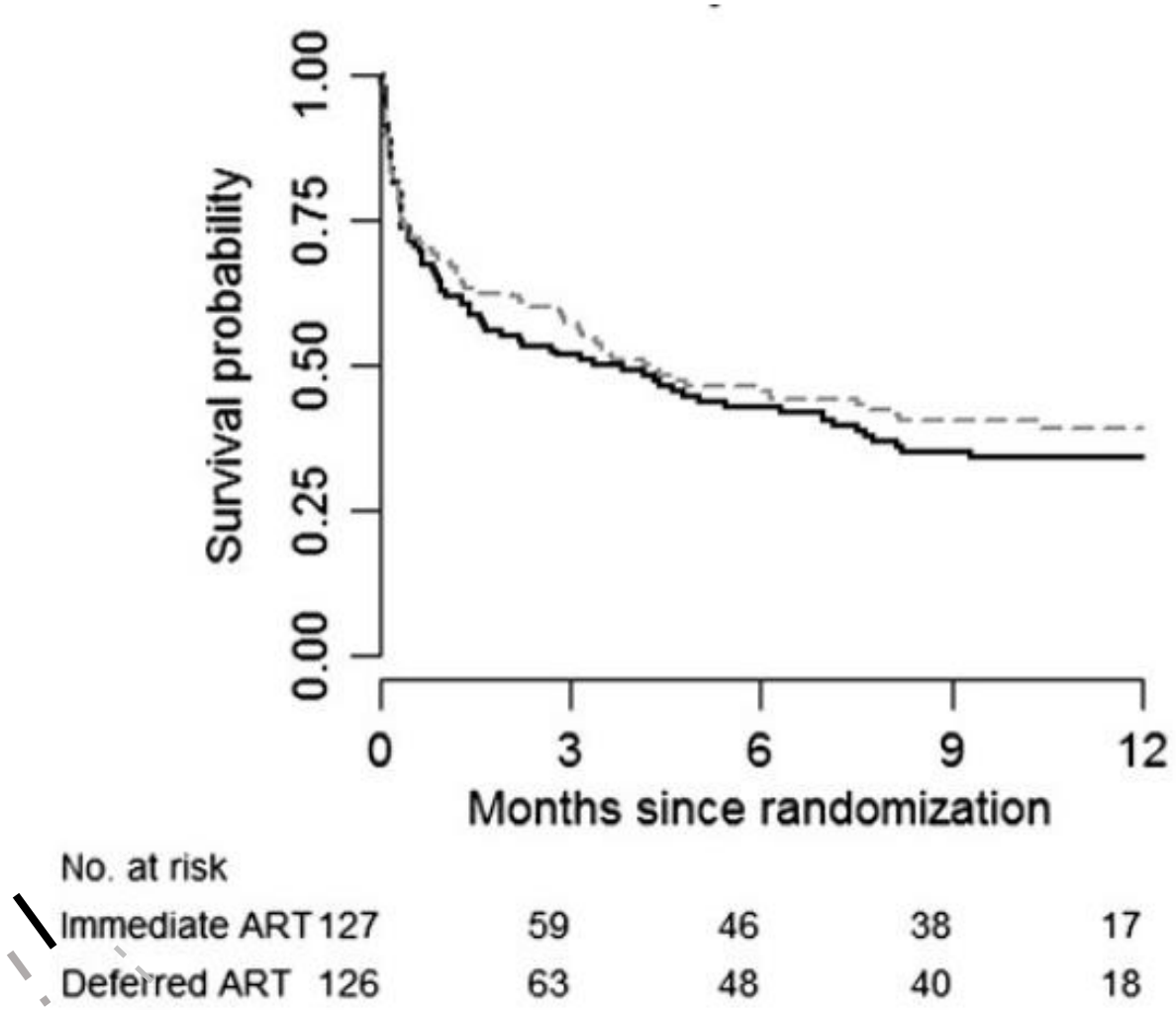
- 253 patients included (Vietnam)
- Randomization:
  - Immediate: ≤7 days after initiation of TB treatment
  - Deferred: 2 months after initiation of TB treatment

- Median CD4 count: 41 cells/mm^3
- 146 deaths; 57.7%

  ½

  Grade 4 adverse events:
  - Immediate: 80.3%
  - Deferred: 69.0%

  - p=0.04, but no difference in neurological events



Török, *CID* 2011

When to start ART?

When to start ART in Persons with Opportunistic Infections (OIs)

	Initiation of ART	Comments
General recommendation	As soon as possible within 2 weeks after starting treatment for the opportunistic infection	
TB meningitis	In persons with CD4 < 50 cells/μL, ART should be initiated within the first 2 weeks after initiation of TB treatment, if close monitoring and optimal TB treatment can be ensured ART initiation should be delayed for 4 weeks in all other cases	Corticosteroids are recommended as adjuvant treatment Where very close monitoring and optimal treatment are available, ART could be initiated early in selected cases
Cryptococcal meningitis	Defer initiation of ART for at least 4 weeks	Corticosteroids are not recommended as adjuvant treatment Where very close monitoring and optimal treatment are available, earlier ART start could be considered in selected cases

EACS guidelines 2023

Case

- Starts TB treatment (old regimen)
- Starts HIV treatment 5 days later
- 2 weeks later, she is admitted in the ID department due to development of
  - Severe headache
  - Tiredness
  - Photophobia

What is the most likely diagnosis?

