Opportunistic infections

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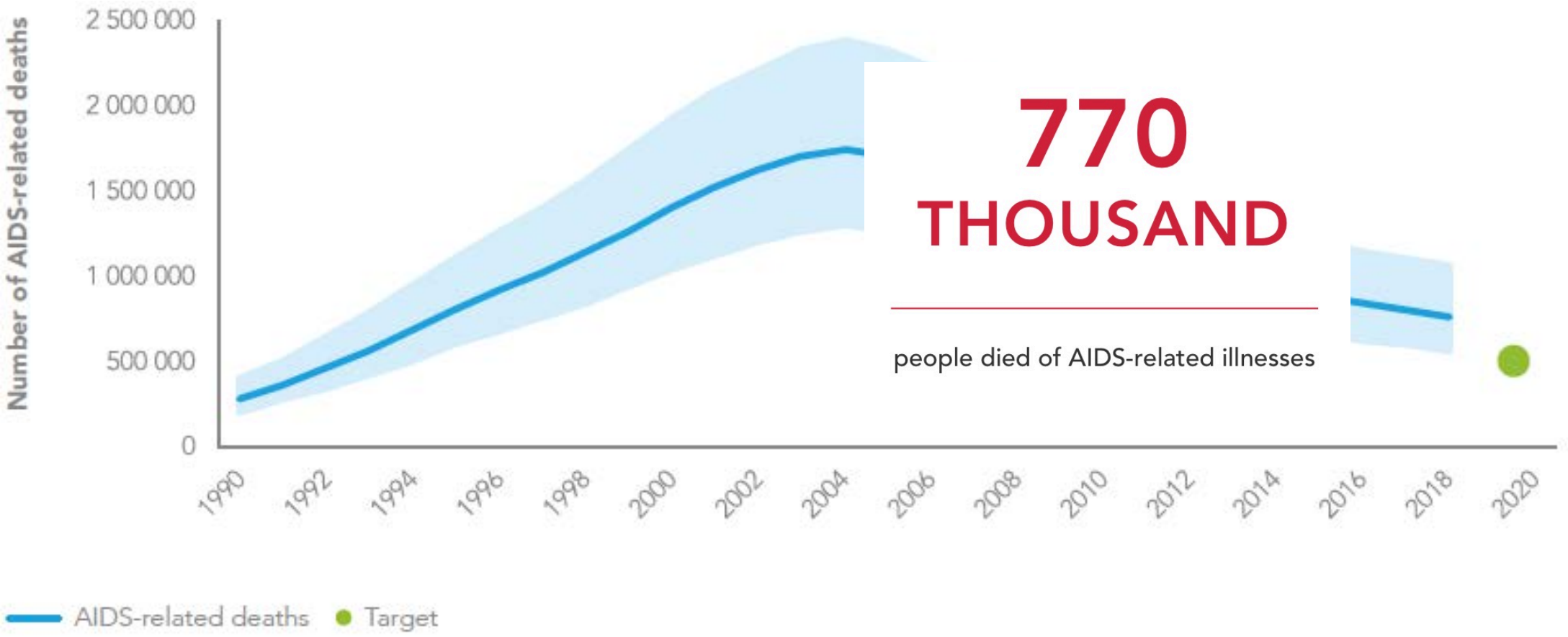
Outline

- The problem
- Mycobacterial
- Fungal
- Viral
- Protozoal
- Bacterial

AIDS related deaths globally: The ART impact



UNAIDS data 2019

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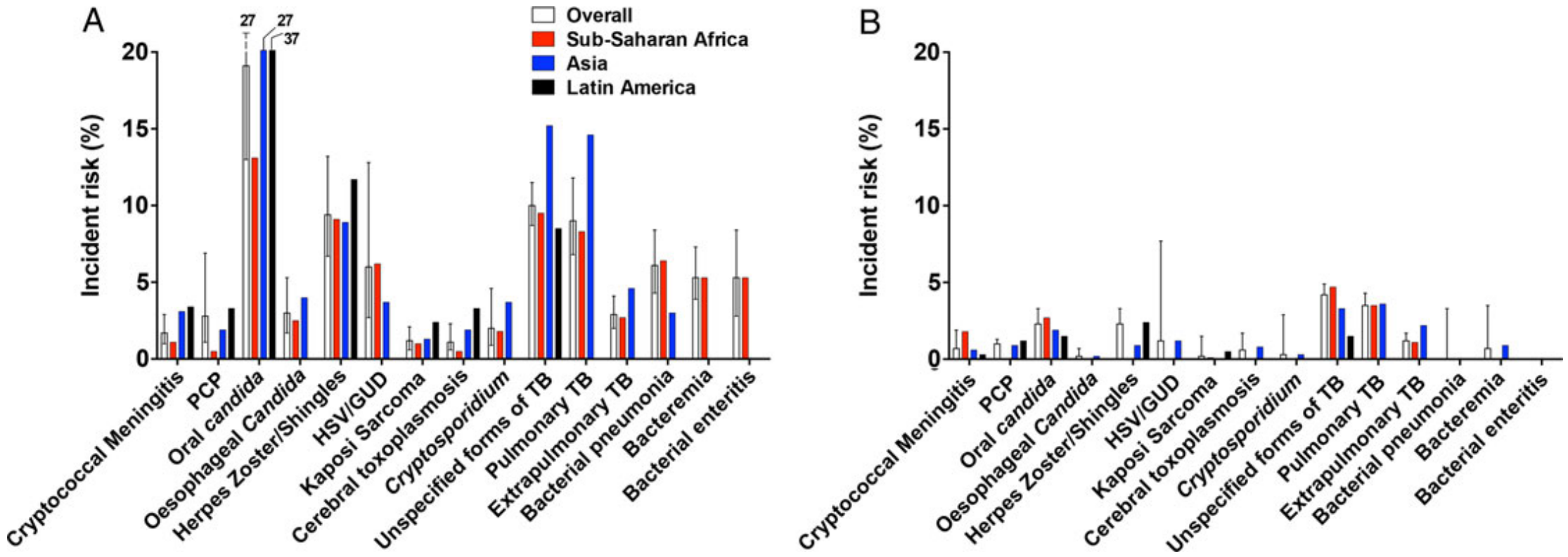
Incidence of OI's in the ART era



Clin Infect Dis 2016;62:595-603

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Late presenters in single center Belgian center

	N (%)
Non LP	385 (56.0)
LP[(a)]	302 (44.0)
LP-AD[(b)]	165 (24.0)

Sci Rep. 2018 Jun 5;8(1):8594

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Factors associated with late presentation

	Coefficient ± SE	Odds ratio (95% CI)	p-value
Intercept	21.6 ± 56.6	—	—
Year of presentation for care	−0.011 ± 0.028	1.0 (0.94–1.1)	0.69
Age (by 10 years older)	**0.23 ± 0.084**	**1.3 (1.1–1.5)**	**0.0069**
Sex (0 = Female, 1 = Male)	**0.35 ± 0.11**	**2.0 (1.3–3.1)**	**0.0021**
SSA[a] origin (0 = No, 1 = Yes)	**0.61 ± 0.14**	**3.4 (1.9–5.9)**	**< 0.0001**
Other[a] non belgian origin (0 = No, 1 = Yes)	**0.31 ± 0.16**	**1.9 (1.0–3.4)**	**0.044**
Hetetosexual[b] mode of acquisition (0 = No, 1 = Yes)	**0.43 ± 0.14**	**2.4 (1.4–4.1)**	**0.0024**
Other (non sexual) mode of acquisition (0 = No, 1 = Yes)	0.11 ± 0.26	1.2 (0.45–3.4)	0.68
Context of screening = Refugee (0 = No, 1 = Yes)	0.12 ± 0.12	1.3 (0.78–2.1)	0.34
Context of screening = Medical problem (0 = No, 1 = Yes)	0.17 ± 0.11	1.4 (0.90–2.2)	0.14
Context of screening = Voluntary screening (0 = No, 1 = Yes)	−0.036 ± 0.14	0.93 (0.53–1.6)	0.81

Sci Rep. 2018 Jun 5;8(1):8594

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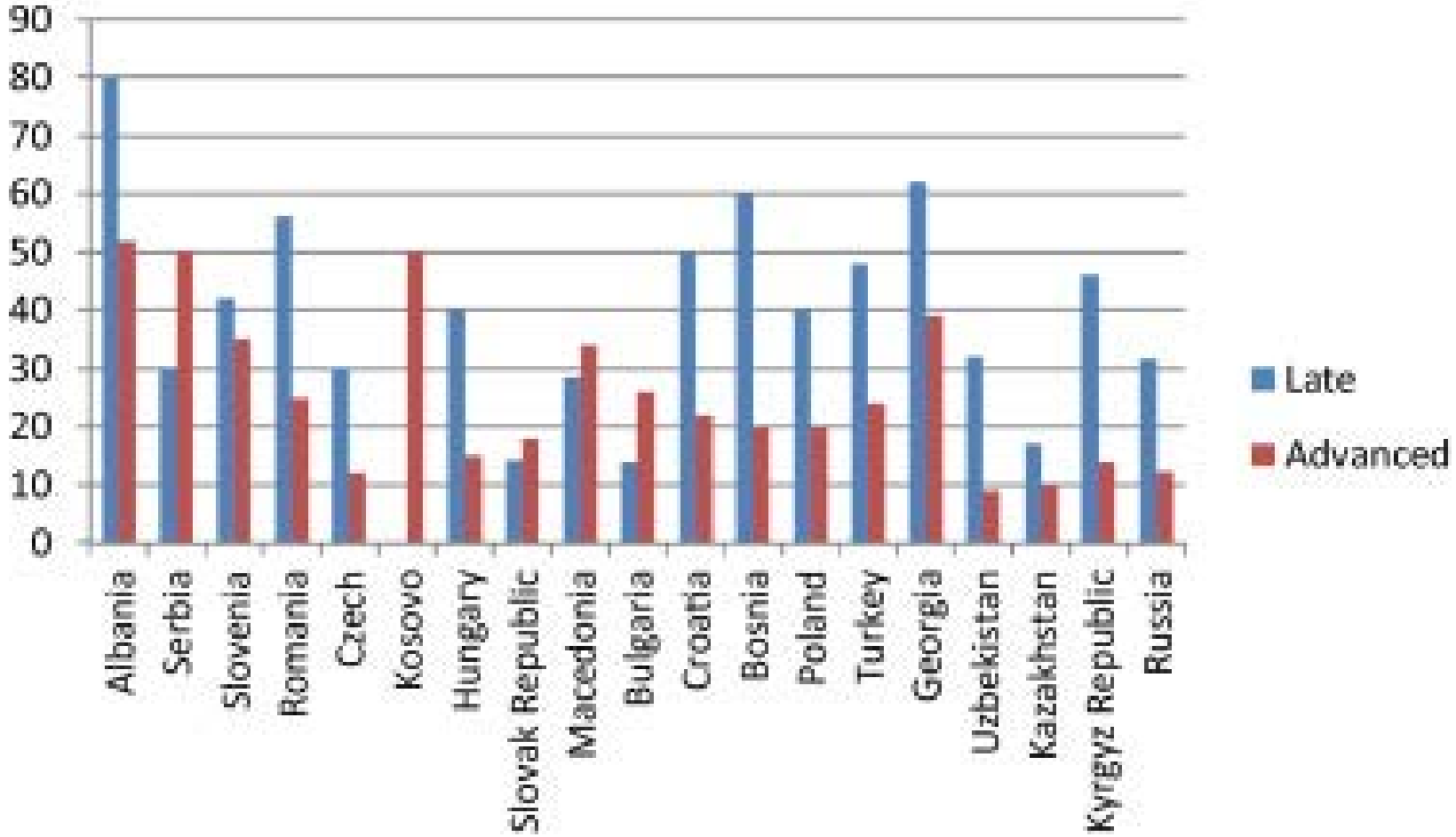
Late/Advanced presentation to care: Central/Eastern Europe (2014)



Int J Infect Dis. 2018 May;70:121-130

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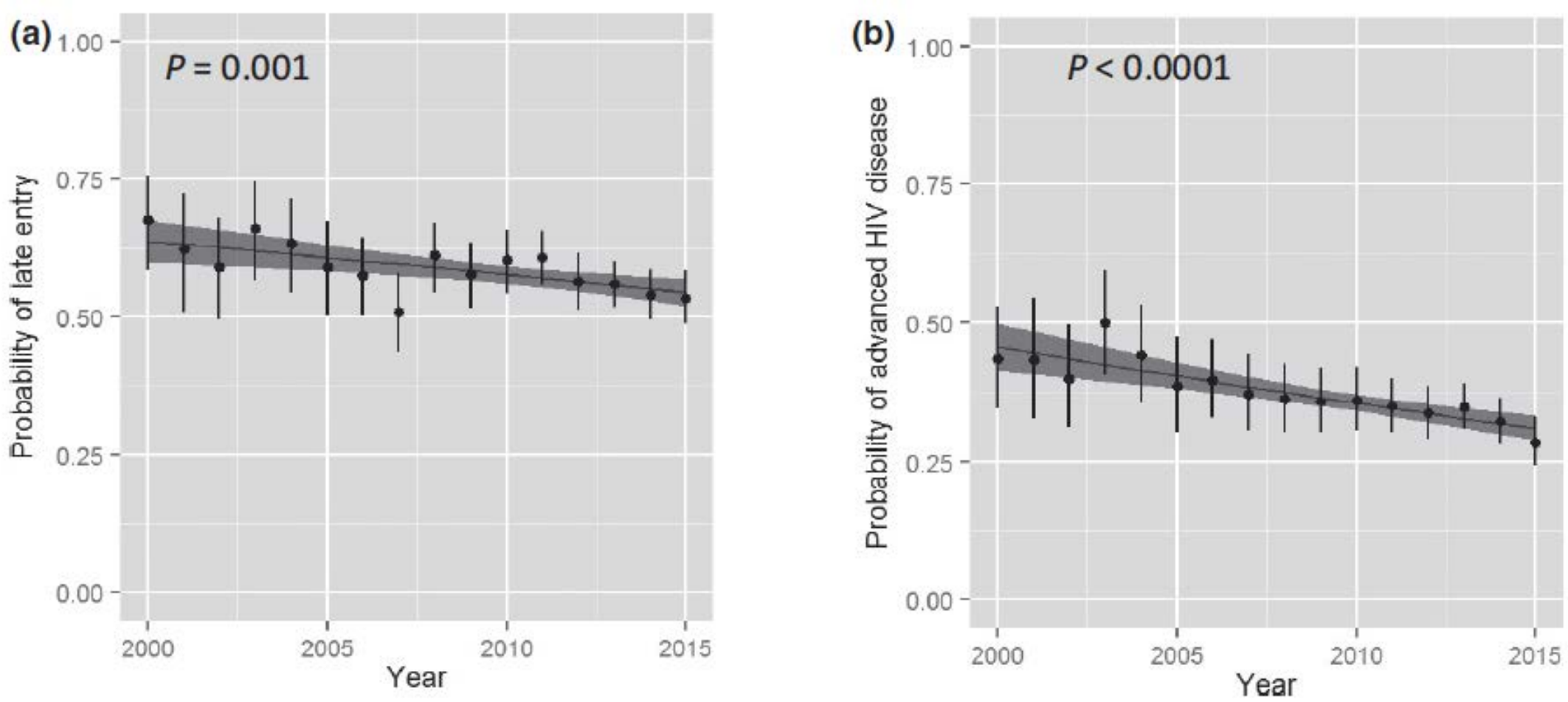
Late entry into care: Poland



HIV Med 2019 Jun 28. [Epub ahead of print]

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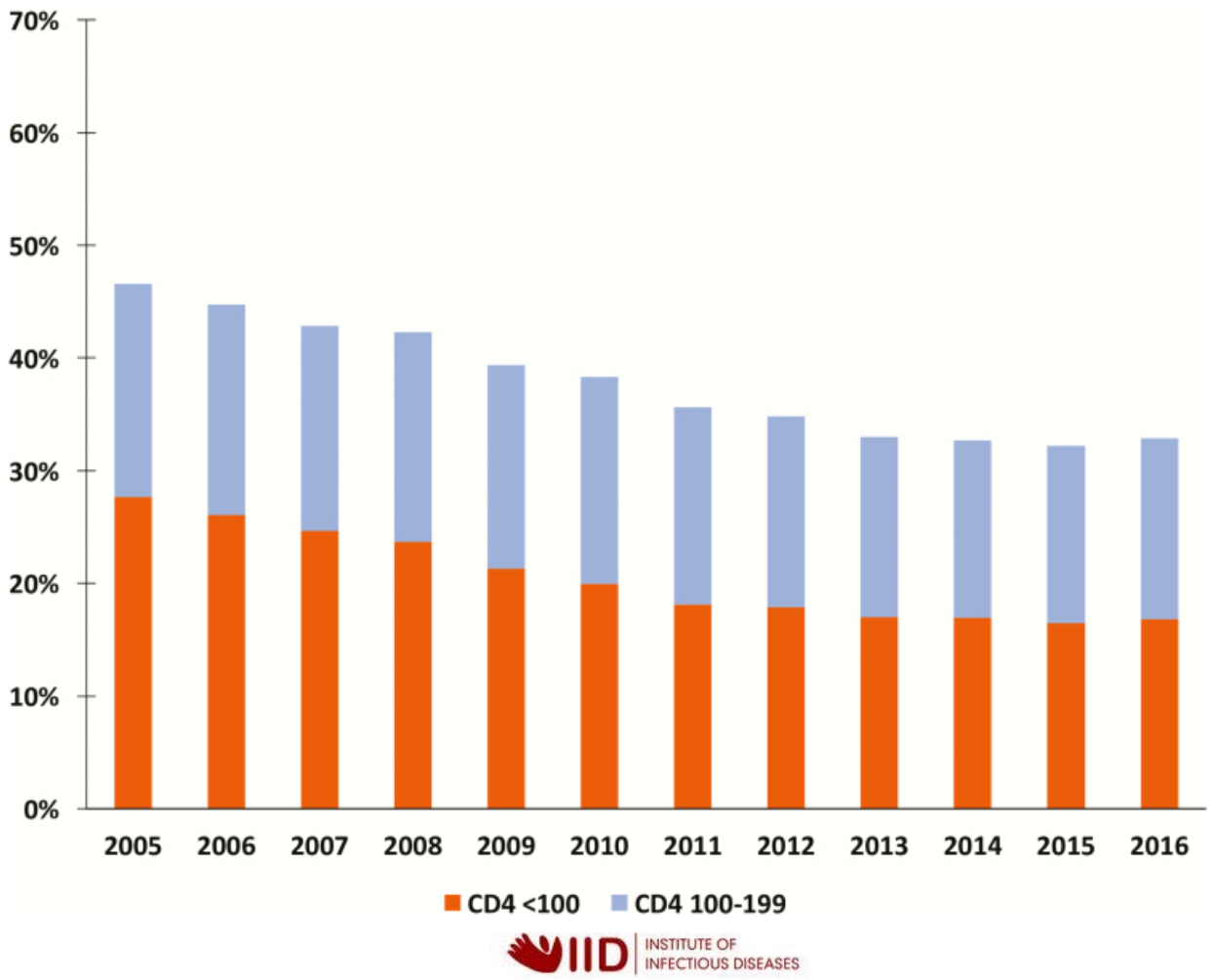
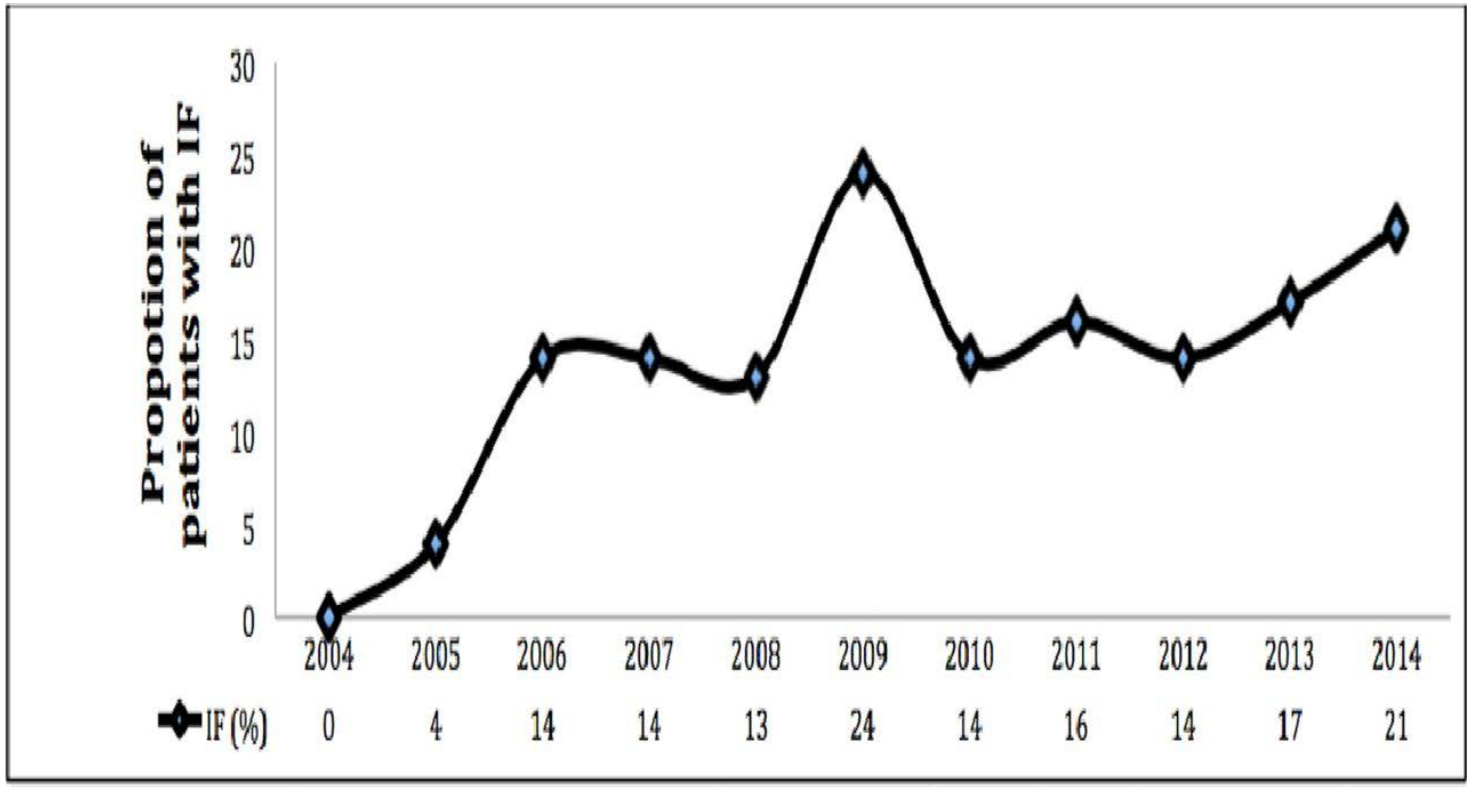
Late/advanced presentation to care: South Africa



Trends in IF on ART: Ethiopia



Absolute number	0/ 34	17/ 381	160/ 1109	229/ 1581	266/ 1977	587/ 2406	402/ 2792	519/ 3158	501/ 3455	646/ 3689	775/ 3768

