Opportunistic infections

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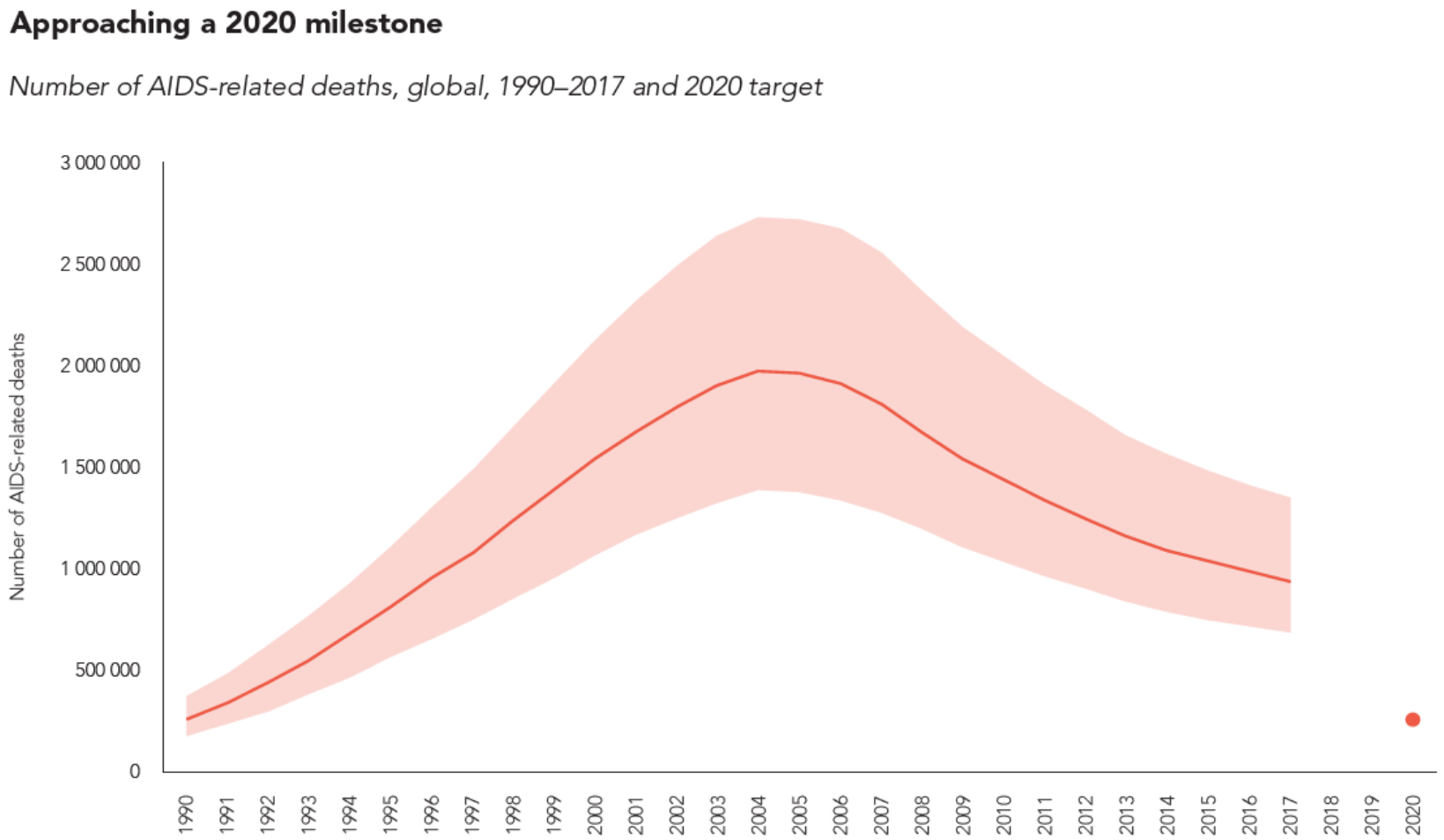
Disclosures

- Advisory board, Speaker fees: Mylan, Hetero, Cipla ltd

Outline

- Why OI's still occur?
- Mycobacterial
- Fungal
- Viral
- Protozoal

Decline in deaths esp d/t AIDS related illnesses



UNAIDS Data 2018

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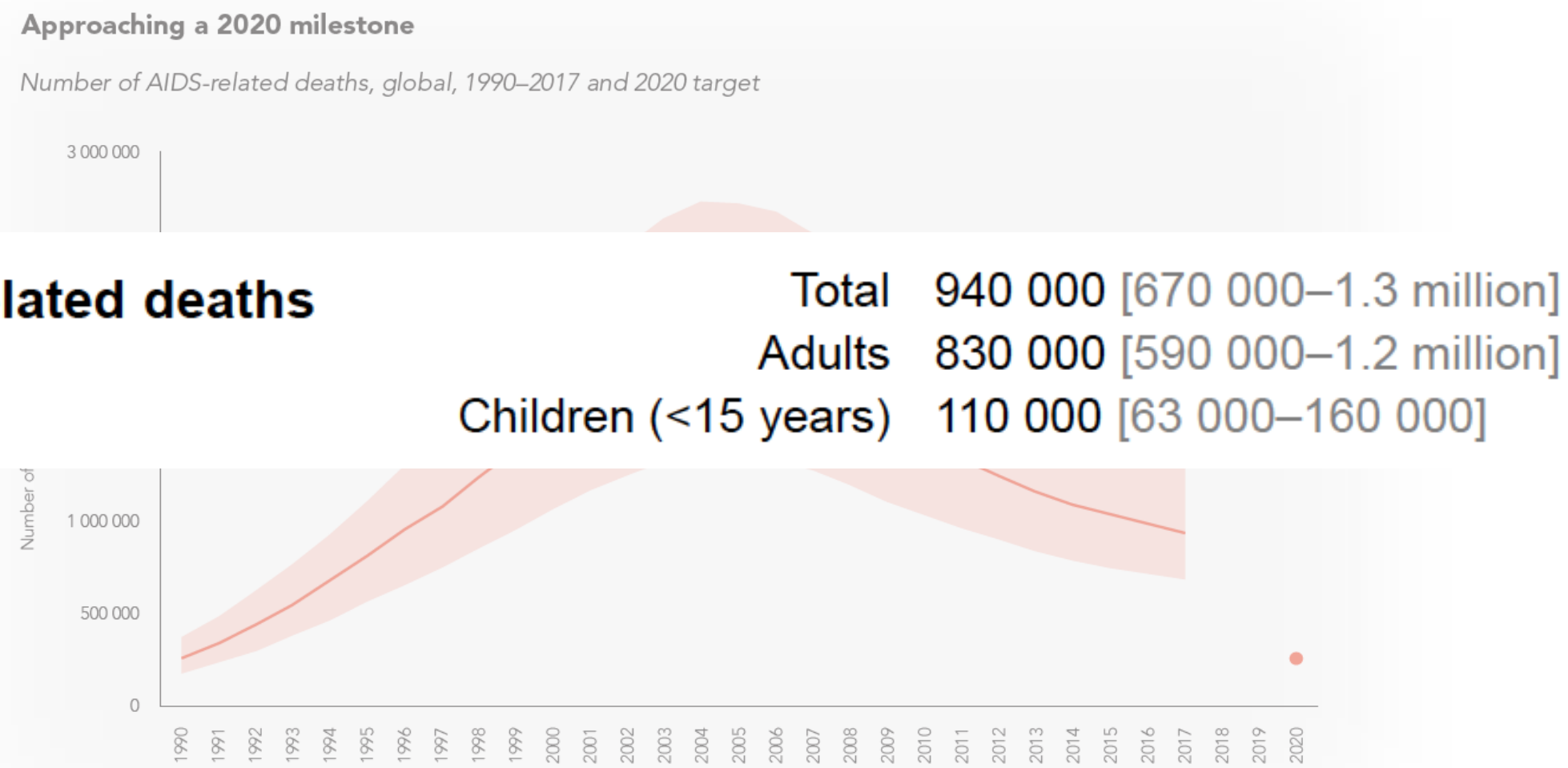
However,



AIDS-related deaths in 2017

Total	940 000 [670 000–1.3 million]
Adults	830 000 [590 000–1.2 million]
Children (<15 years)	110 000 [63 000–160 000]

UNAIDS Data 2018

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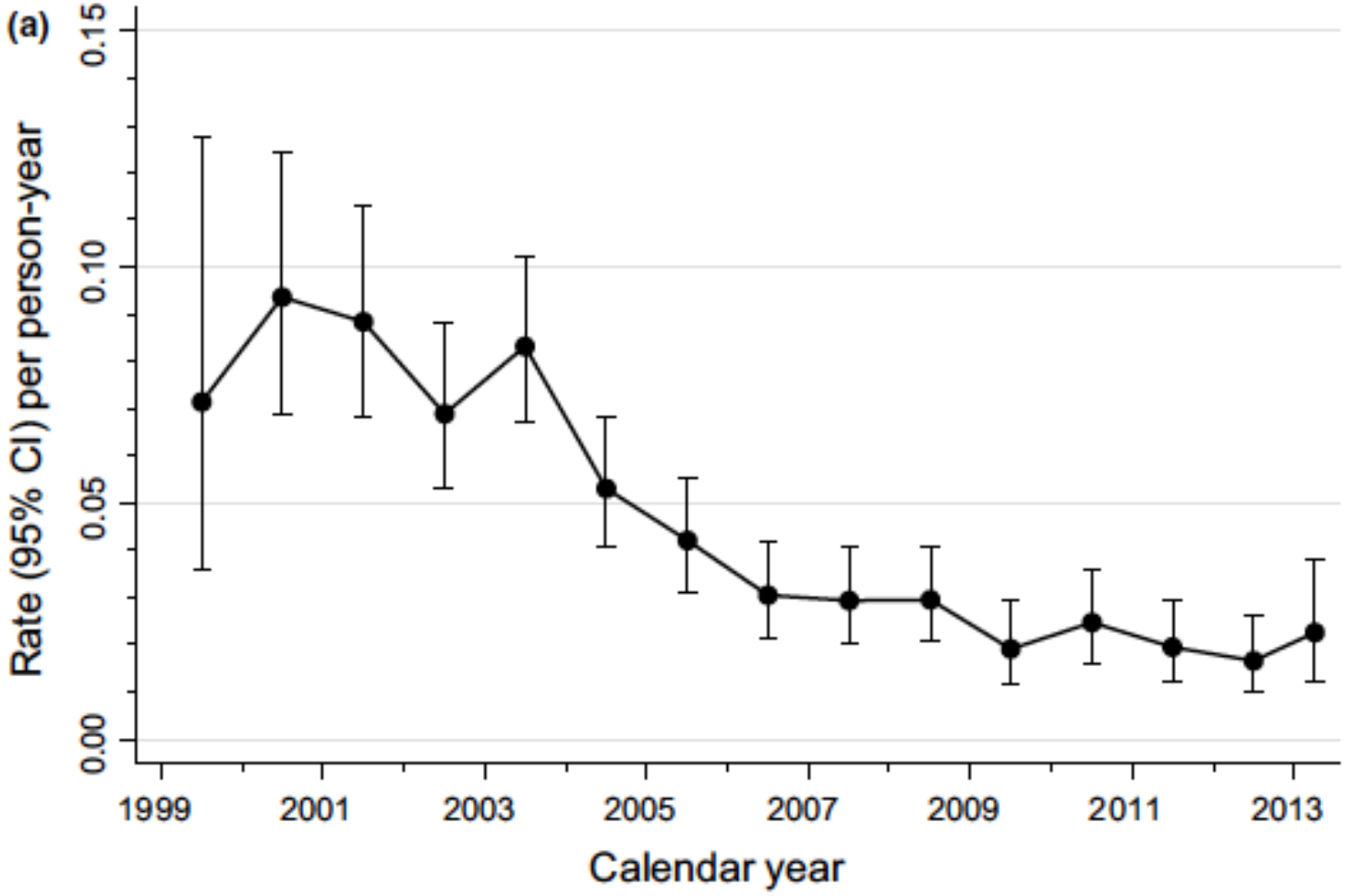
Impact of cART on late presenters: LSOCA cohort



HIV Medicine 2018, *19*, 411--419

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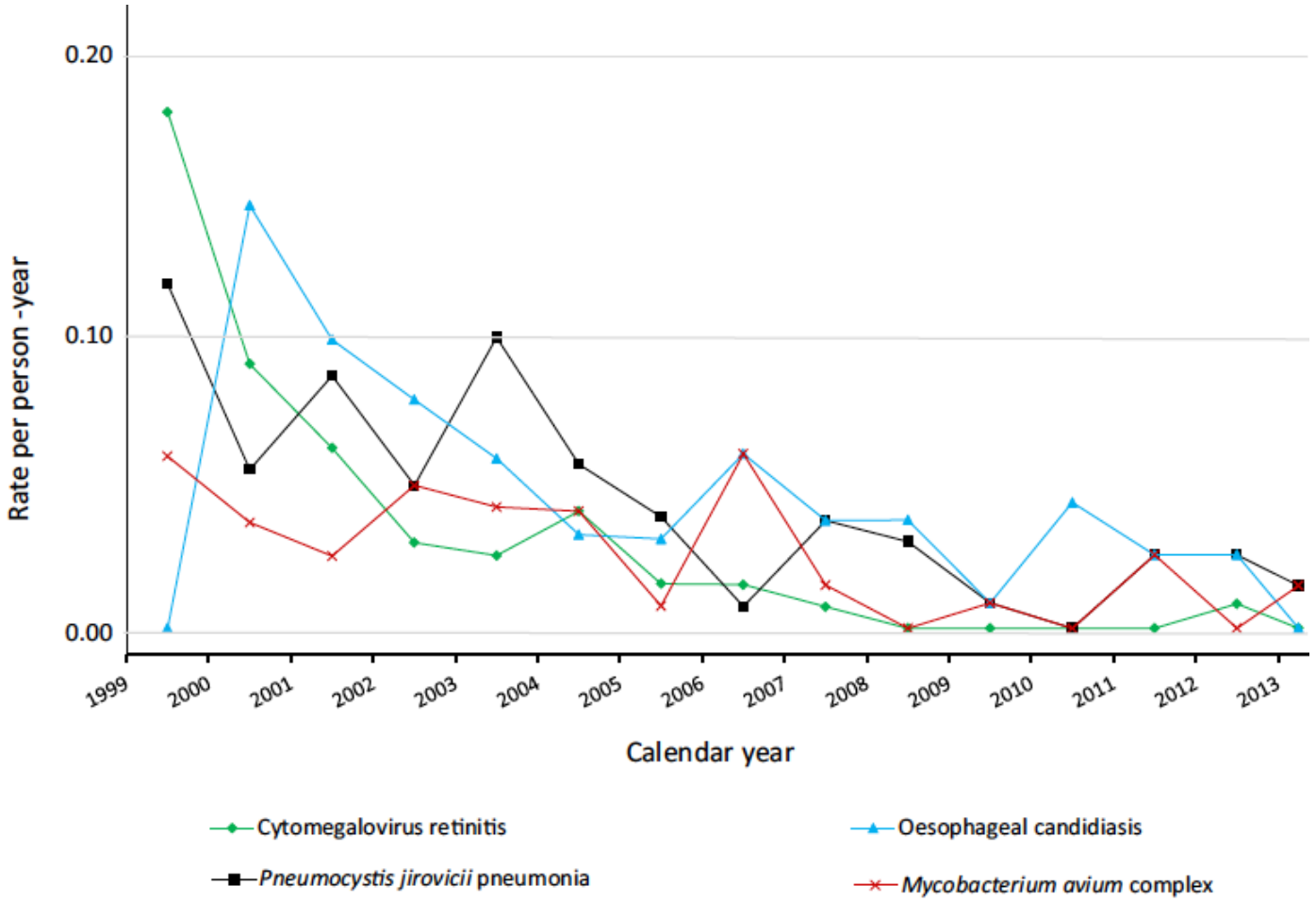

HIV Medicine 2018, *19*, 411--419

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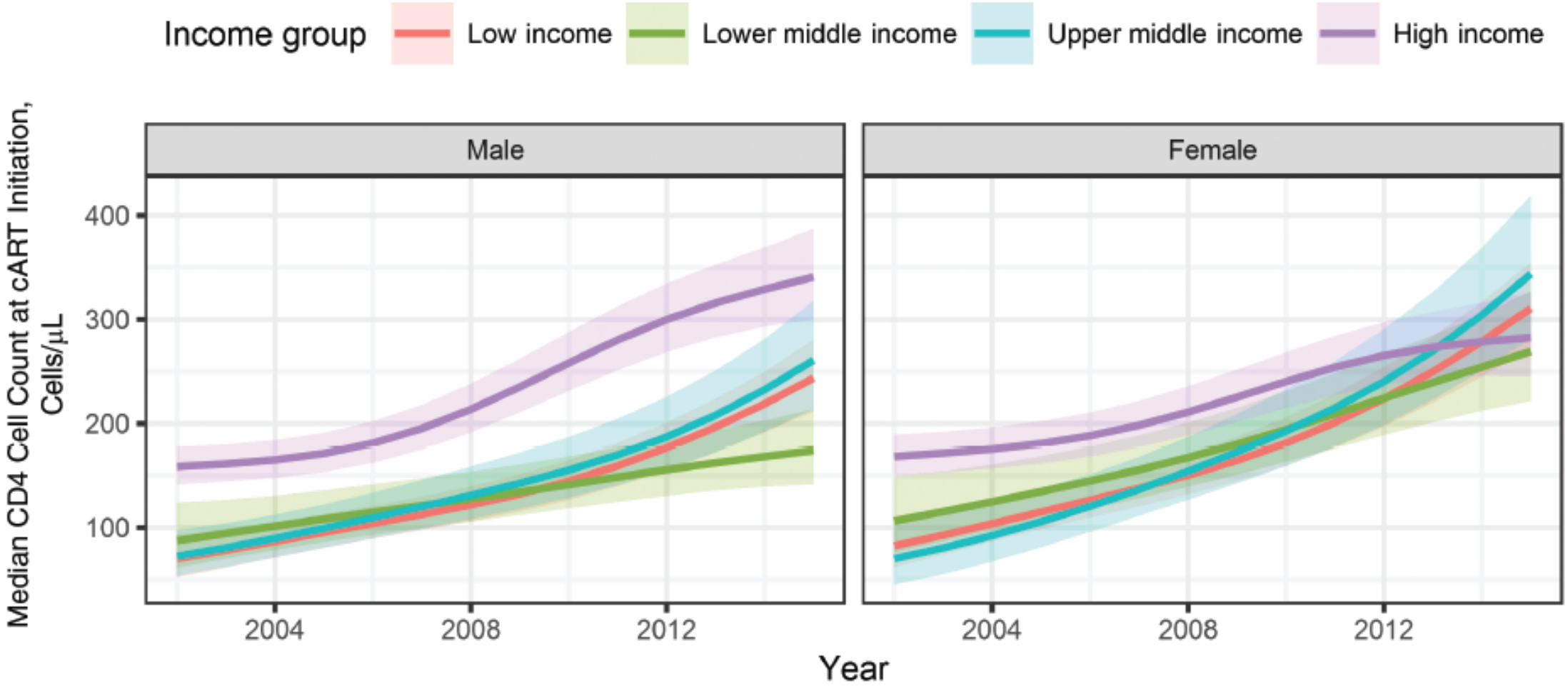
Median CD4 counts at cART initiation