- Paradoxical reaction after initiation of TB and HIV treatment/IRIS
- Treatment failure and development of TB meningitis
- Adverse events due to TB and HIV drugs
- Watching too much television

What is next step?

What is the most likely diagnosis?

- Paradoxical reaction after initiation of TB and HIV treatment/IRIS
- Treatment failure and development of TB meningitis
- Adverse events due to TB and HIV drugs
- Watching too much television

What is next step?

- MRI-brain
- Lumbar puncture
- Genotypic susceptibility testing

Case - follow-up

- MRI: leptomeningeal and basal cistern enhancement

- Lumbar puncture:
  - Monocytic pleocytosis 100/129 cells/mL
  - Csv-glucose: 0.7 mmol/l
  - Csv-protein: 1.3 g/L

  - Negativ sputum microscopy
  - Positive PCR for *m. tuberculosis*

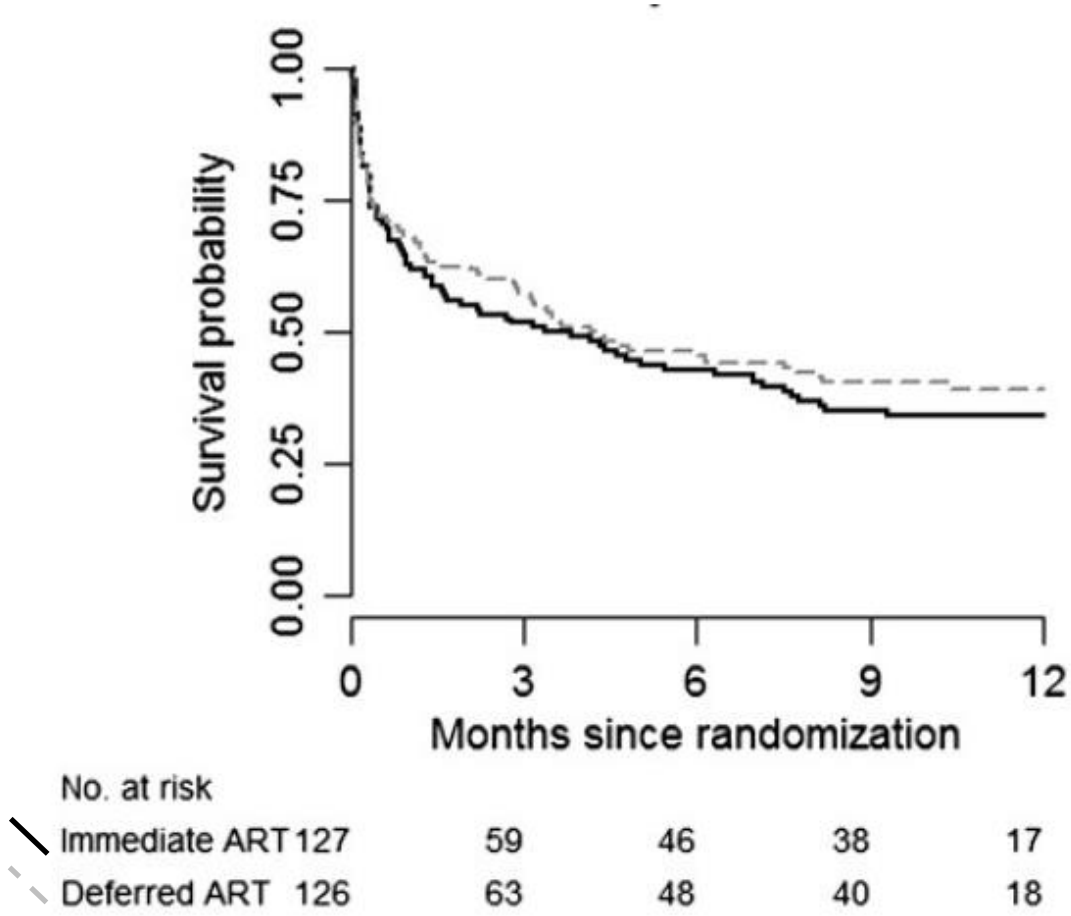
Is early initiation of ART a problem? -TB meningitis and ART

- 253 patients included (Vietnam)
- Randomization:
  - Immediate: ≤7 days after initiation of TB treatment
  - Deferred: 2 months after initiation of TB treatment