*BMJ Open 2018;**8:**e017413.*

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- Protozoal
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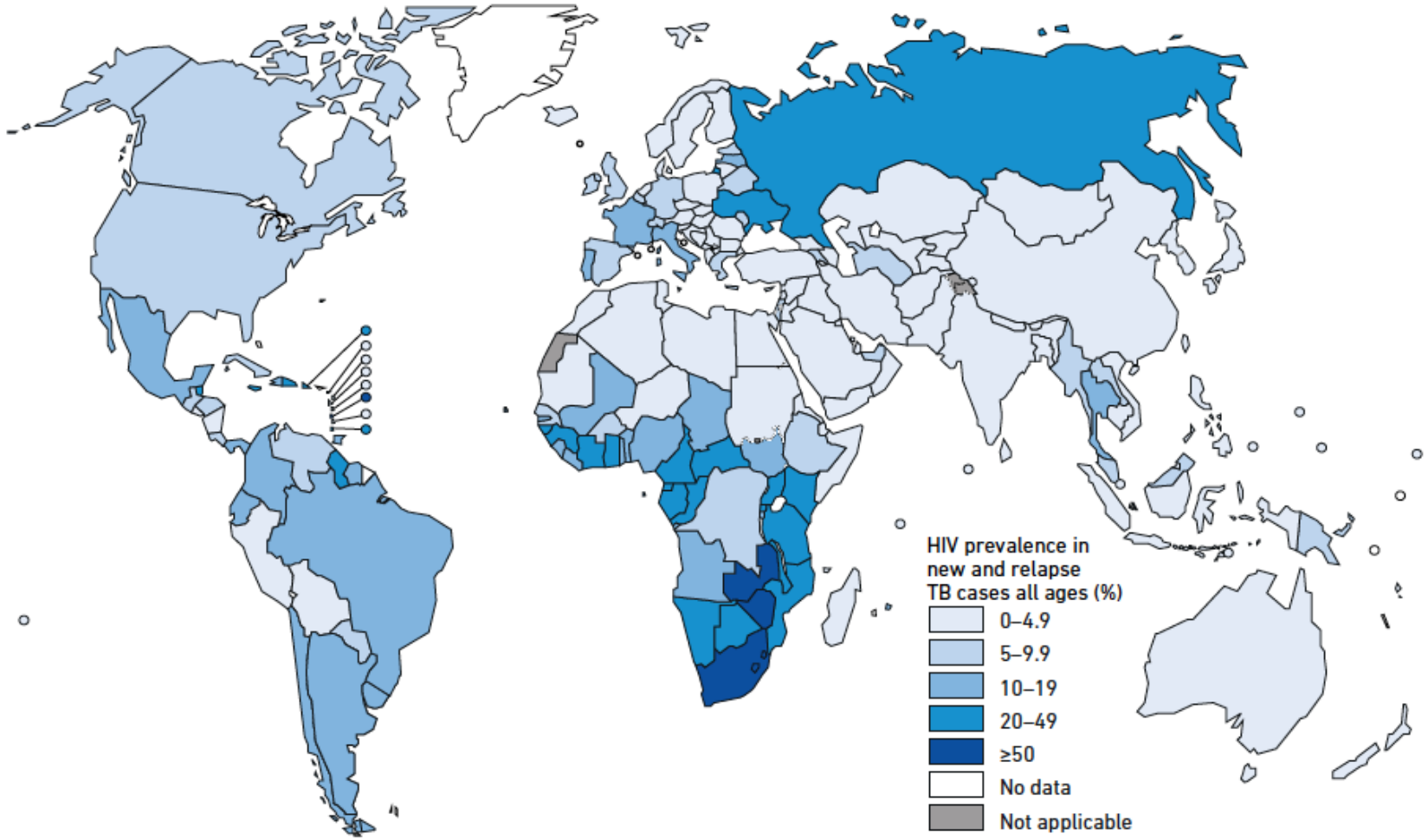
HIV prevalence in new and relapsed TB: 2017



Global TB report 2018

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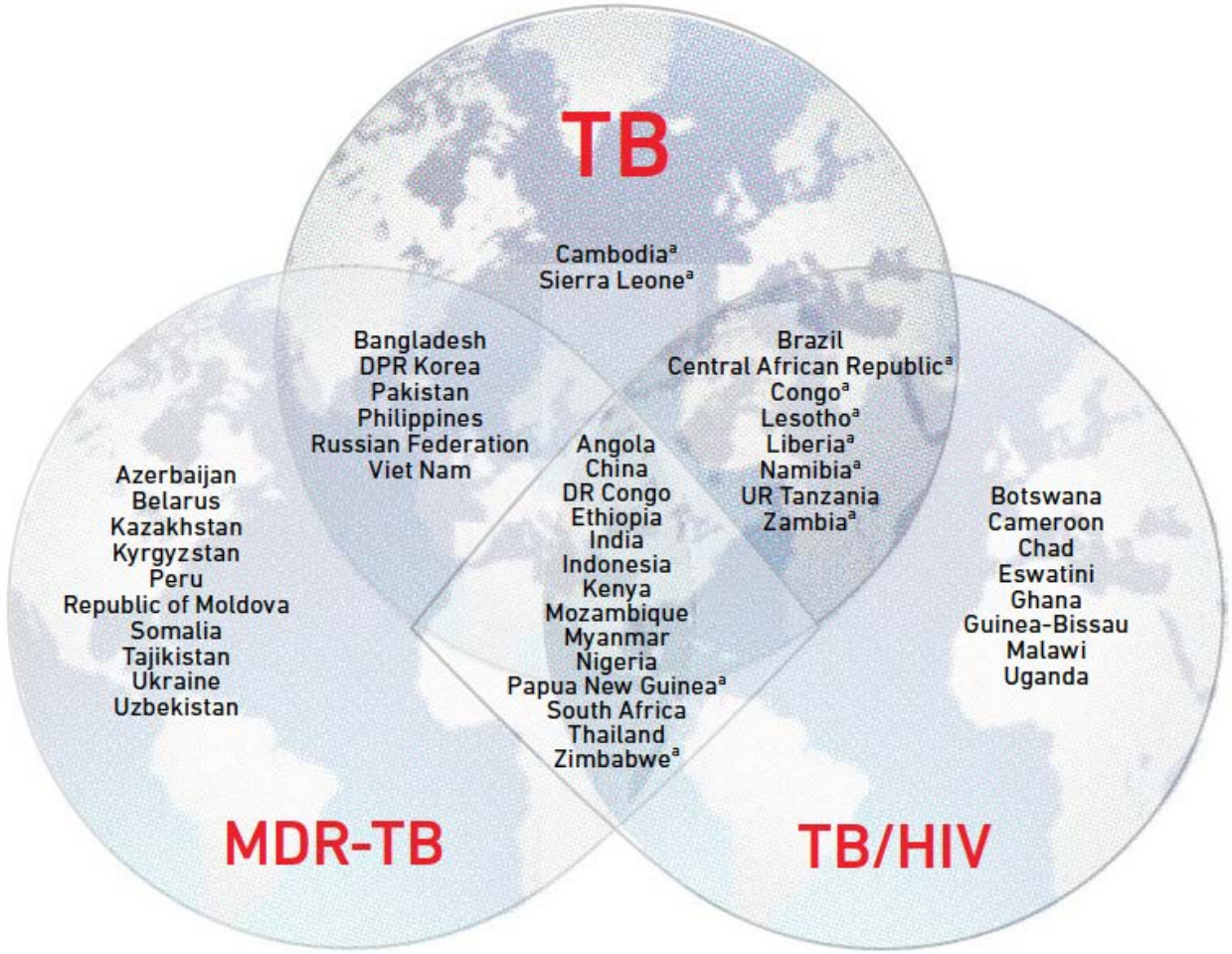
Countries with major burden of TB/MDRTB/HIV



Global TB report 2018

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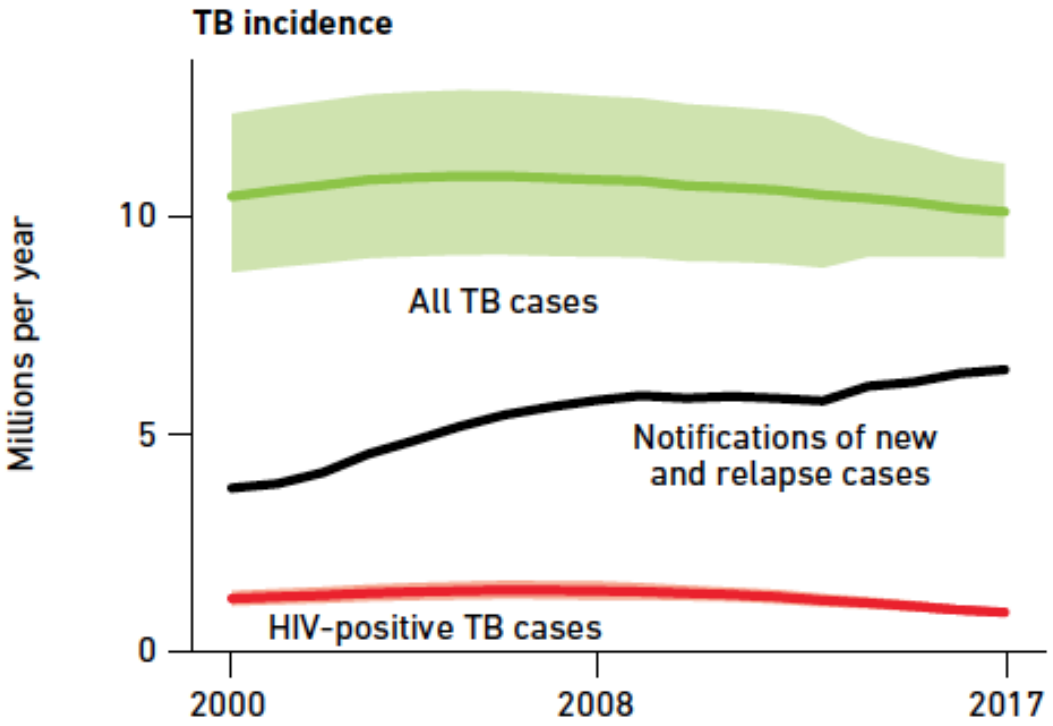
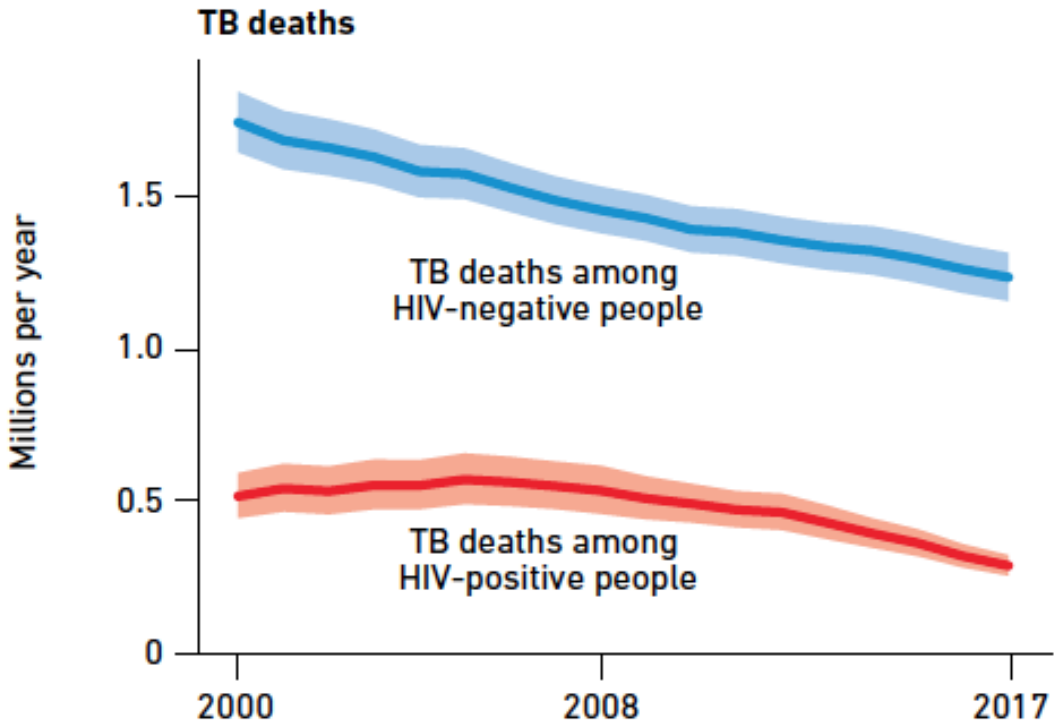
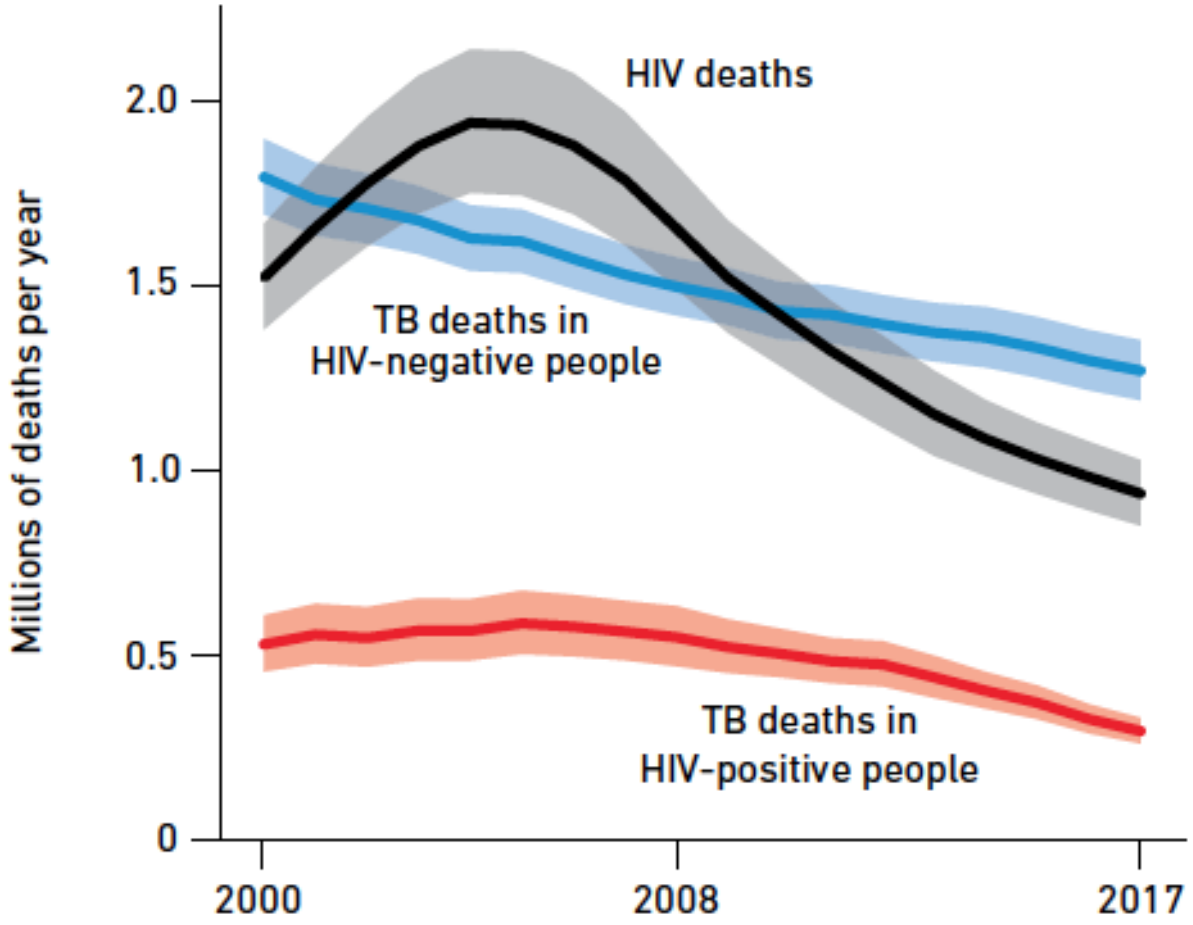
Trends in HIV/TB incidence and deaths





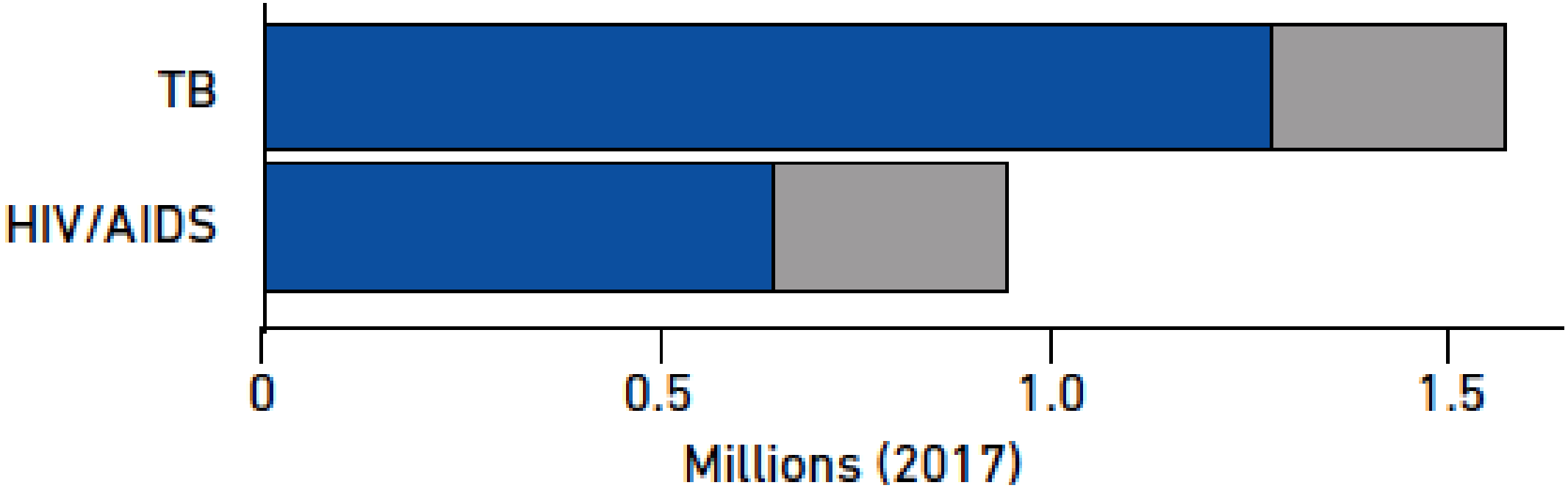
Global TB report 2018

Mortality amongst HIV/TB



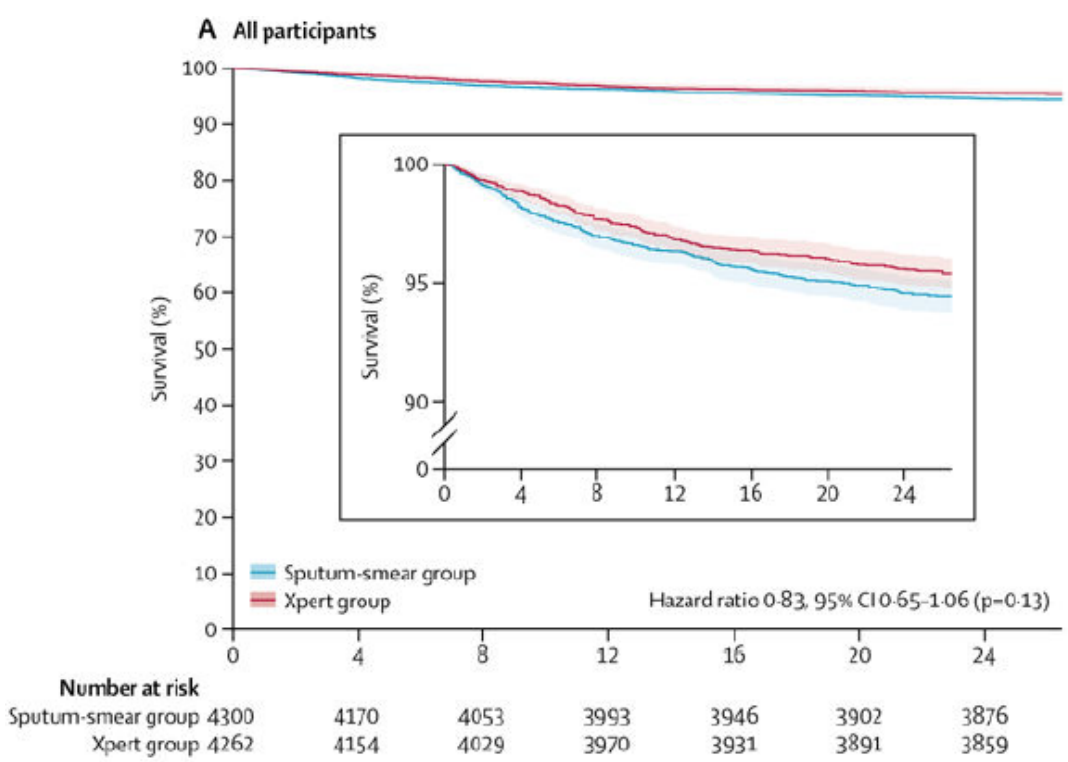
Global TB report 2018

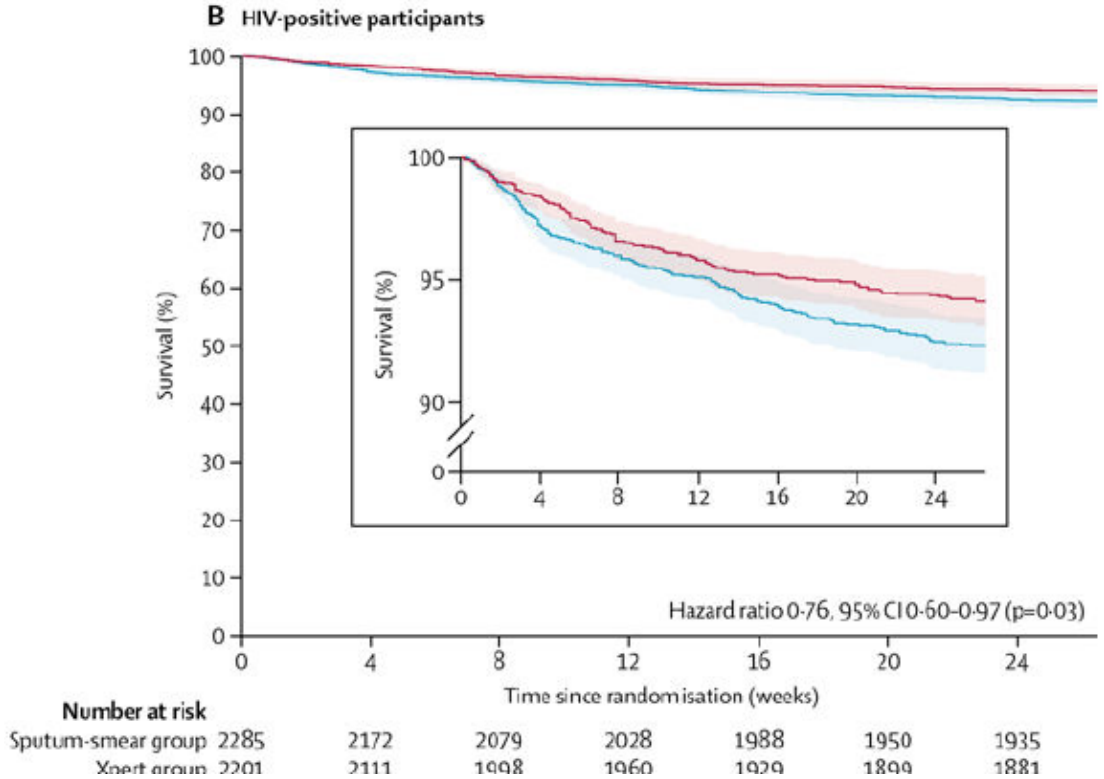
Estimated number of deaths



Global TB report 2018

XpertMTB/Rif and mortality



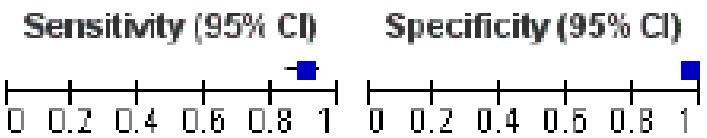


Lancet Glob Health. 2019 February ; 7(2): e191–e199.