Clinical Infectious Diseases 2018;66(6):893–903

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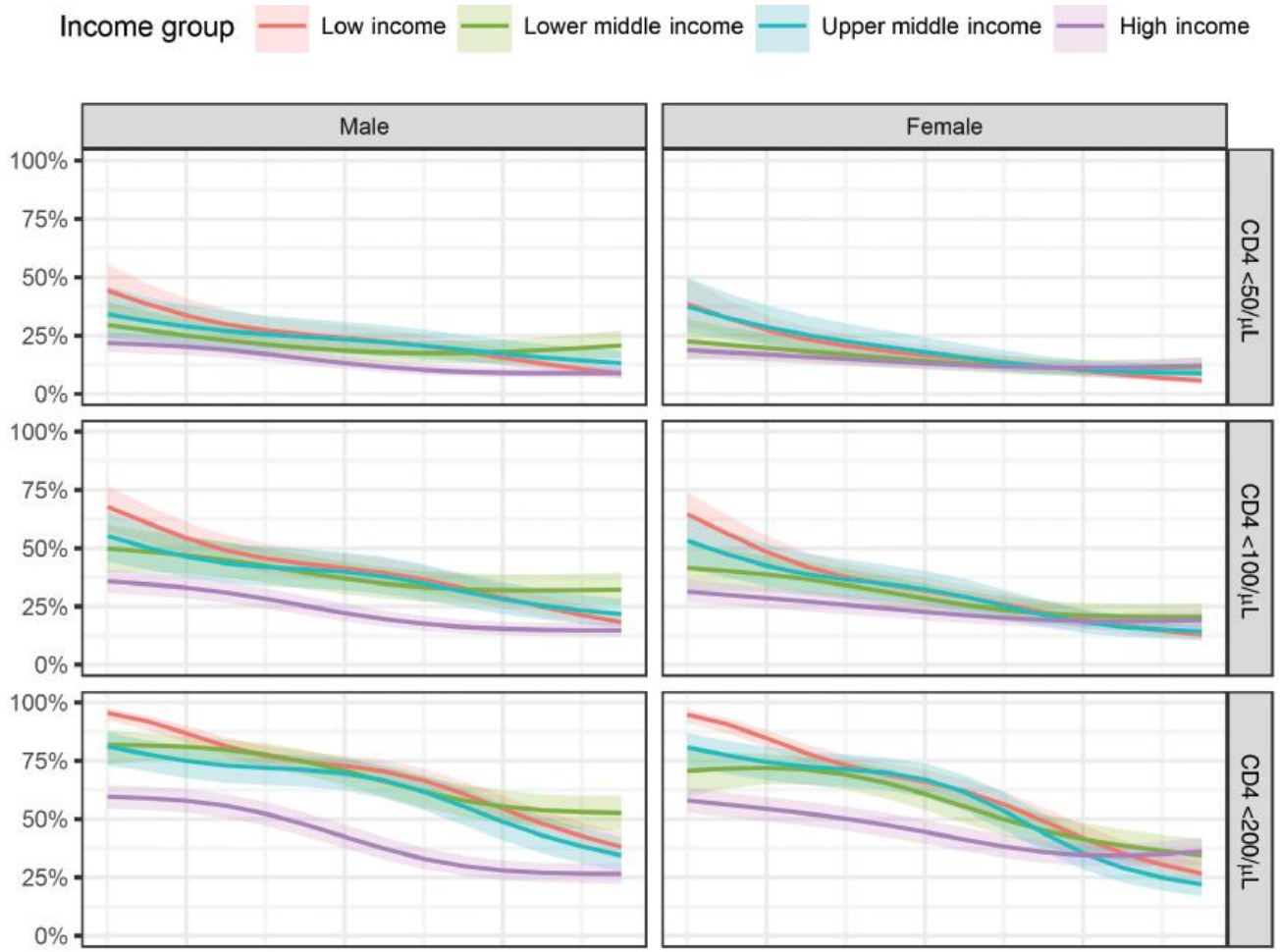
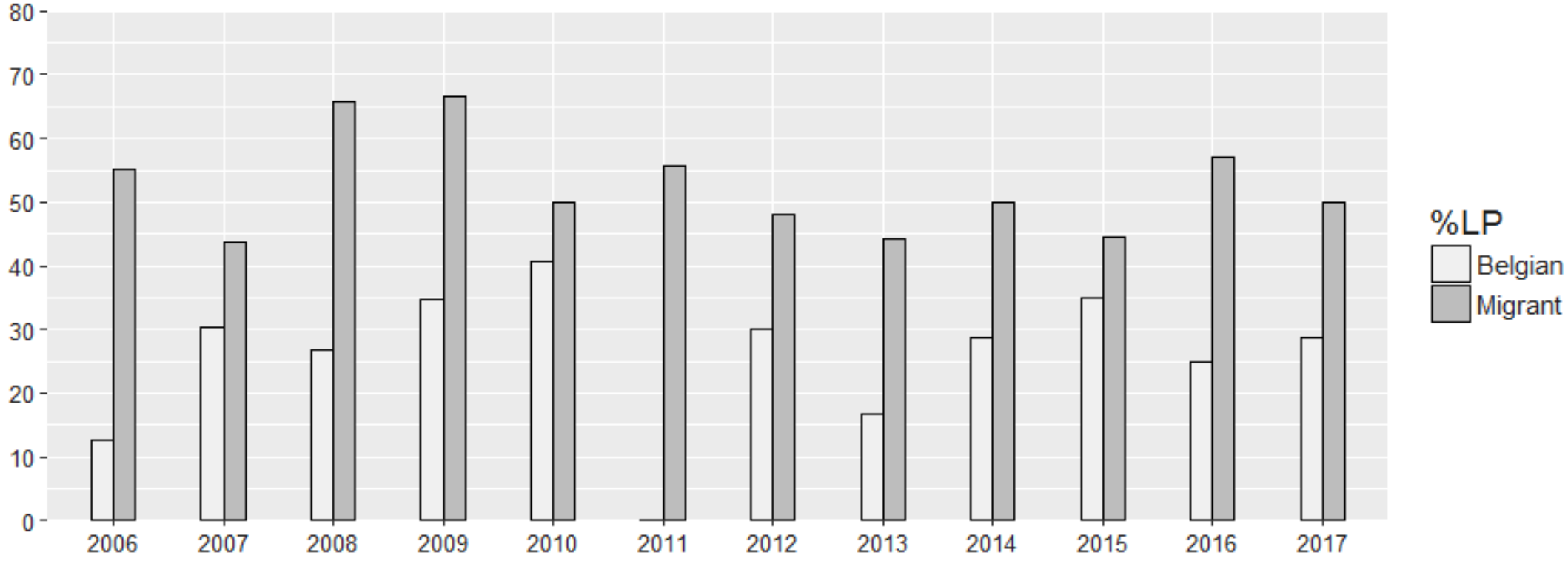
Late initiation of cART



Clinical Infectious Diseases 2018;66(6):893–903

Late presentation (CD4<350) to HIV care: Belgium



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

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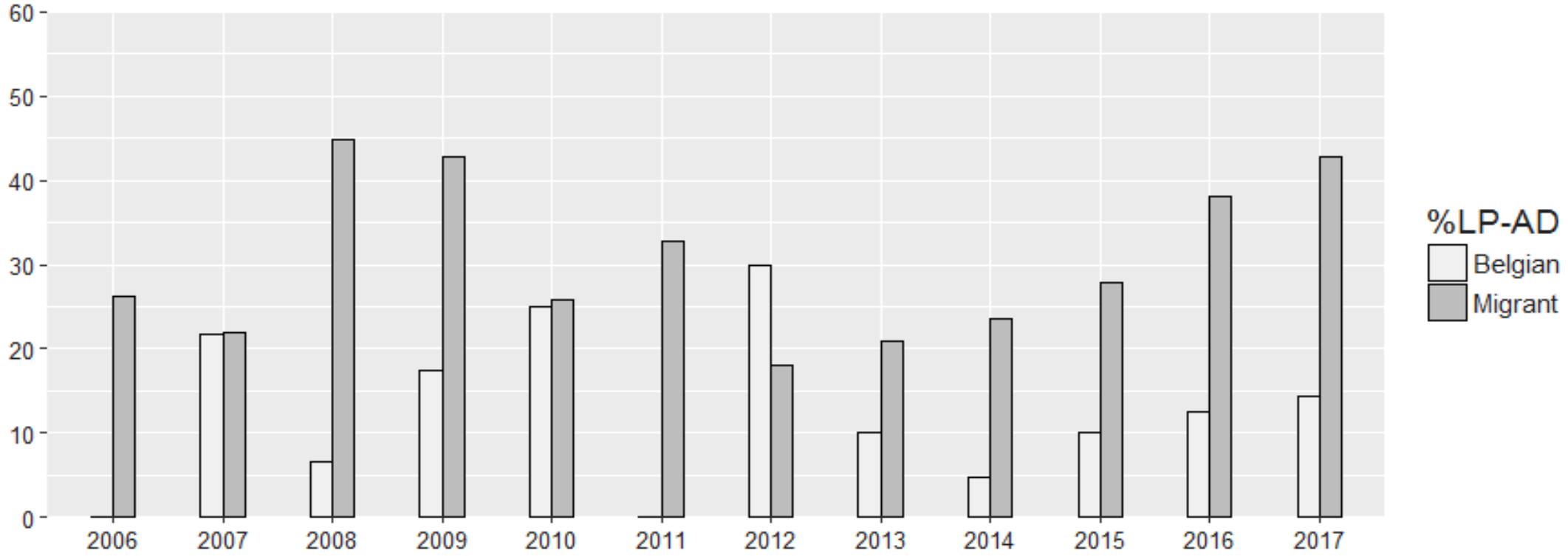
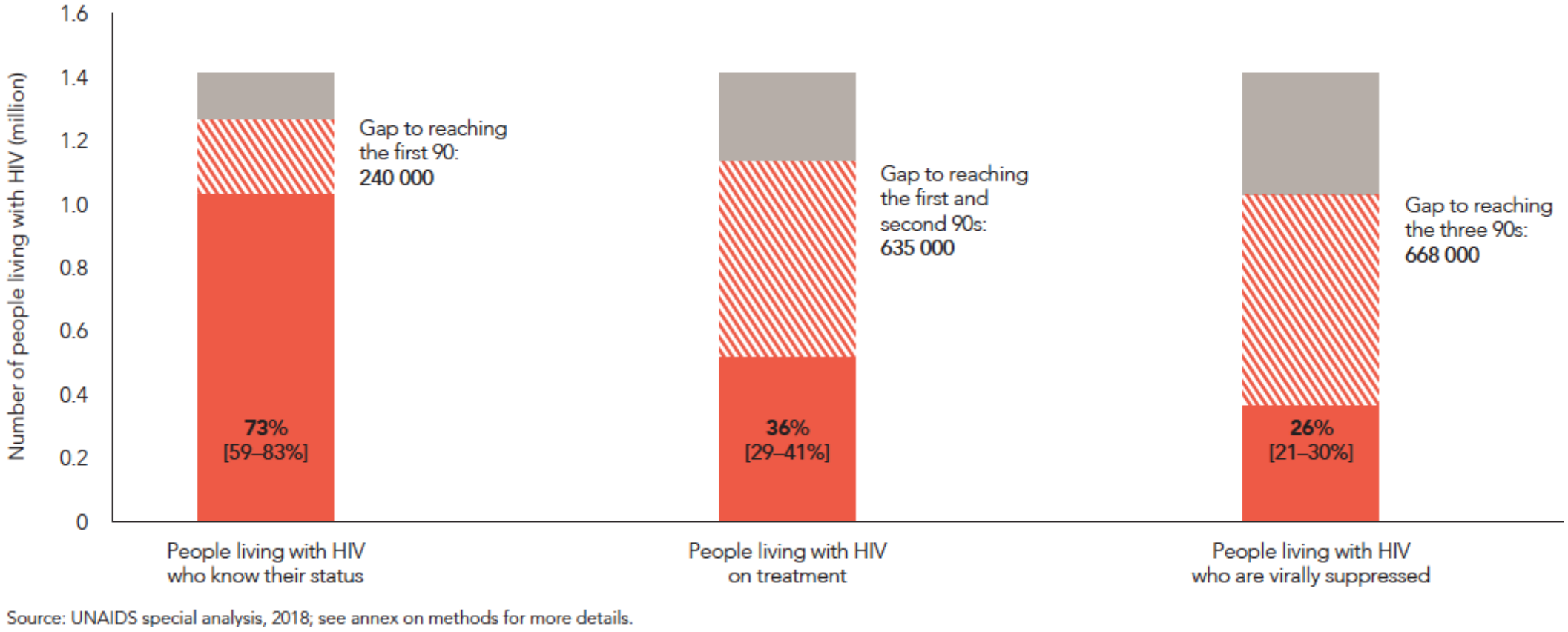
Advanced disease (CD4<200) at presentation: Belgium



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

The 90-90-90 status: Eastern Europe/Central Asia

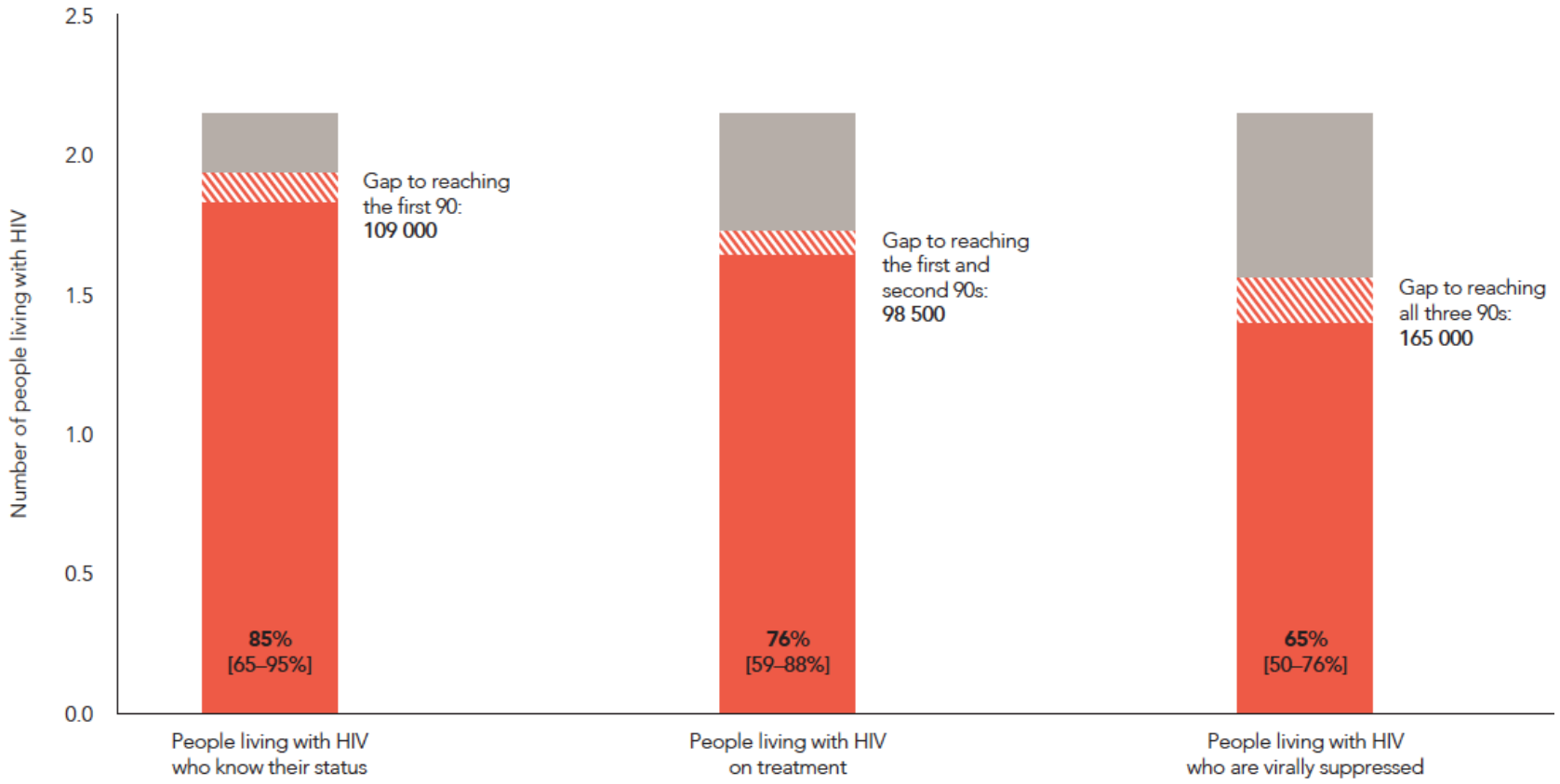


Source: UNAIDS special analysis, 2018; see annex on methods for more details.

UNAIDS Data 2018

The 90-90-90 status: Western Europe/Central Europe/North America

HIV testing and treatment cascade, western and central Europe and North America, 2016



UNAIDS Data 2018

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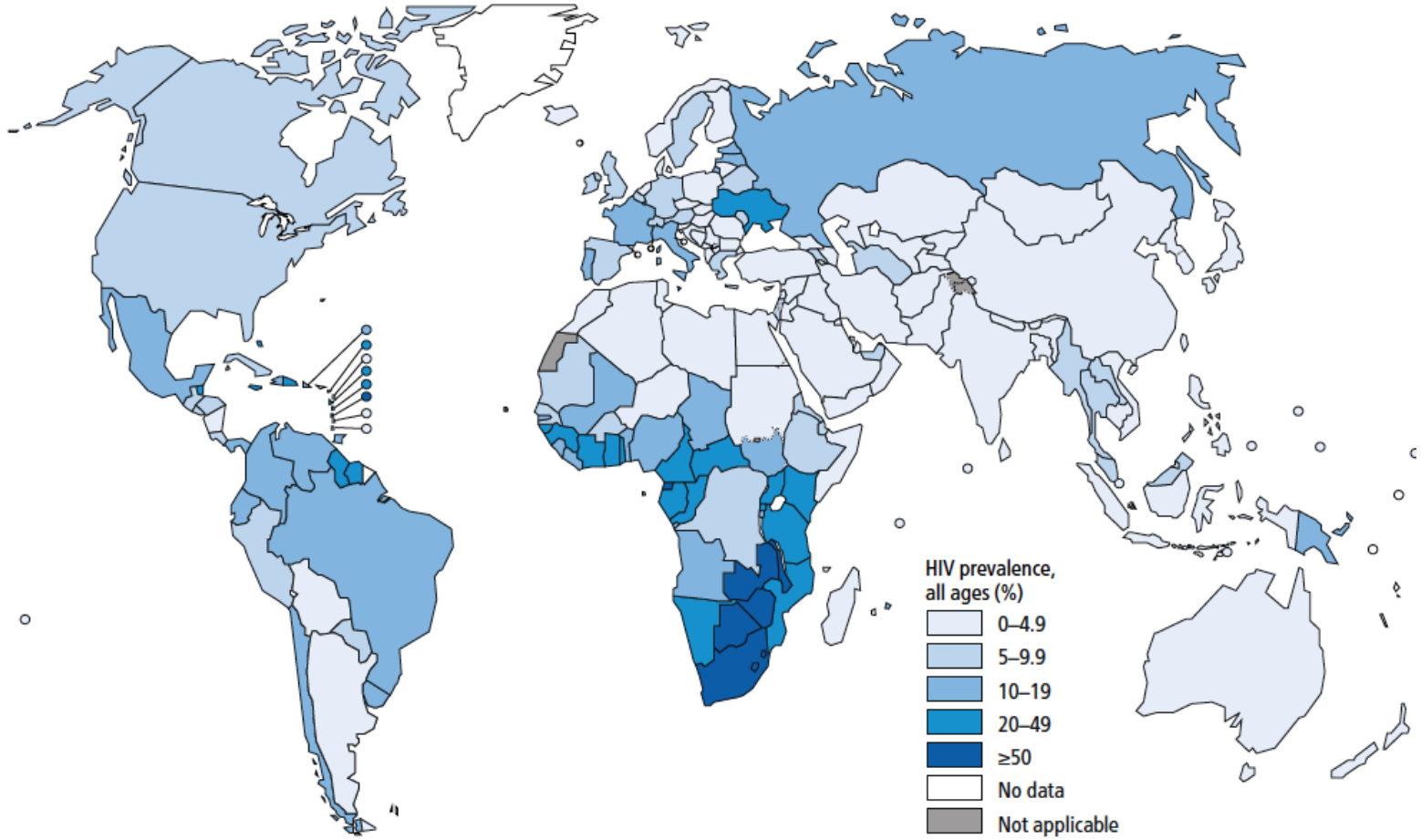
Outline

- Why OI's still occur?
- Mycobacterial
- Fungal
- Viral
- Protozoal

Prevalence of HIV in Individuals with TB



Global TB report 2017
http://www.who.int/tb/publications/global_report/en/

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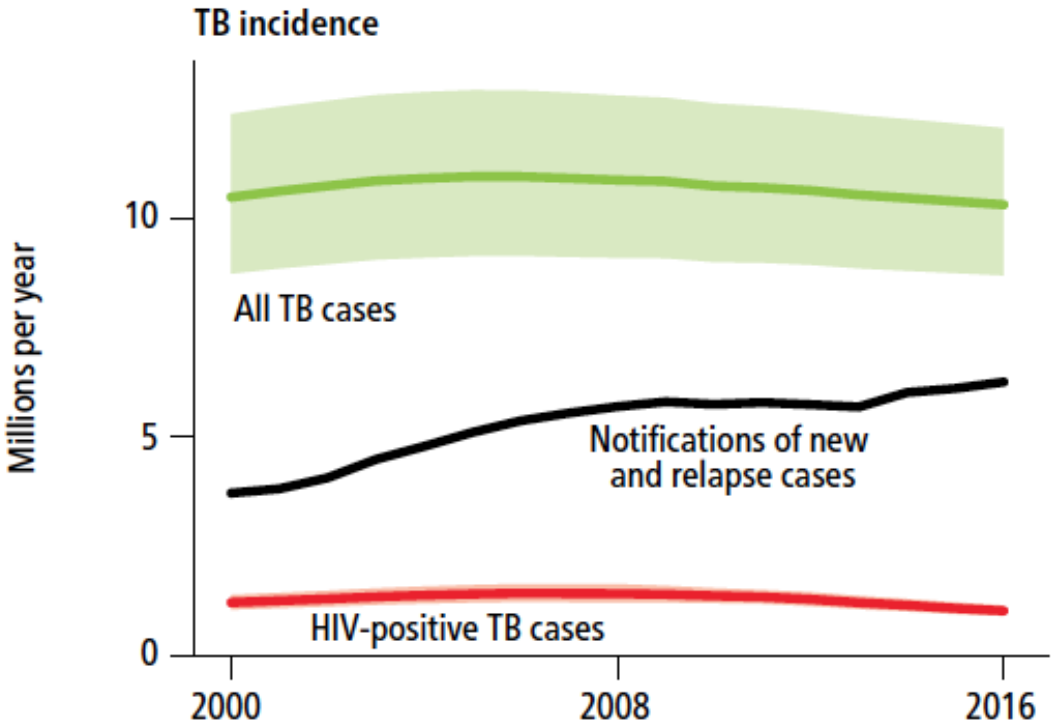
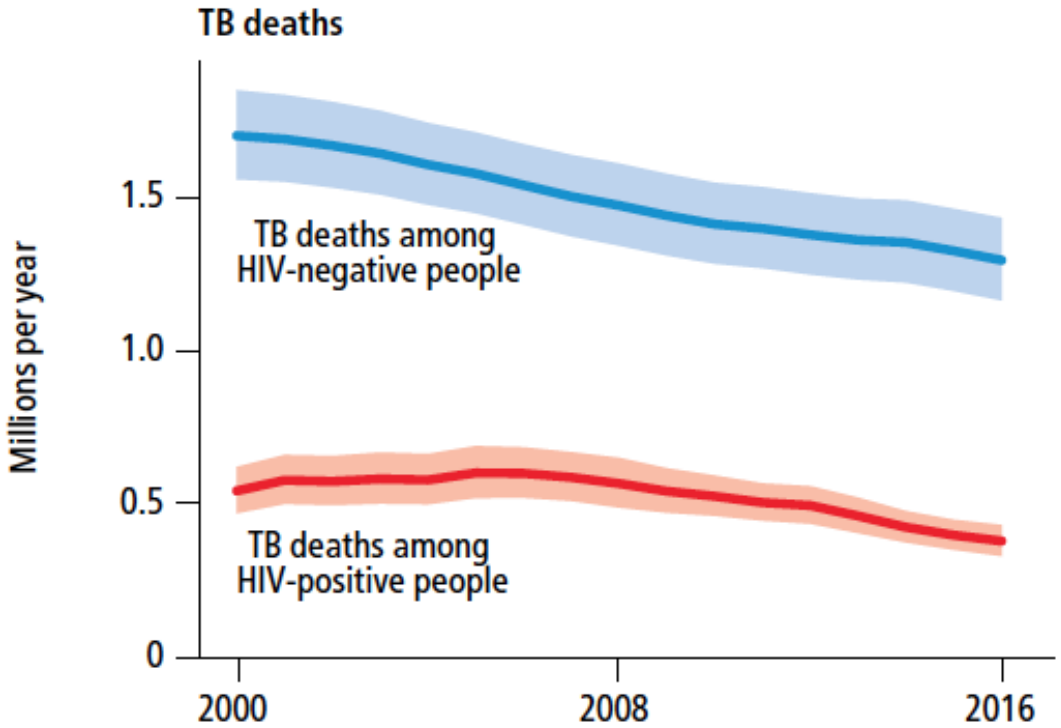
TB incidence and deaths: 2000-2016