- Median CD4 count: 41 cells/mm^3
- 146 deaths; 57.7%

Grade 4 adverse events:
- Immediate: 80.3%
- Deferred: 69.0%

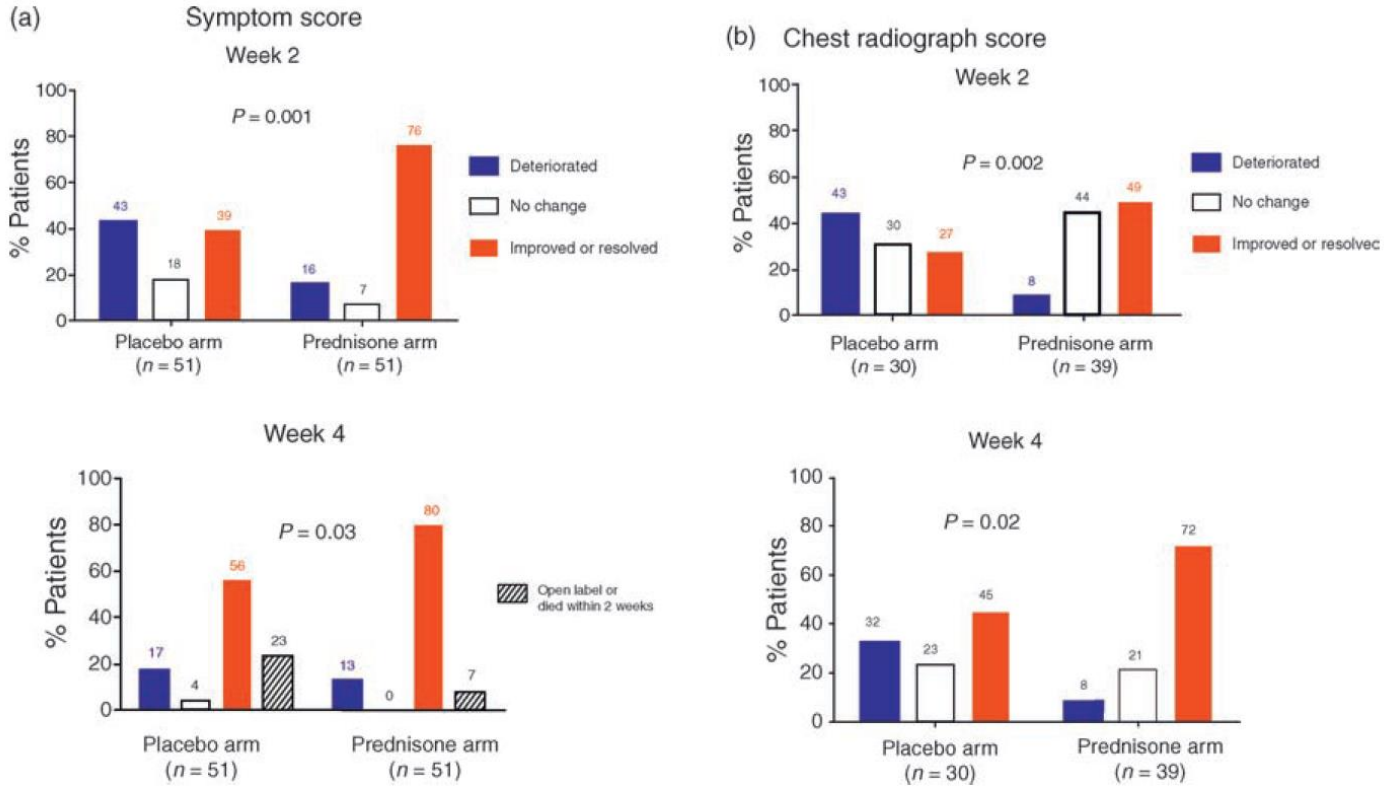
- p=0.04, but no difference in neurological events



Török, *CID* 2011

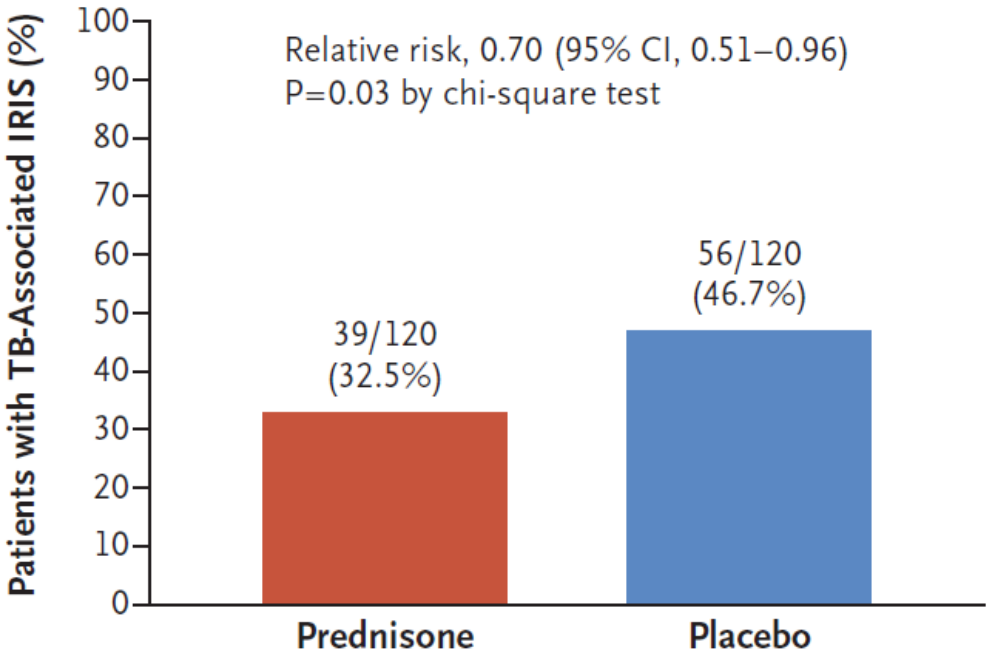
Immune reconstitution inflammatory syndrome (IRIS) and TB