XpertMTB/Rif vs XpertMTB/Rif ultra in PLHIV

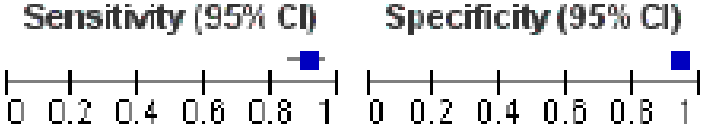
HIV-negative, Xpert MTB/RIF, direct comparison Xpert MTB/RIF vs Xpert Ultra

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	143	9	16	315	0.90 [0.84, 0.94]	0.97 [0.95, 0.99]



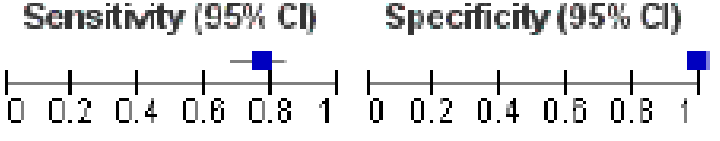
HIV-negative, Xpert Ultra, direct comparison Xpert MTB/RIF vs Xpert Ultra

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	145	17	14	307	0.91 [0.86, 0.95]	0.95 [0.92, 0.97]



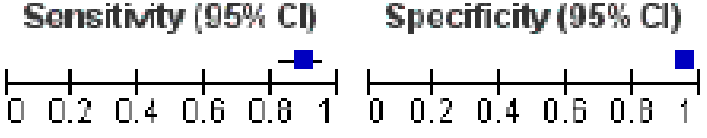
HIV-positive, Xpert MTB/RIF, direct comparison Xpert MTB/RIF vs Xpert Ultra

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	88	2	27	315	0.77 [0.68, 0.84]	0.99 [0.98, 1.00]



HIV-positive, Xpert Ultra, direct comparison Xpert MTB/RIF vs Xpert Ultra

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	103	14	12	303	0.90 [0.82, 0.94]	0.96 [0.93, 0.98]

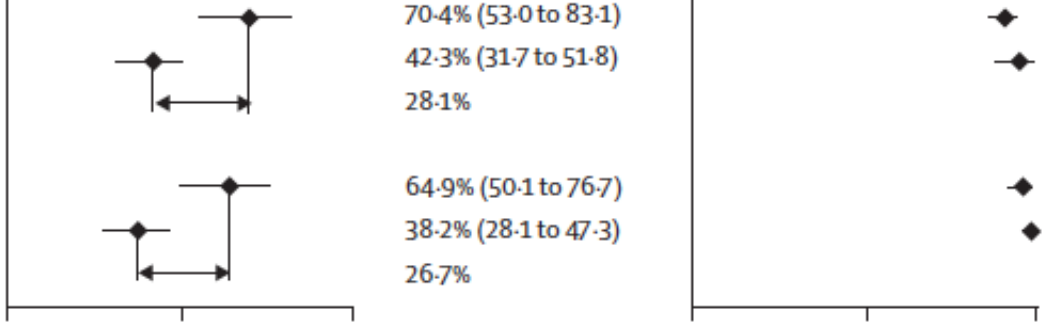


Cochrane Databse Syst Rev 2019 Jun; 2019(6): CD009593

FujiLAM vs AlereLAM for diagnosing TB

A

	Test	n	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
MRS	FujiLAM	968	455	33	145	335	70·4% (53·0 to 83·1)	90·8% (86·0 to 94·4)
	AlereLAM	968	268	18	332	350	42·3% (31·7 to 51·8)	95·0% (87·7 to 98·8)
	Difference						28·1%	−4·2%
CRS								
	FujiLAM	968	477	11	214	266	64·9% (50·1 to 76·7)	95·7% (92·0 to 98·0)
	AlereLAM	968	281	5	410	272	38·2% (28·1 to 47·3)	98·2% (95·7 to 99·6)
	Difference						26·7%	−2·5%



Lancet Infect Dis 2019;19:852-61

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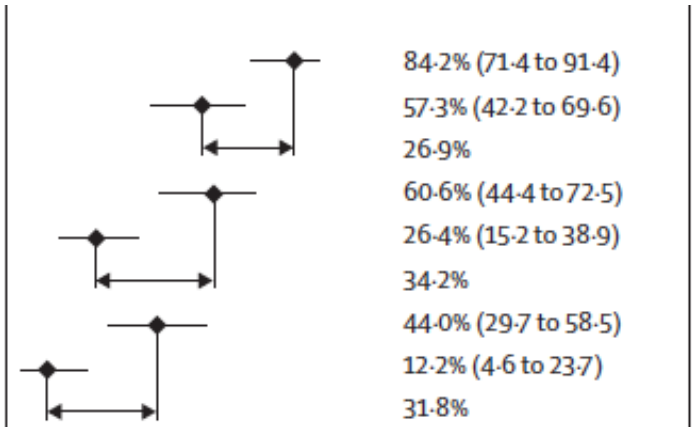
FujiLAM vs AlereLAM for diagnosing TB

MRS								
0–100 cells per µL	FujiLAM	516	332	20	49	115	84·2% (71·4 to 91·4)	85·0% (75·8 to 91·7)
	AlereLAM	516	221	8	160	127	57·3% (42·2 to 69·6)	94·1% (88·3 to 97·7)
	Difference						26·9%	−9·1%
101–200 cells per µL	FujiLAM	216	83	9	49	75	60·6% (44·4 to 72·5)	89·6% (78·5 to 98·1)
	AlereLAM	216	35	7	97	77	26·4% (15·2 to 38·9)	92·8% (69·2 to 99·9)
	Difference						34·2%	−3·2%
>200 cells per µL	FujiLAM	231	37	4	46	144	44·0% (29·7 to 58·5)	97·0% (92·5 to 99·3)
	AlereLAM	231	10	3	73	145	12·2% (4·6 to 23·7)	97·2% (88·4 to 100)
	Difference						31·8%	−0·2%



Lancet Infect Dis 2019;19:852-61

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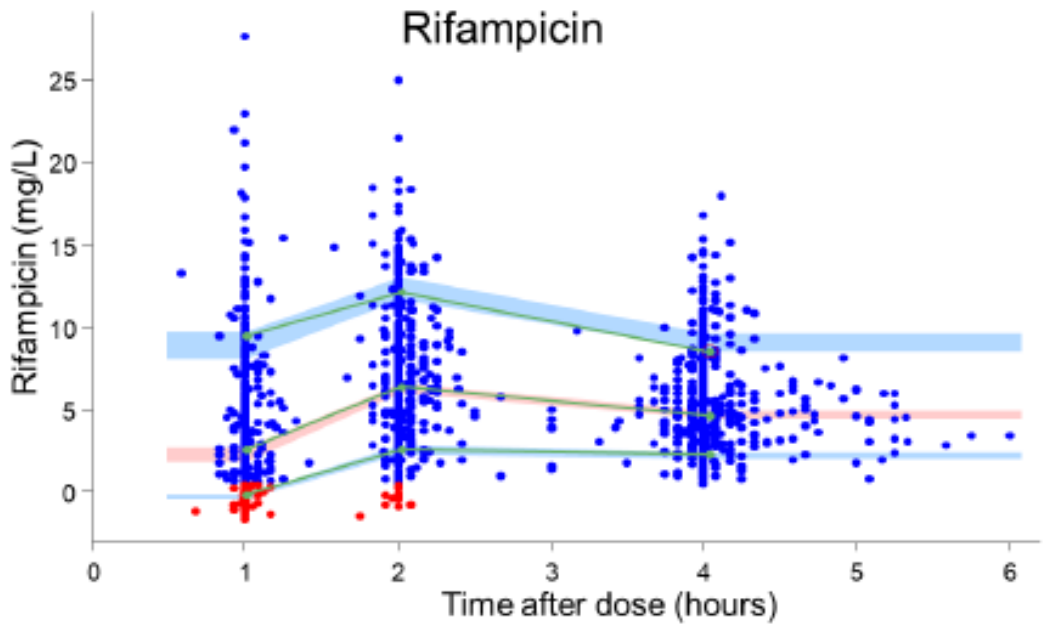
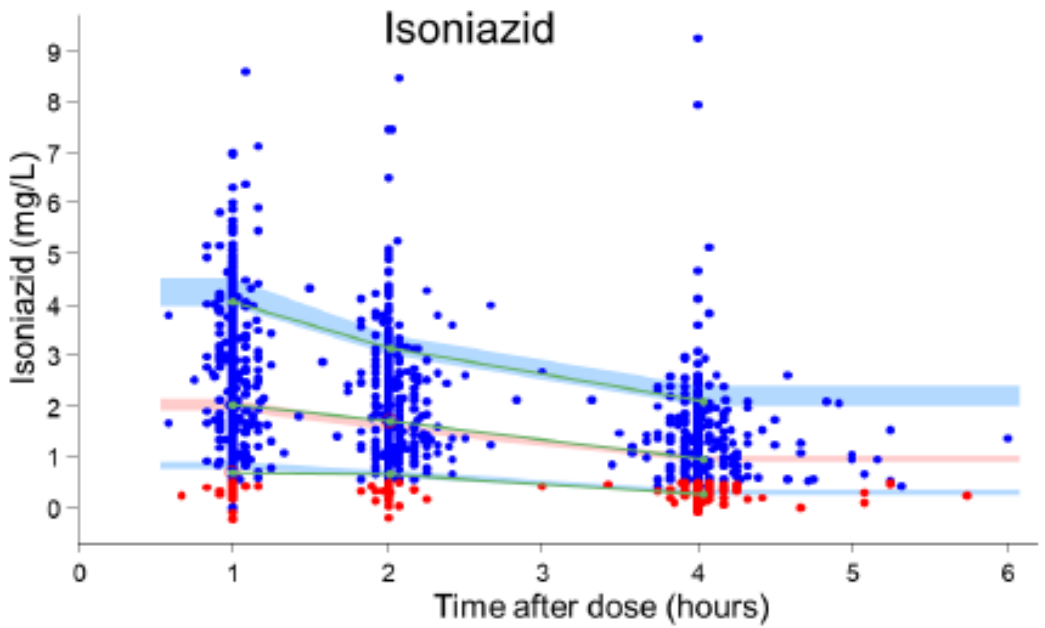
WGS for TB diagnosis

Low body weight leads to sub-optimal TB drug concentrations





Antimicrob Agents Chemother 2019 May 24;63(6).

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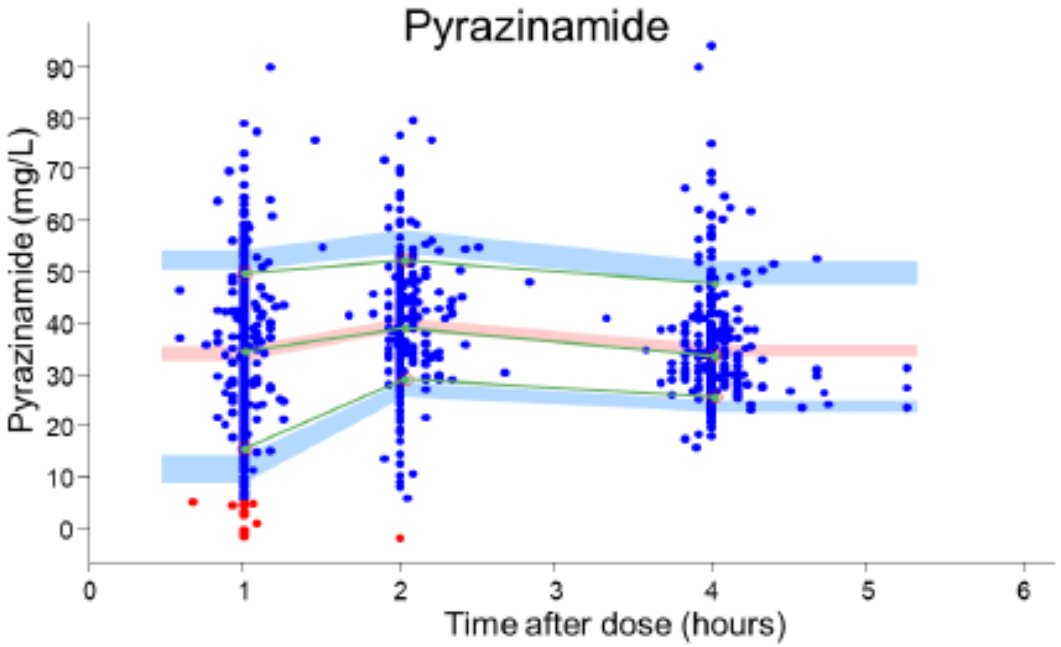
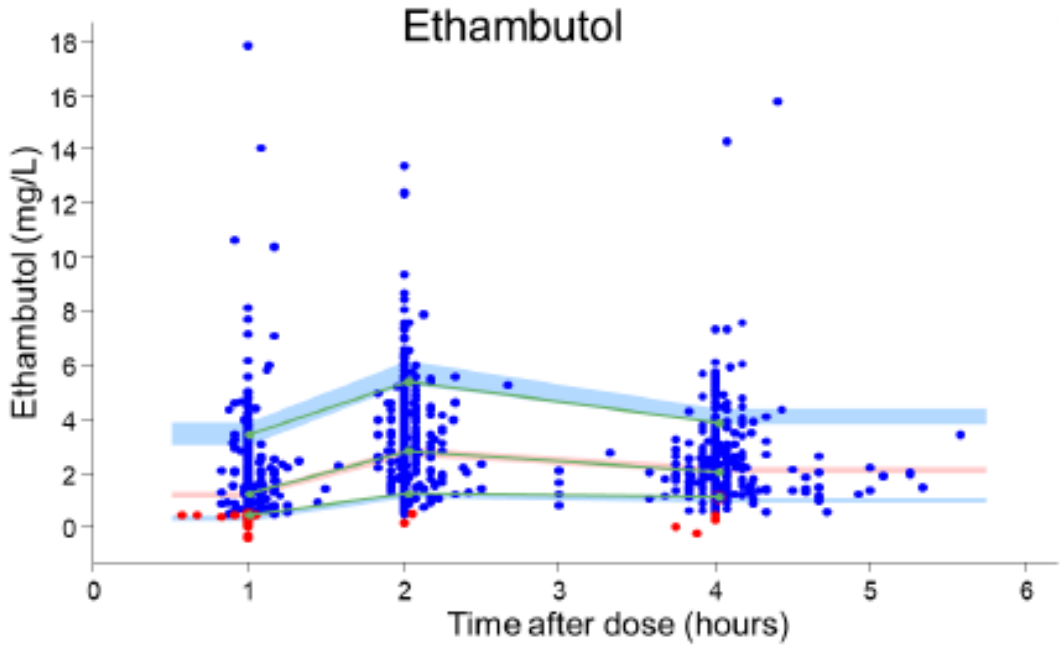
Low body weight leads to sub-optimal TB drug concentrations





Antimicrob Agents Chemother 2019 May 24;63(6).

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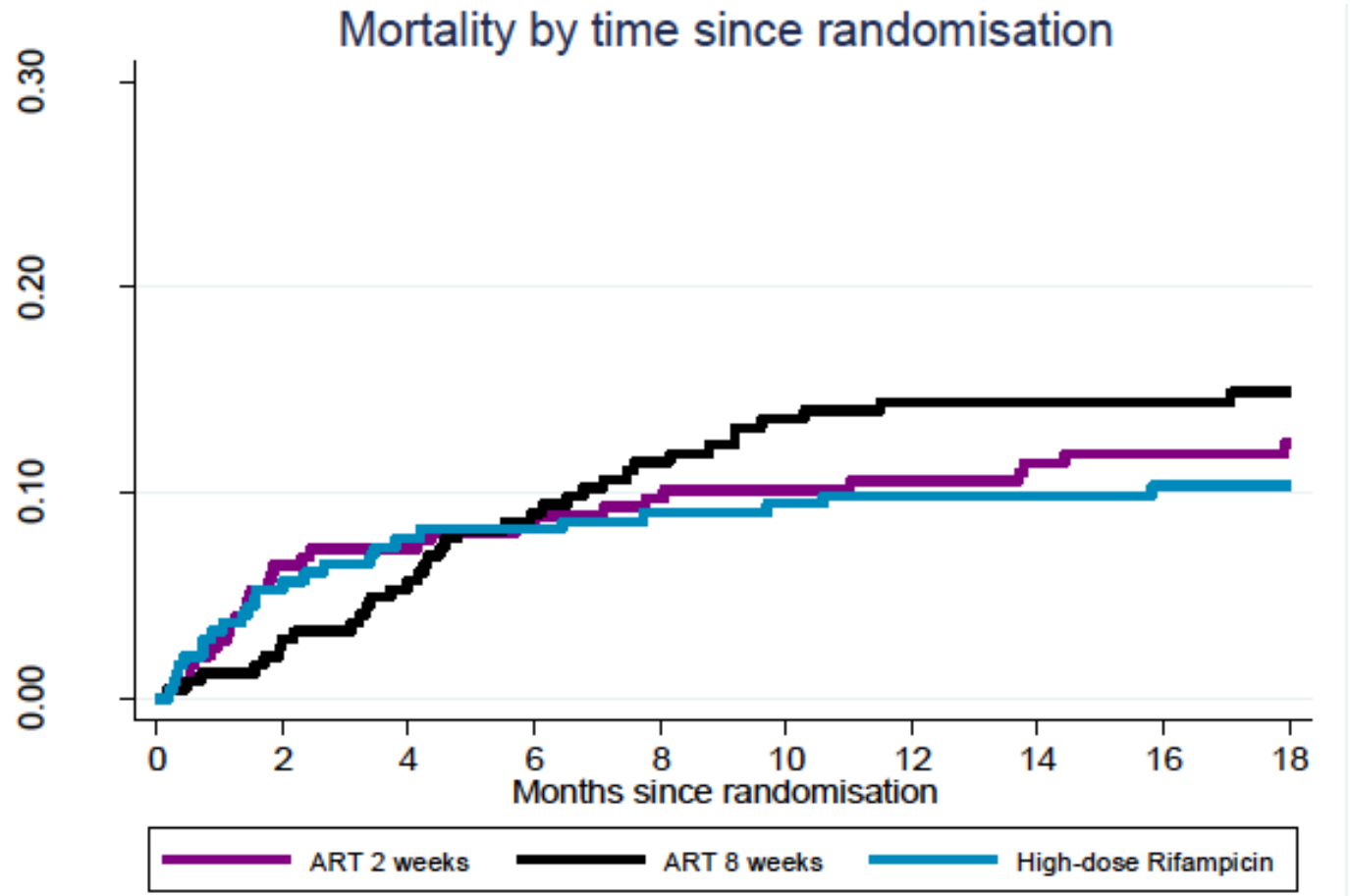
RAFA: High dose RMP in induction phase



Interaction between treatment arm & CD4 level
p= 0.005

2017 INTERTB Symposium, London, UK;

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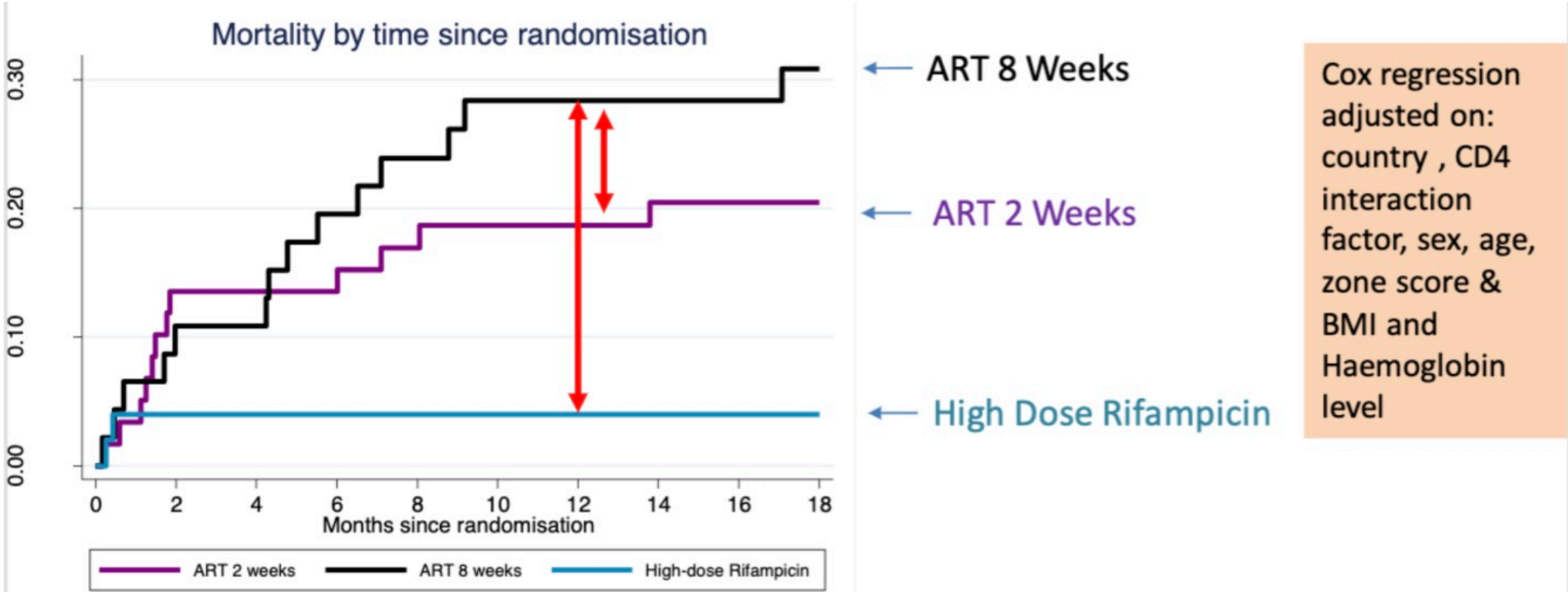
RAFA: High dose RMP in intensive phase (CD4<100)