Global TB report 2017
http://www.who.int/tb/publications/global_report/en/

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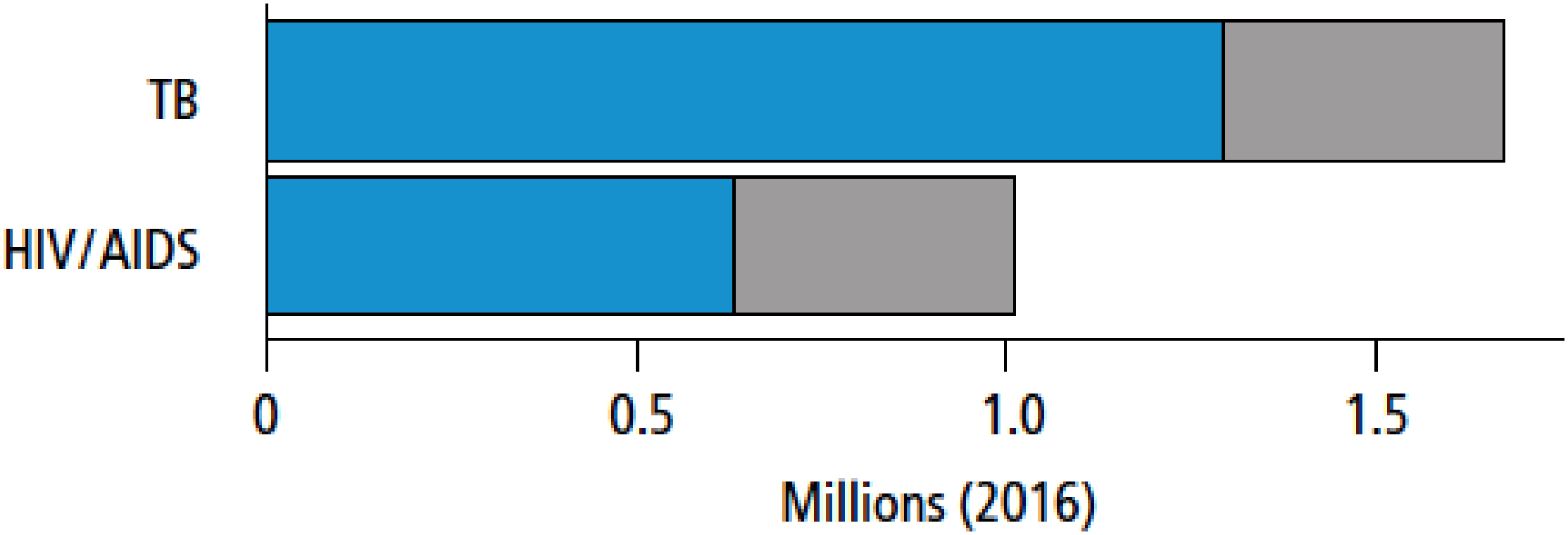
Estimated deaths d/t HIV, TB: 2016



Global TB report 2017
http://www.who.int/tb/publications/global_report/en/

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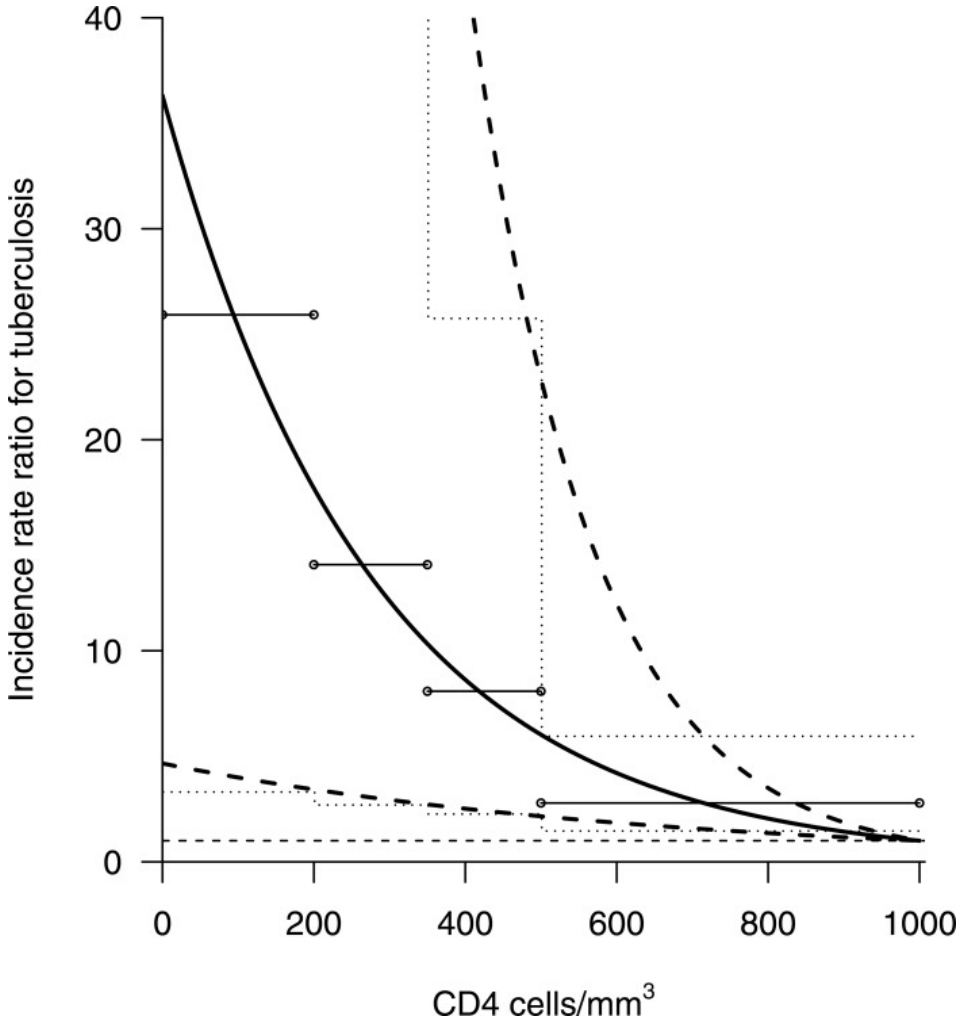
TB incidence and CD4 counts: PLHIV not on cART



Peer J. 2017 Dec 14;5:e4165

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Clinical Scoring system for prioritizing investigation for TB: XPHACTOR score

Risk factor	Category	Select one	Associated points	Assigned score
ART status	Pre-ART	☐	3	
	ART < 3 months	☐	3	
	ART ≥ 3 months	☐	0	⊕
BMI	< 18.5	☐	6	
	18.5-24.9	☐	2	
	≥ 25	☐	0	⊕
CD4	<200	☐	3	
	200-349	☐	1	
	≥ 350	☐	0	⊕
Number of WHO symptoms	>1	☐	4	
	1	☐	0	⊖
			TOTAL SCORE	

PloS One 2017; 12:e0181519

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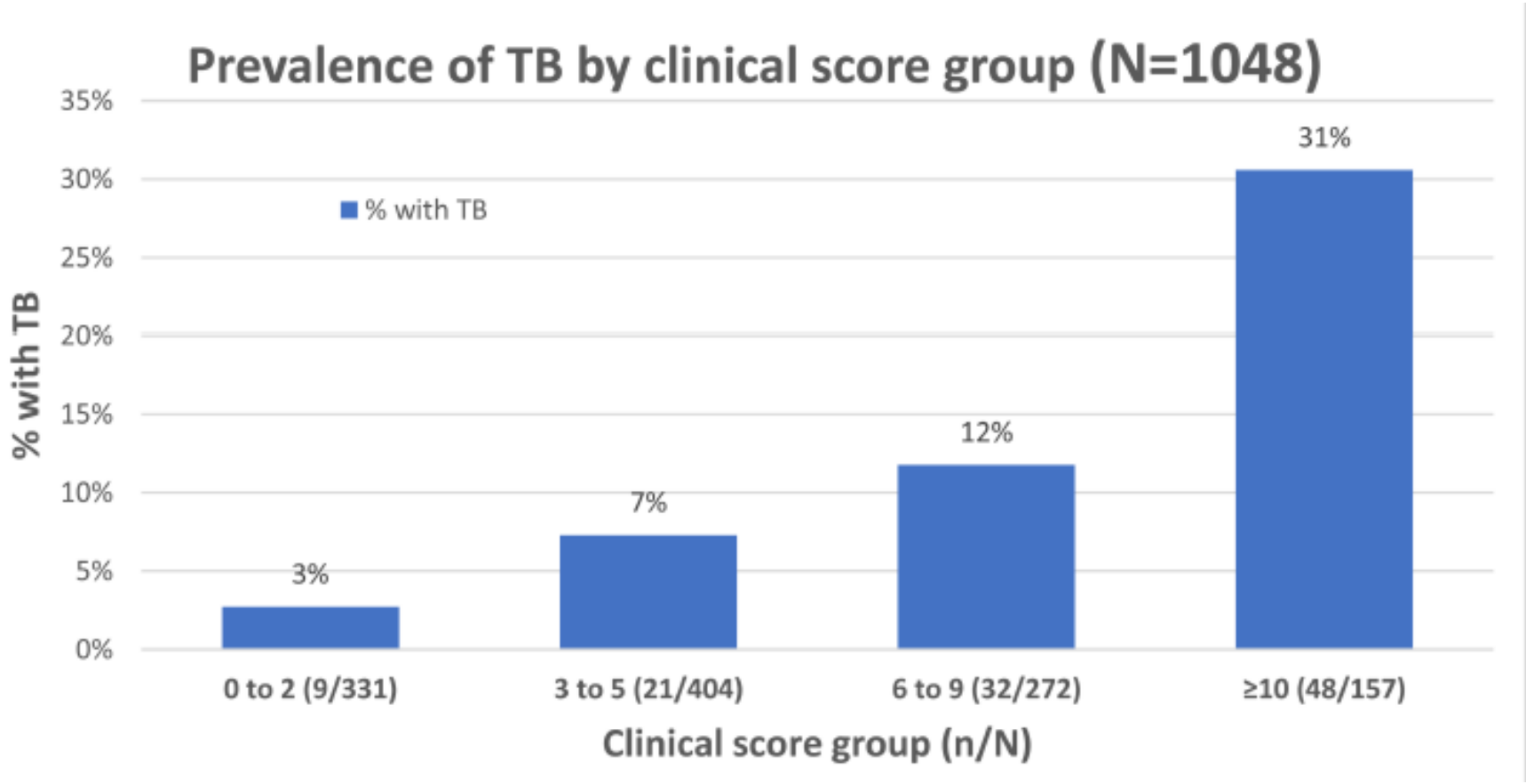

PloS One 2017; 12:e0181519

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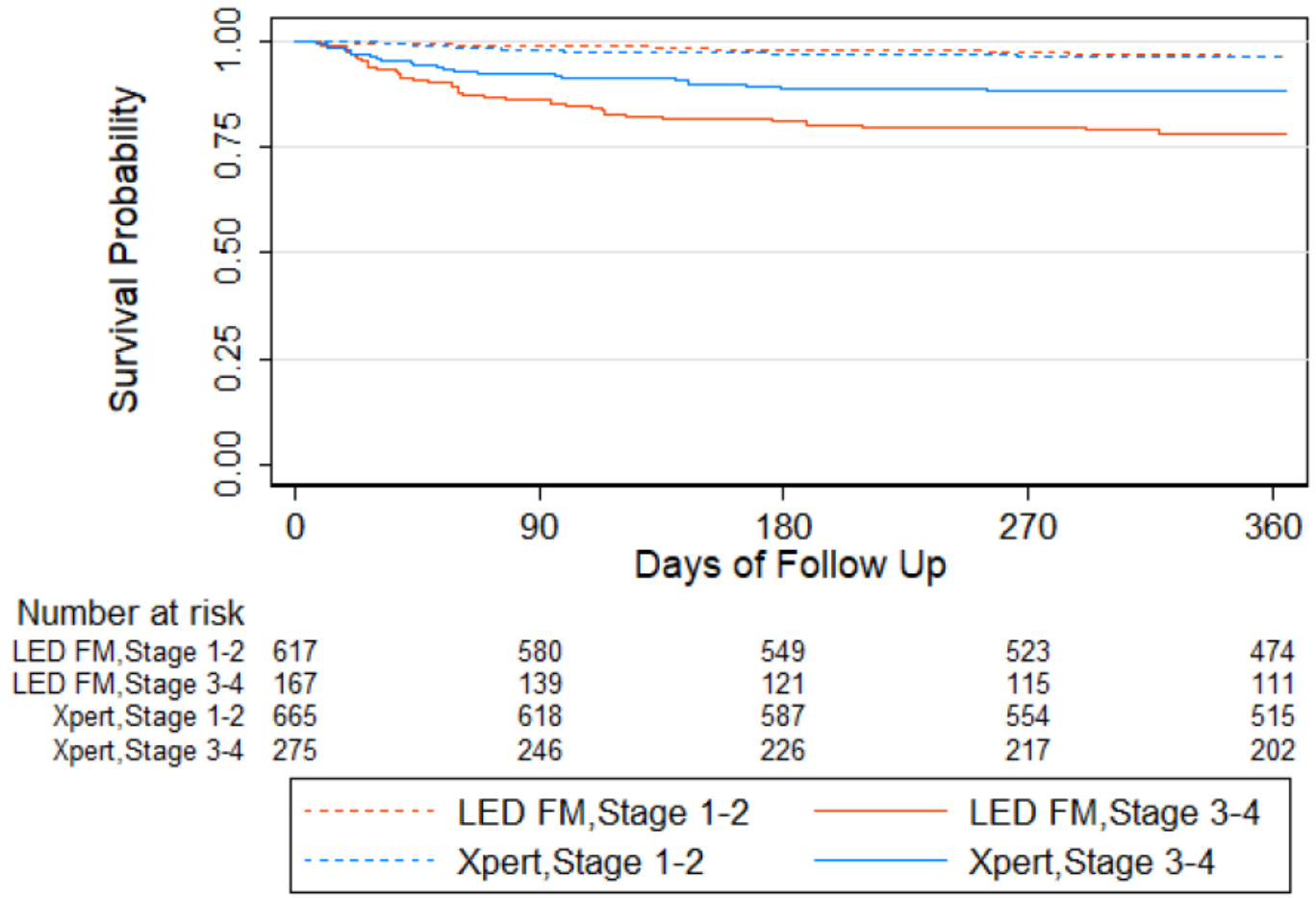
Screening with Xpert MTB and mortality: CHEPETSA trial



Clin Infect Dis. 2018 Jul 27 (epub ahead of print)

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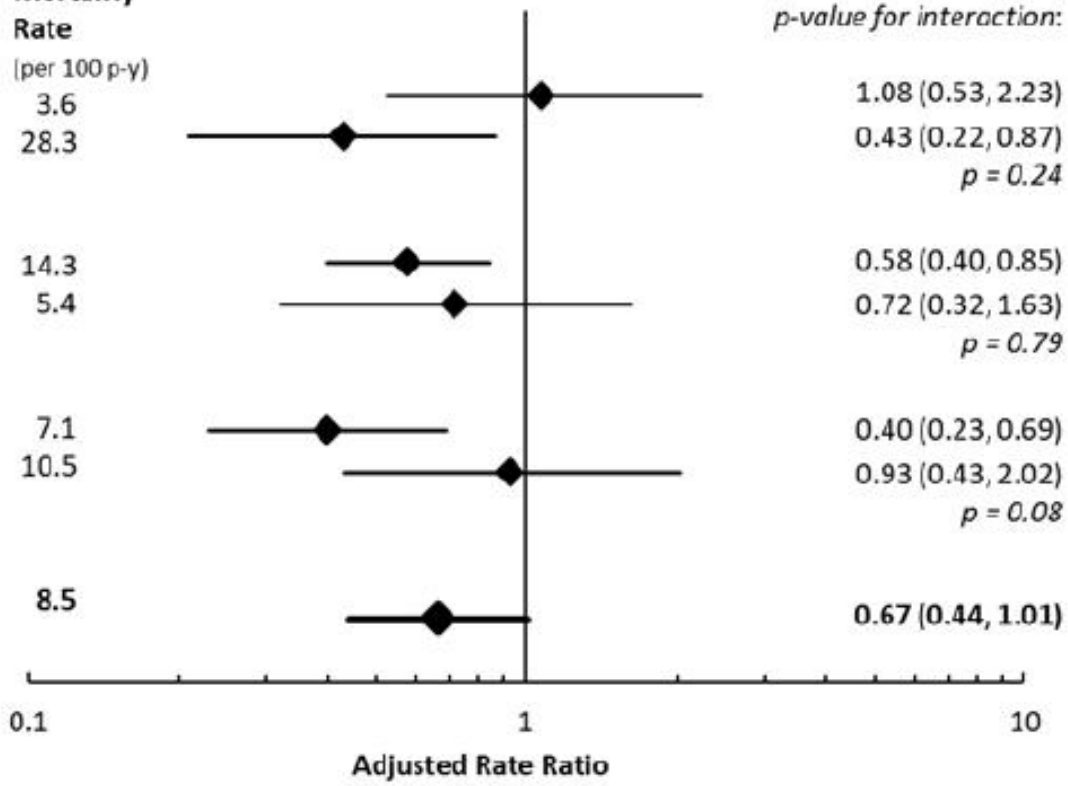
Screening with Xpert MTB and mortality: CHEPETSA trial

	Xpert MTB/RIF			LED FM			
	Person-Years	Deaths	Mortality Rate (per 100 p-y)	Person-Years	Deaths	Mortality Rate (per 100 p-y)	Adjusted rate ratio (aRR) *p-value for interaction:*
WHO Clinical Stage							
Stage 1-2	587	23	3.9	550	20	3.6	1.08 (0.53, 2.23)
Stage 3-4	231	32	13.9	127	36	28.3	0.43 (0.22, 0.87) *p = 0.24*
Sex							
Male	315	35	11.1	238	34	14.3	0.58 (0.40, 0.85)
Female	503	20	4.0	447	24	5.4	0.72 (0.32, 1.63) *p = 0.79*
Age							
≤35 Years	484	20	4.1	408	29	7.1	0.40 (0.23, 0.69)
>35 Years	333	35	10.5	276	29	10.5	0.93 (0.43, 2.02) *p = 0.08*
Overall	**818**	**55**	**6.7**	**685**	**58**	**8.5**	**0.67 (0.44, 1.01)**



Clin Infect Dis. 2018 Jul 27 (epub ahead of print)