Treatment



P: 1.5 mg/kg for 2 w,
then 0.75 mg/kg for 2 w

Prophylaxis

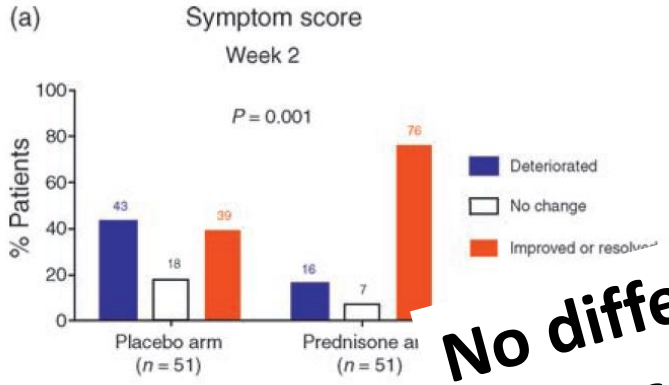


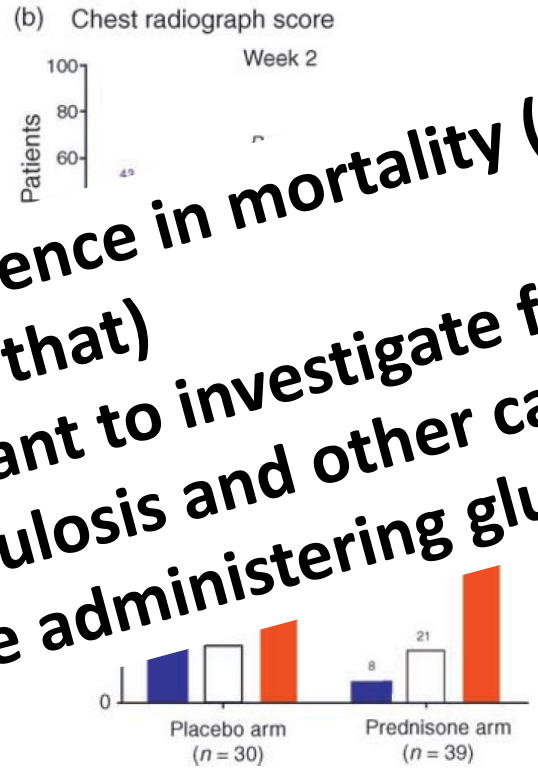
P: 40 mg for 2 w,
then 20 mg for 2 w

Meintjes *AIDS 2010;* Meintjes *NEJM* 2018

Immune reconstitution inflammatory syndrome (IRIS) and TB