2017 INTERTB Symposium, London, UK;

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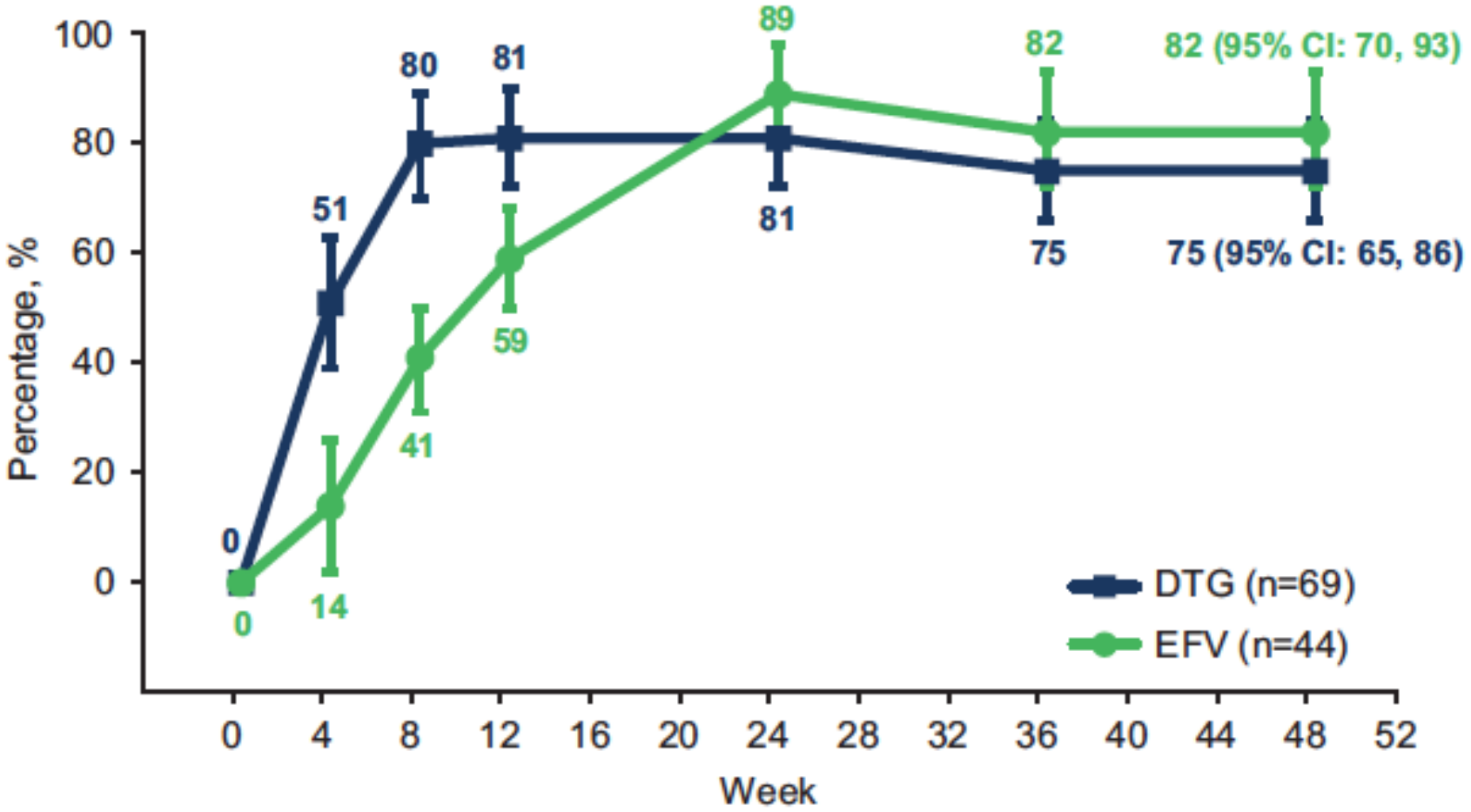
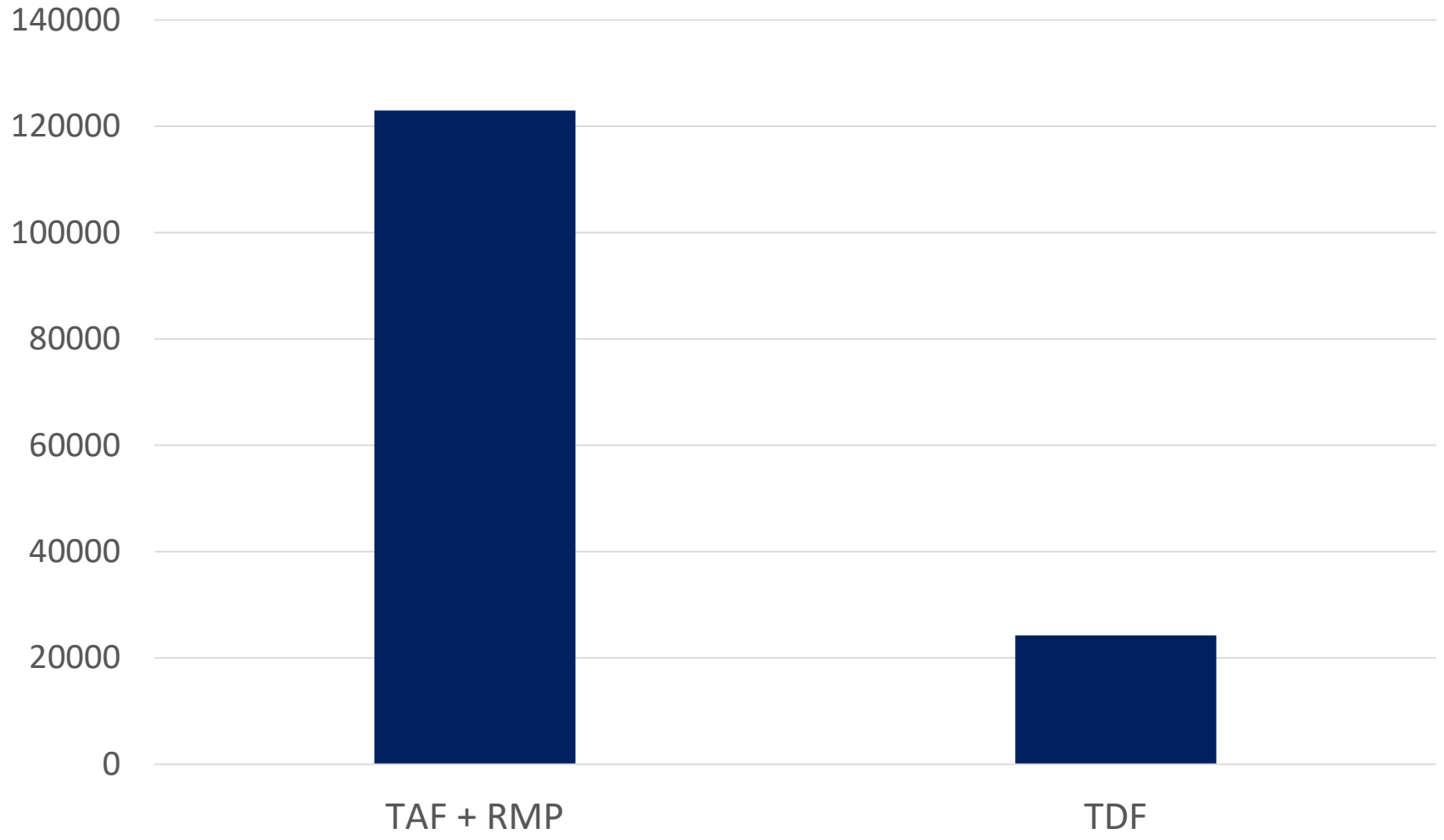
DTG bid efficacy with RMP



Clin Infect Dis March 2019 (epub).

TAF with RMP



Open Forum Infectious Diseases, February 2019, 6:2, ofz035,

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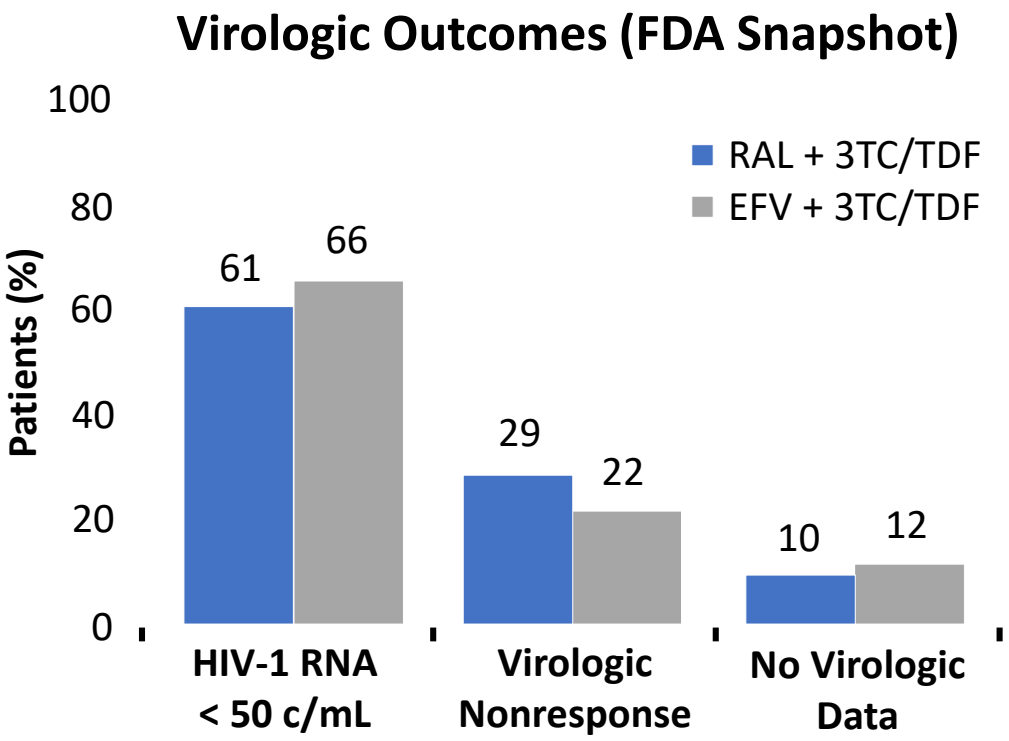
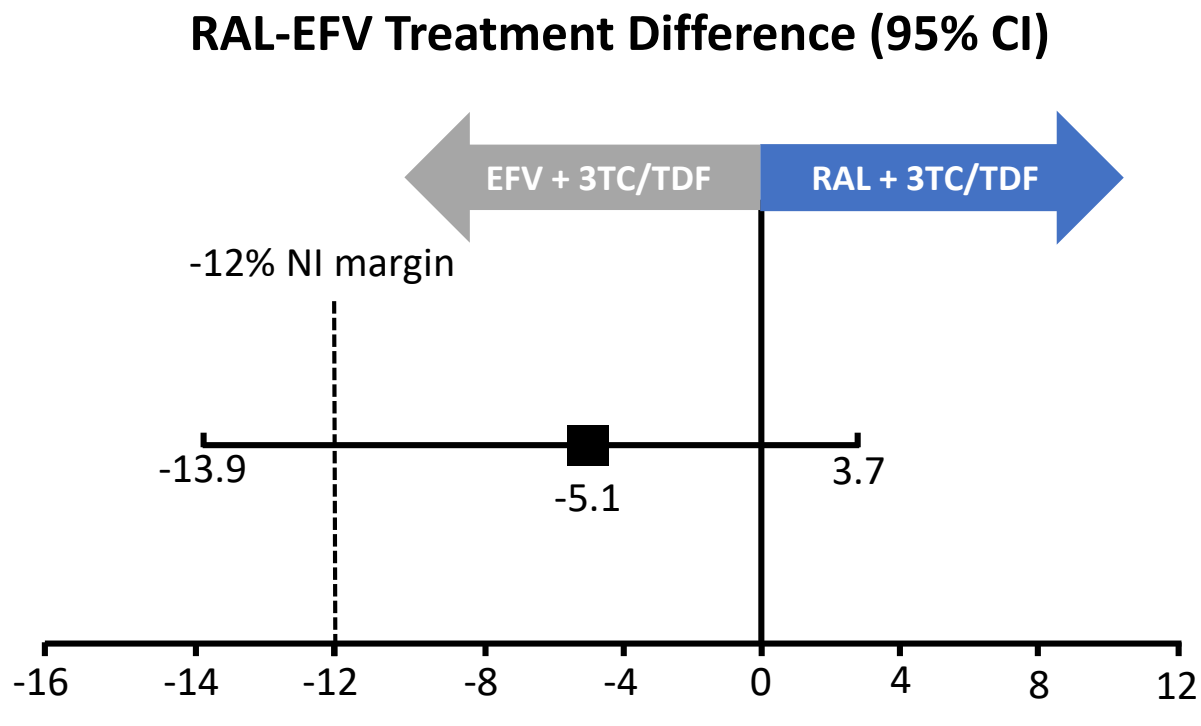
REFLATE 2 trial: RAL + RMP

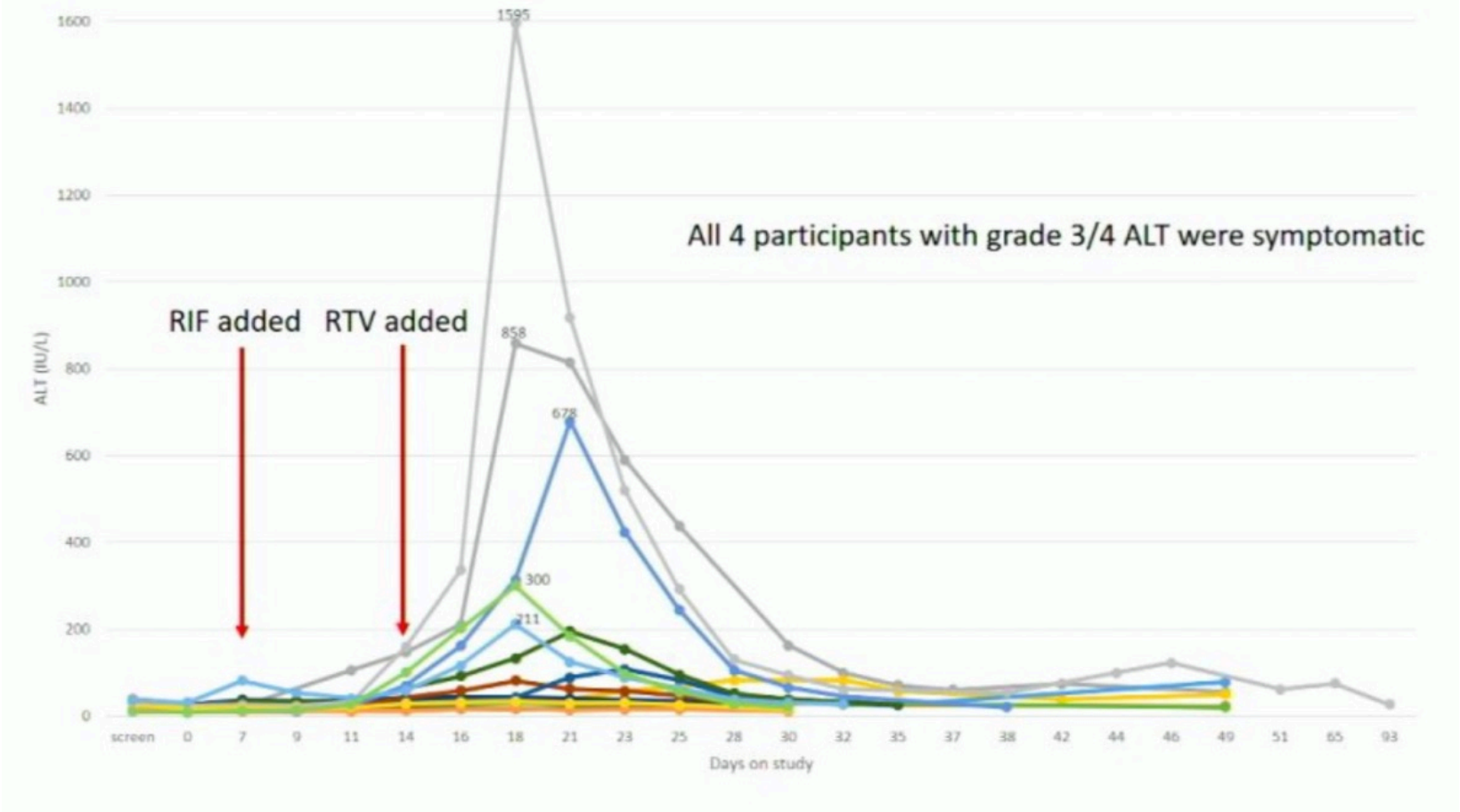
- RAL 400 mg BID + 3TC/TDF did not meet criteria for noninferior efficacy vs EFV 600 mg QD + 3TC/TDF





De Castro. IAS 2019. Abstr MOAB0101. Reproduced with permission.

Doubling DRV/r with RMP: Liver safety (ALT)



CROI 2019; abstr 81

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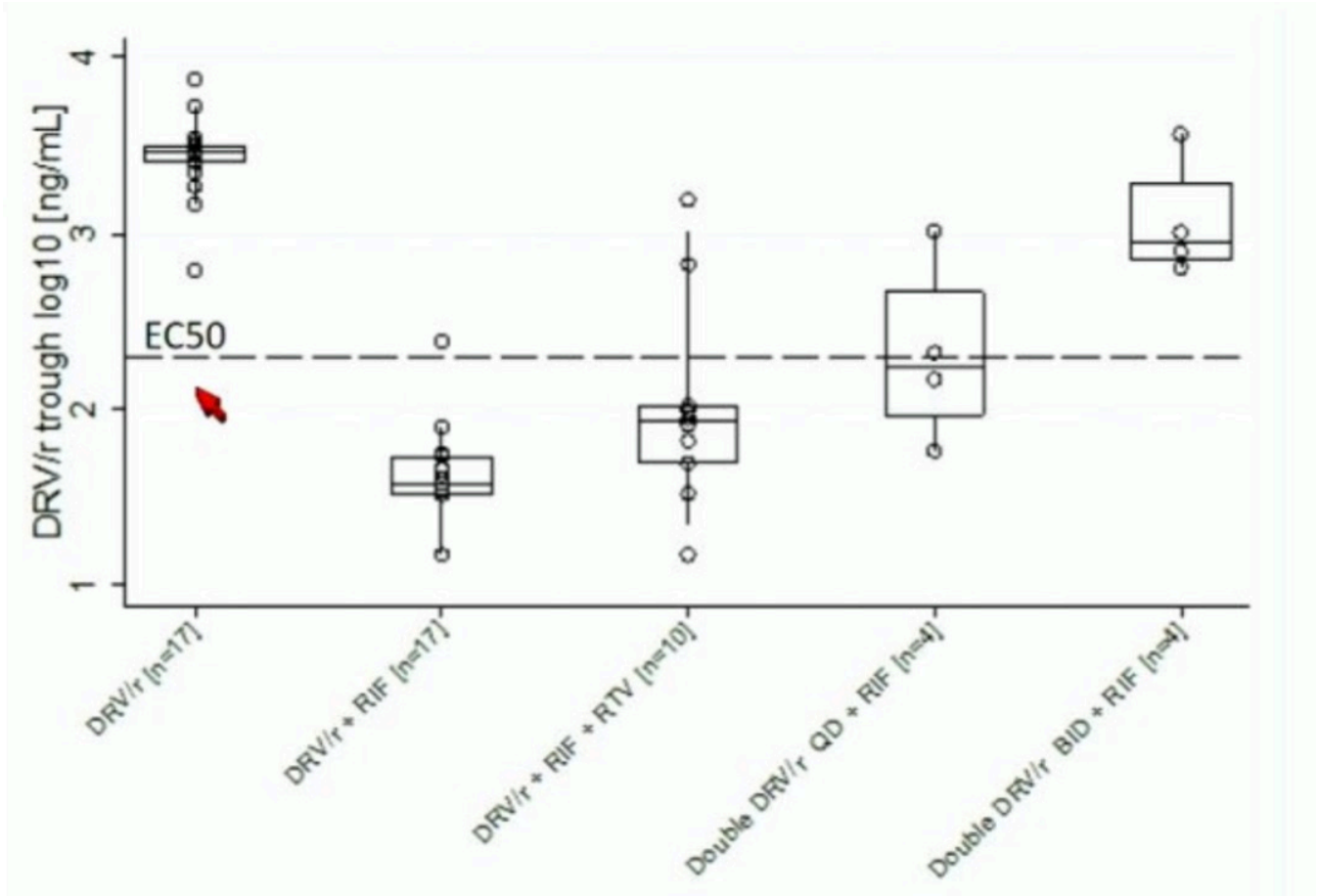
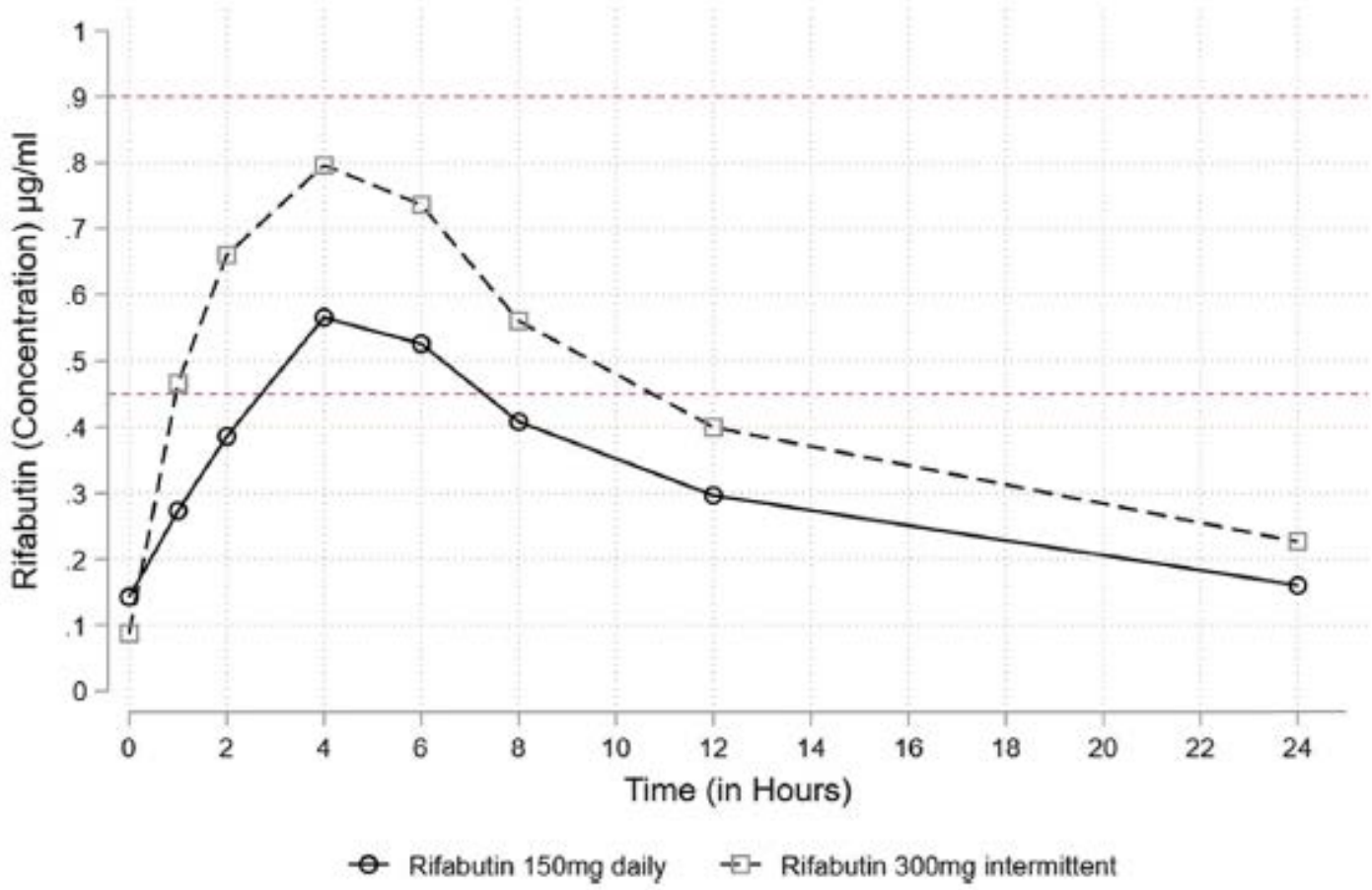
DRV trough concs across dosing regimens with RMP