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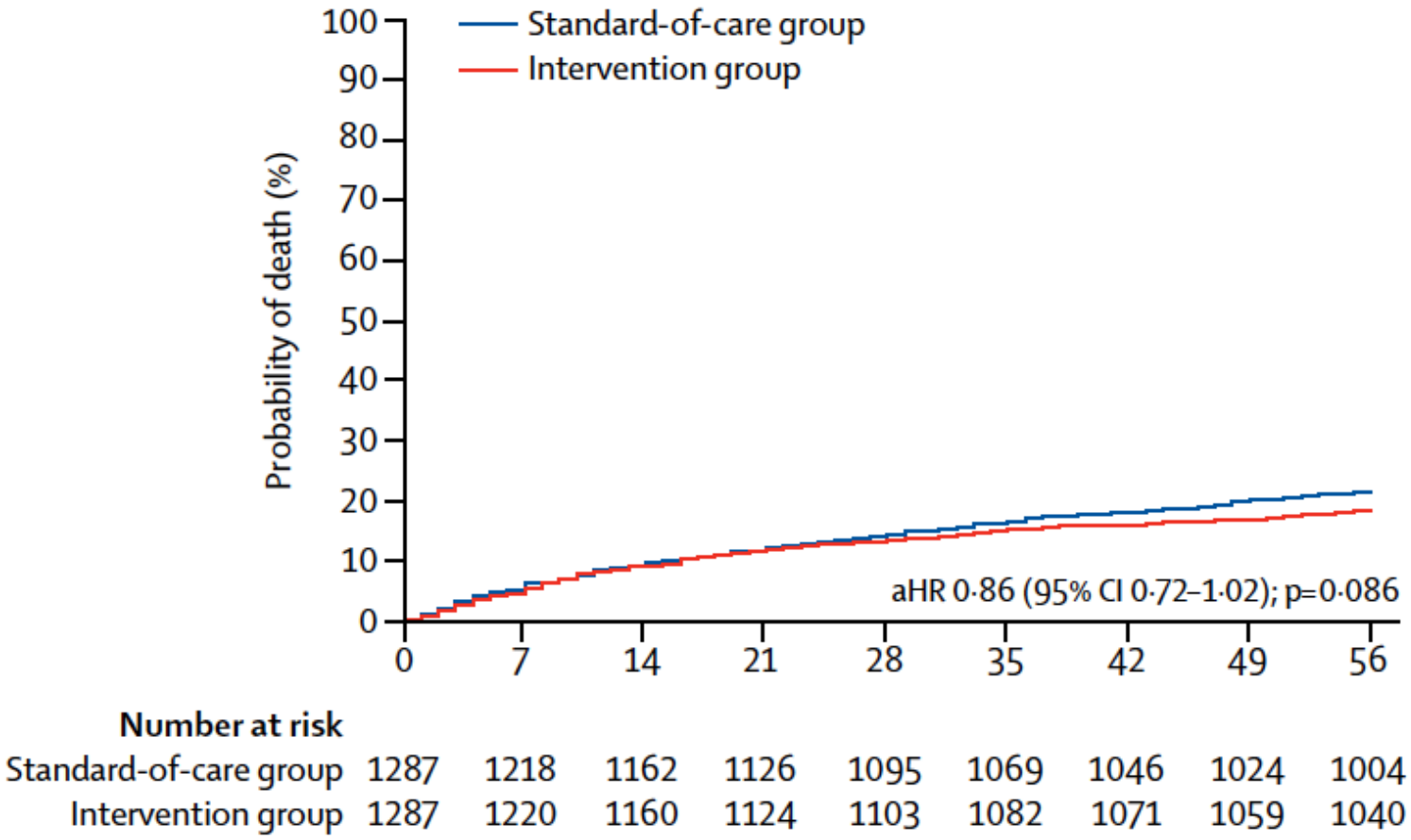
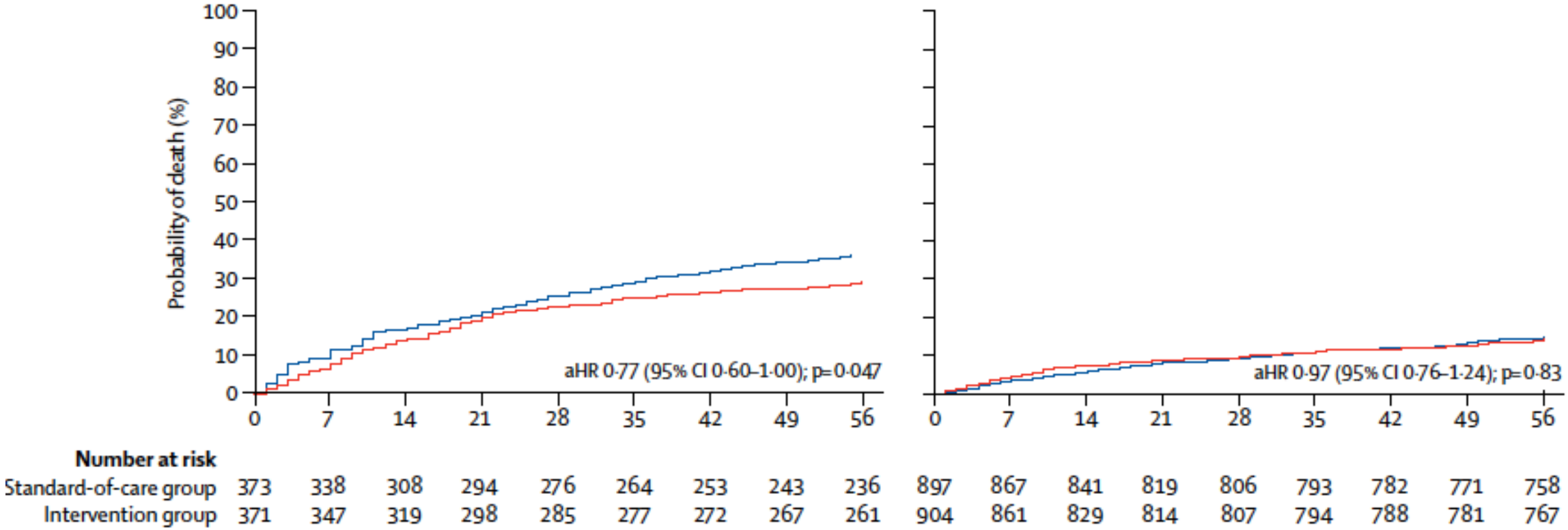
Urinary LAM + Xpert MTB screening for all inpatients: STAMP trial



Lancet 2018; 392: 292–301

IID INSTITUTE OF INFECTIOUS DISEASES

Urinary LAM + Xpert MTB screening for all inpatients: CD4<100 vs >100



Lancet 2018; 392: 292–301

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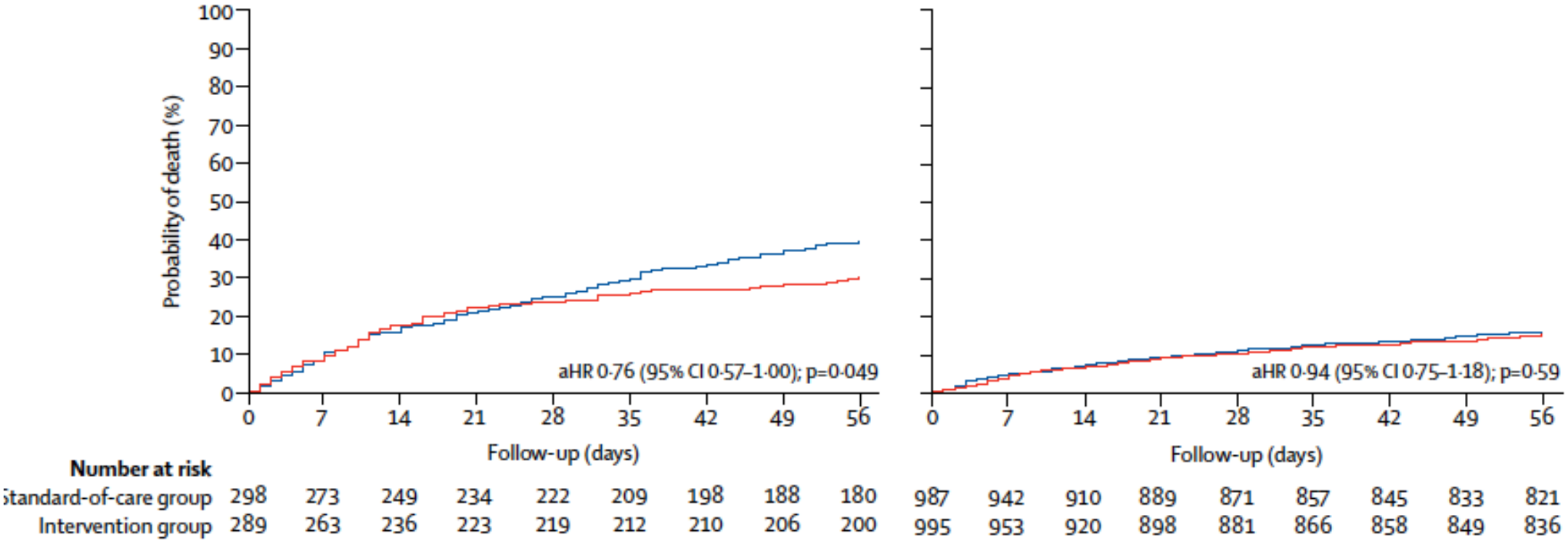
Urinary LAM + Xpert MTB screening for all inpatients: Hb < 8 vs > 8



Lancet 2018; 392: 292–301

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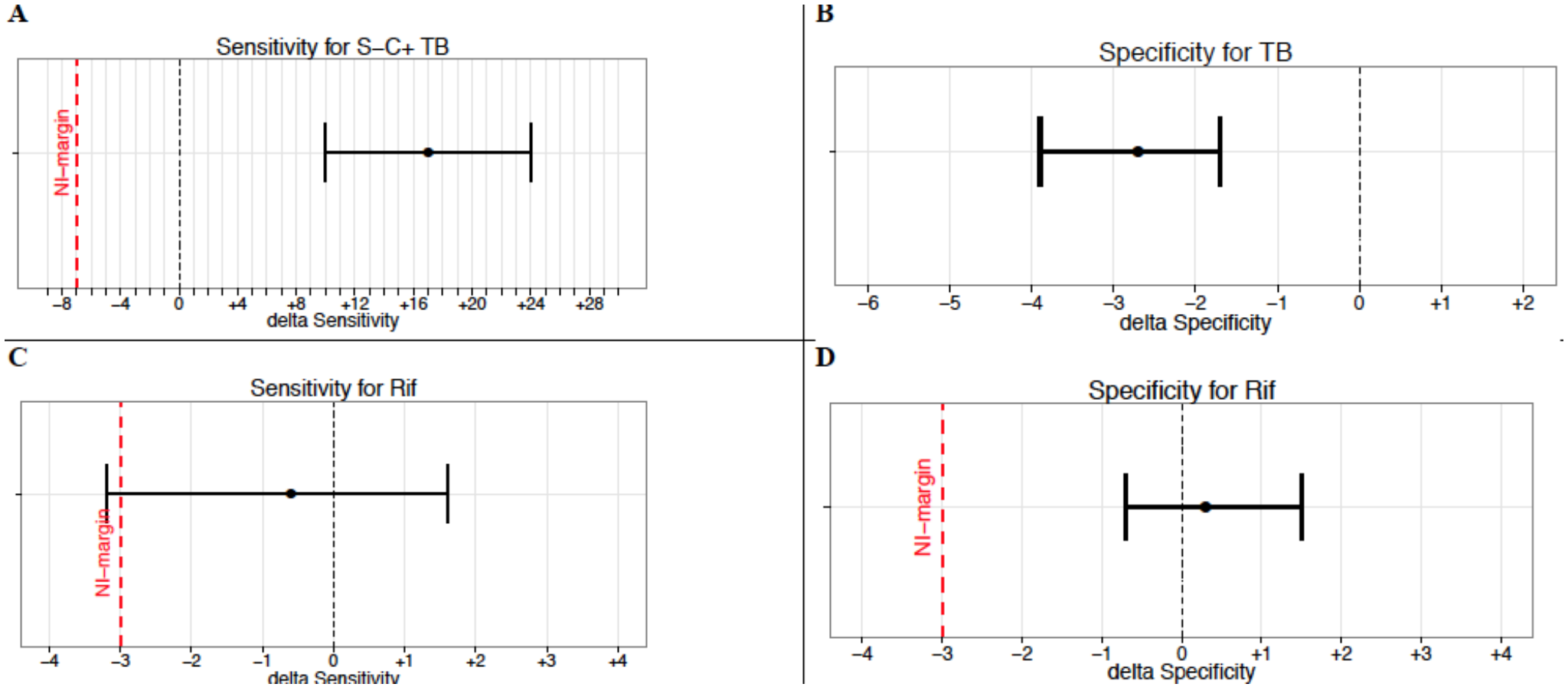
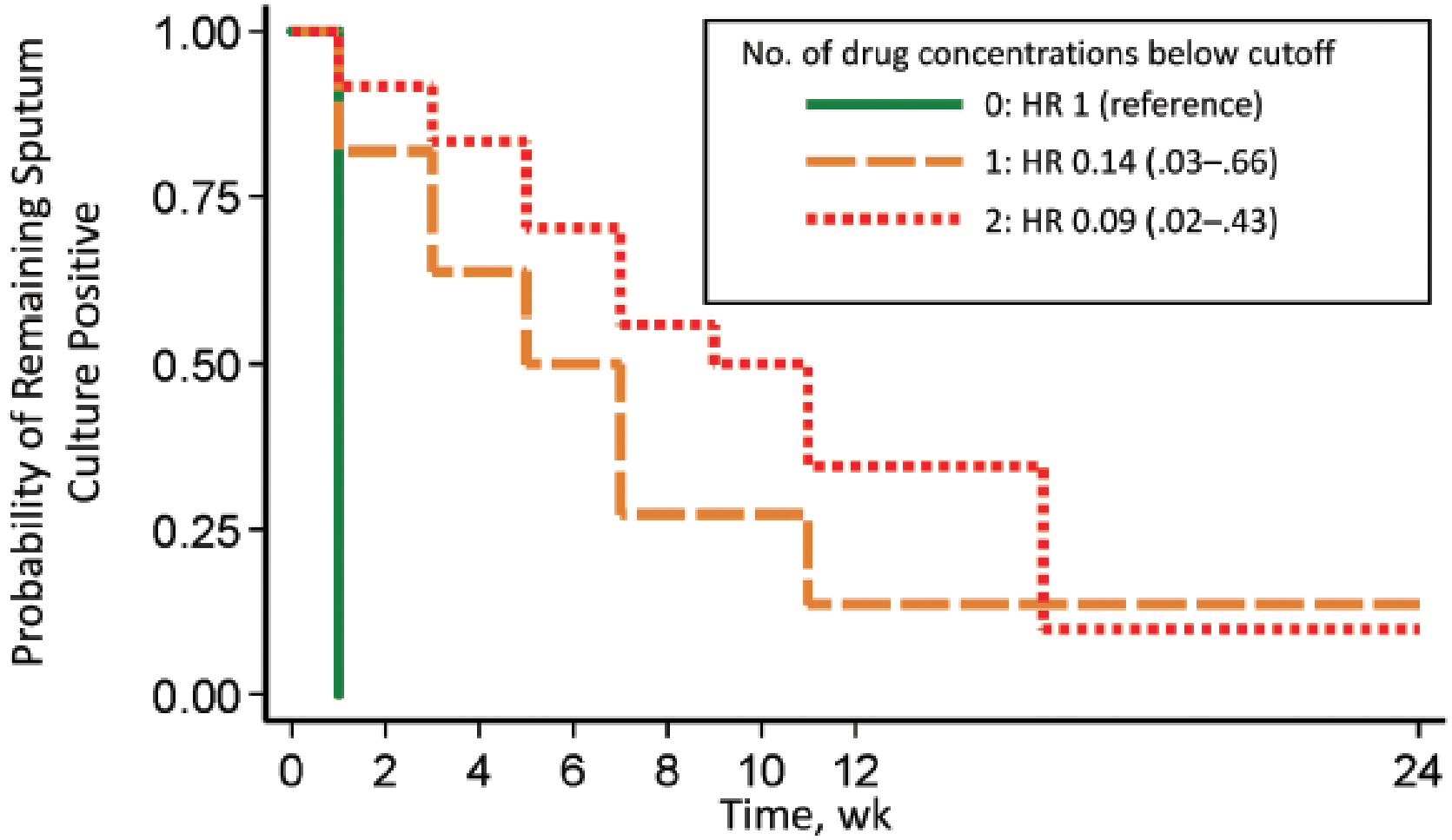
Ultra-Xpert: S-ve, culture +, PTB

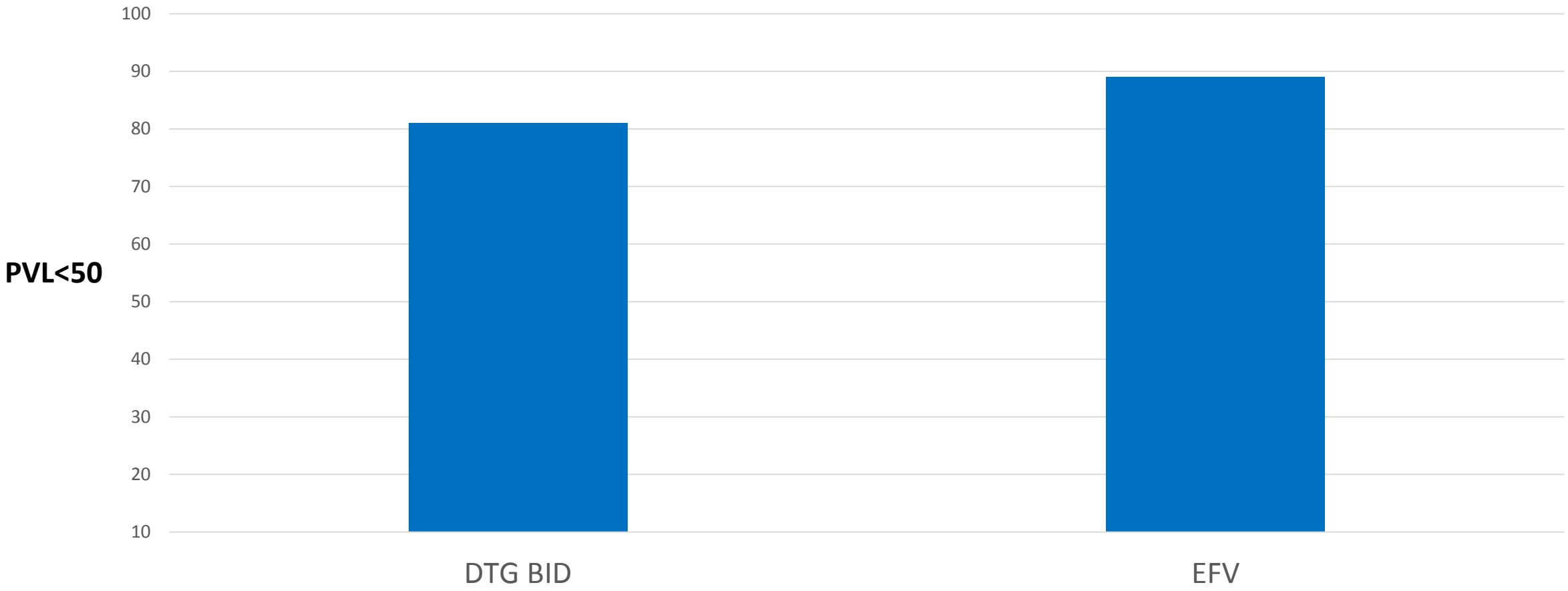


Lancet Infect Dis 2018;18:76–84.

HR drug concentrations and culture conversion



DTG bid with RMP: INSPIRING study



CROI 2018 abstr 28LB

BIC with RMP

Mean BIC PK (% CV)	Cohort 1 BIC/FTC/TAF QD (n = 26)	Cohort 2 BIC/FTC/TAF BID + RIF QD (n = 26)
AUC_{0-24}, ng*h/mL	115,200 (21)	45,600 (23)
C_{max}, ng/mL	8530 (16)	4560 (19)
C_{trough}, ng/mL	3070 (28)	608 (30)

CROI 2018, abstr 34

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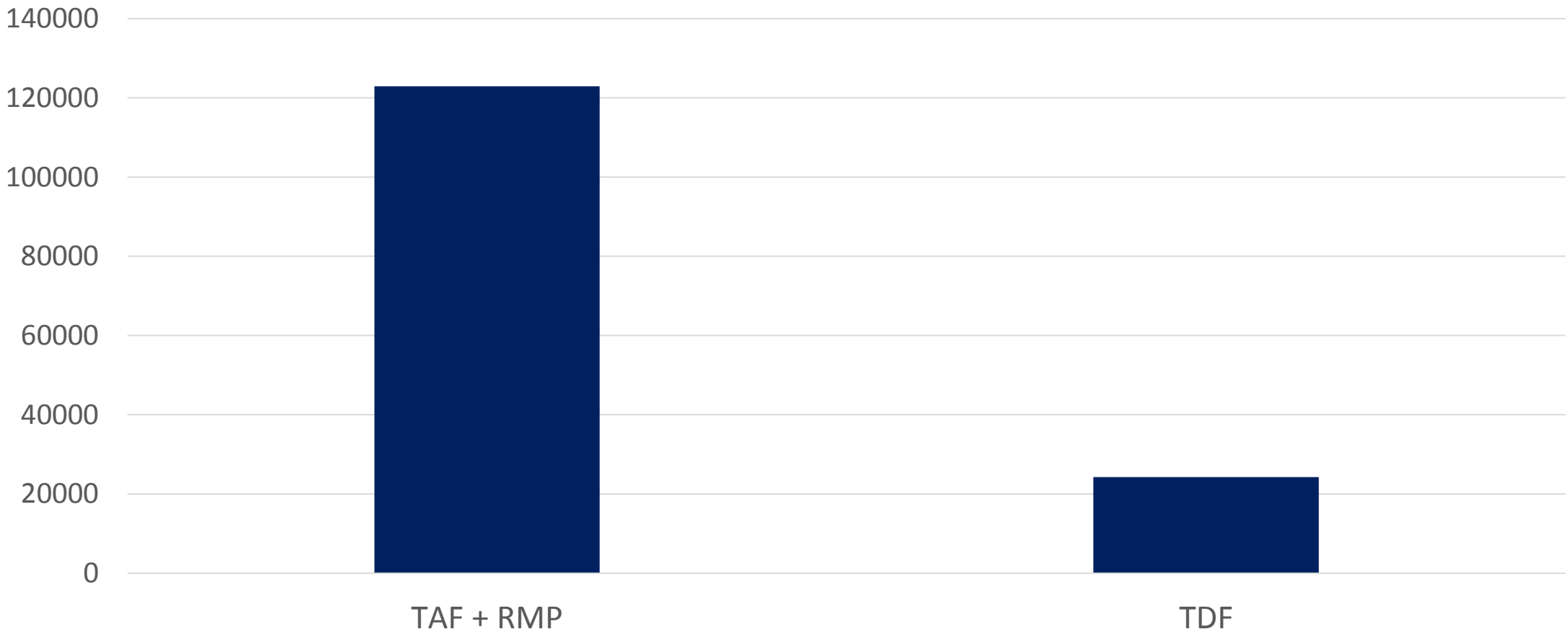
TAF + RMP vs TDF- IC-TFV-DP: RIFT study