Treatment

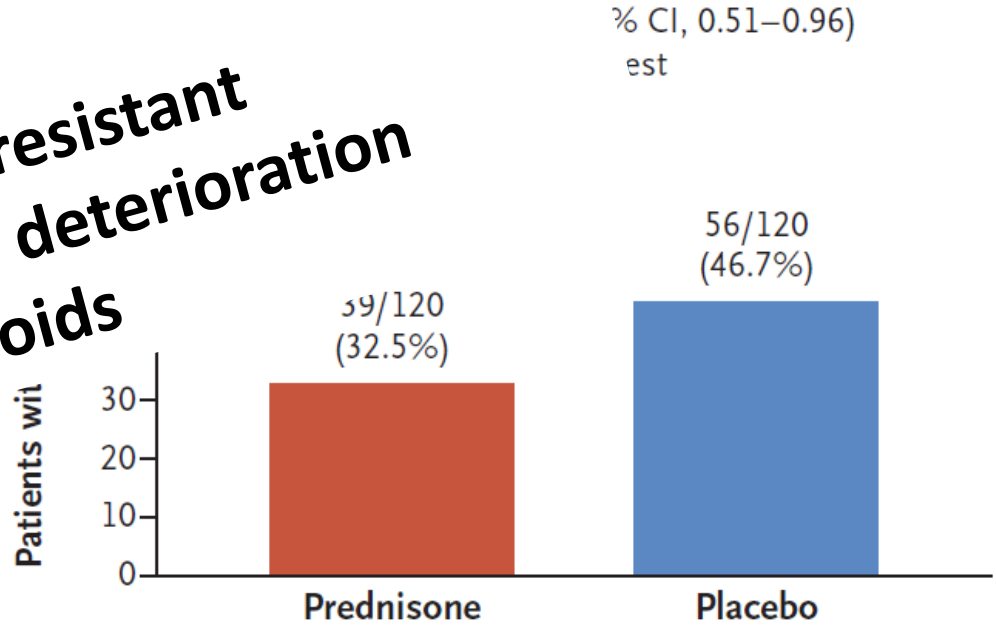




No difference in mortality (RCTs not powered to address that)

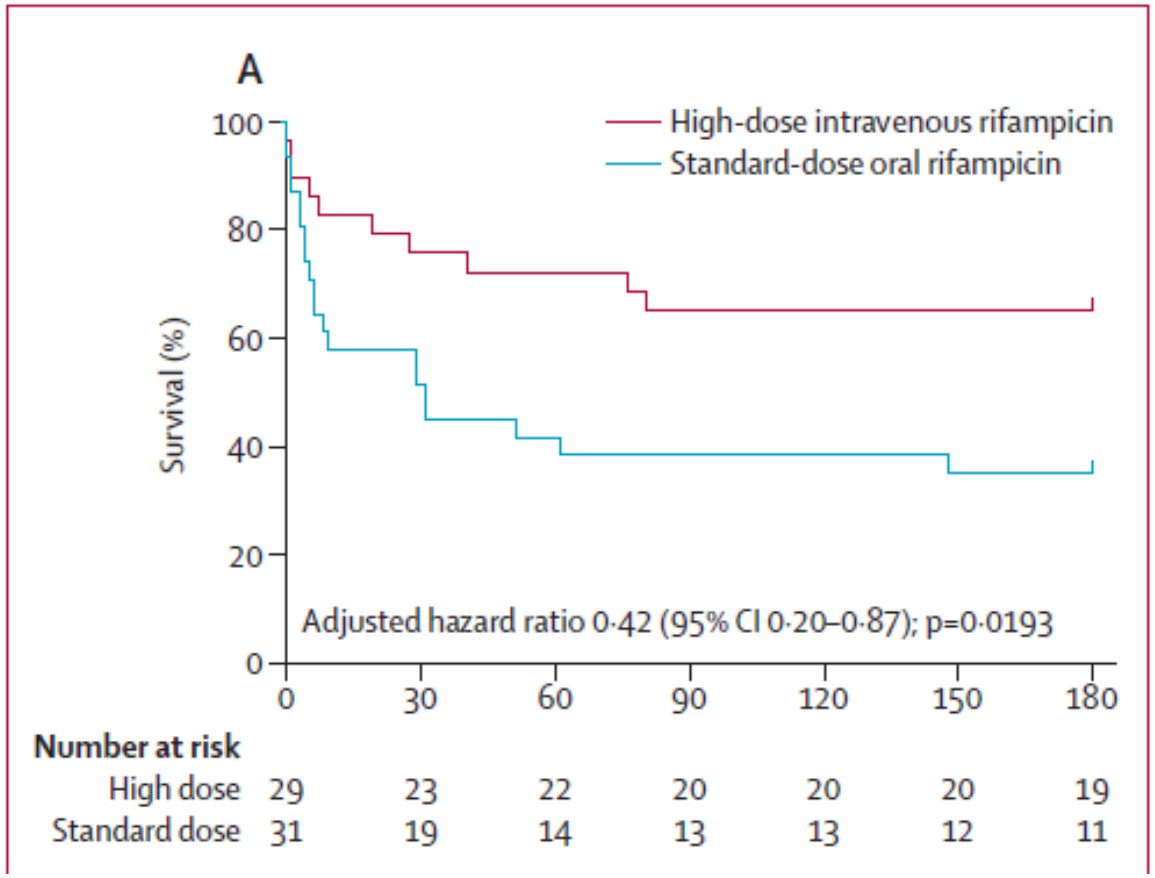
Important to investigate for drug-resistant tuberculosis and other causes for deterioration before administering glucocorticoids