CROI 2019; abstr 81

RBT concentrations with ATV/r



Indian J Tuberc. 2019 Jan;66(1):129-133

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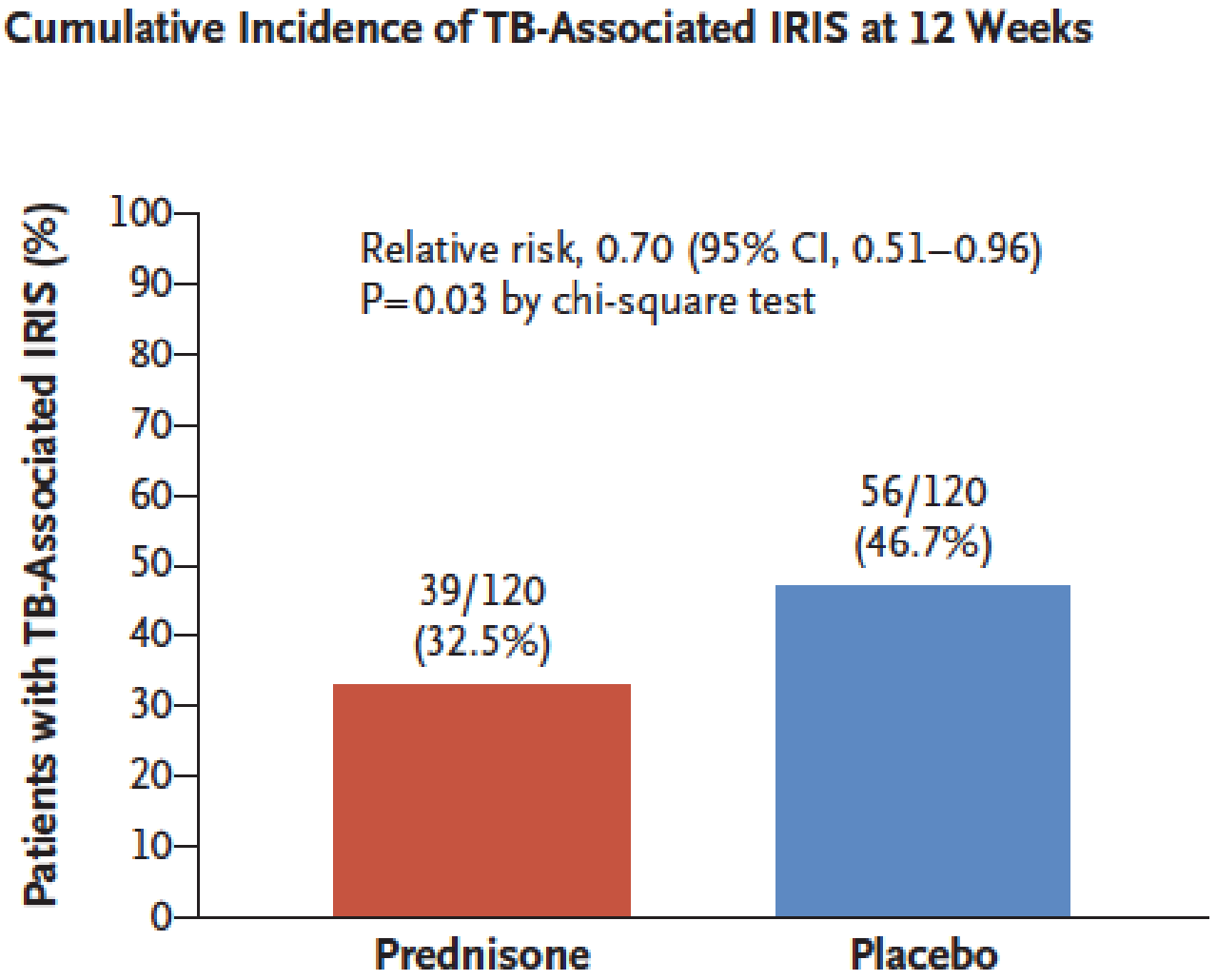
PRED-IRIS study



N Engl J 2018 Nov 15;379(20):1915-1925

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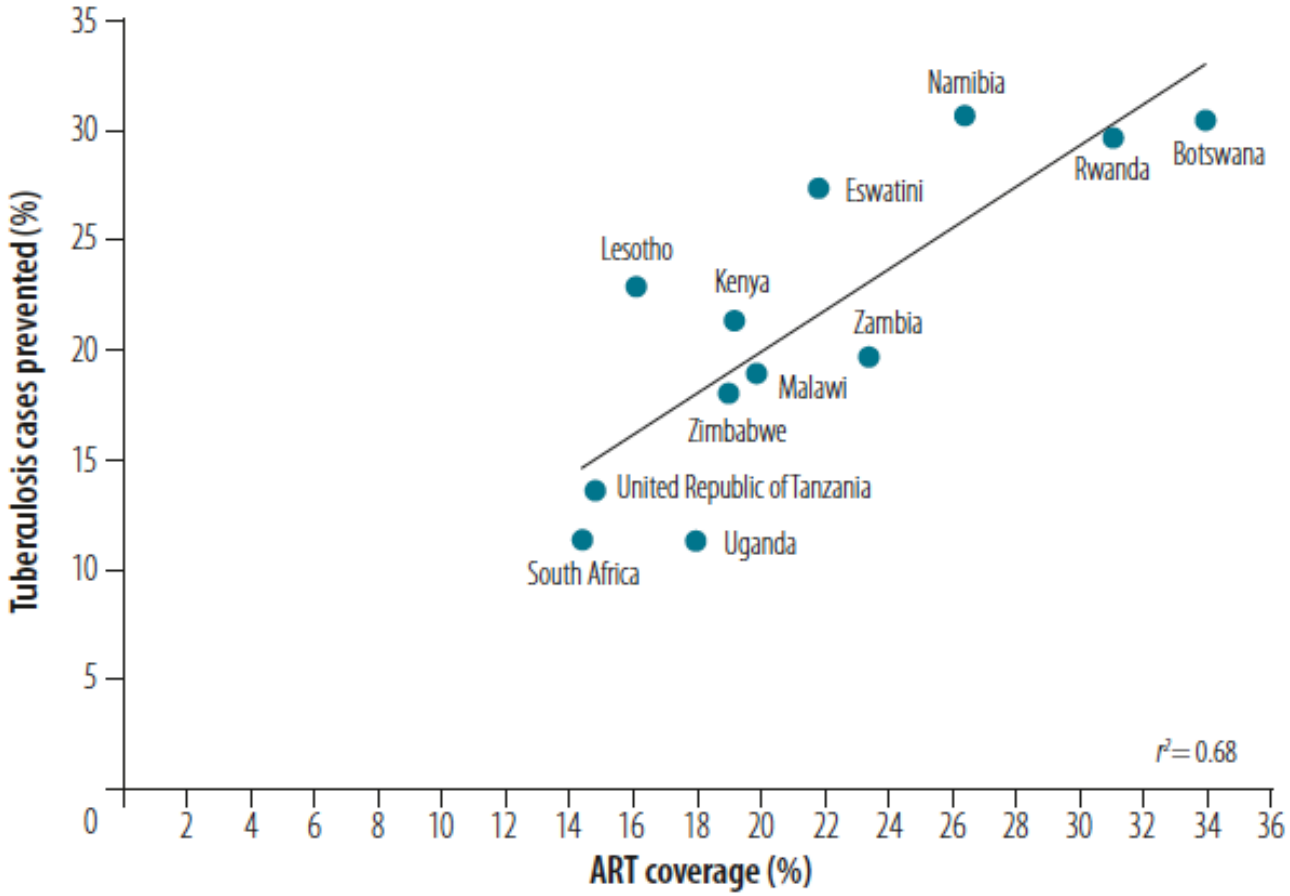
ART coverage and TB incidence



Bull World Health Organ 2019;97:405–414

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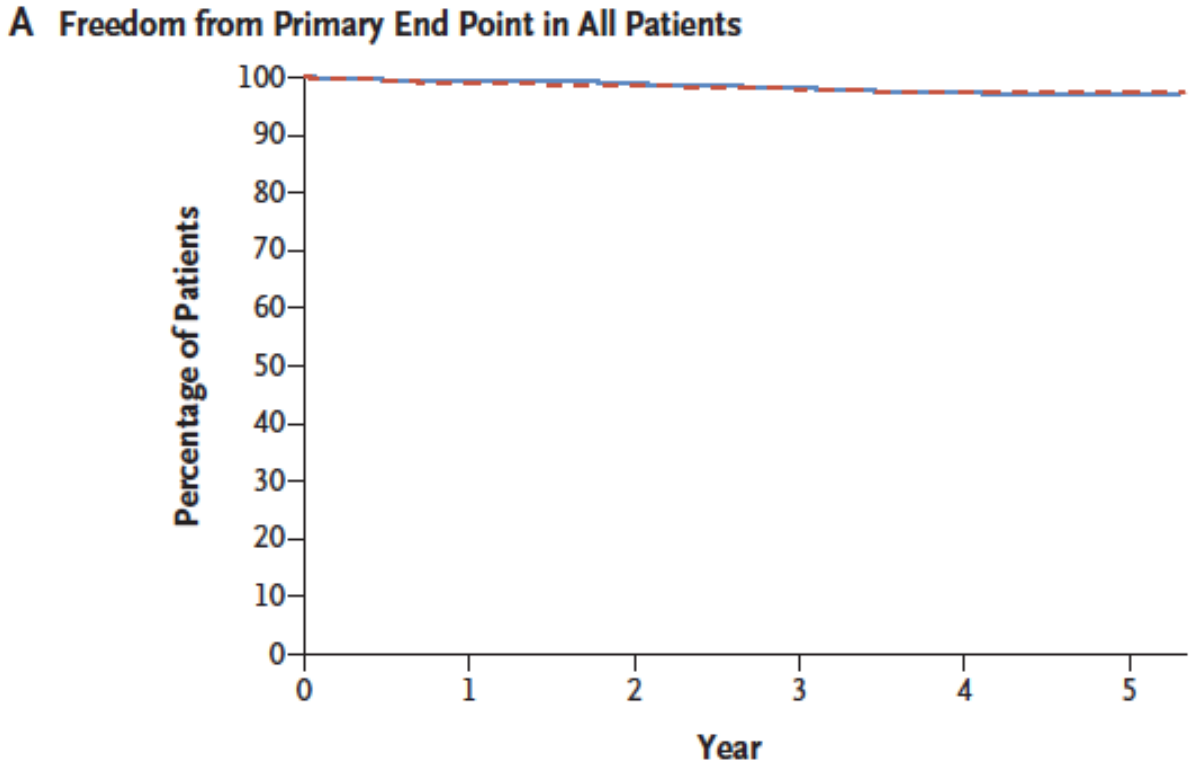
BRIEF TB/A5279: INH/RPT x 1 mo for preventing TB



N Engl J Med 2019;380:1001-11.

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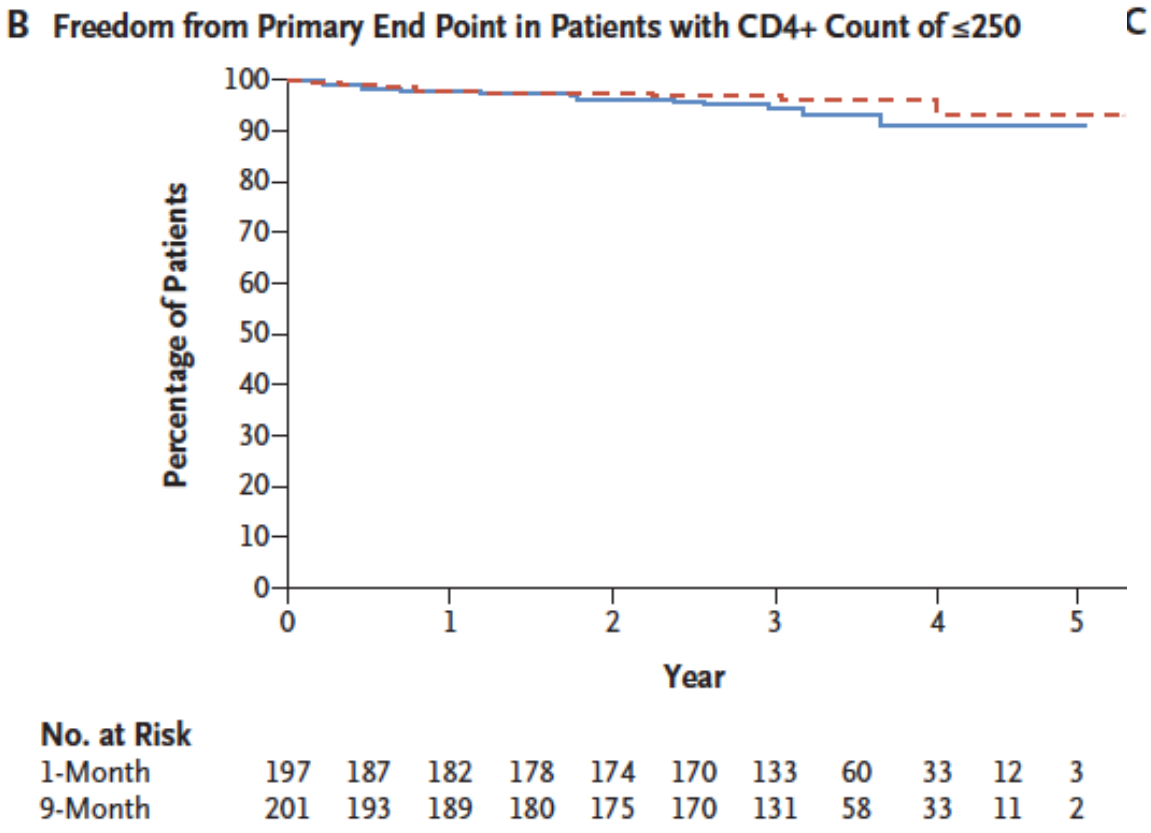
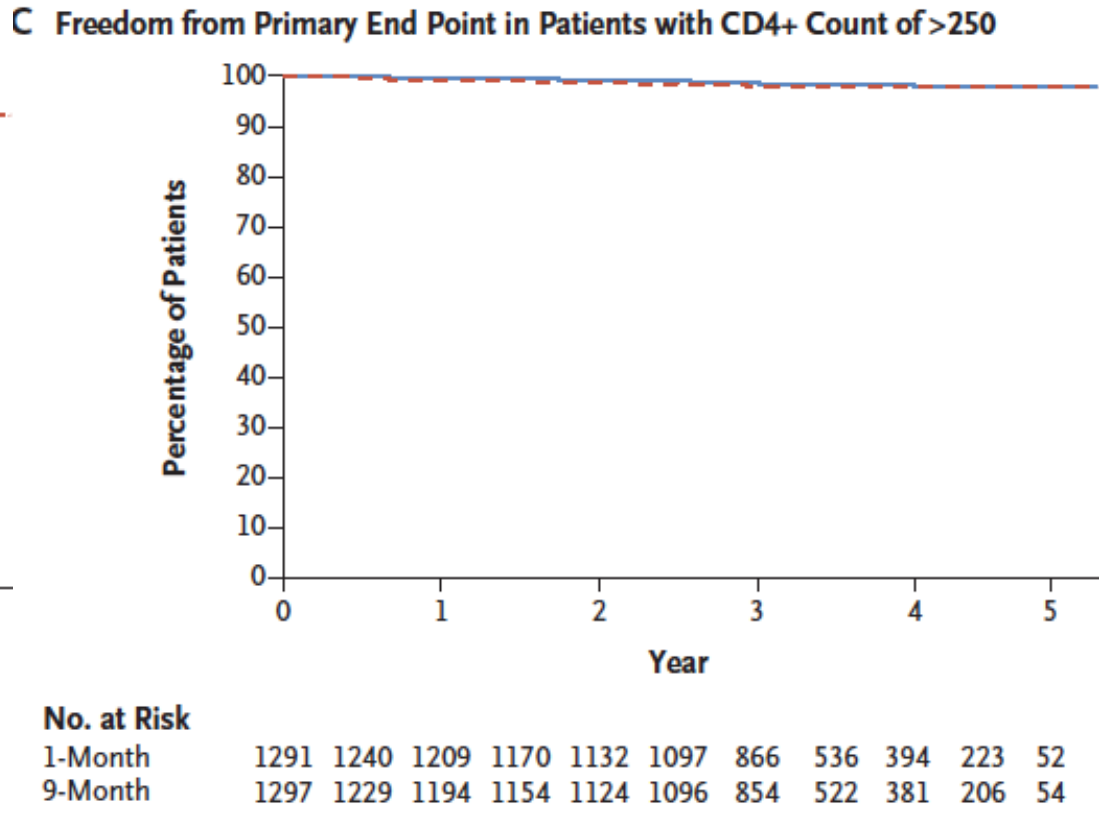
BRIEF TB/A5279: INH/RPT x 1 mo for preventing TB





N Engl J Med 2019;380:1001-11.

DOLPHIN: 3HP + DTG

	Total n	Prior to 1st HP dose n	After 1st HP dose n
AE Severity	CROI 2019; abstr 80		
Grade 2	2	1[a]	1[b]
Grade 3	3	1[c]	2[d]
Grade 4	0	0	0
Death	0	0	0

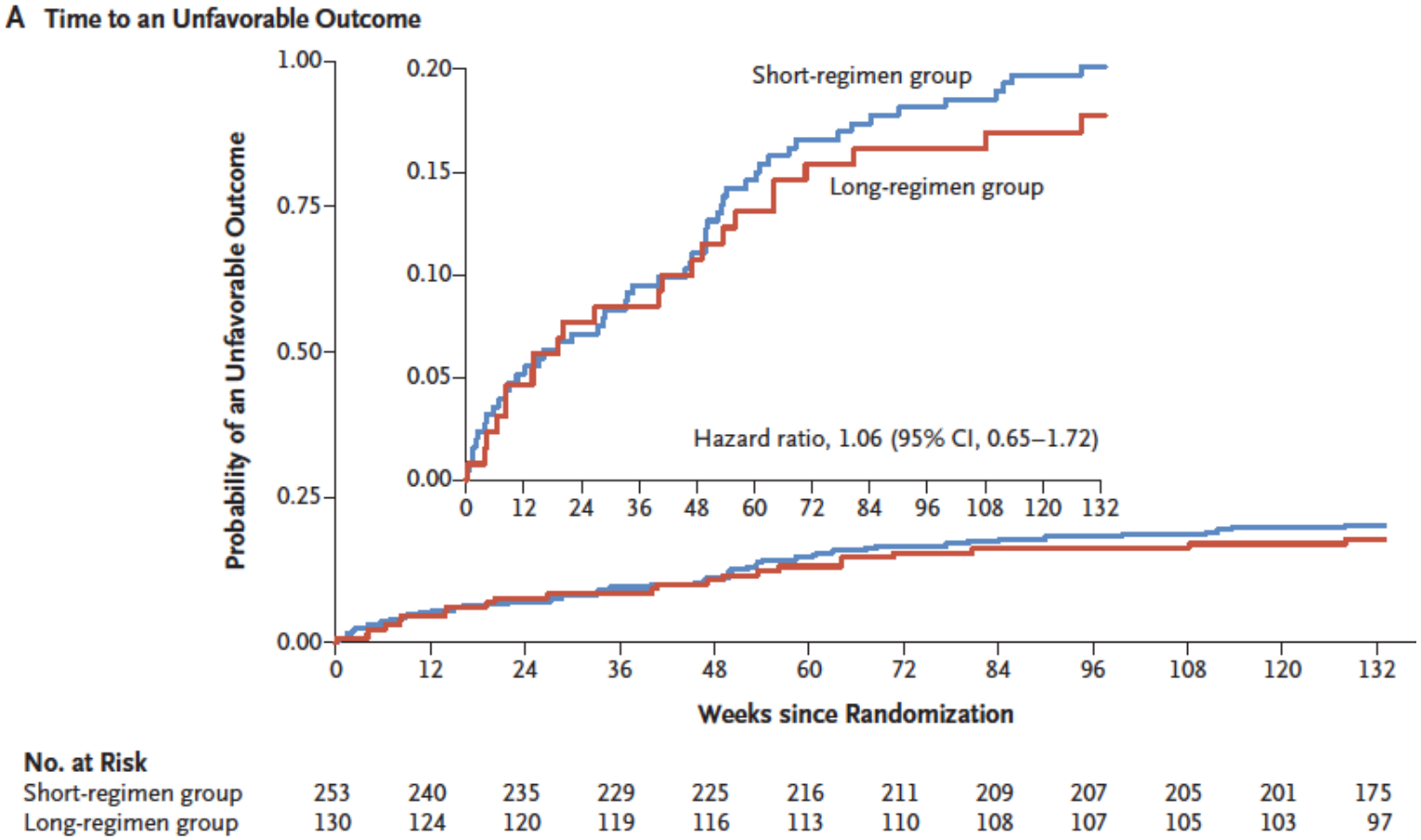
CROI 2019; abstr 80

DTG trough concs: alone and with 3HP

Study Day	Week on 3HP	N	Day Post HP Dose	Geometric mean	Troughs, 5th and 95th %	Regimen
57/58		60	0	1003	500 -2080	DTG alone
59	Week 1	30	1	1053	412 - 1834	DTG+HP
72	Week 2	30	7	492	200-1063	DTG+HP
73	Week 3	60	1	657	295-1502	DTG+HP
74	Week 3	60	2	355	134-933	DTG+HP
78	Week 3	30	6	388	140 - 794	DTG+HP
108	Week 8	60	1	703	289 - 1603	DTG+HP
109	Week 8	60	2	394	121 - 1079	DTG+HP

CROI 2019; abstr 80

STREAM: short regimen for MDRTB



N Engl J Med 2019;380:1201-13.