CROI 2018; abstr 28LB

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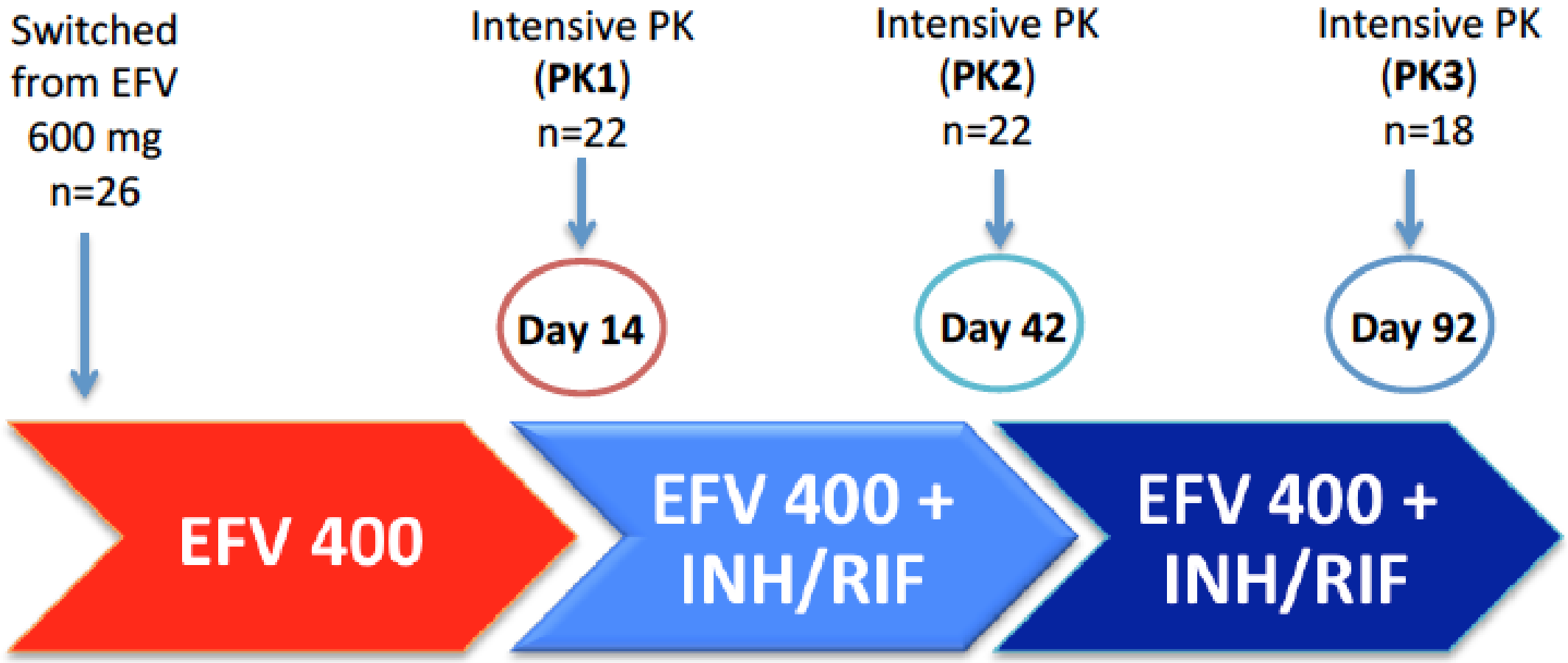
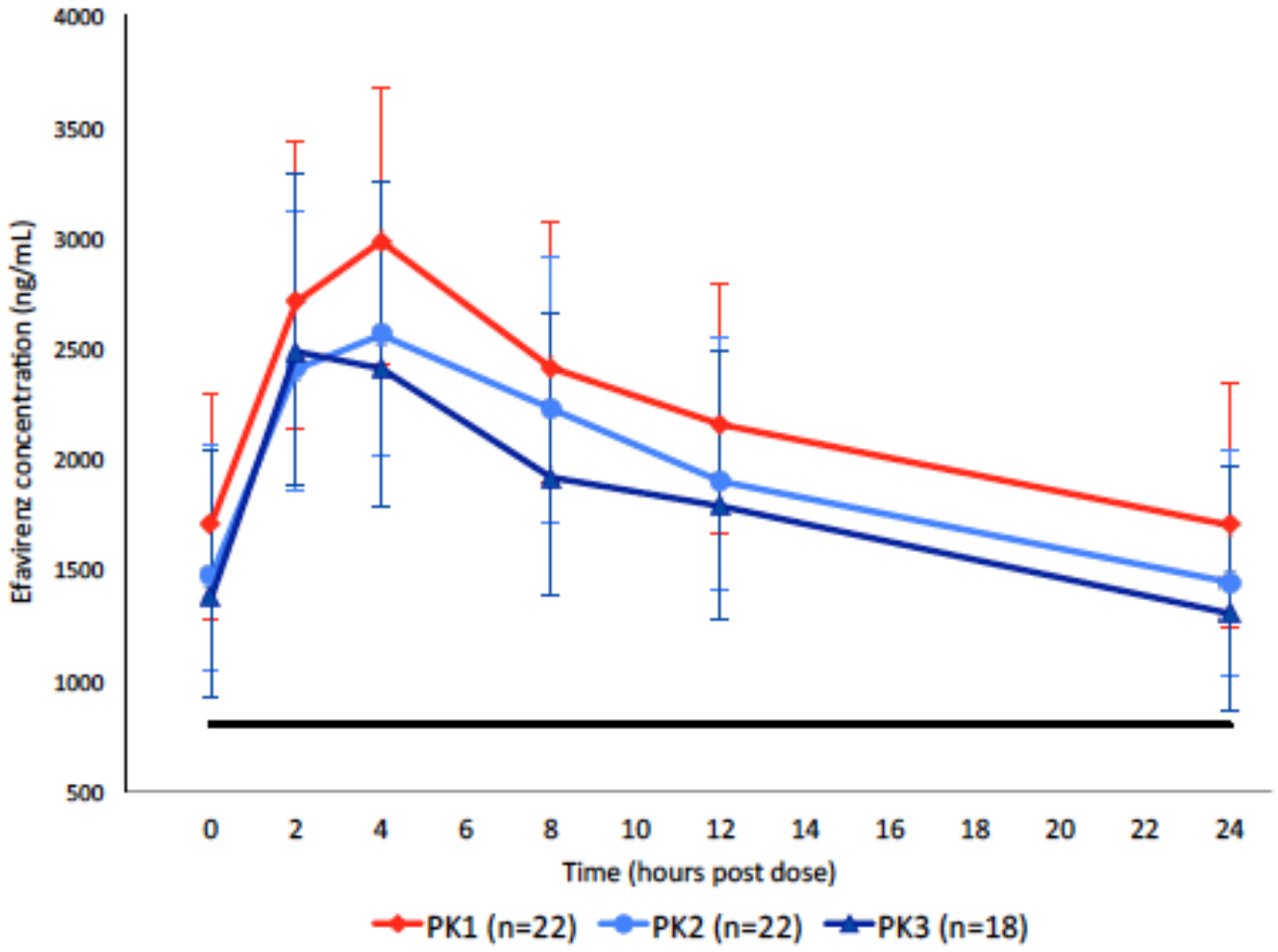
EFV_{400} with HR: study design



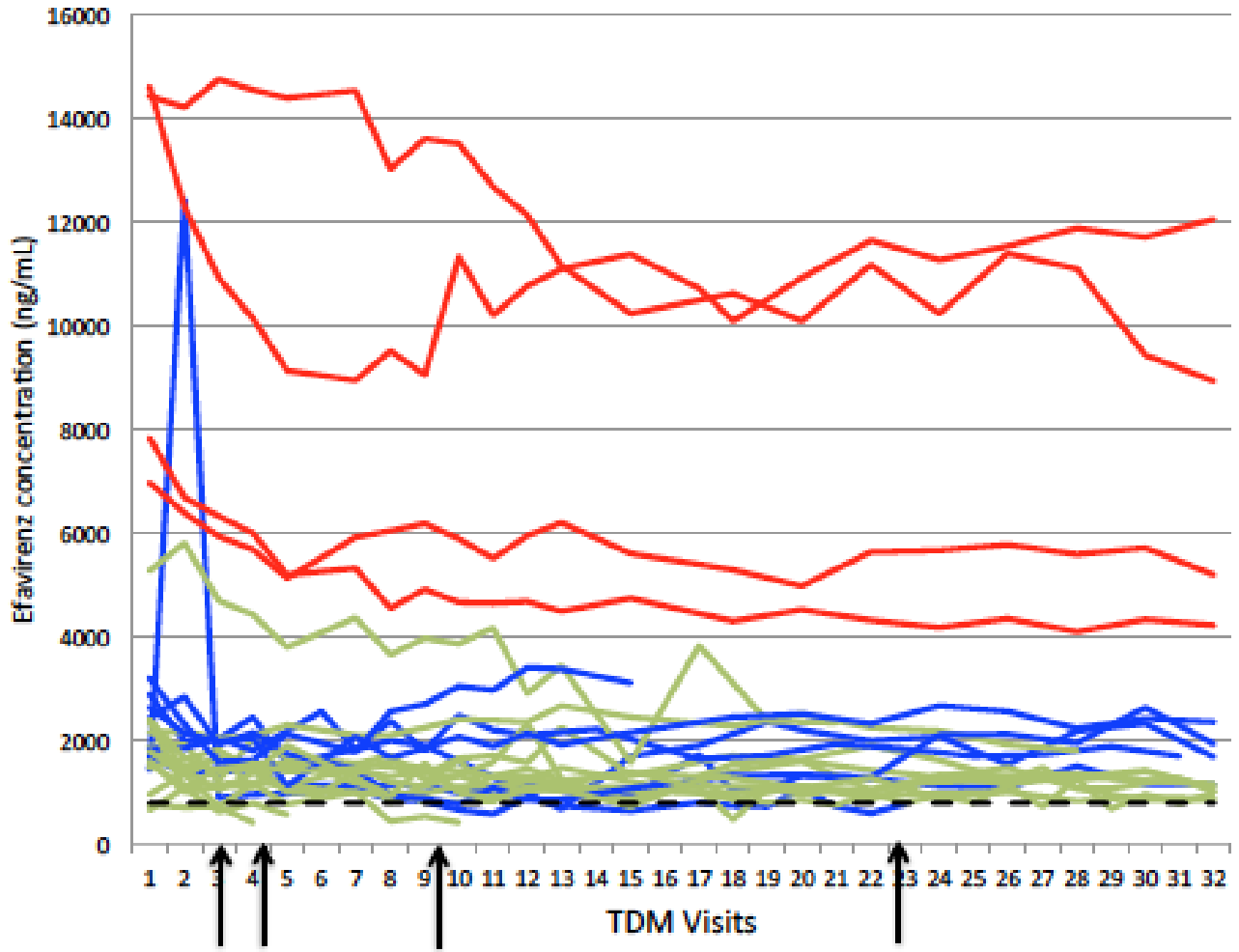
CROI 2018 abstr 457

EFV concentrations with HR + EFV_{400}



CROI 2018 abstr 457

EFV + HR: Metabolizer status



CROI 2018 abstr 457

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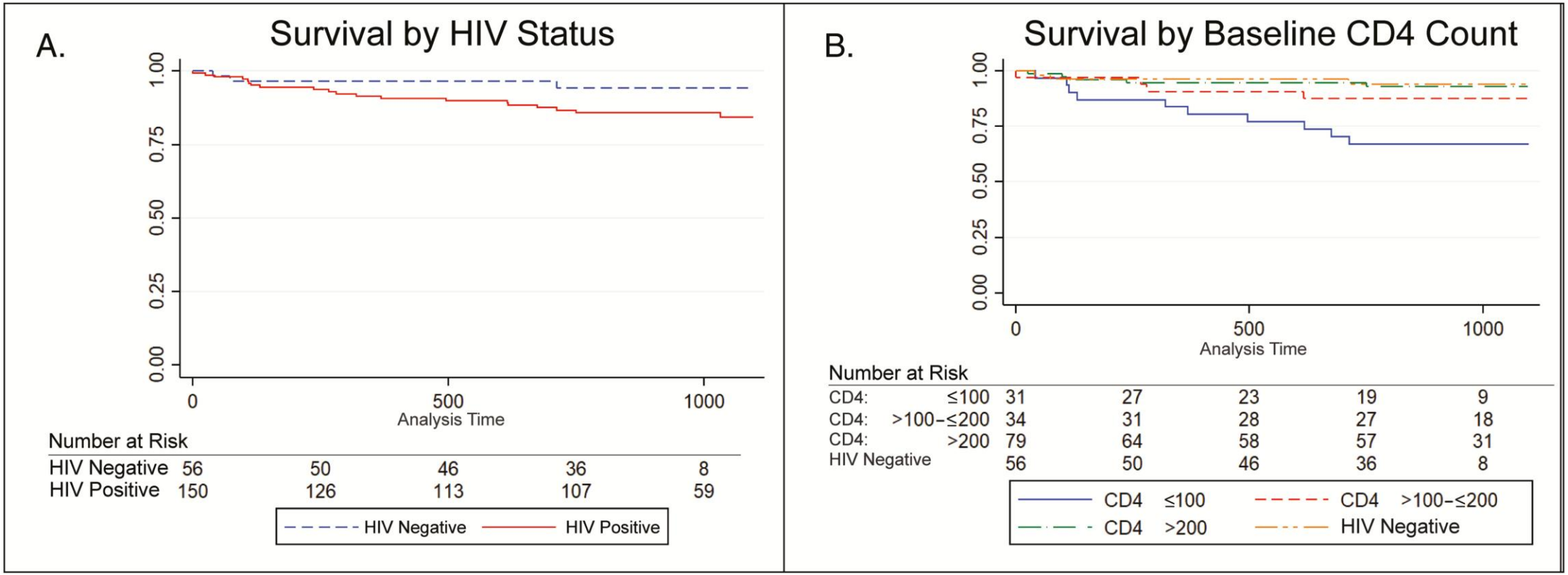
Concurrent MDRTB and HIV treatment: SHOUT-MDRTB study



Clin Infect Dis 2018;66:1246–1253.

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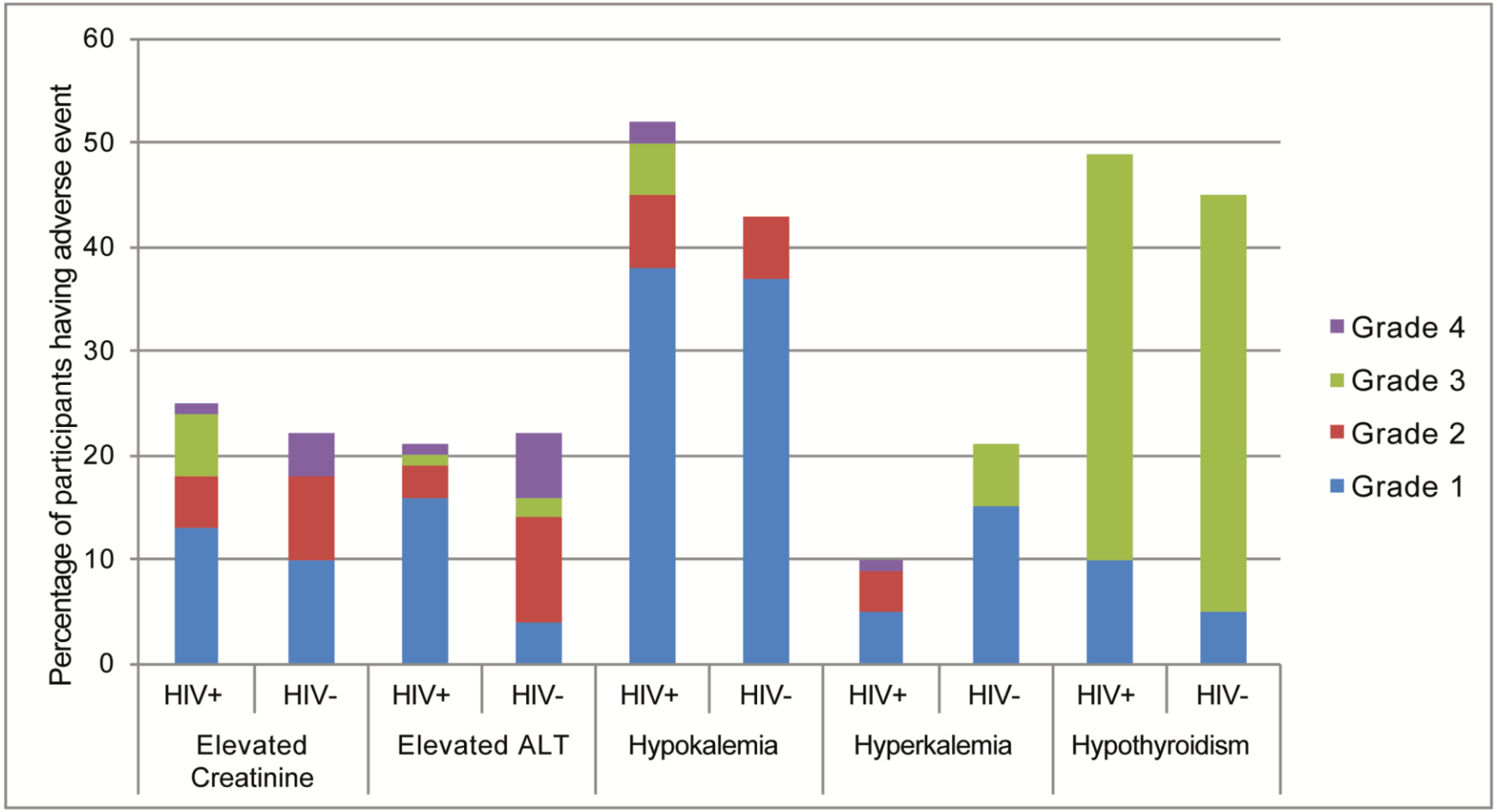

Clin Infect Dis 2018;66:1246–1253.

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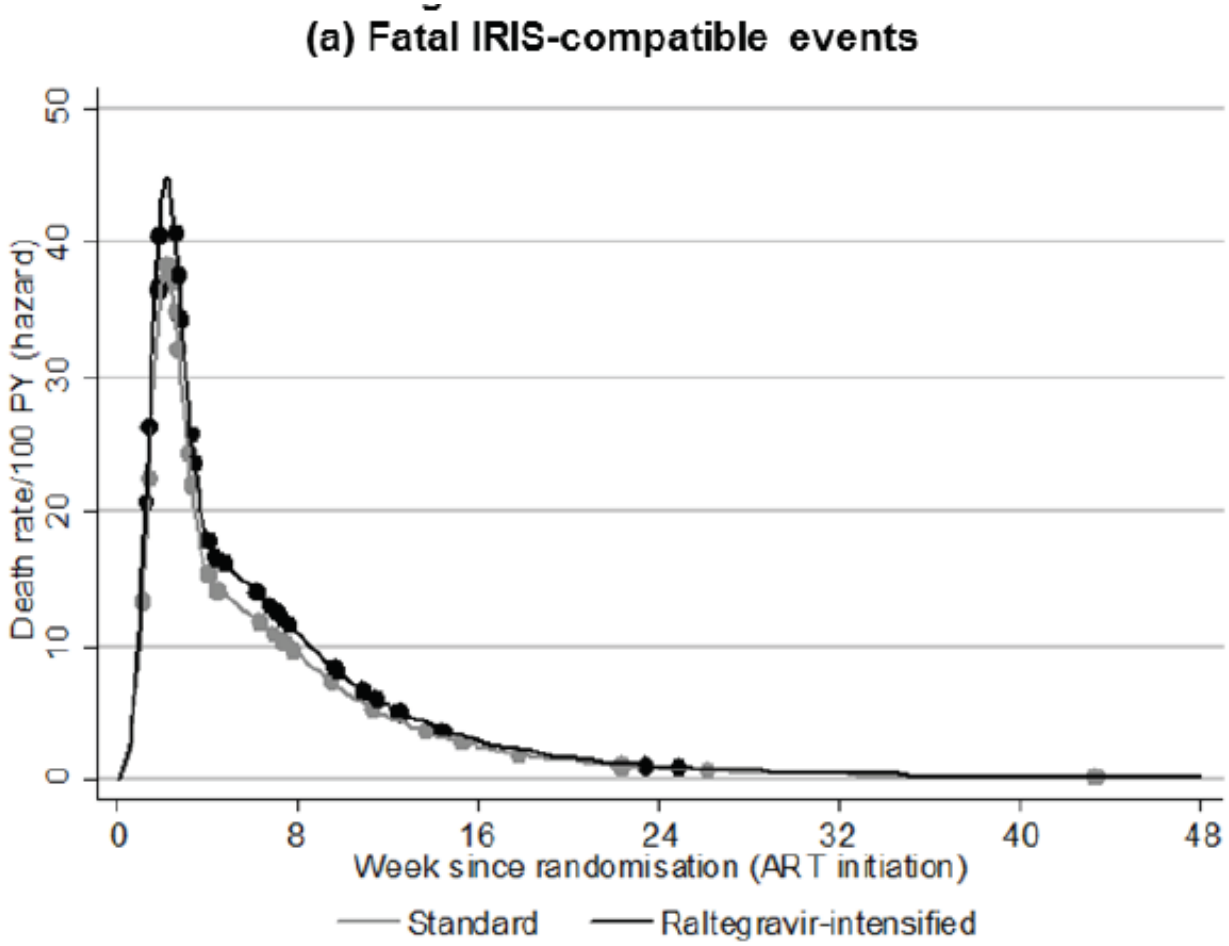
No higher IRIS with RAL intensification: REALITY trial