Prophylaxis



Meintjes *AIDS 2010;* Meintjes *NEJM* 2018

TB meningitis - treatment



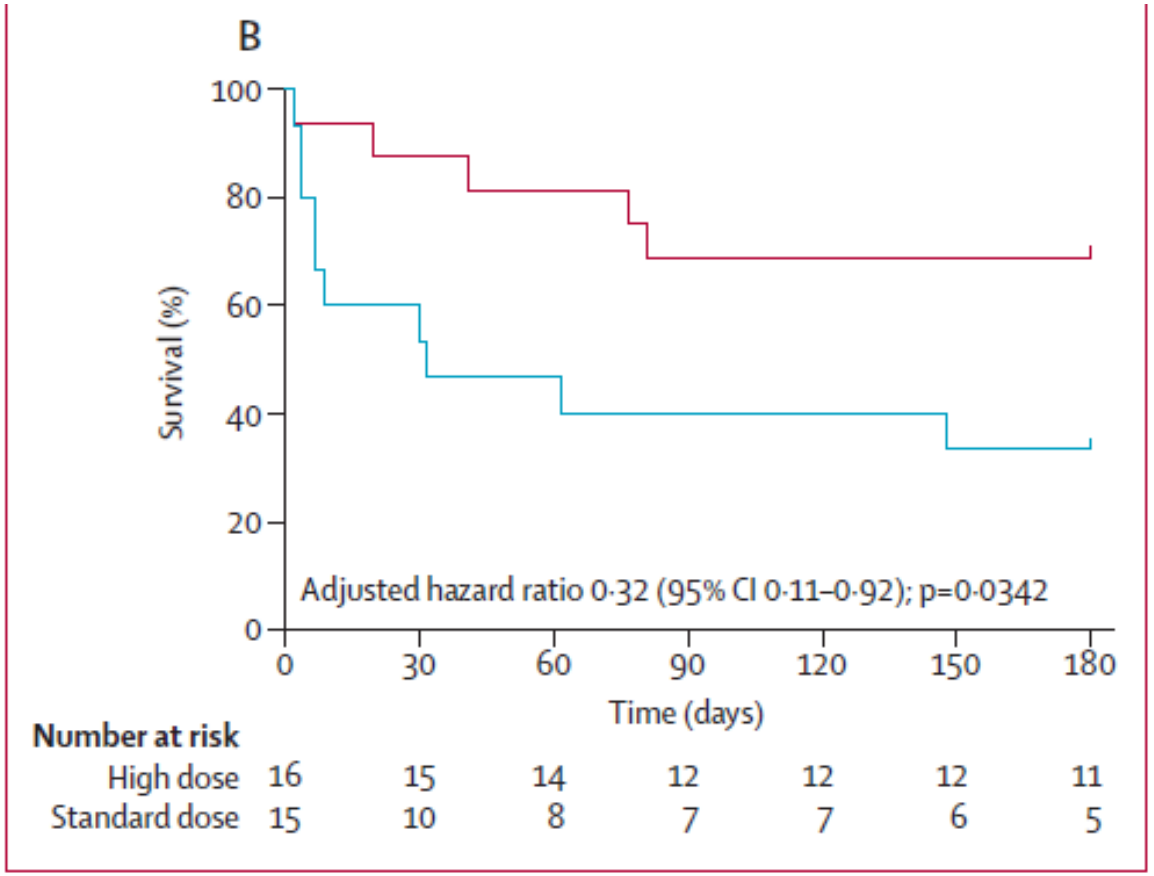
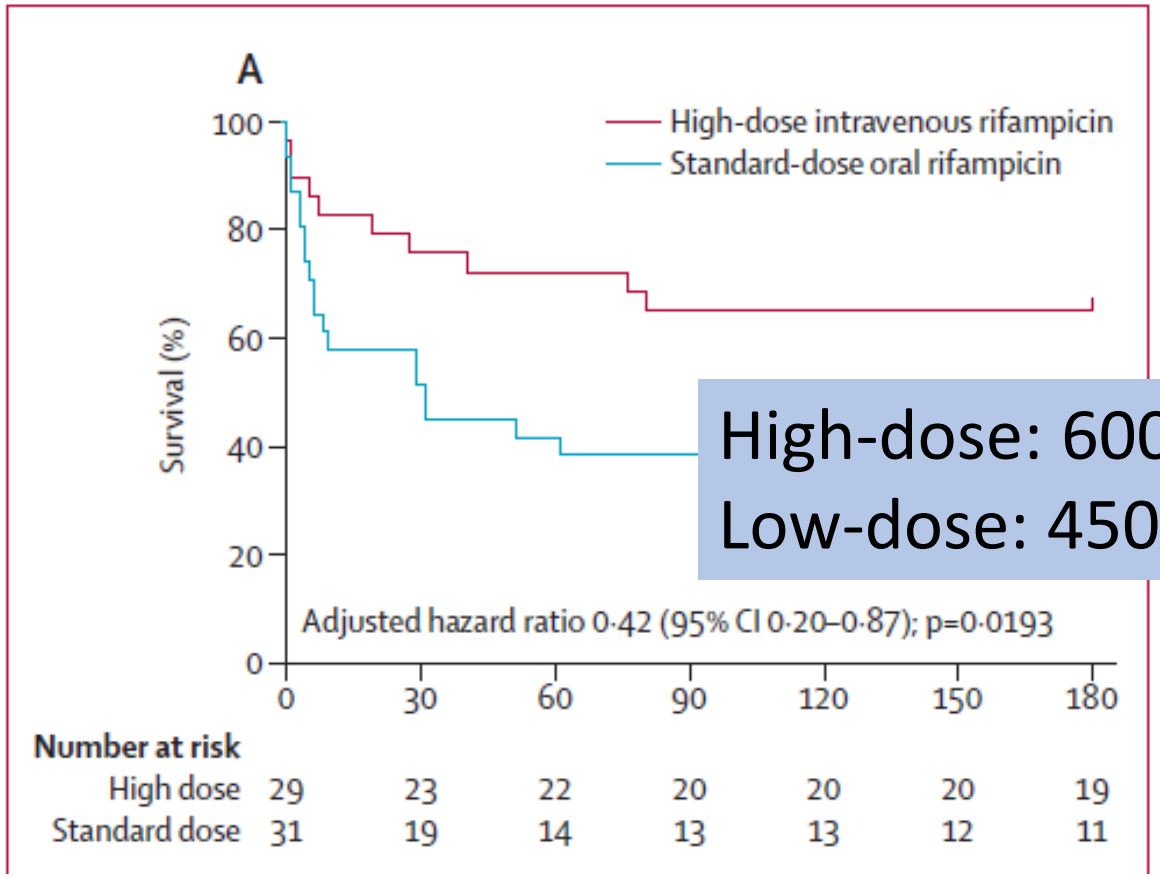
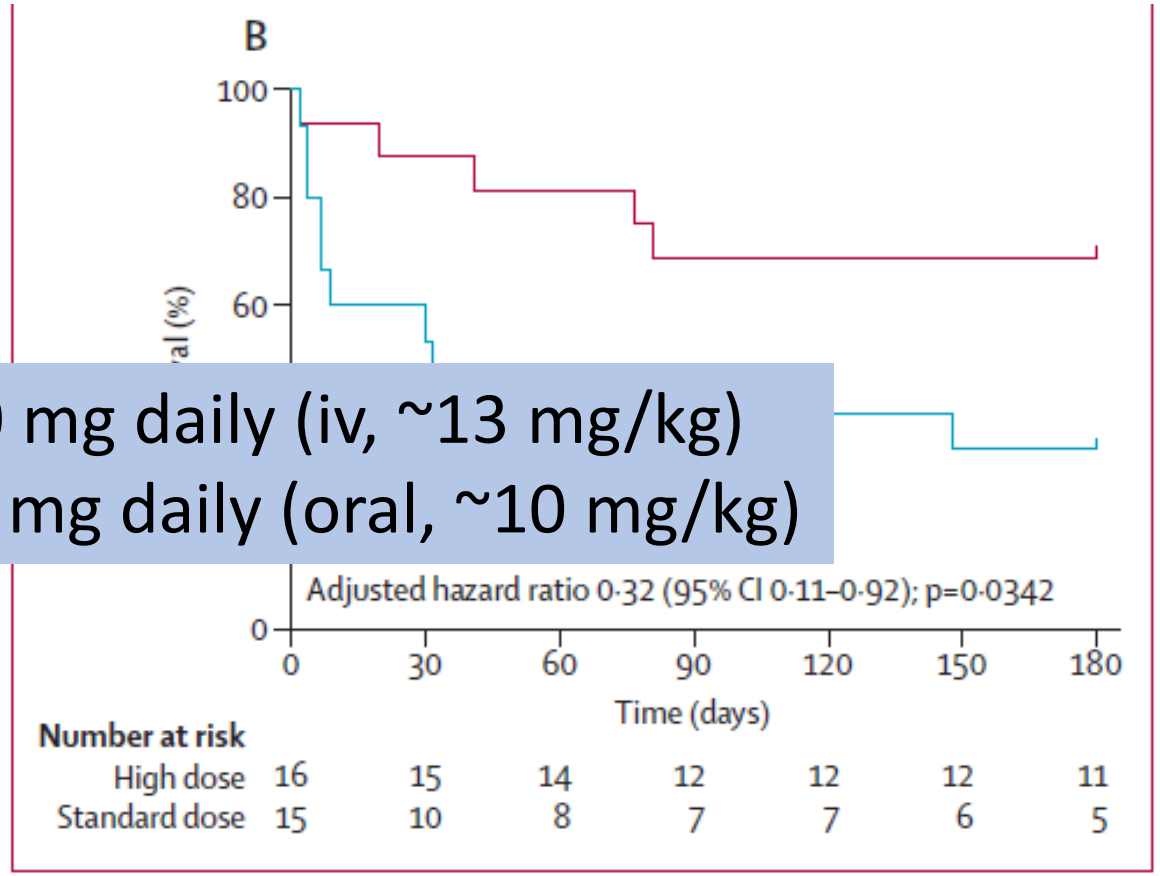