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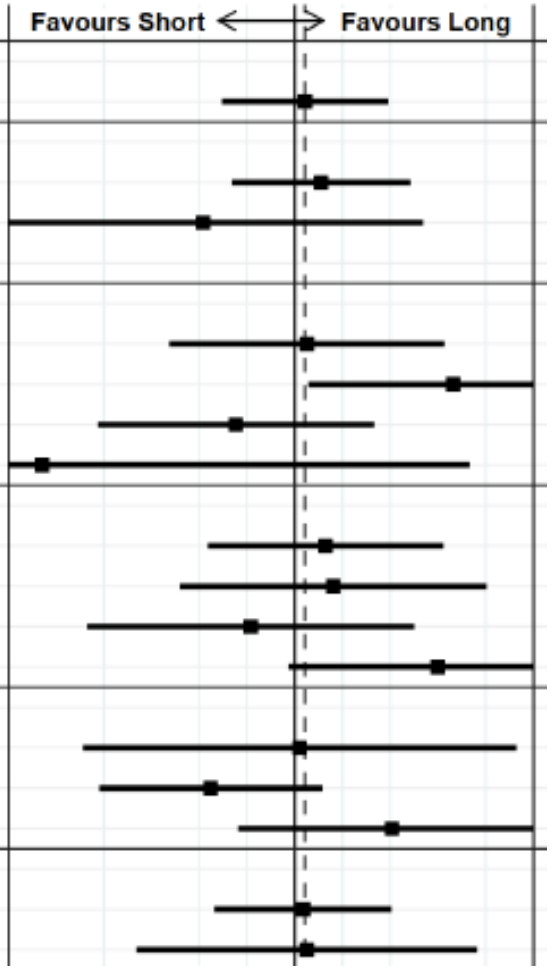
STREAM: short regimen for MDRTB

	Long regimen	Short regimen	Unadjusted difference (95% CI)
Overall			
Unstratified	25 (20.2%) / 124	52 (21.2%) / 245	1.1% (-7.7%, 9.8%)
Age			**Interaction p = 0.317**
<45 years	19 (18.3%) / 104	41 (21.0%) / 195	2.8% (-6.6%, 12.1%)
45-<65 years	6 (30.0%) / 20	10 (20.4%) / 49	-9.6% (-32.6%, 13.4%)
≥65 years	0 (0.0%) / 0	1 (100.0%) / 1	N/A
BMI			**Interaction p = 0.130**
<18kg/m²	11 (22.4%) / 49	23 (23.7%) / 97	1.3% (-13.2%, 15.7%)
18-<20kg/m²	2 (8.0%) / 25	15 (24.6%) / 61	16.6% (1.4%, 31.8%)
20-<25kg/m²	9 (20.5%) / 44	10 (14.3%) / 70	-6.2% (-20.6%, 8.3%)
≥25kg/m²	3 (50.0%) / 6	4 (23.5%) / 17	-26.5% (-71.3%, 18.3%)
Study site			**Interaction p = 0.276**
Ethiopia	4 (10.5%) / 38	11 (13.8%) / 80	3.2% (-9.1%, 15.6%)
Vietnam	5 (15.6%) / 32	12 (19.7%) / 61	4.0% (-12.0%, 20.1%)
South Africa	16 (35.6%) / 45	26 (31.0%) / 84	-4.6% (-21.7%, 12.5%)
Mongolia	0 (0.0%) / 9	3 (15.0%) / 20	15.0% (-0.6%, 30.6%)
Extent of disease			**Interaction p = 0.184**
None/minimal	2 (14.3%) / 14	4 (14.8%) / 27	0.5% (-22.2%, 23.2%)
Moderate	16 (23.2%) / 69	18 (14.4%) / 125	-8.8% (-20.5%, 2.9%)
Advanced	7 (18.9%) / 37	23 (29.1%) / 79	10.2% (-5.9%, 26.3%)
HIV status			**Interaction p = 0.970**
Negative	12 (14.3%) / 84	25 (15.2%) / 165	0.9% (-8.4%, 10.1%)
Positive	13 (32.5%) / 40	27 (33.8%) / 80	1.3% (-16.6%, 19.1%)



N Engl J Med 2019;380:1201-13.

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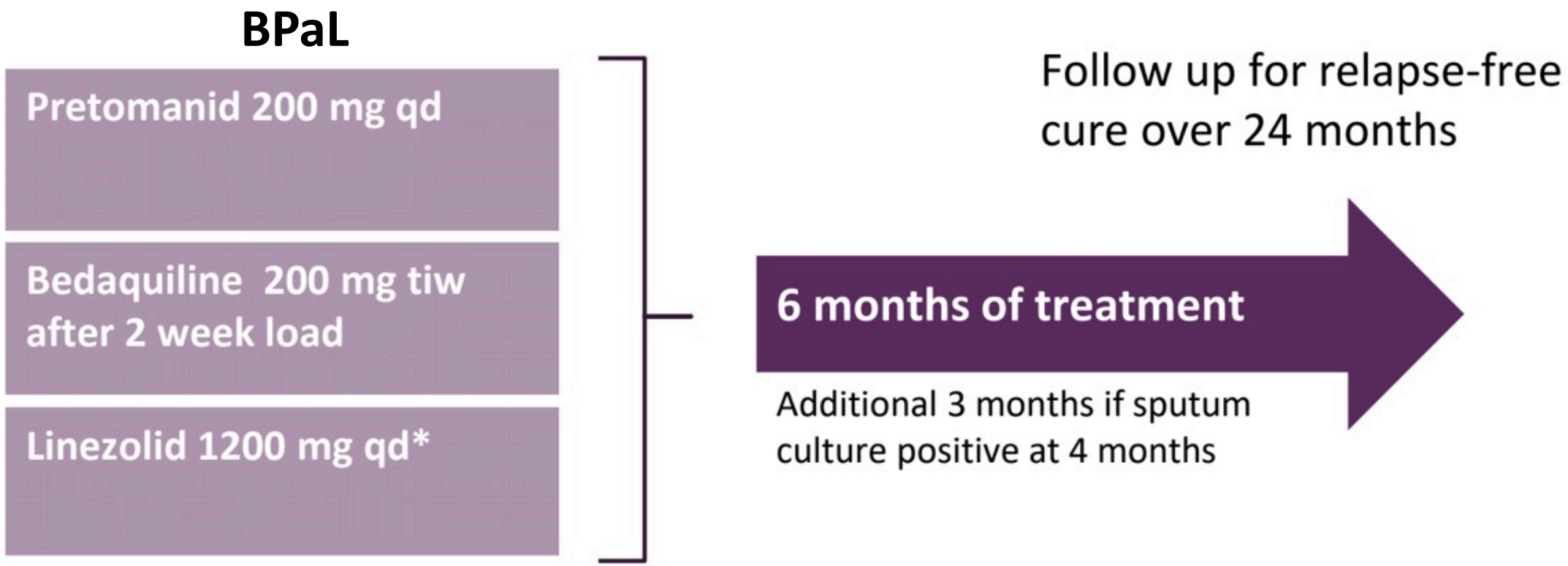
WHO: Components of longer MDRTB regimens

Groups & steps	Medicine	
Group A: **Include all three medicines**	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: **Add one or both medicines**	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

WHO consolidated guidelines 2019

N_{IXTB} trial: design



TB alliance, 2018

N_{IXTB} trial: Primary outcome (mITT)

	Total	XDR	MDR
Total for interim analysis	75	51	24
Unassessable*	1	1	0
Total Assessable	74	50	24
Favourable	66 (89%)	44 (88%)	22 (92%)
Unfavourable**	8 (11%)	6 (12%)	2 (8%)
95% CI for Favourable	(79.8%, 95.2%)	(75.7%, 95.5%)	(73.0%, 99.0%)

TB alliance, 2018

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N_{IXTB} trial: Primary efficacy by HIV status (mITT)

	Total	HIV negative	HIV positive
Total for interim analysis	75	37	38
Unassessable	1	0	1
Total Assessable	74	37	37
Favourable	66 (89%)	33 (89%)	33 (89%)
Unfavourable	8 (11%)	4 (11%)	4 (11%)
95% CI for Favourable	(79.8%, 95.2%)	(74.6%, 97.0%)	(74.6%, 97.0%)

TB alliance, 2018

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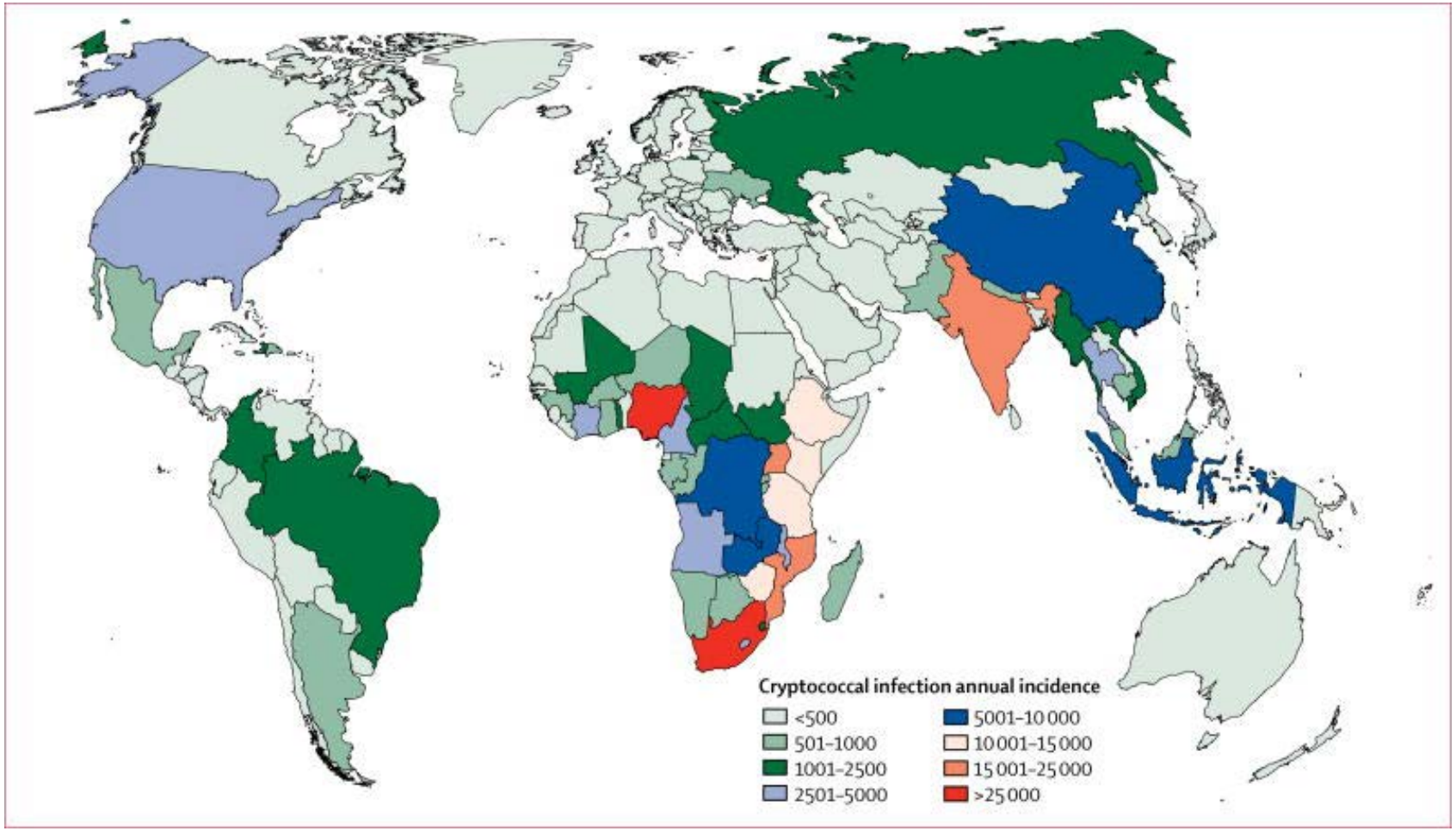
TB: Some research ideas

- High dose Anti-TB drugs to optimize treatment
  - DDIs of high dose RMP with ARVs
- Outcomes of rifabutin based treatment for TB
- Impact of newer rapid POC screening tests on morbidity/mortality
- Outcomes of newer recommended MDRTB regimens in PLHIV

Outline

- The problem
- Mycobacterial
- Fungal
- Viral
- Protozoal
- Bacterial

Annual incidence of cryptococcal infection



Lancet Infect Dis 2017 Aug;17(8):873-881

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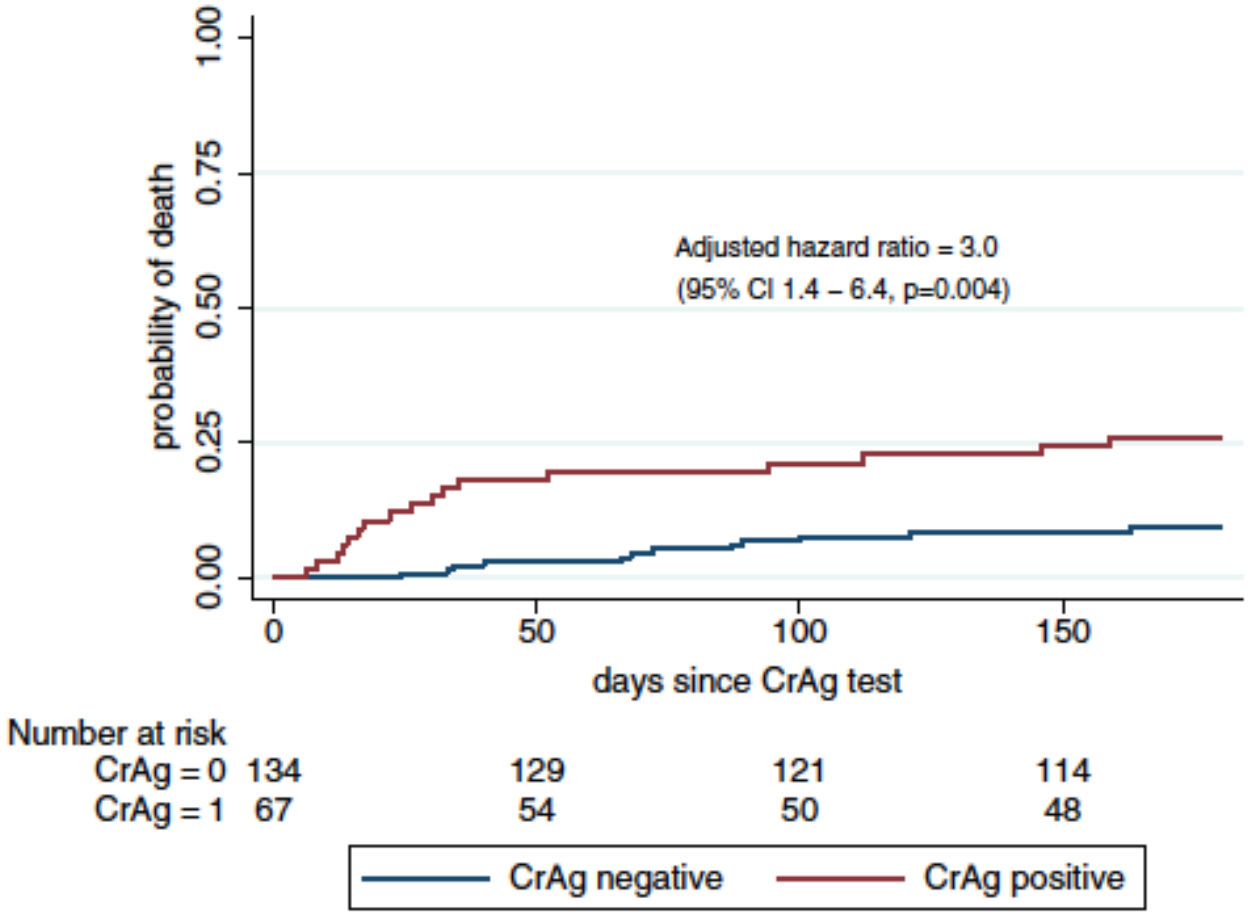
ScRAG positive mortality



Clin Infect Dis. 2019 Jun 8

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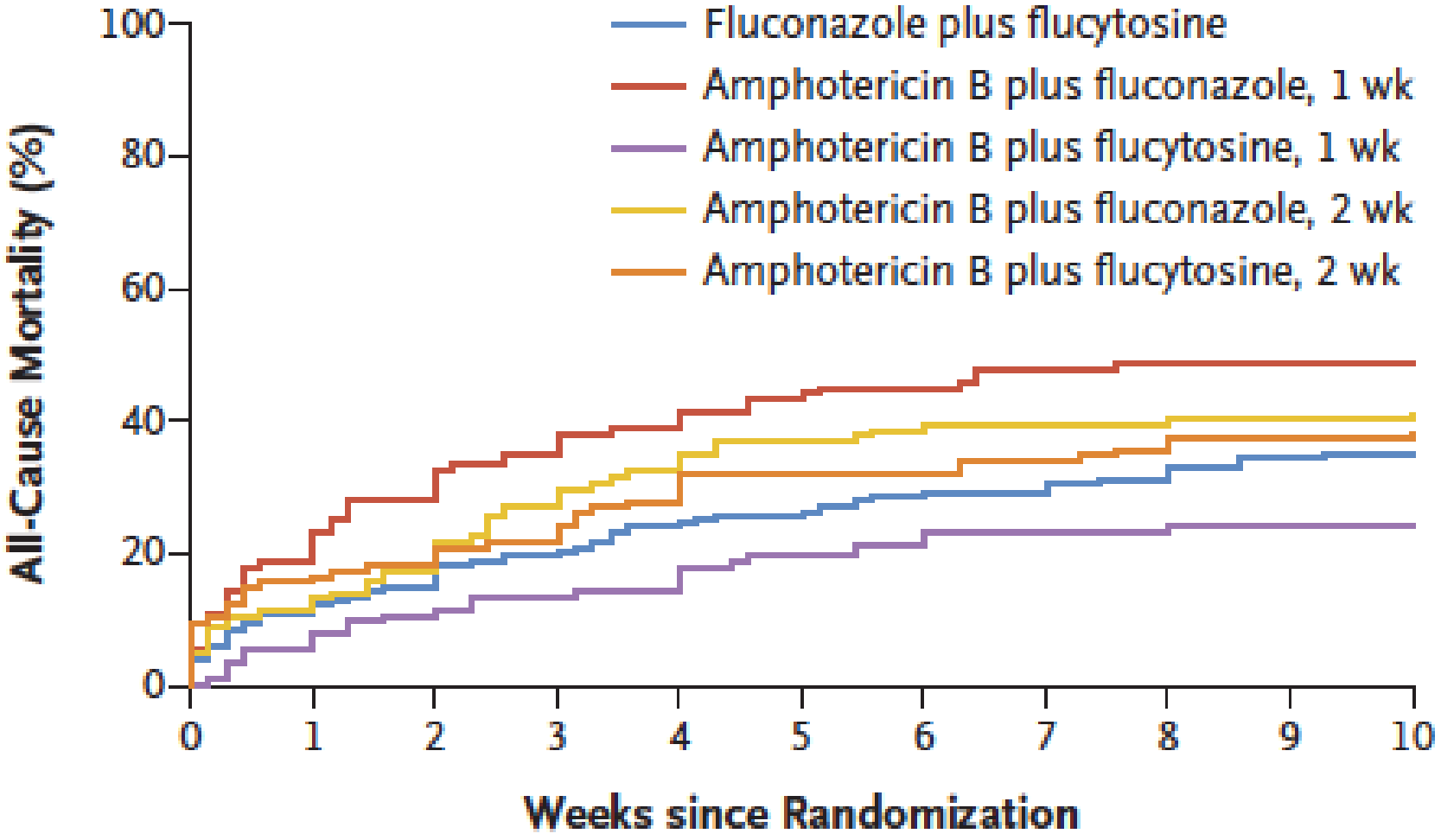
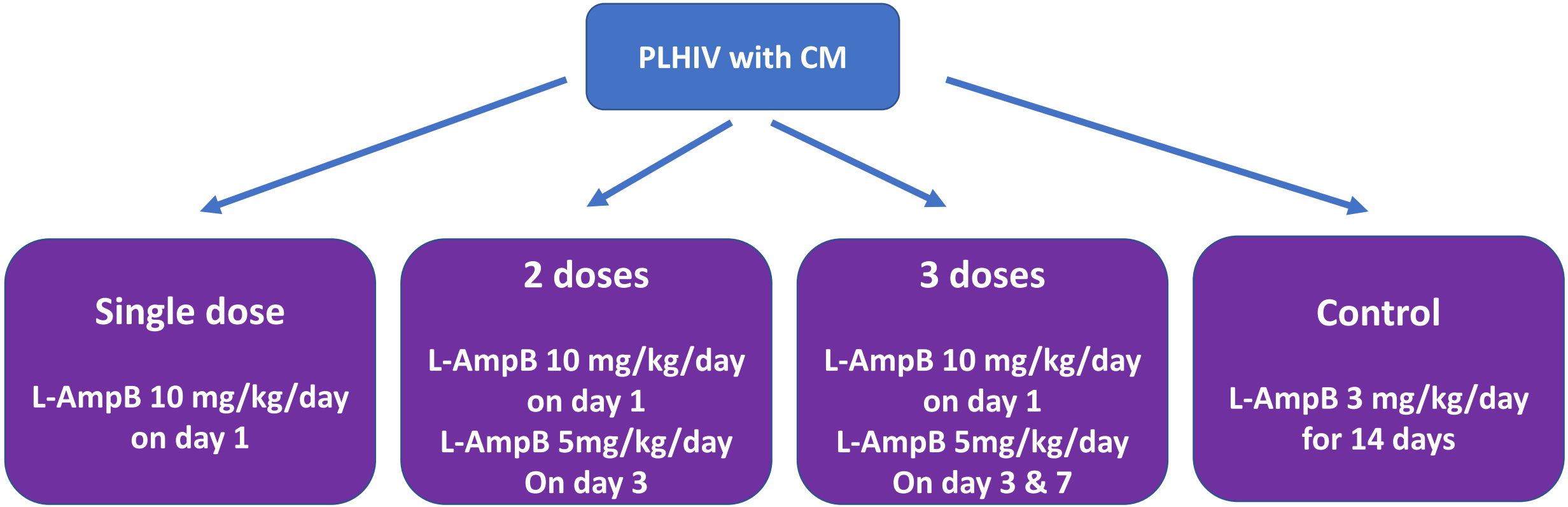
ACTA: Treatment of CM in PLHIV