CROI 2018, Abstr 23

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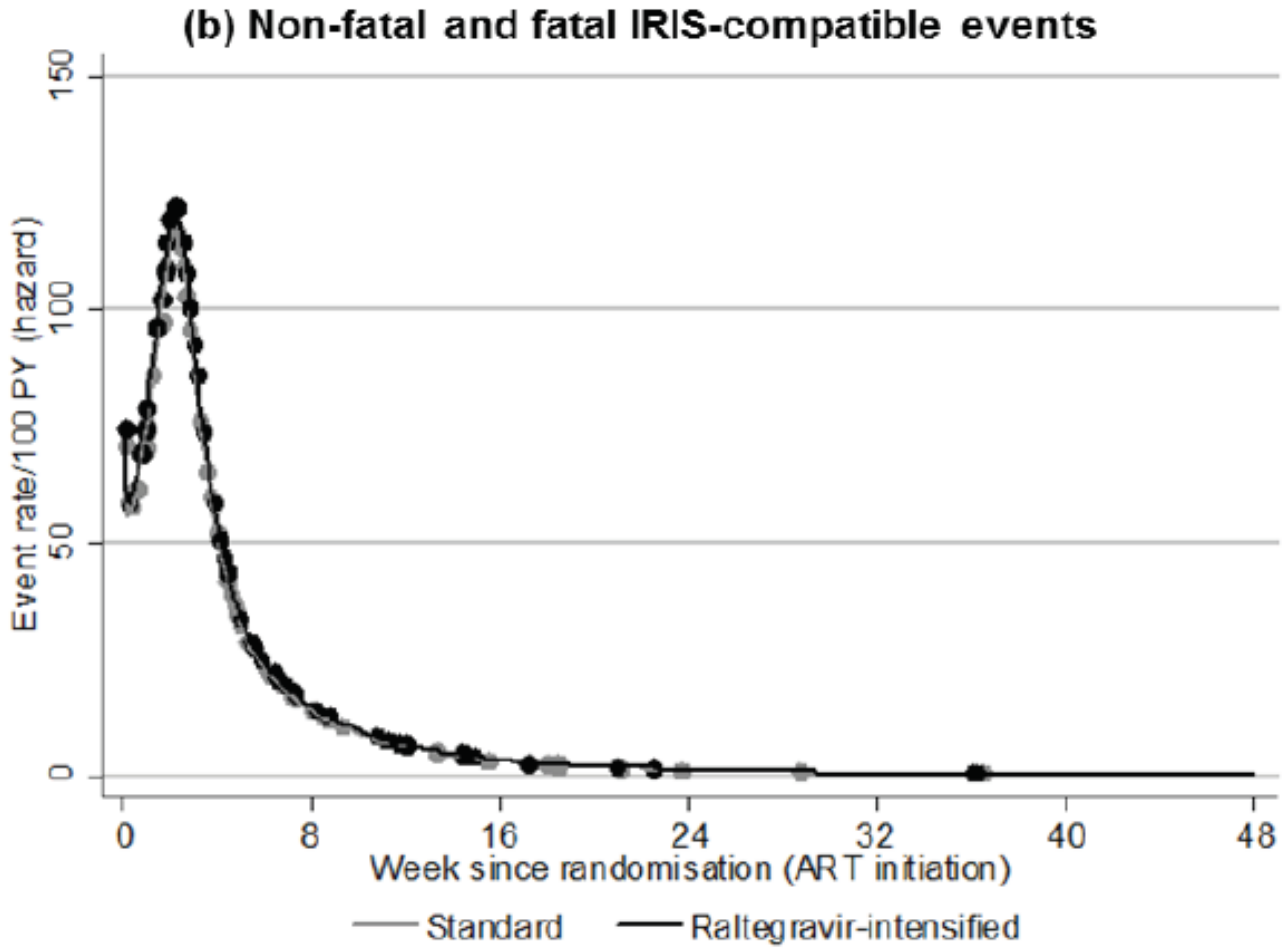
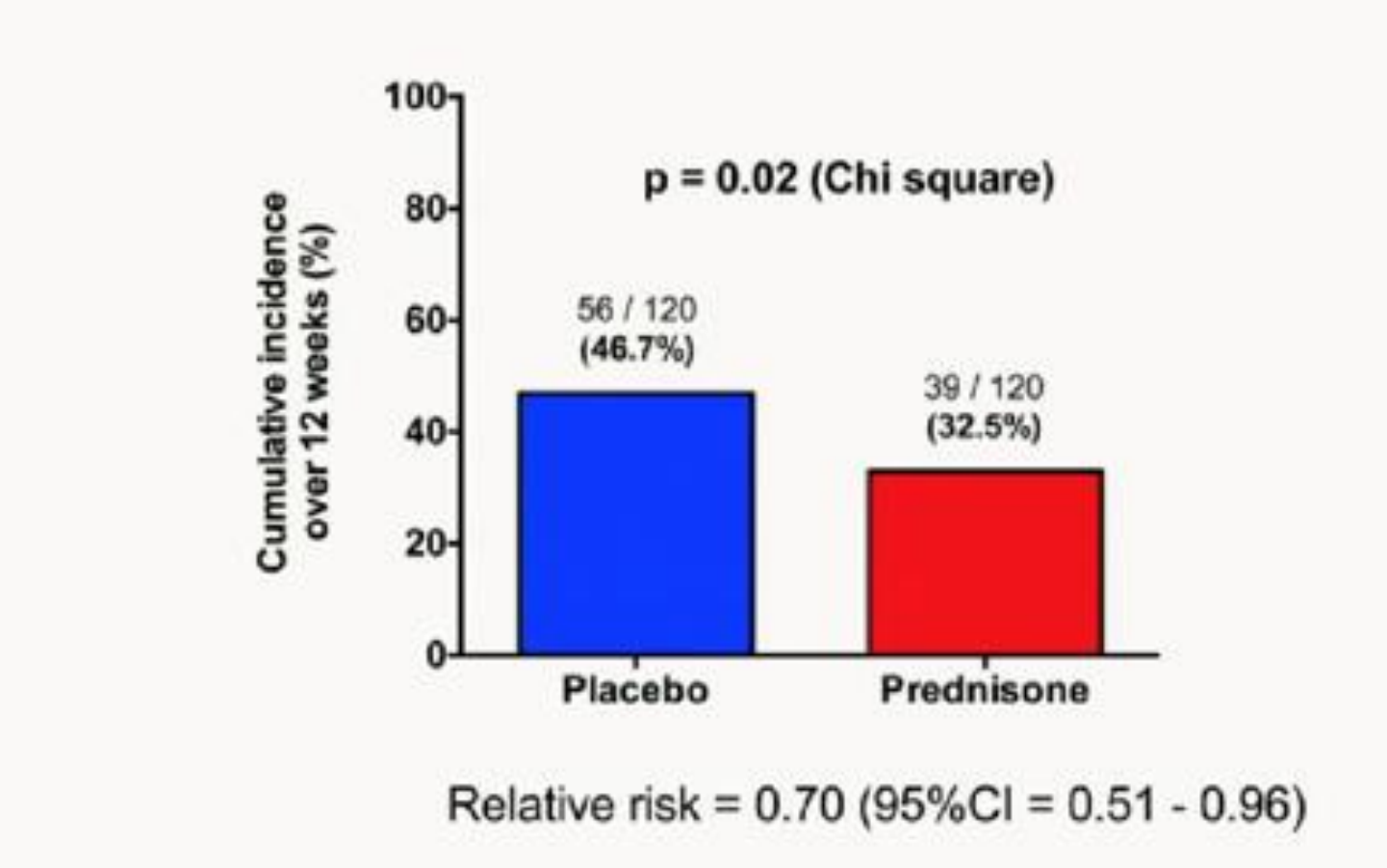


CROI 2018, Abstr 23

Prophylactic steroids for paradoxical TB-IRIS: PRED-IRIS study



CROI 2017, abstr 81LB

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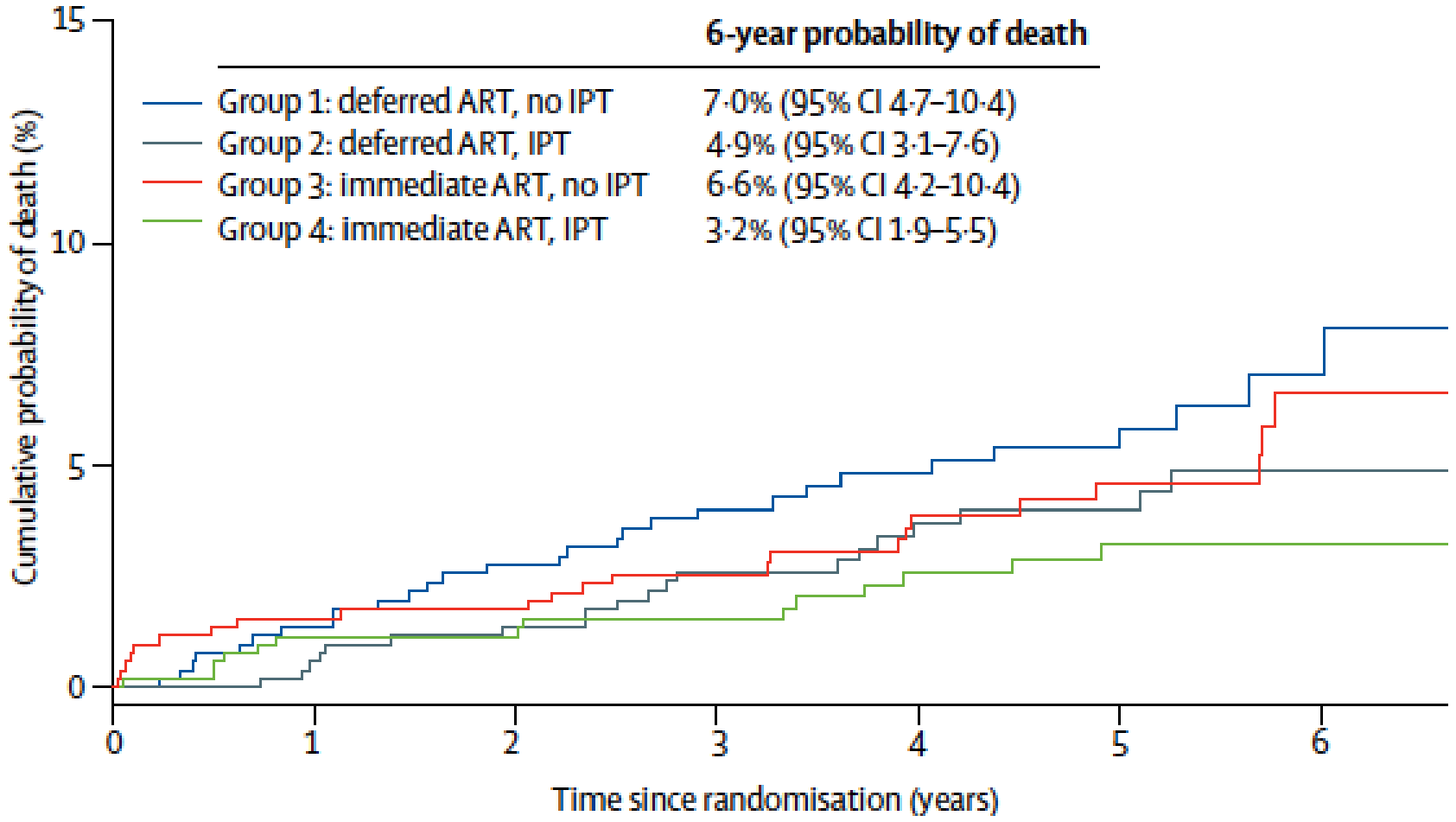
IPT and mortality benefit: TEMPARANO



Lancet Glob Health 2017; 5:e1080–e1089.

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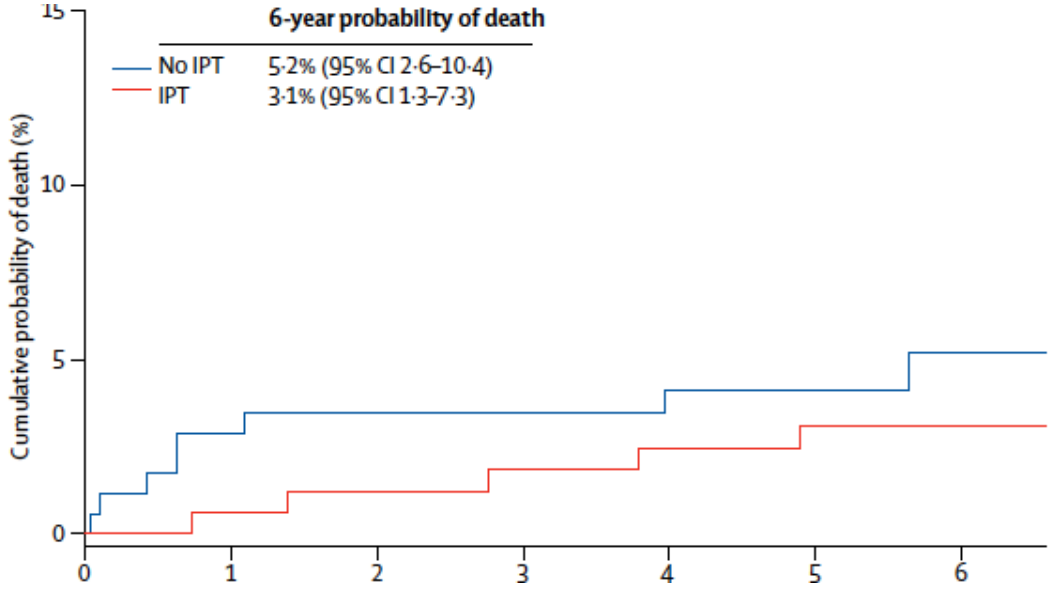
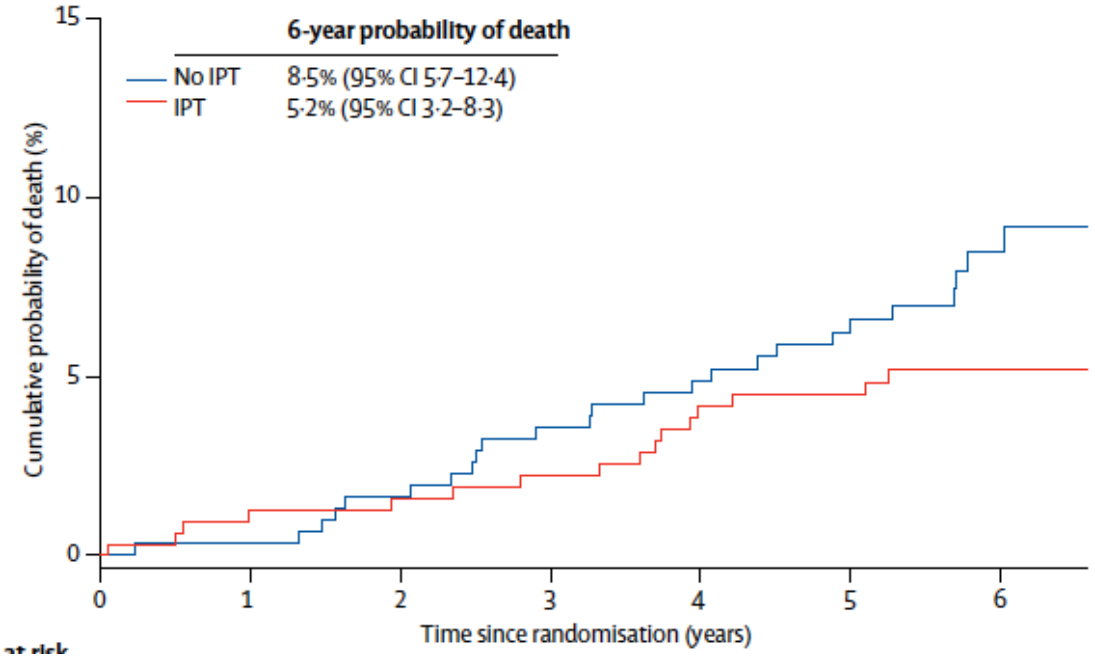
IPT benefit according to QuantiFERON status

QunatiFERON-TB Gold +ve



QuantiFERON-TB Gold -ve



Lancet Glob Health 2017; 5:e1080–e1089.

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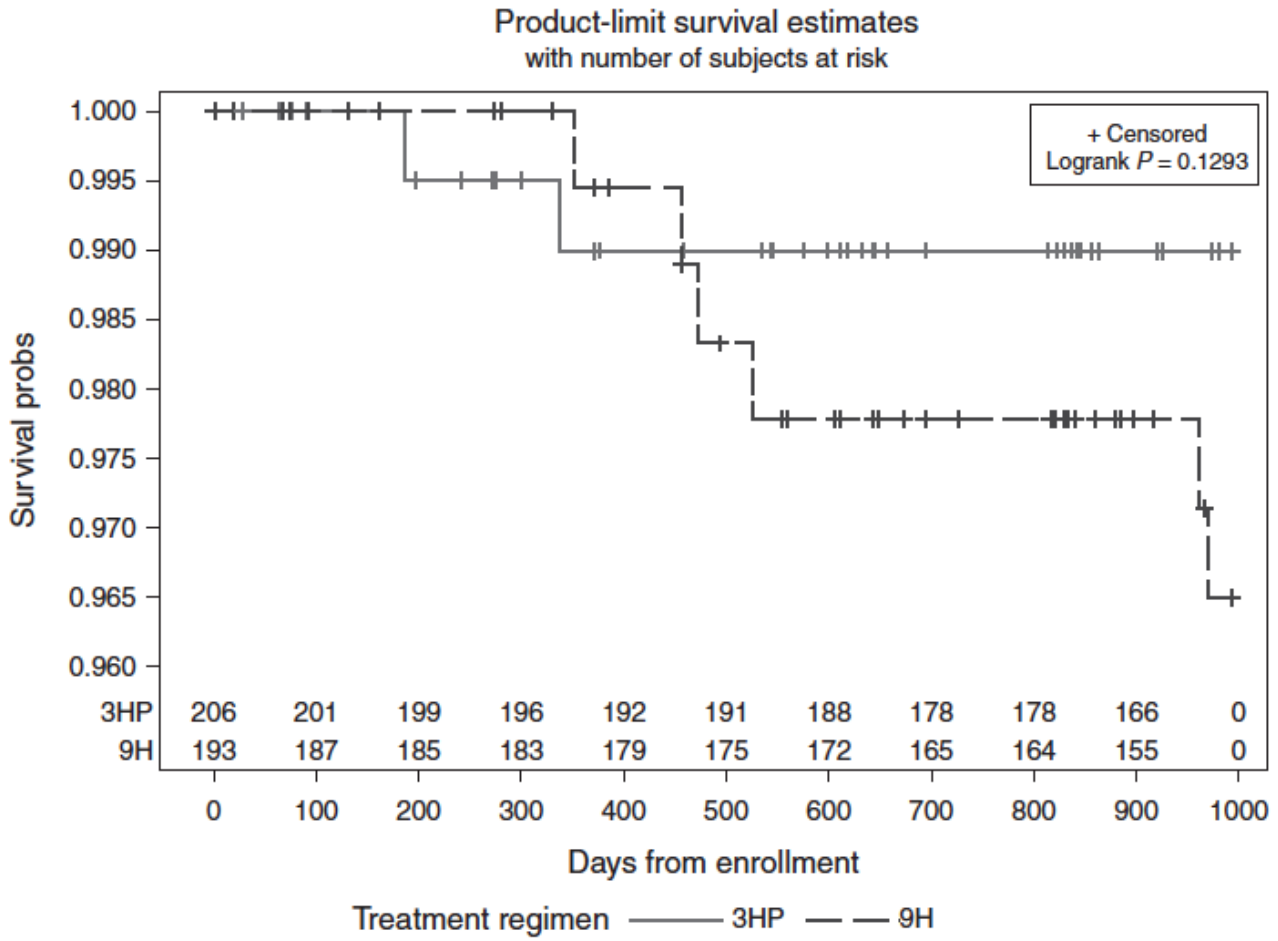
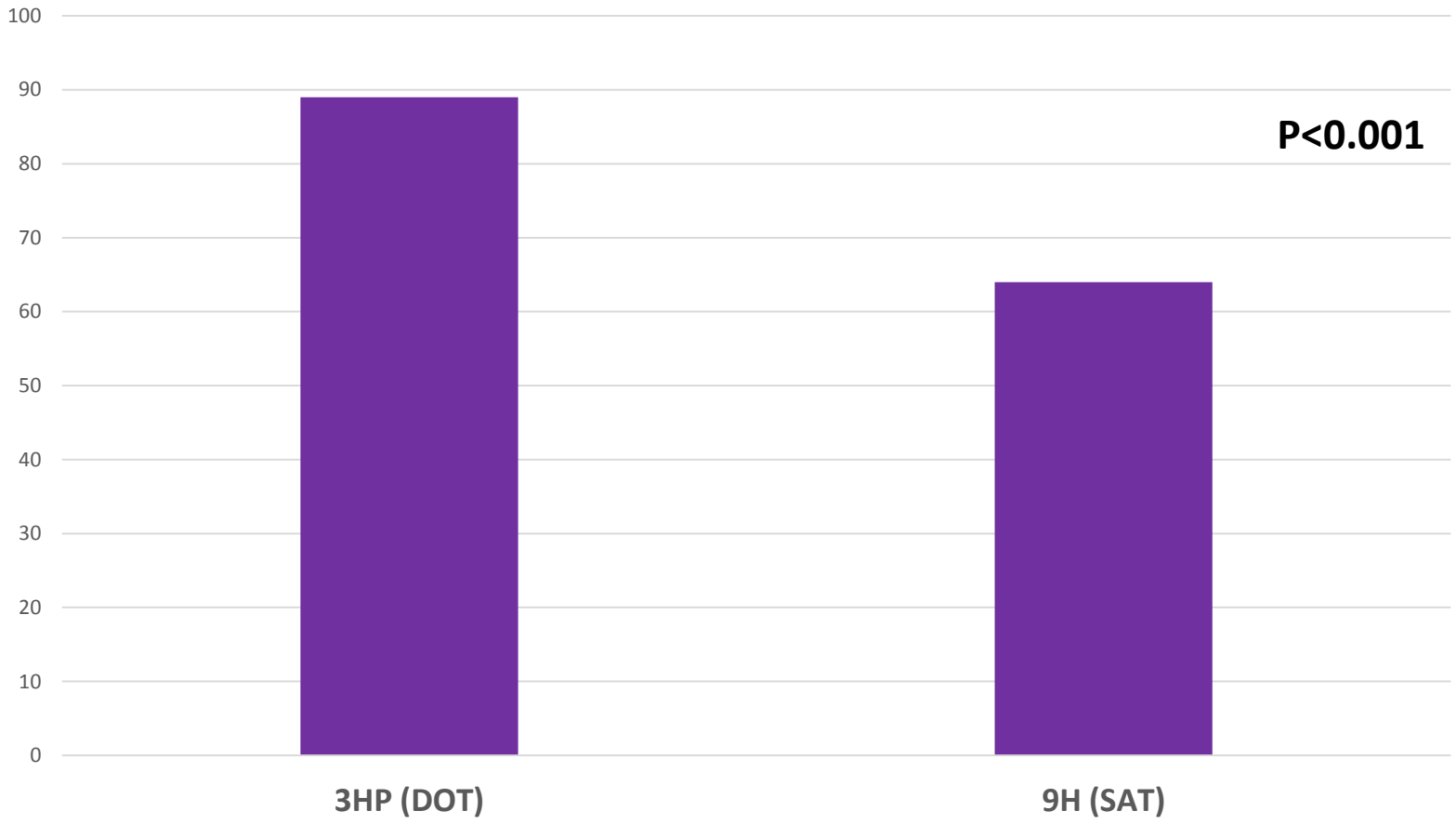
3HP vs 9H for LTBI treatment: PREVENT TB trial