Figure 2: Survival according to rifampicin treatment in all 60 patients (A) and in 31 bacteriologically proven cases of tuberculous meningitis (B)

Ruslami *Lancet Inf Dis* 2013

TB meningitis - treatment





High-dose: 600 mg daily (iv, ~13 mg/kg)
Low-dose: 450 mg daily (oral, ~10 mg/kg)

Figure 2: Survival according to rifampicin treatment in all 60 patients (A) and in 31 bacteriologically proven cases of tuberculous meningitis (B)

Ruslami *Lancet Inf Dis* 2013

Resistant TB!

- Genotypic resistance testing (at TB diagnosis):
  - Rifampin R, Isoniazid R
- The patient starts a regimen of Bedaquiline, Pretomanid, Linezolid, Moxifloxacin and Pyrazinamide
- Phenotypic resistance testing (results available after 6 weeks):
  - Rifampin R, Isoniazid R, Moxifloxacin R
  - Pyrazinamide S, Ethambutol S, Bedaquiline S, Pretomanid S, Linezolid S, Clofazimine S
- Moxifloxacin discontinued
- After 8 weeks, Pyrazinamide discontinued – Bedaquiline, Pretomanid, Linezolid continued
- Currently treated for 6½ months without major adverse events (linezolid reduced to 300 mg daily) - – plan 12 months of treatment **NB: no strong evidence for extrapulmonary TB, but WHO Rapid Communication June 2024**

Resistant TB!

- Genotypic resistance testing (at TB diagnosis):
  - Rifampin R, Isoniazid R
- The patient starts a regimen of Bedaquiline, Pretomanid, Linezolid, Moxifloxacin and Pyrazinamide
- Phenotypic resistance testing (results available after 6 weeks):
  - Rifampin R, Isoniazid R, Moxifloxacin R
  - Pyrazinamide S, Ethambutol S, Bedaquiline S, Pretomanid S, Linezolid S, Clofazimine S

Pre-XDR-TB

- Moxifloxacin discontinued
- After 8 weeks, Pyrazinamide discontinued – Bedaquiline, Pretomanid, Linezolid continued
- Currently treated for 6½ months without major adverse events (linezolid reduced to 300 mg daily) - – plan 12 months of treatment **NB: no strong evidence for extrapulmonary TB, but WHO Rapid Communication June 2024**

Treatment of resistant TB

- Guided by drug susceptibility testing (incl. X-pert MTB/RIF)
- Treatment for **pulmonary** multi-drug resistant TB: all-oral regimens, 6 months:
  - Bedaquiline
  - Pretomanid
  - Linezolid
  - Moxifloxacin

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population	
	Standard-Care Group (N=73)	BPaLM Group (N=72)
Favorable outcome — no. (%)	34 (47)	55 (76)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)
Death — no. (%)	2 (3)	0
Early discontinuation — no. (%)	35 (48)	15 (21)
Adherence issues — no./total no. (%)	3/35 (9)	0
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0
Other reason — no./total no. (%)†	2/35 (6)	0
Treatment failure — no.	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)
Recurrence — no.	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)

Conradie *NEJM* 2020; Conradie *NEJM* 2022; Nyang'wa *NEJM* 2022

Treatment of resistant TB

- Guided by drug susceptibility testing (incl. X-pert MTB/RIF)
- Treatment for **pulmonary** multi-drug resistant TB: all-oral regimens, 6 months:
  - Bedaquiline
  - Pretomanid
  - Linezolid
  - Moxifloxacin

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population	
	Standard-Care Group (N=73)	BPaLM Group (N=72)
Favorable outcome — no. (%)	34 (47)	55 (76)
Primary outcome: un		17 (24)
Death — no. (%)		0
Early discontinua		15 (21)
Adherence iss		0
Adverse event		5/15 (33)
Did not meet detected		10/15 (67)
Withdrew cor no./total no. (%)		0
Other reason — no./total no. (%)†	2/35 (6)	0
Treatment failure — no.	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)
Recurrence — no.	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)

Favorable outcome — no. (%)
Intention-to-Treat Population
Standard-Care Group (N=73)
BPaLM Group (N=72)
34 (47)
55 (76)

Conradie *NEJM* 2020; Conradie *NEJM* 2022; Nyang'wa *NEJM* 2022

Resistant TB

- Treatment:
  - If BPaLM not possible-> Construct a regimen of at least 4 likely effective drugs - guided by drug susceptibility testing (incl. X-pert MTB/RIF)

Drug choices	
Each empiric regimen should be reassessed and modified if needed once drug sensitivity results become available	
Group A: **Include all three drugs**	• **levofloxacin** or **moxifloxacin** • **bedaquiline** • **linezolid**
Group B: **Add one or both drugs**	• **clofazimine** • **cycloserine** or **terizidone**
Group C: **Add to complete the regimen and when drugs from Groups A and B cannot be used**	• **ethambutol** • **delamanide** • **pyrazinamide** • **amikacin** (or **streptomycin** – only if susceptible) • **imipenem–cilastatin** or **meropenem** • **ethionamide** or **prothionamide** • **para-aminosalicylic acid**
Pretomanid is recommended but not yet included in Group A drugs	

WHO, EACS guidelines etc

Thank you!