N Engl J Med 2018; 378:1004-1017

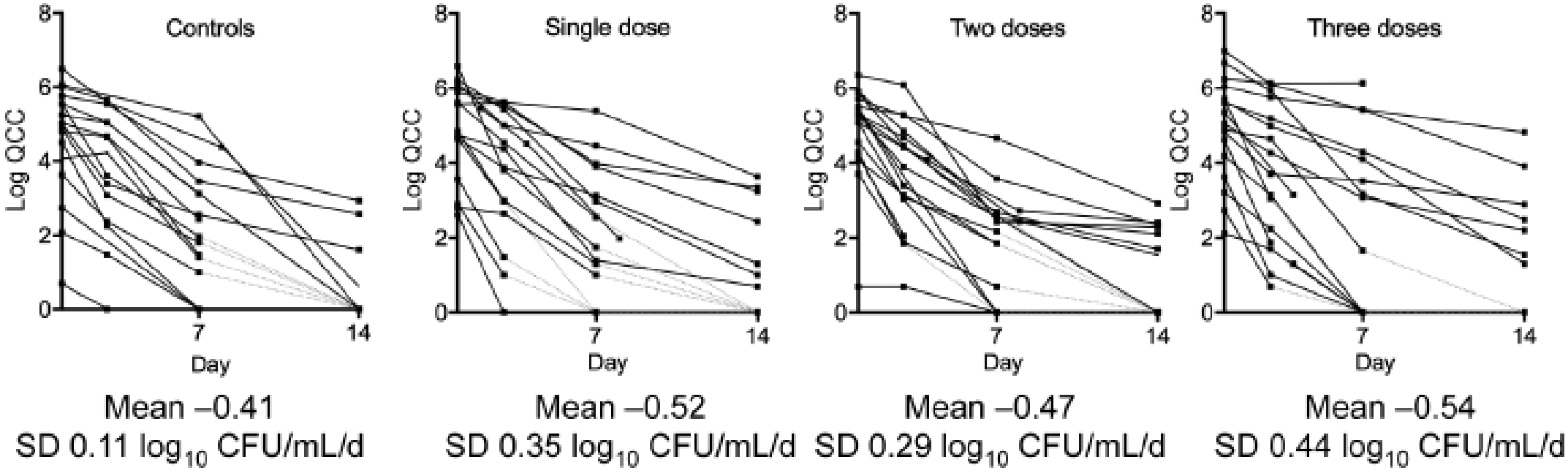
Ambition-CM trial: design



+ fluconazole 1200 mg/day x 14 days

Clin Infect Dis 2019 Feb;68:3:393-401

EFA with L-AmB short course



Clin Infect Dis 2019 Feb;68:3:393-401

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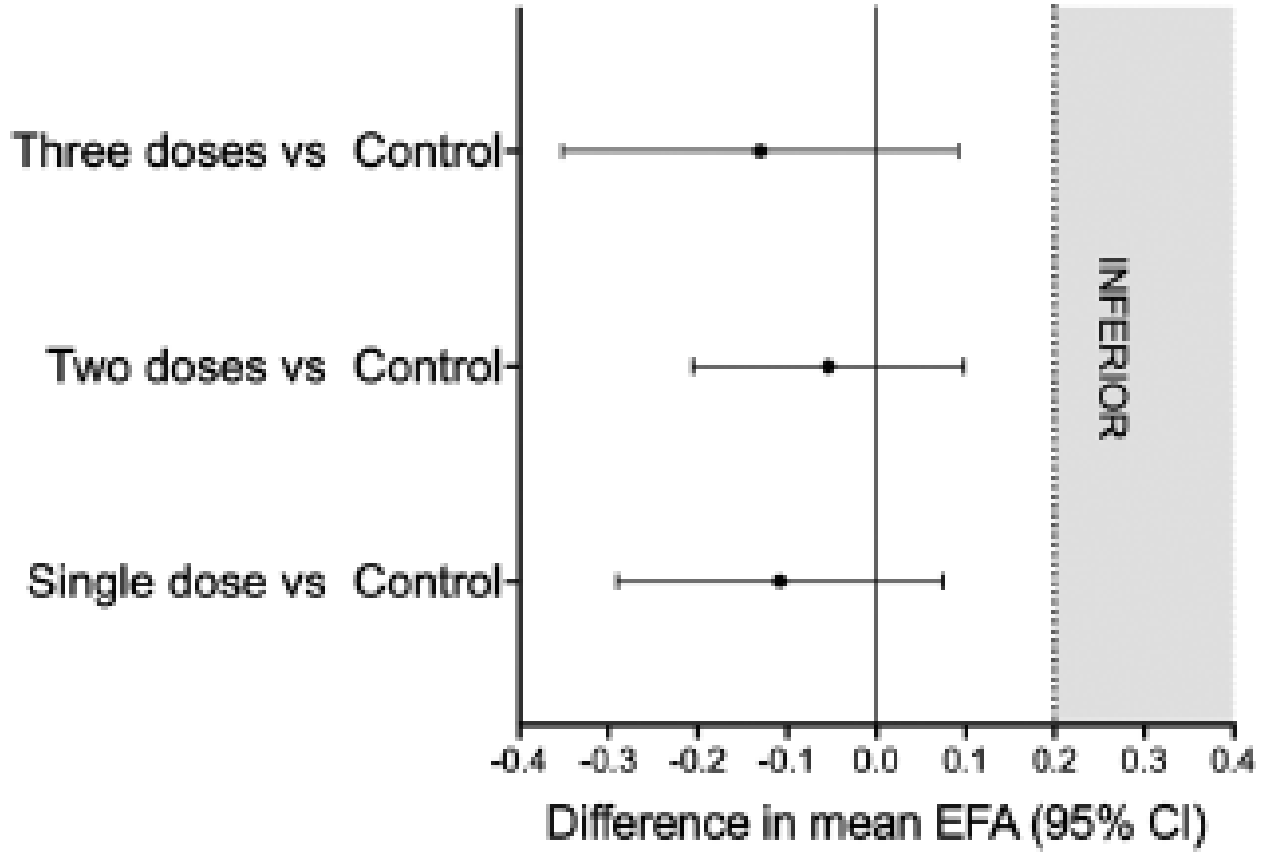
Efficacy of short course L-AmpB



Clin Infect Dis 2019 Feb;68:3:393-401

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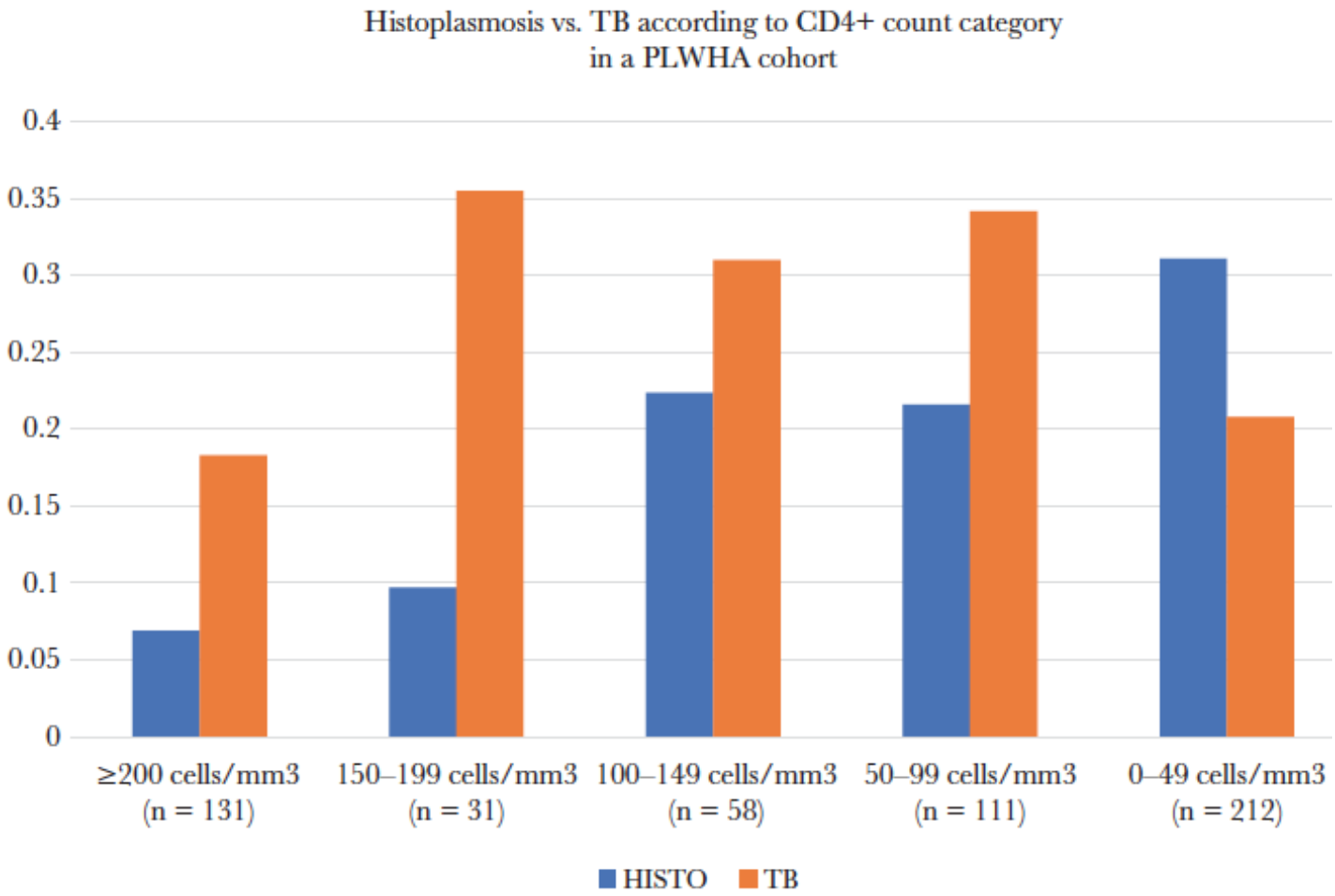
Histoplasmosis vs TB in Brazil



Open Forum Infect Dis 2019 Apr 13;6(4):ofz073

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Clinical prediction of histoplasmosis

Clinical Variable	Odds Ratio (95% Confidence Interval)
CD4+ <50 cells/mm^3	2.11 (1.17–3.82)
Pancytopenia	1.79 (1.00–3.21)
Miliary pattern on thorax imaging	2.72 (1.35–5.46)
Hepatomegaly on clinical examination	2.47 (1.28–4.76)
Generalized lymphadenopathy	0.37 (0.11–0.96)
Lactate dehydrogenase >1000 IU/L	3.60 (1.94–6.69)

Abbreviation: PLWHA, people living with HIV/AIDS.

Open Forum Infect Dis 2019 Apr 13;6(4):ofz073

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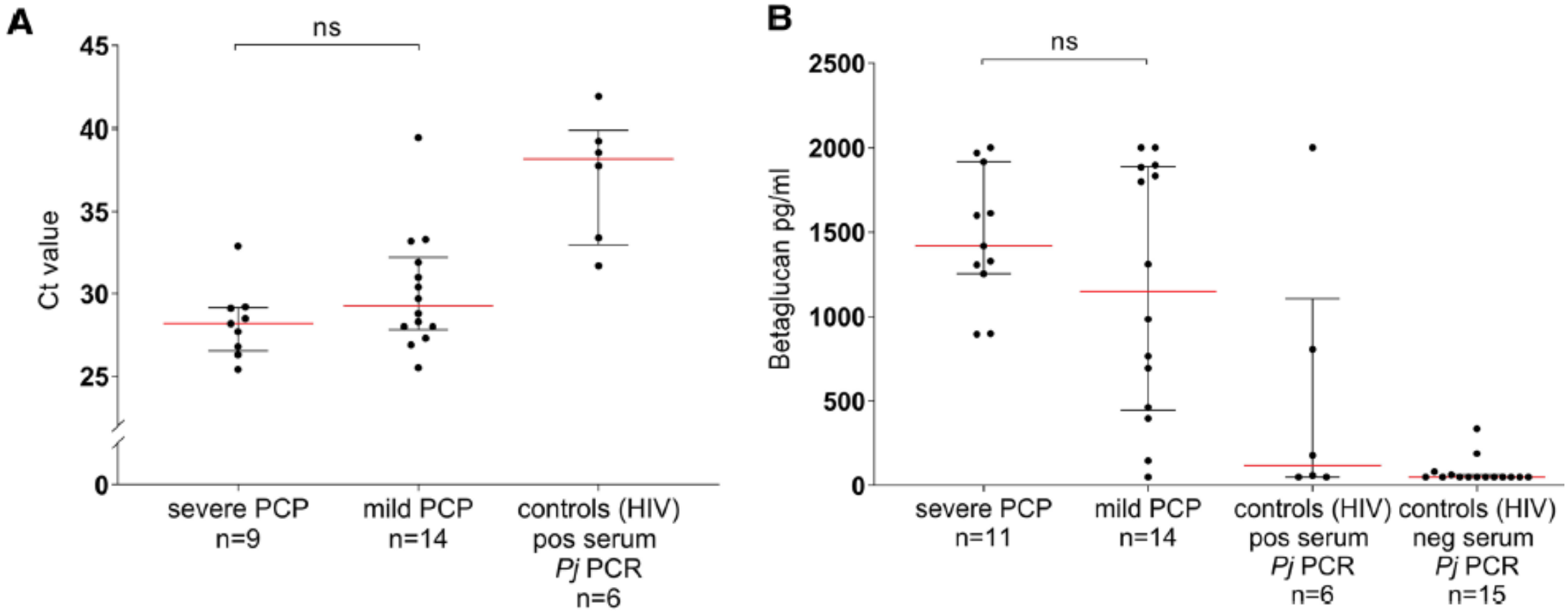
PjPCR and Betaglucan in serum in PCP

Index tests in serum	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	
	Patients with PCP	HIV-infected control patients	Blood donors
	$n = 26$	$n = 21$	$n = 18$
Pj PCR positive	100 (87–100)	71 (50–86)	100 (87–100)
Pj PCR with Ct ≤34[a]	96 (79–100)	90 (71–98)	100 (82–100)
BG ≥80 pg/ml[b]	96 (80–100)	71 (50–86)	100 (82–100)
BG ≥200 pg/ml[b]	92 (75–99)	86 (65–95)	100 (82–100)
BG ≥400 pg/ml[b]	88 (70–96)	90 (71–98)	100 (82–100)
Pj PCR positive *and* BG ≥200 pg/ml[b]	92 (75–99)	90 (71–98)	100 (82–100)

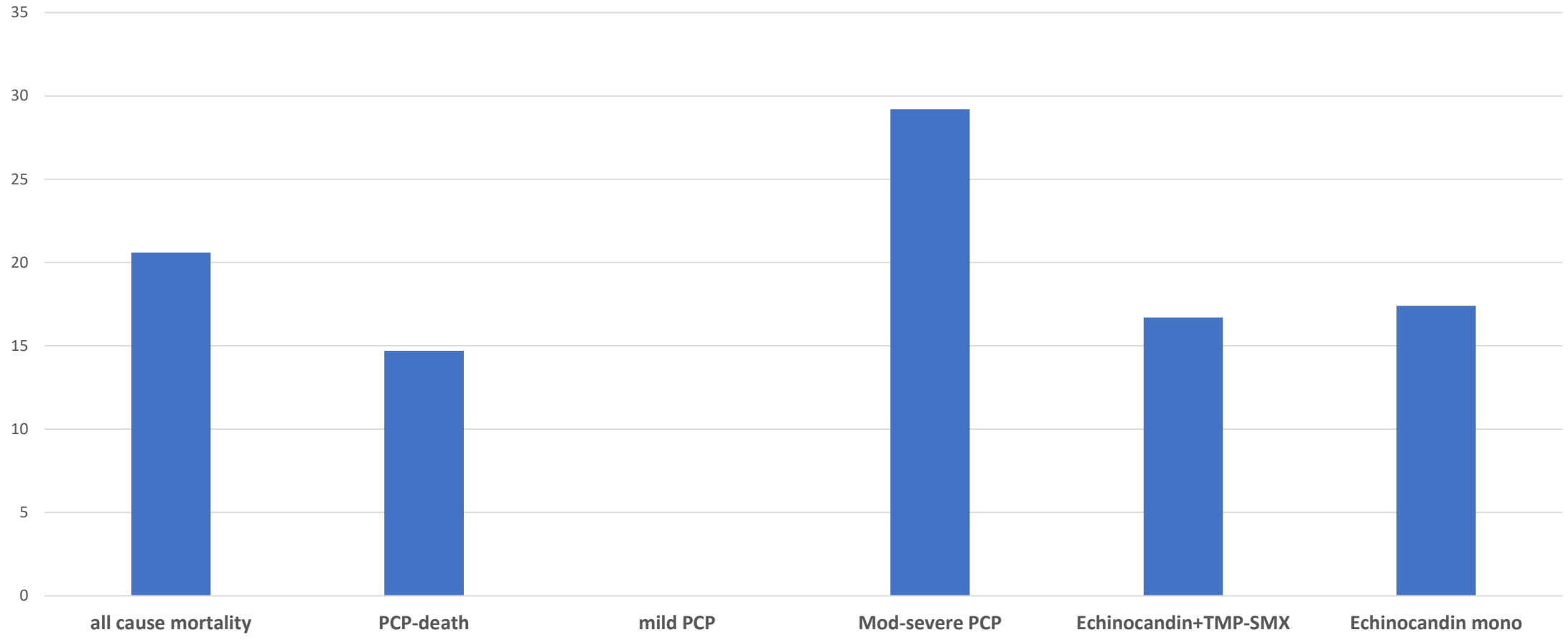
BMC Infect Dis 2019 Jul 23;19(1):658

PCRct values and B-glucan levels and severity of PCP



BMC Infect Dis 2019 Jul 23;19(1):658

Echinocandins for PCP



AIDS 2019, 33:1345–1351

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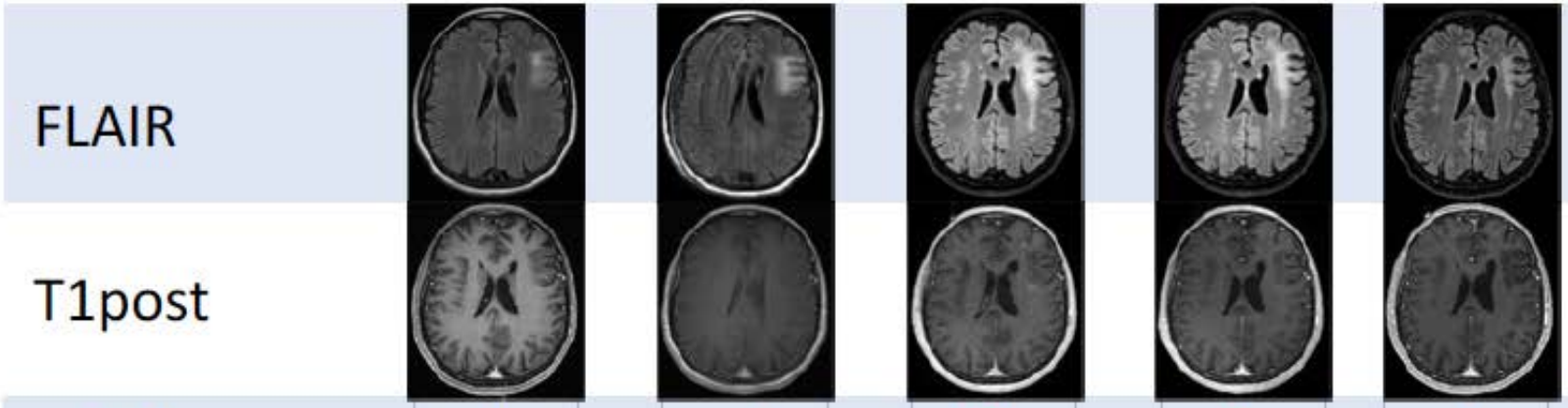
Fungal: Some research ideas

- Optimal regimen for pre-emptive treatment of cryptococcemia
- Clinical Scoring tool for differentiating histoplasma vs TB
- Optimal management of histoplasmosis in PLHIV
- Non-invasive diagnosis of PCP

Outline

- The problem
- Mycobacterial
- Fungal
- Viral
- Protozoal
- Bacterial

Pembrolizumab for PML



month	-4	-3	0	1	6
MRS	-	-	3	3	2
JCV#	-	-	63	15	*und*

- Left upper extremity weakness
- Transcortical motor aphasia
- Cortical visual impairment
- Cognitive changes

New Engl J Med 2019 Apr 25;380(17):1597-1605

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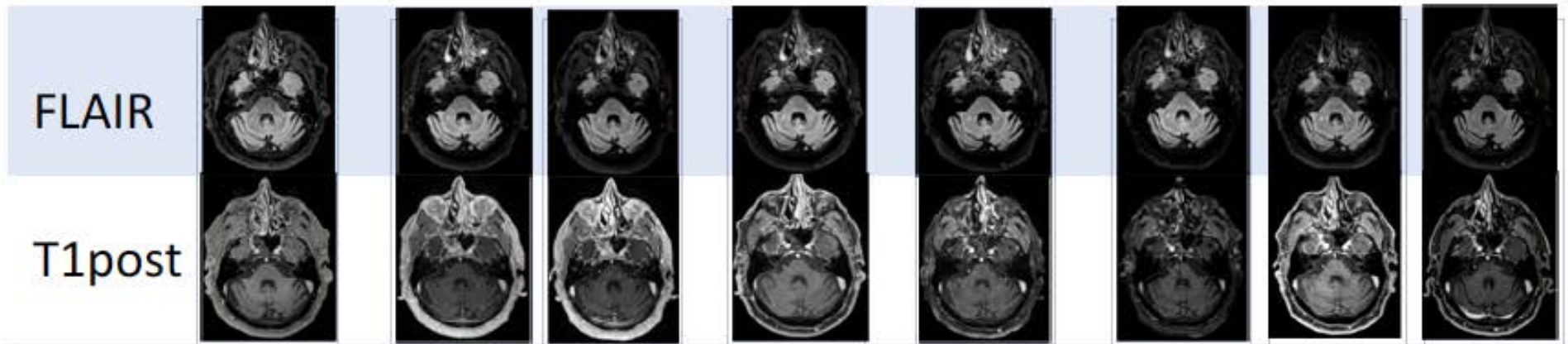
Pembrolizumab for PML



month	-5	0	1	3	6	11	12	13
MRS	-	2	2	2	2	2	-	2
JCV#	-	286	119	229	53	404	-	273

- Appendicular ataxia
- Truncal ataxia
- Dysarthria

New Engl J Med 2019 Apr 25;380(17):1597-1605

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Zostavax in PLHIV with CD4>200: Efficacy

GMT/GMFR	ZOSTAVAX (n = 296)	Placebo (n = 99)	*P* Value[a]
No. missing	12	3	
Week 6 GMT, mean (95% CI)	534.4 (480.0–594.9)	263.7 (204.0–340.8)	<.001
Week 6 GMFR, mean (95% CI)	1.78 (1.64–1.92)	1.05 (.98–1.12)	
No. missing	23	9	
Week 12 GMT, mean (95% CI)	530.3 (477.8–588.6)	250.3 (191.7–326.8)	<.001
Week 12 GMFR, mean (95% CI)	1.80 (1.66–1.95)	1.04 (.96–1.13)	

Clin Infect Dis 2018 Nov 13;67(11):1712-1719

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Zostavax in PLHIV with CD4>200: Safety

Endpoint/Adverse Event	ZOSTAVAX (n = 295) Estimate, % (95% CI)	Placebo (n = 97) Estimate, % (95% CI)	*P* Value[a]
Primary safety endpoints[b]	n = 15 5.1 (2.9–8.2)	n = 2 2.1 (.3–7.3)	.261
Injection site reactions	n = 124 42.0 (36.3–47.9)	n = 12 12.4 (6.6–20.6)	<.001
Rashes (generalized, varicella-like, or HZ-like)	n = 15 5.1 (2.9–8.2)	n = 4 4.1 (1.1–10.2)	1.00
Fever >38.3°C	n = 12 4.1 (2.1–7.0)	n = 6 6.2 (2.3–13.0)	.405