AIDS 2016, 30:1607–1615

3HP vs 6H for LTBI treatment: completion rates PREVENT TB trial



AIDS 2016, 30:1607–1615

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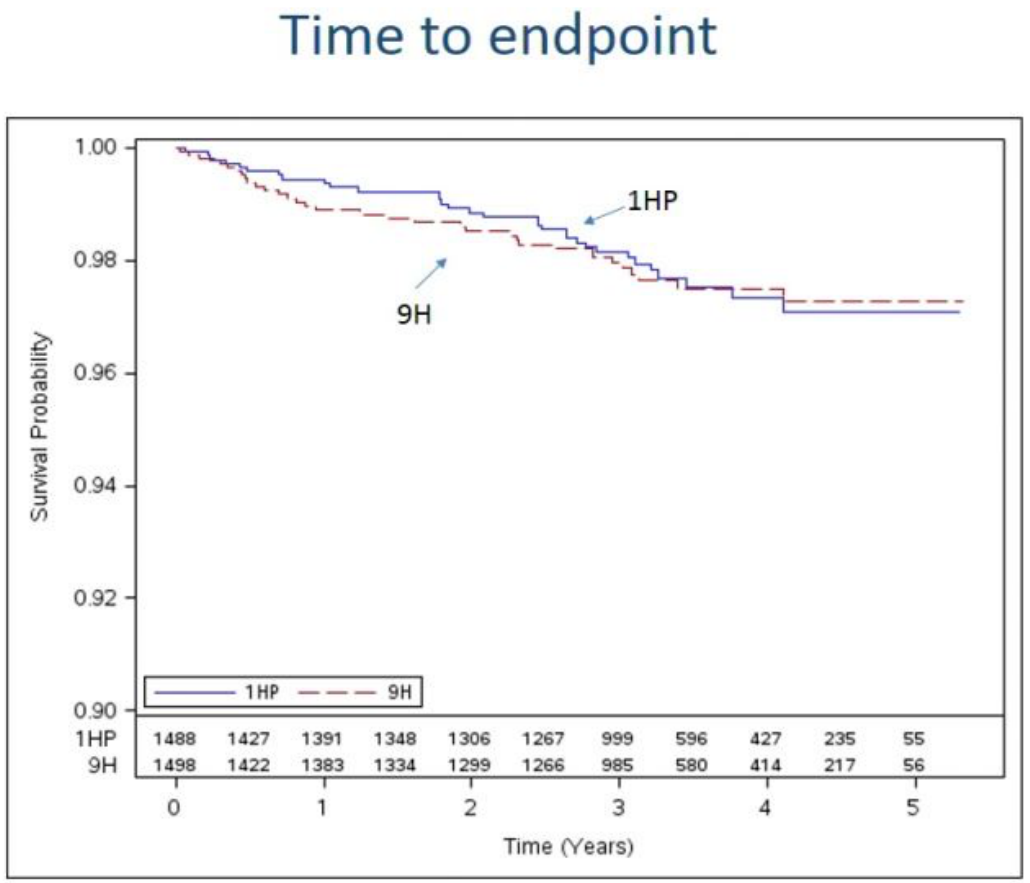
1HP vs 9H for preventing TB amongst PLHIV: BRIEF-TB/A5279

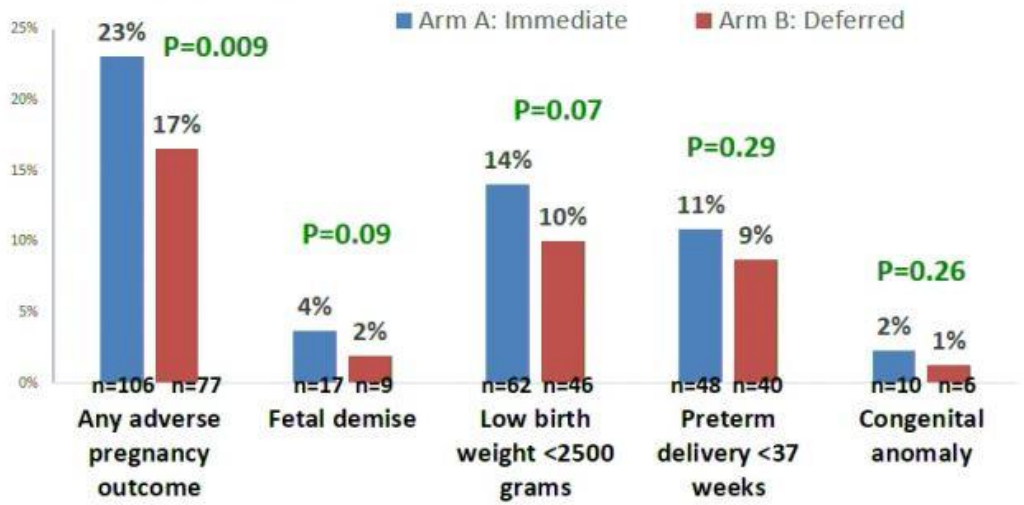


CROI 2018; Abstract 37LB

Immediate IPT and pregnancy/birth outcomes: TB APPRISE study

Secondary Outcomes: Pregnancy and Birth Outcomes

- 926 deliveries (460 in immediate arm vs 466 in deferred arm)
  - 915 singletons, 11 twins for total of 937 fetuses/infants
  - 26 stillbirths (fetal demise)
  - 2 abortions (1 spontaneous, 1 induced)
  - 909 live births



CROI 2018; Abstract 142LB

HIV/TB: Research ideas

- Evaluation of
  - Next generation urinary LAM assays
  - Diagnostic accuracy and Clinical outcomes of screening with Xpert-Ultra vs Xpert in PTB and EPTB across different settings

- Efficacy and durability of shorter LTBI regimens (3HP, 1HP, 3R) in PLHIV with advanced disease initiating ART

- Operational research for TDM of anti-TB drugs in high HIV/TB areas

Outline

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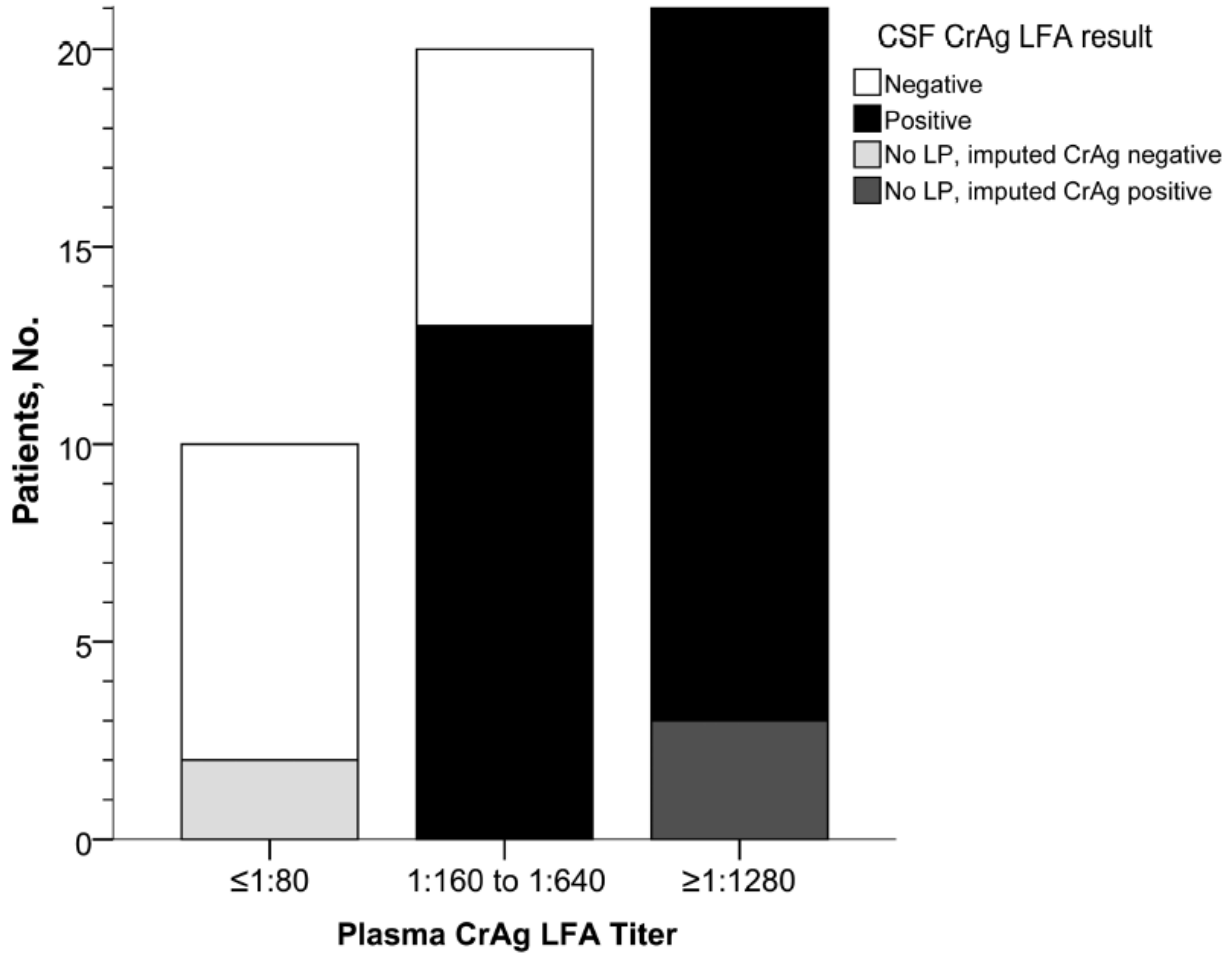
- Mycobacterial
- Fungal
- Viral
- Protozoal

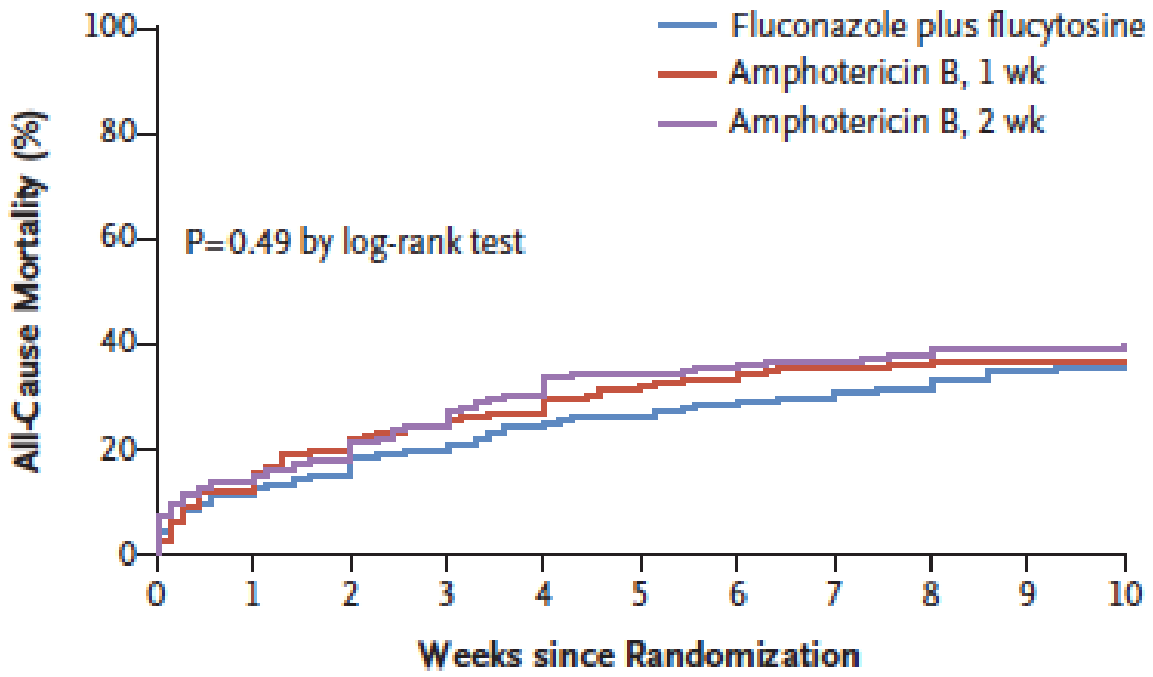
sCrAG titers and CSF CrAG positivity



Clin Infect Dis. 2017 Nov 29;65(12):2126-2129

IID INSTITUTE OF INFECTIOUS DISEASES

Alternative regimens for CM induction treatment: ACTA trial



No. at Risk											
Fluconazole plus flucytosine	225	200	192	181	171	167	161	159	155	147	144
Amphotericin B, 1 wk	224	196	180	169	164	152	148	143	142	141	139
Amphotericin B, 2 wk	229	198	188	173	160	150	147	144	142	139	136

N Engl J Med. 2018 Mar 15;378(11):1004-1017

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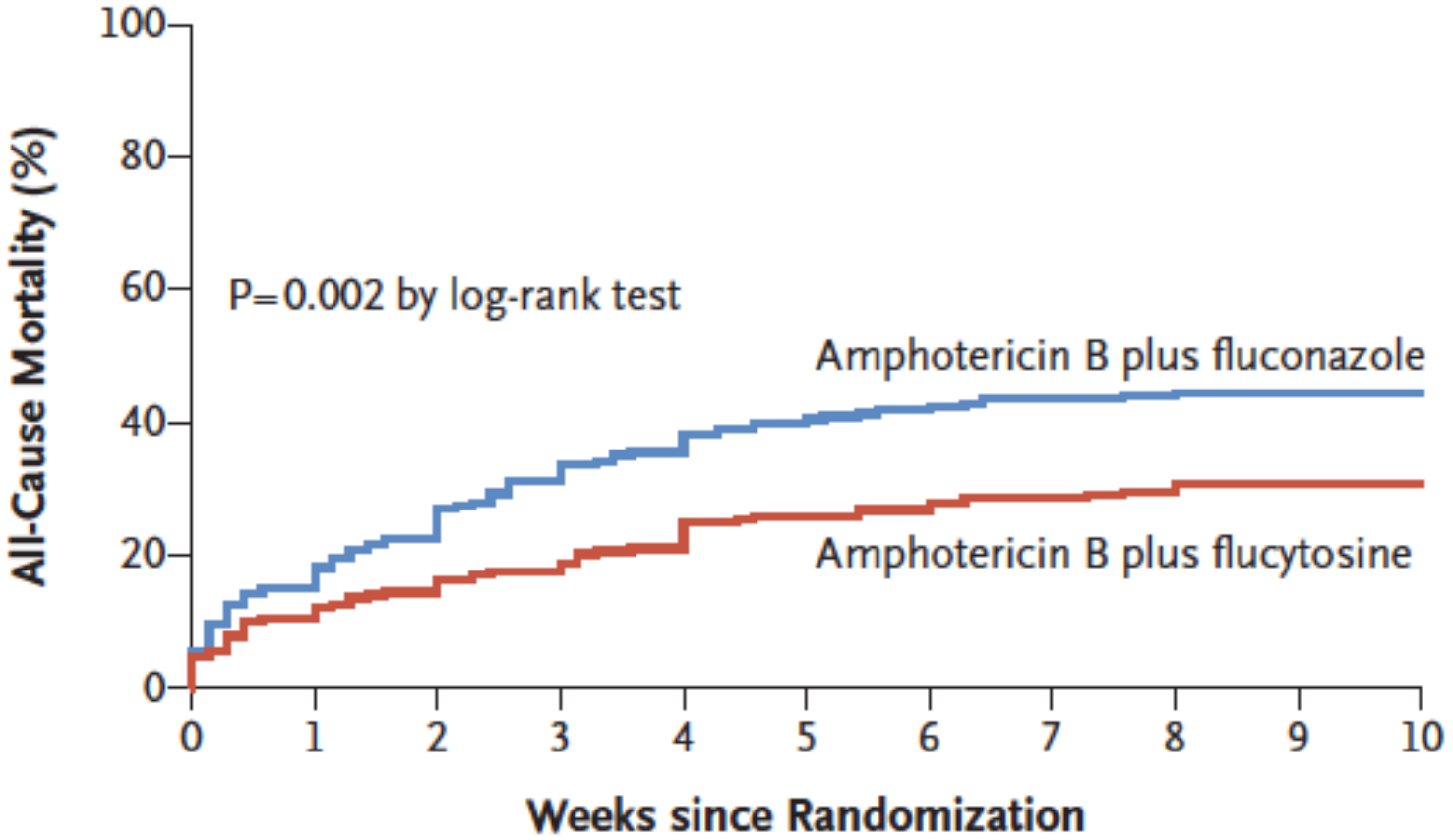
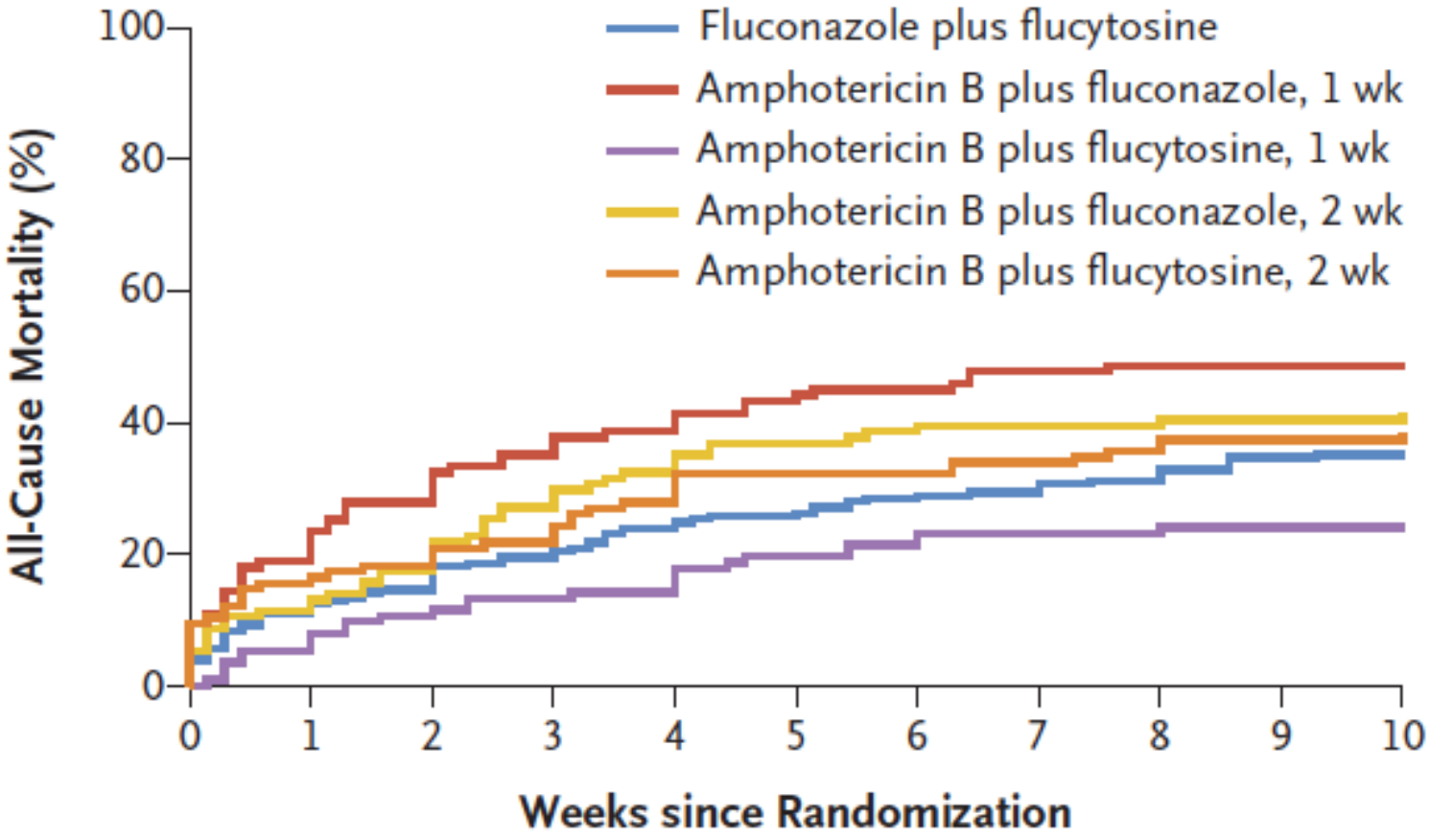
ACTA:
Alternative regimens for CM induction treatment



N Engl J Med. 2018 Mar 15;378(11):1004-1017

Alternative regimens for CM induction treatment: ACTA trial



N Engl J Med. 2018 Mar 15;378(11):1004-1017

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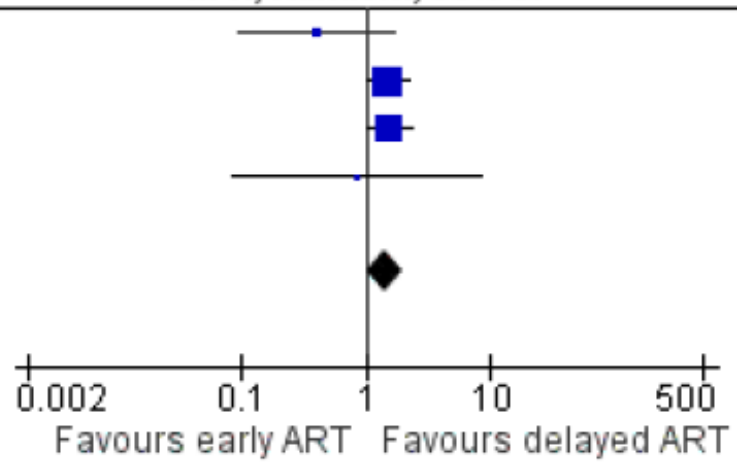
ART timing in CM: All cause mortality

Study or Subgroup	Early ART Events	Early ART Total	Delayed ART Events	Delayed ART Total	Weight	Risk Ratio M-H, Random, 95% CI
Bisson 2013	2	14	5	14	4.9%	0.40 [0.09, 1.73]
Boulware 2014	40	88	27	89	49.9%	1.50 [1.02, 2.21]
Makadzange 2010	22	28	13	26	43.2%	1.57 [1.02, 2.42]
Zolopa 2009	1	13	2	22	2.0%	0.85 [0.08, 8.44]
Total (95% CI)		**143**		**151**	**100.0%**	**1.42 [1.02, 1.97]**
Total events	65		47			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.44$, df = 3 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 2.08 (P = 0.04)