Clin Infect Dis 2018 Nov 13;67(11):1712-1719

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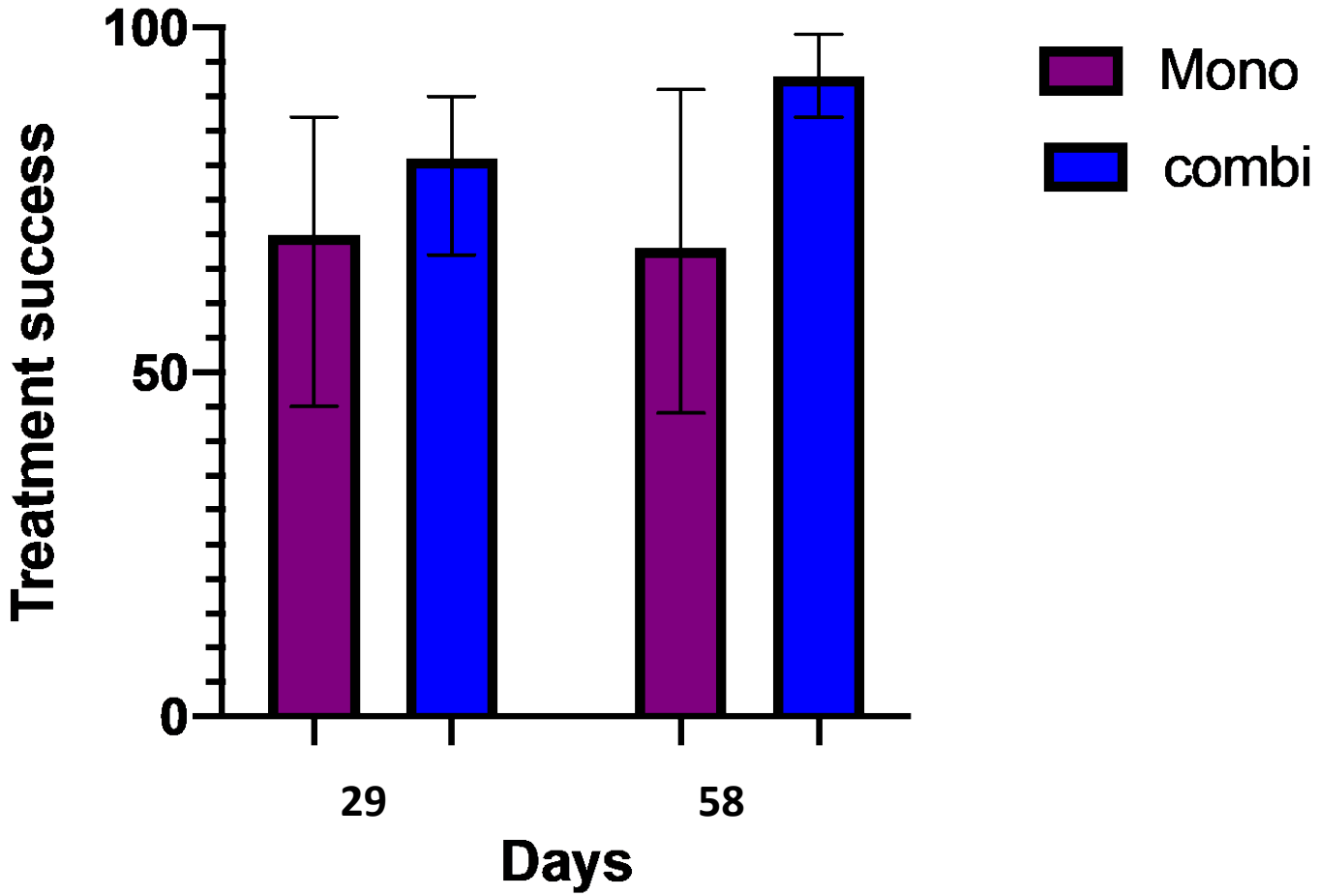
Viral: Some research ideas

- Exploring immunomodulating treatment in PML
- Role of newer HZ vaccine in PLHIV

Outline

- The problem
- Mycobacterial
- Fungal
- Viral
- Protozoal
- Bacterial

Combi LAmB + miltefosine for HIV-VL



PLoS Negl Trop Dis. 2019 Jan 17;13(1):e0006988

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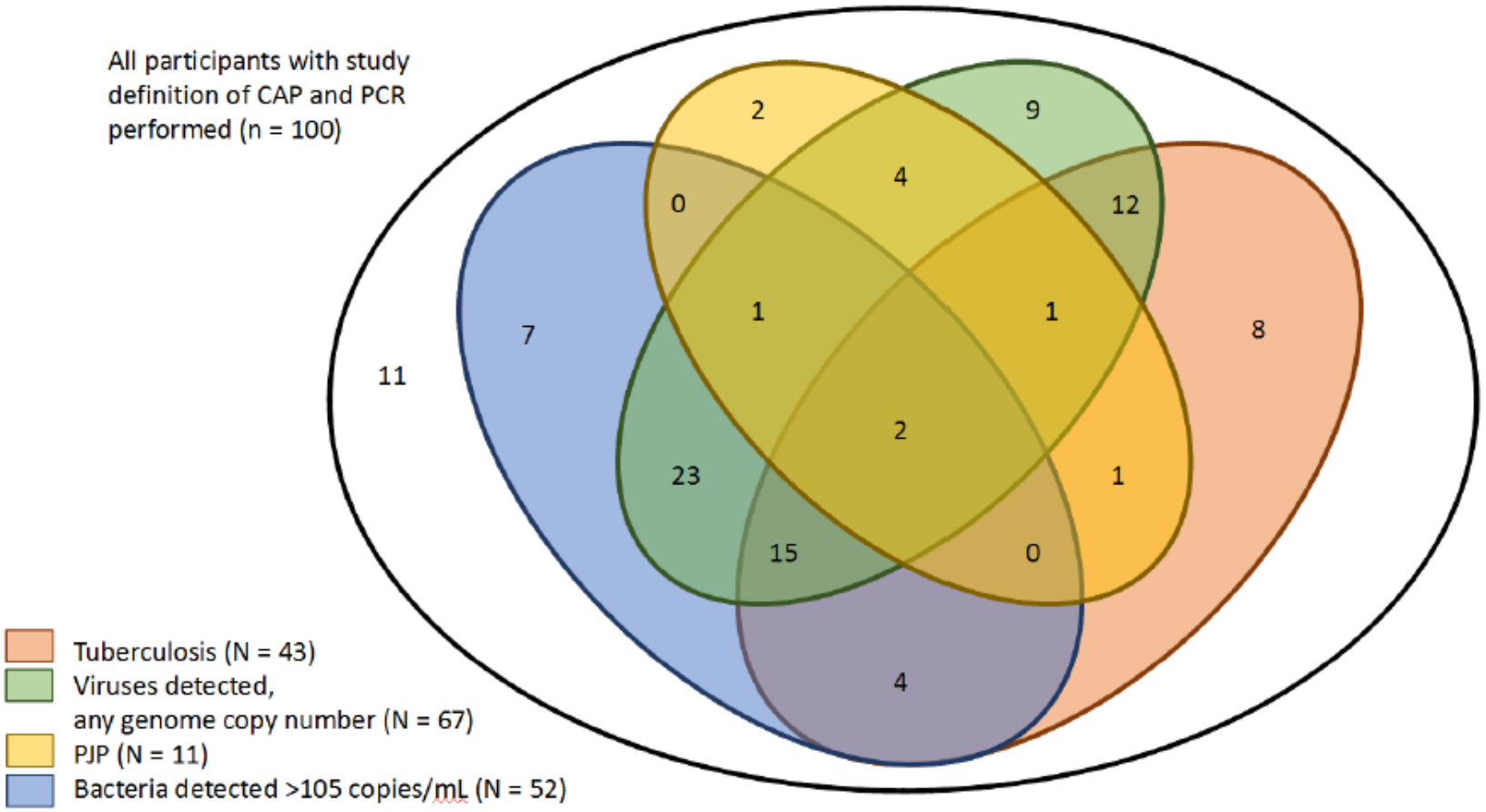
Outline

- The problem
- Mycobacterial
- Fungal
- Viral
- Protozoal
- Bacterial

Pulmonary infections etiology using sputum multiplex PCR



Clin Infect Dis 2019 Apr 26. [Epub ahead of print]

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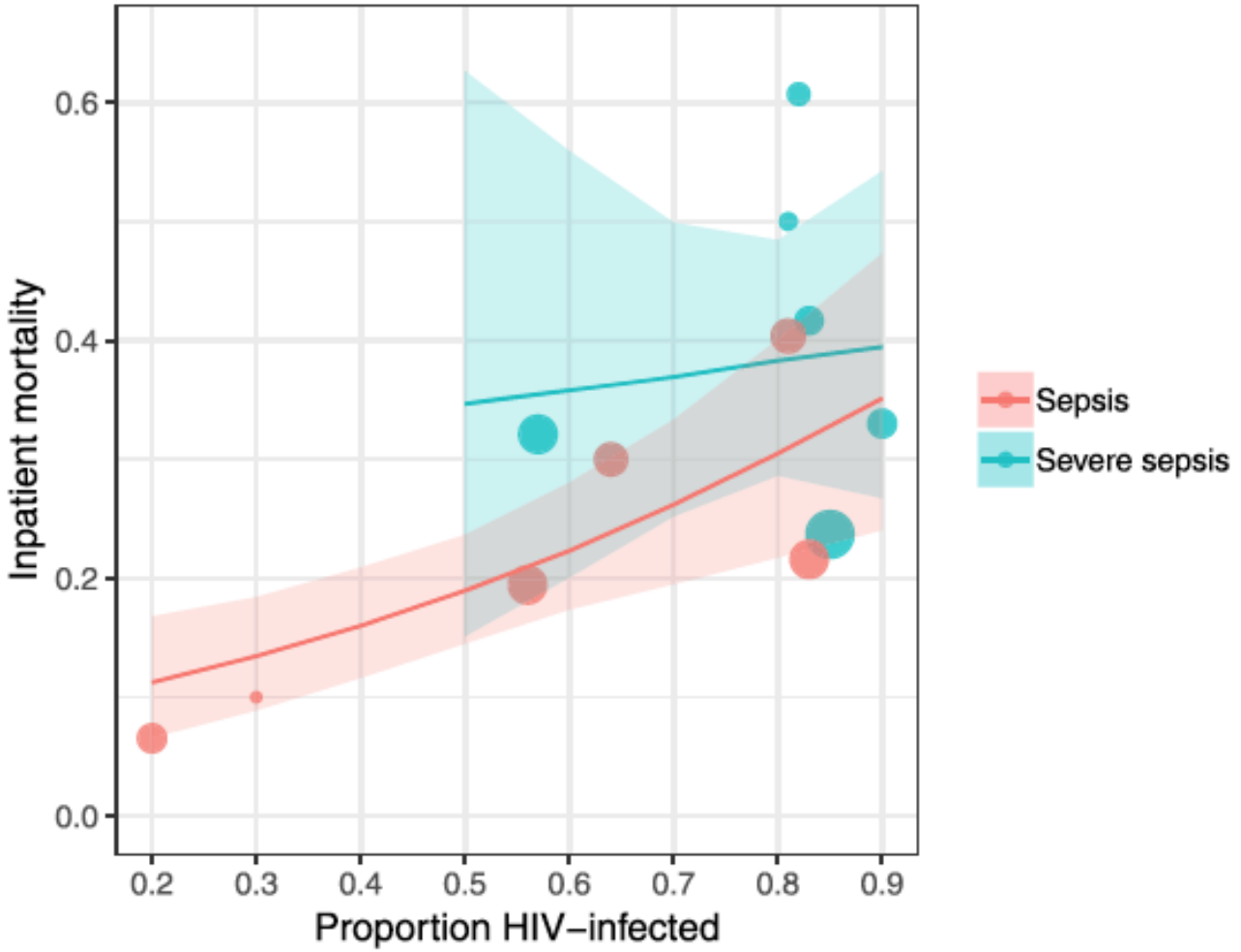
HIV associated with higher mortality in Sepsis: sSA



Critical Care (2019) 23:212

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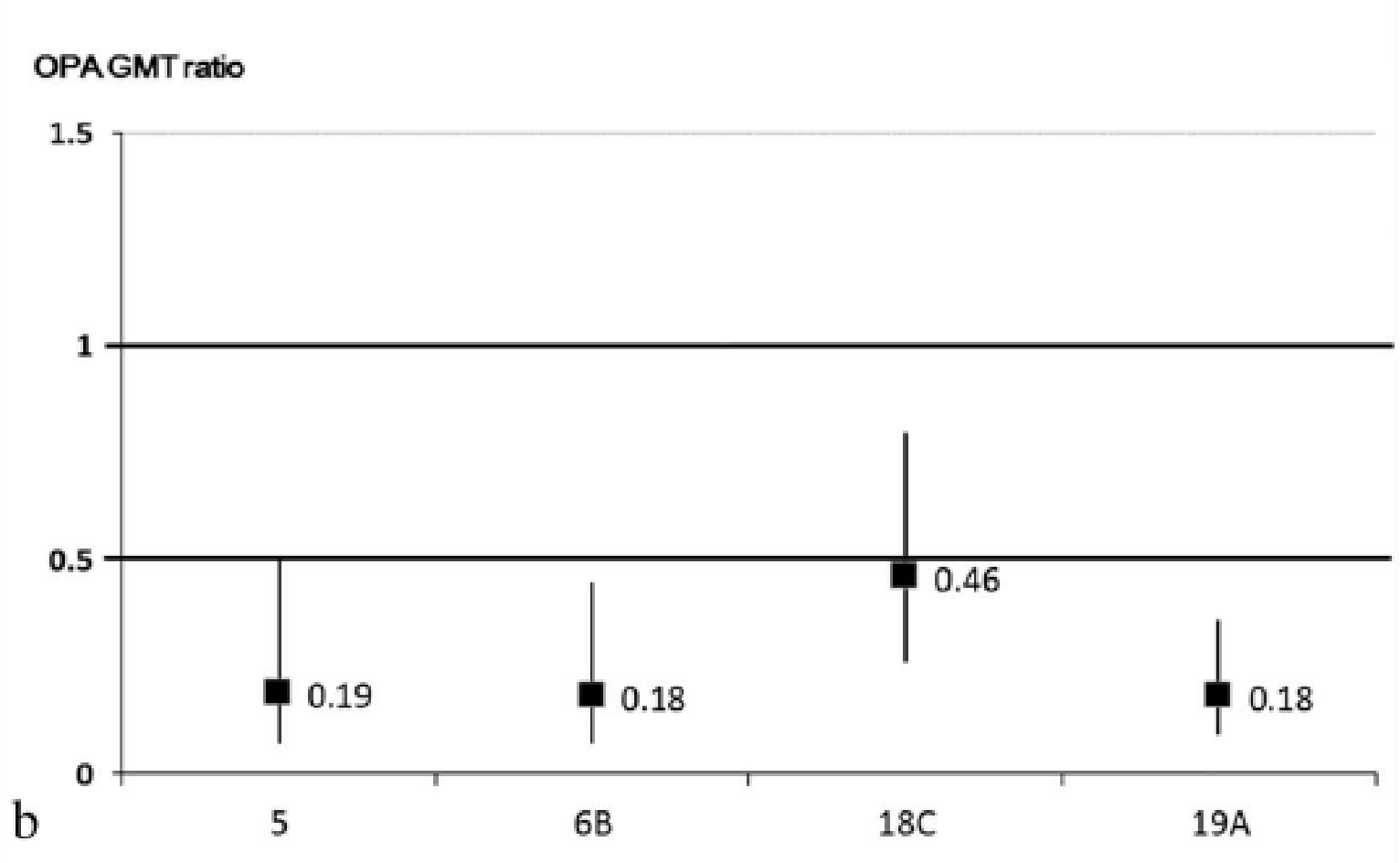
Immunogenicity of PCV-13 with CD4 counts<350



Hum Vaccin Immunother. 2019 Aug 23:1-7

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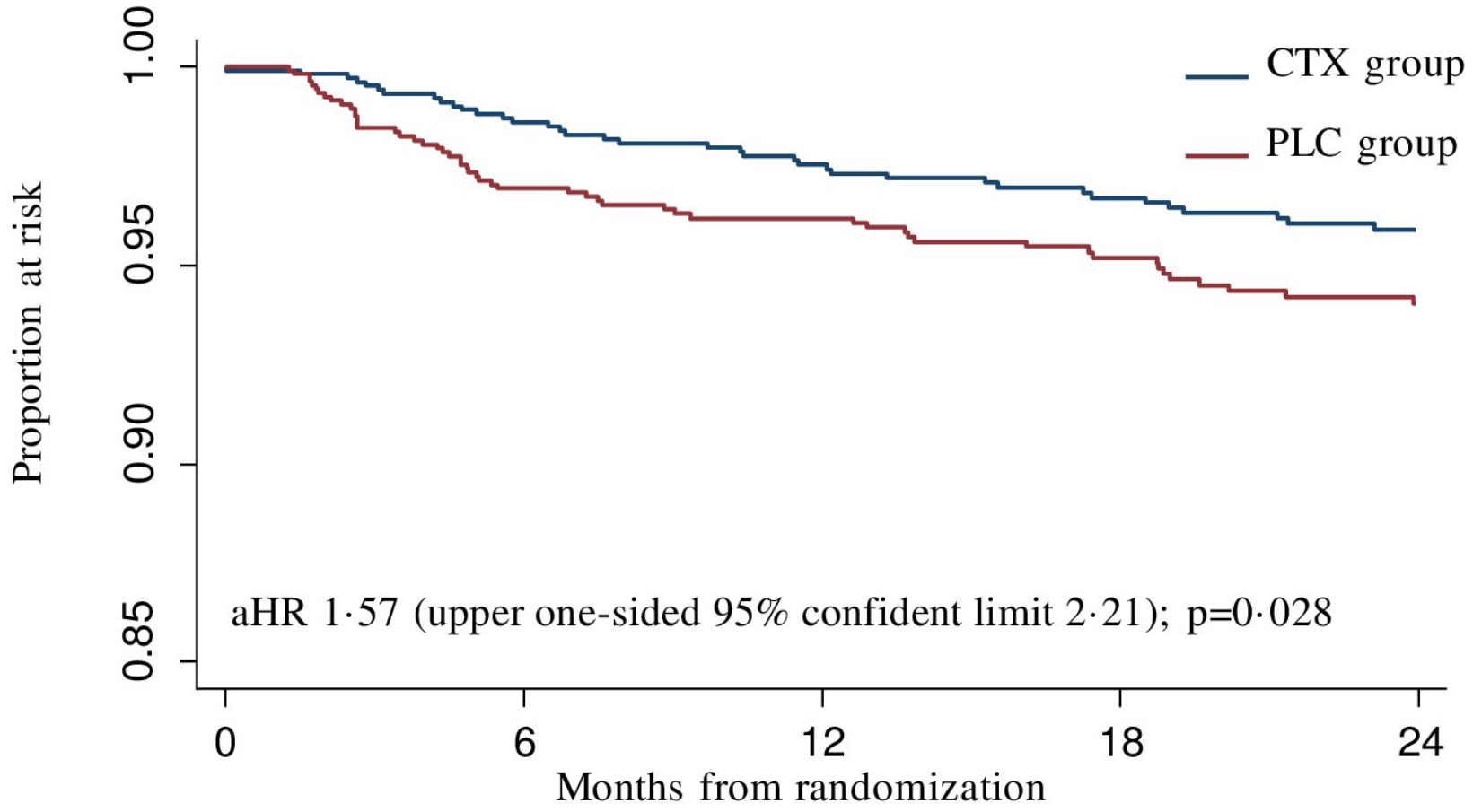
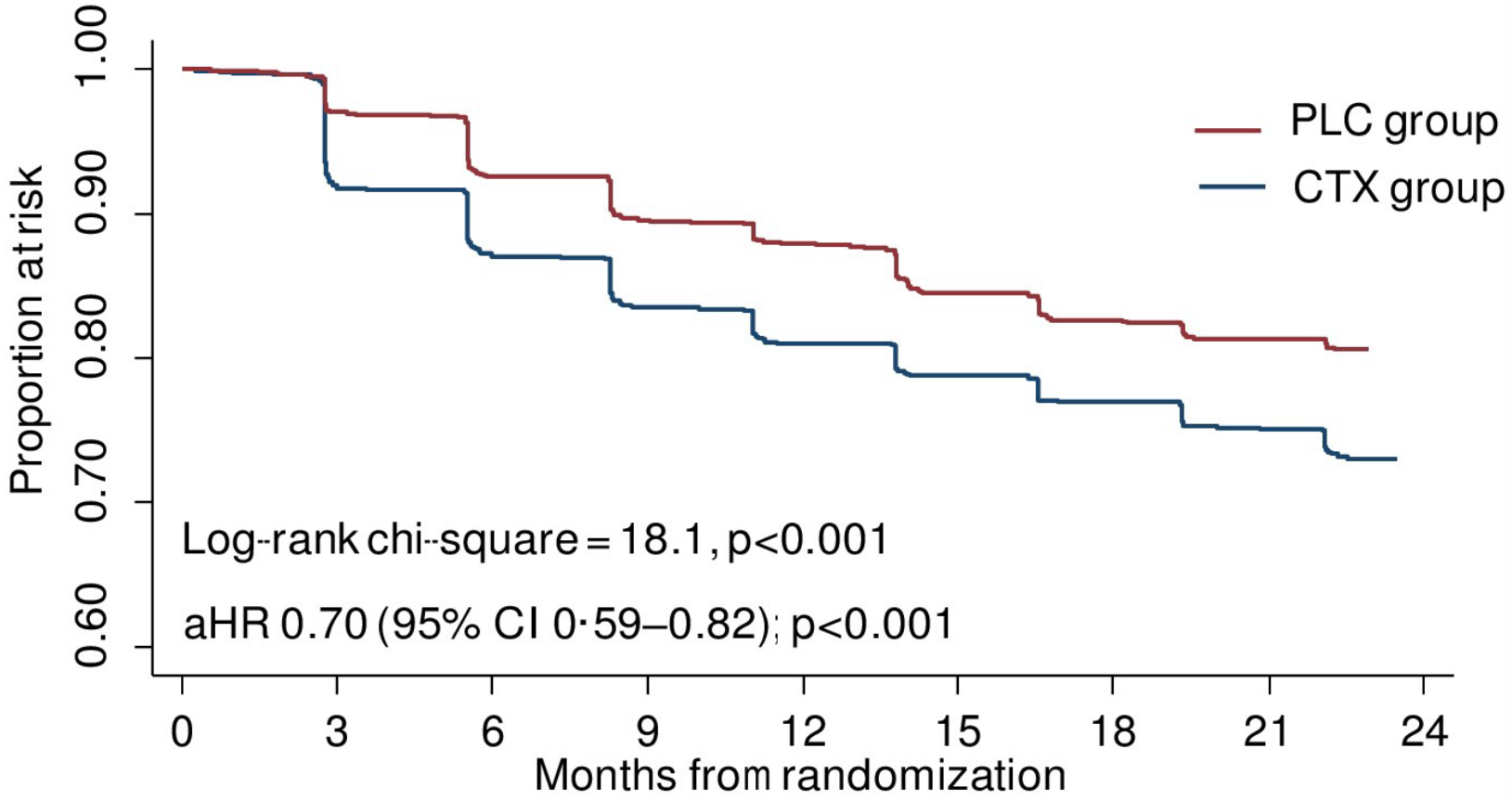
COSTOP:
CTX prophylaxis in PLHIV with CD4>250- efficacy



PLOS One 2018; 13(12): e0206907.

COSTOP:
CTX prophylaxis in PLHIV with CD4>250-safety



PLOS One 2018; 13(12): e0206907.

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Summary

- OI's: Going, going, but not gone

- Continued need to be vigilant
  - Late presentation
  - Failing ART

- Great potential for further refining and optimizing treatment and prevention of OI's