Cochrane Database Syst Rev. 2018 Jul 24;7:CD009012

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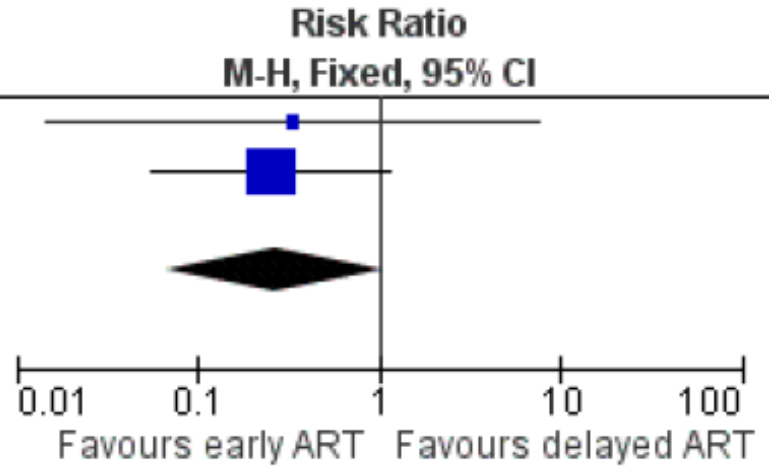
ART timing in CM: CM relapse

Study or Subgroup	Early ART Events	Total	Delayed ART Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bisson 2013	0	14	1	14	15.9%	0.33 [0.01, 7.55]
Boulware 2014	2	88	8	89	84.1%	0.25 [0.06, 1.16]
Total (95% CI)		**102**		**103**	**100.0%**	**0.27 [0.07, 1.04]**
Total events	2		9			

Heterogeneity: $Chi^2 = 0.02$, $df = 1$ ($P = 0.88$); $I^2 = 0\%$

Test for overall effect: $Z = 1.90$ ($P = 0.06$)



Cochrane Database Syst Rev. 2018 Jul 24;7:CD009012

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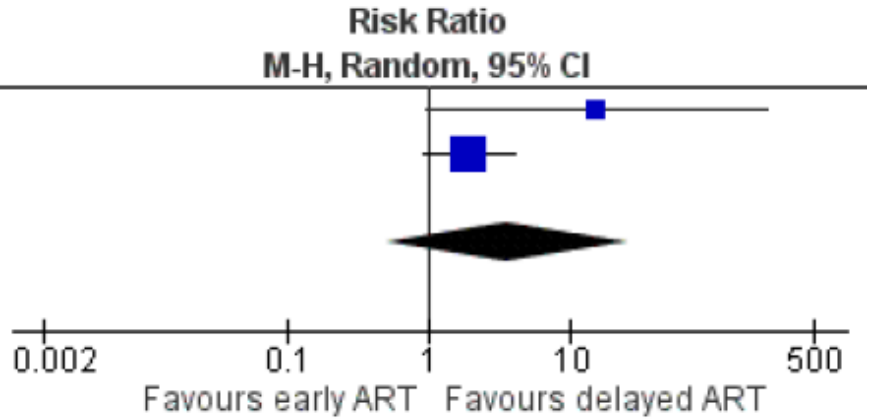
ART timing in CM: Cryptococcal IRIS

Study or Subgroup	Early ART Events	Early ART Total	Delayed ART Events	Delayed ART Total	Weight	Risk Ratio M-H, Random, 95% CI
Bisson 2013	7	14	0	14	30.2%	15.00 [0.94, 239.81]
Boulware 2014	17	88	9	89	69.8%	1.91 [0.90, 4.05]
Total (95% CI)		**102**		**103**	**100.0%**	**3.56 [0.51, 25.02]**
Total events	24		9			

Heterogeneity: $Tau^2 = 1.27$; $Chi^2 = 2.18$, $df = 1$ ($P = 0.14$); $I^2 = 54\%$

Test for overall effect: $Z = 1.28$ ($P = 0.20$)



Cochrane Database Syst Rev. 2018 Jul 24;7:CD009012

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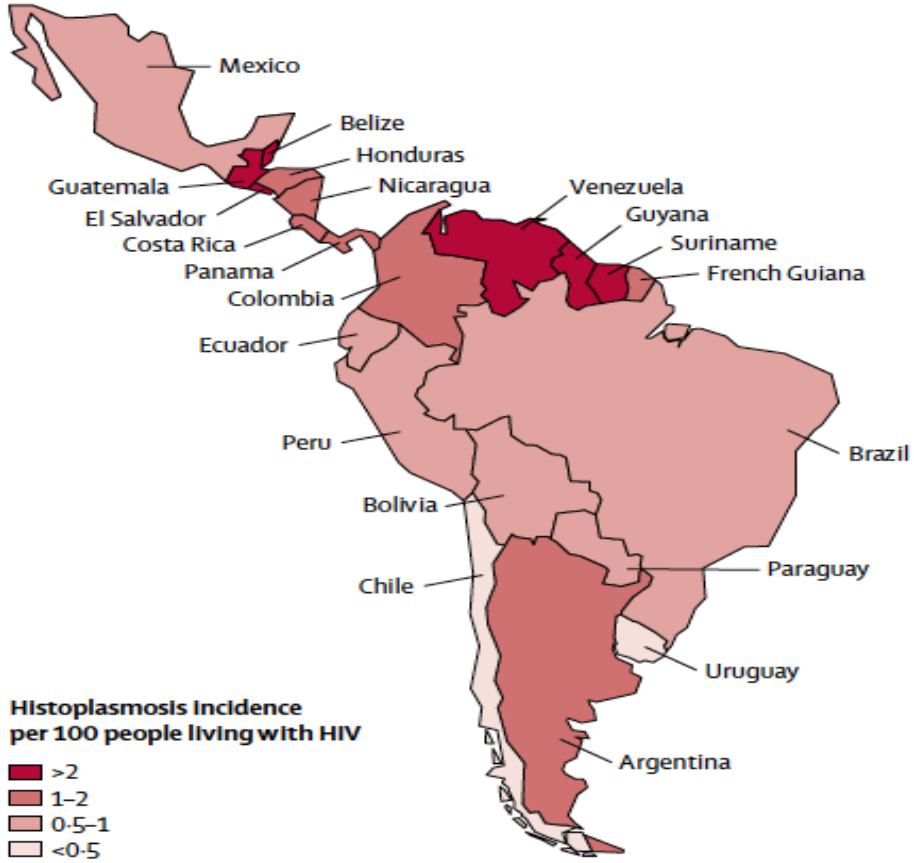
Histoplasma in Latin America



Lancet Infect Dis 2018; Aug 23

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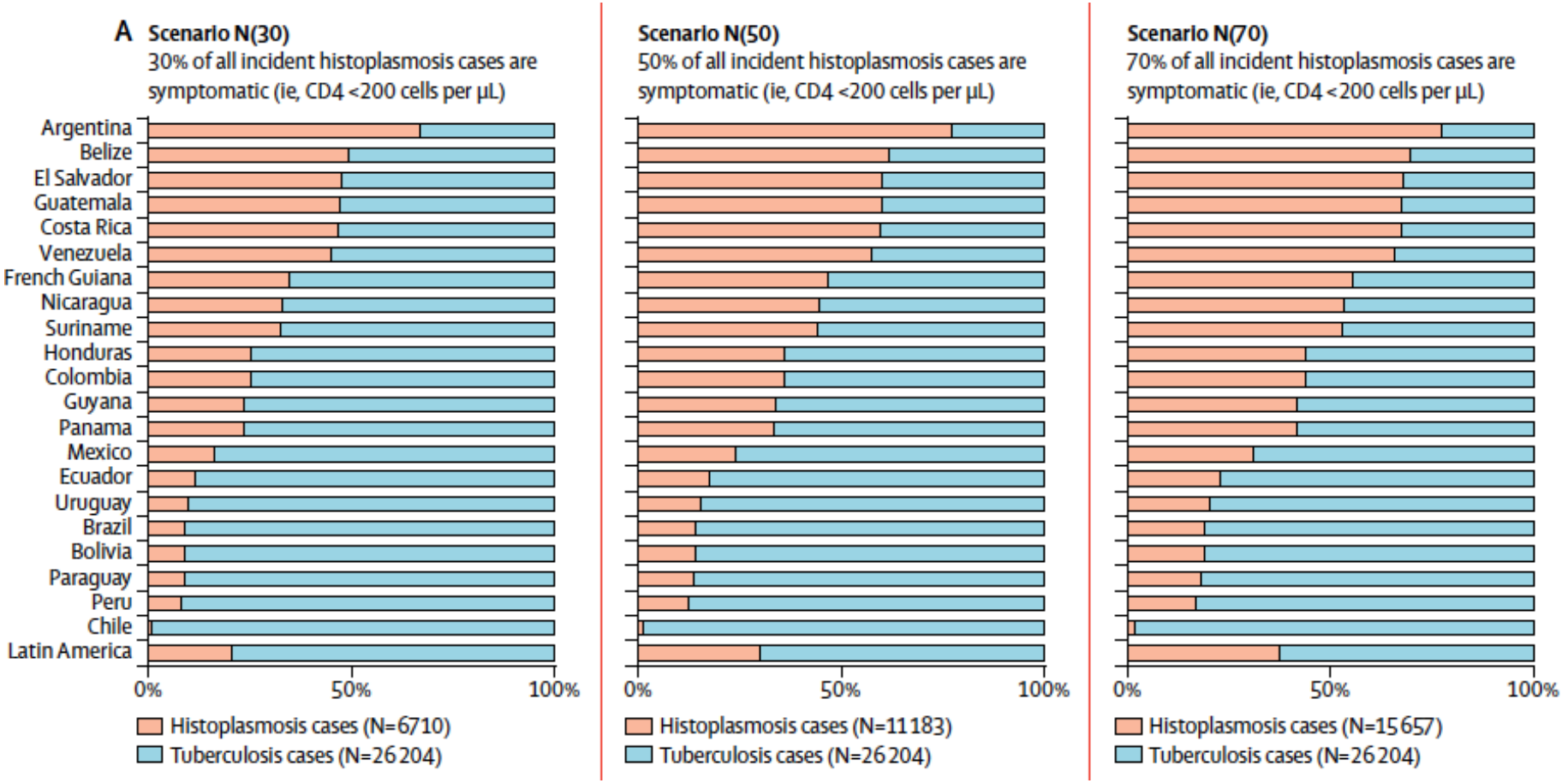
Histo vs TB in Latin America



Lancet Infect Dis 2018; Aug 23

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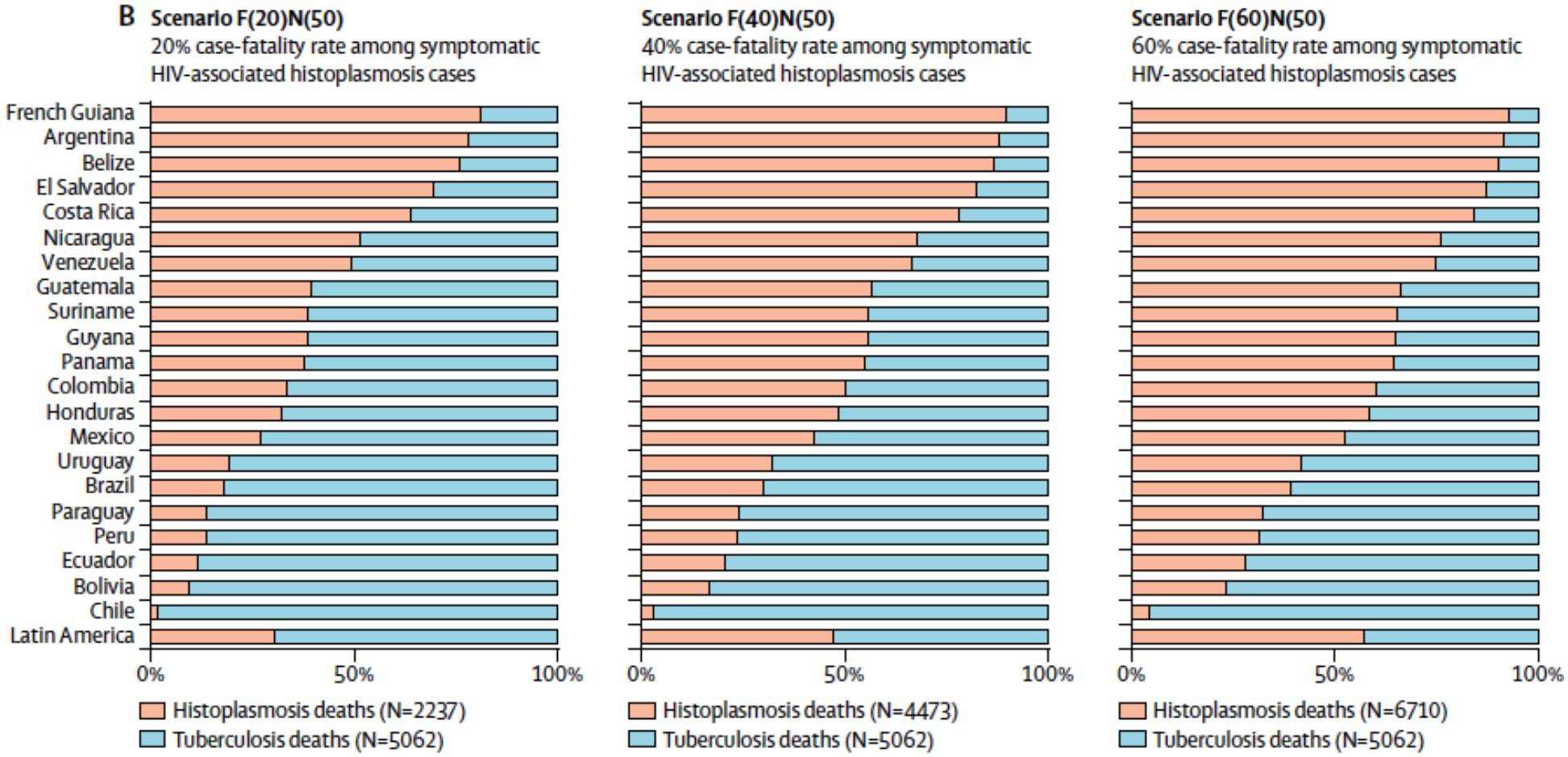
Histo vs TB in Latin America



Lancet Infect Dis 2018; Aug 23

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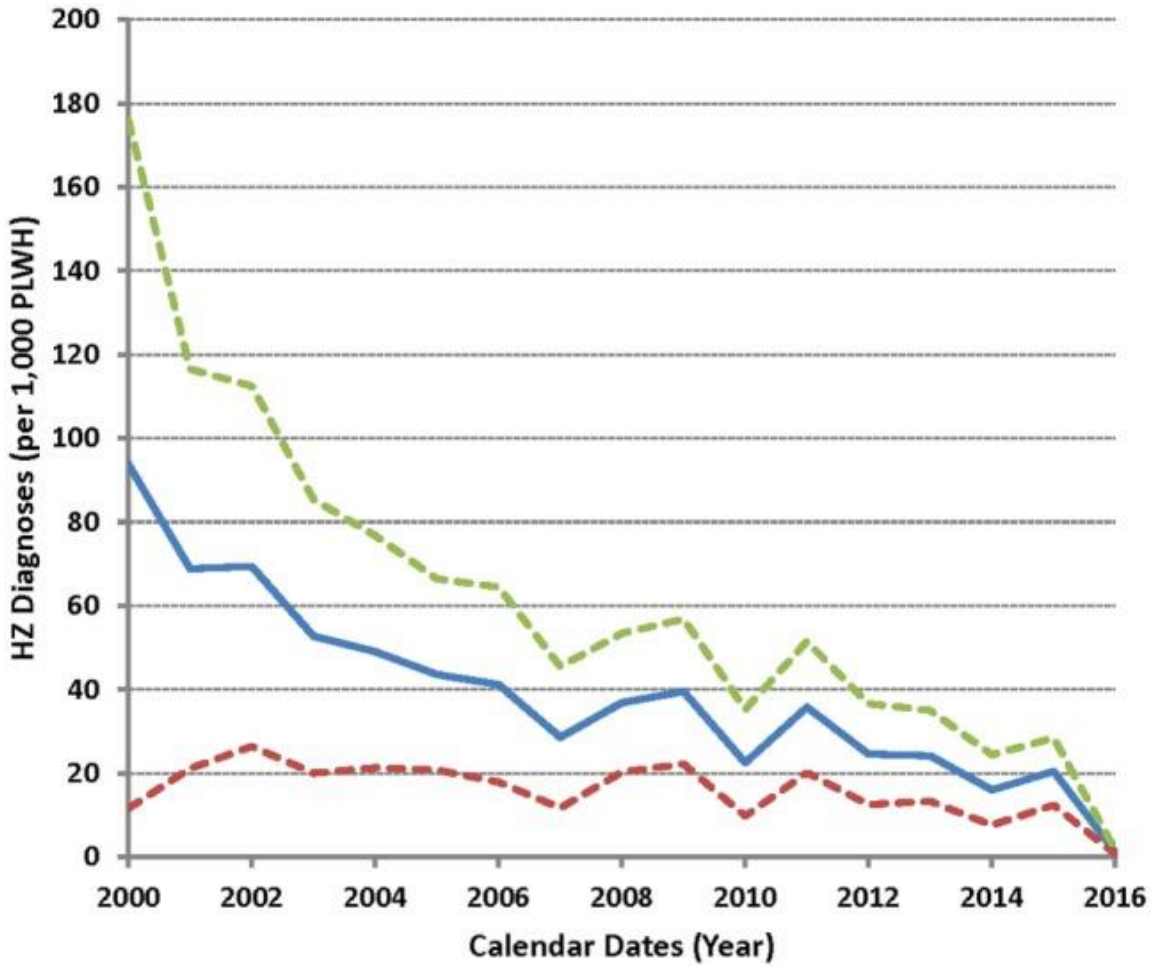
HIV/fungal: Research ideas

- Management of PLHIV developing CM soon after initiating ART
- Evaluation and treatment of CM recurrence
- Flucoanazole for pre-emptive treatment of sCRAG+
- Role of echinocandins in severe PCP

Outline

- Why do OI's still occur?
- Mycobacterial
- Fungal
- Viral
- Protozoal

HZ incidence in the cART era



Front Public Health. 2018 Mar 12;6:70. doi

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VZV live vaccine in PLHIV suppressed on ART and CD4>200/mm^3

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 Mar 26 [Epub ahead of print]

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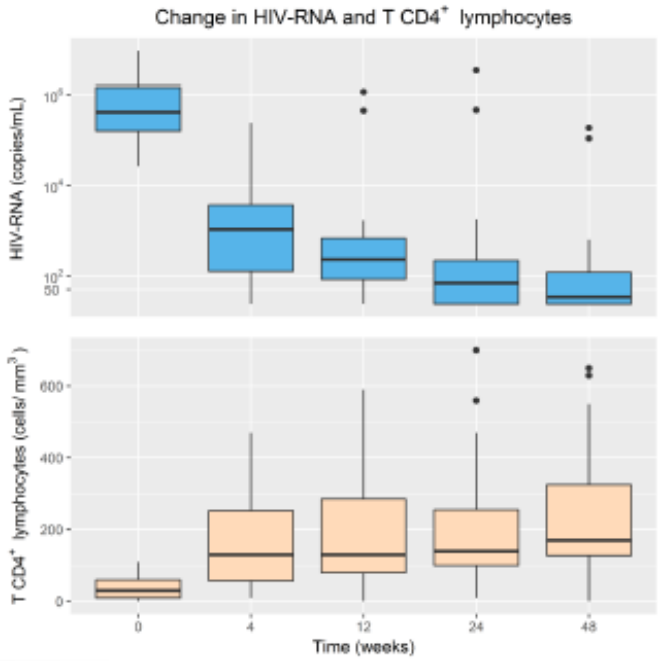
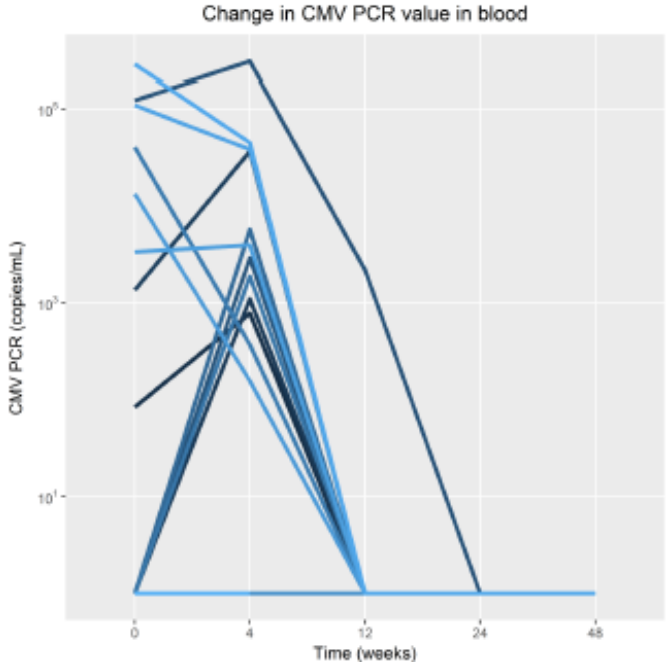
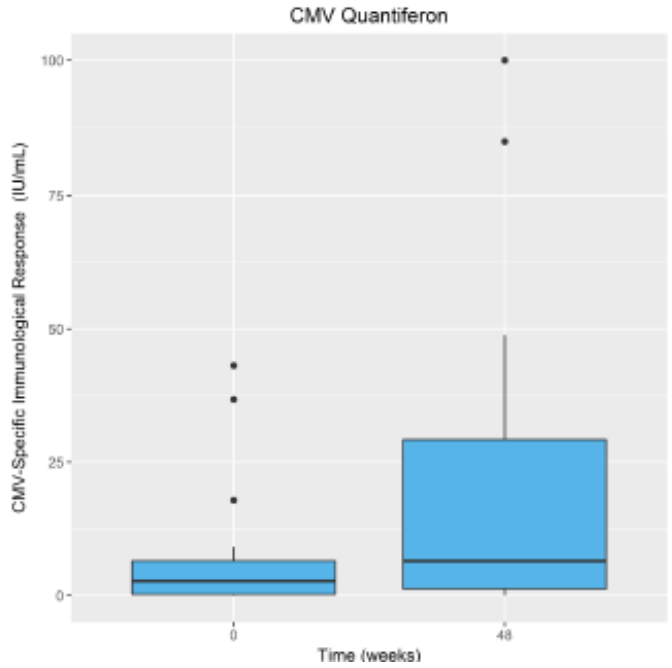
CMV viremia in advanced HIV improves with ART without anti-CMV treatment







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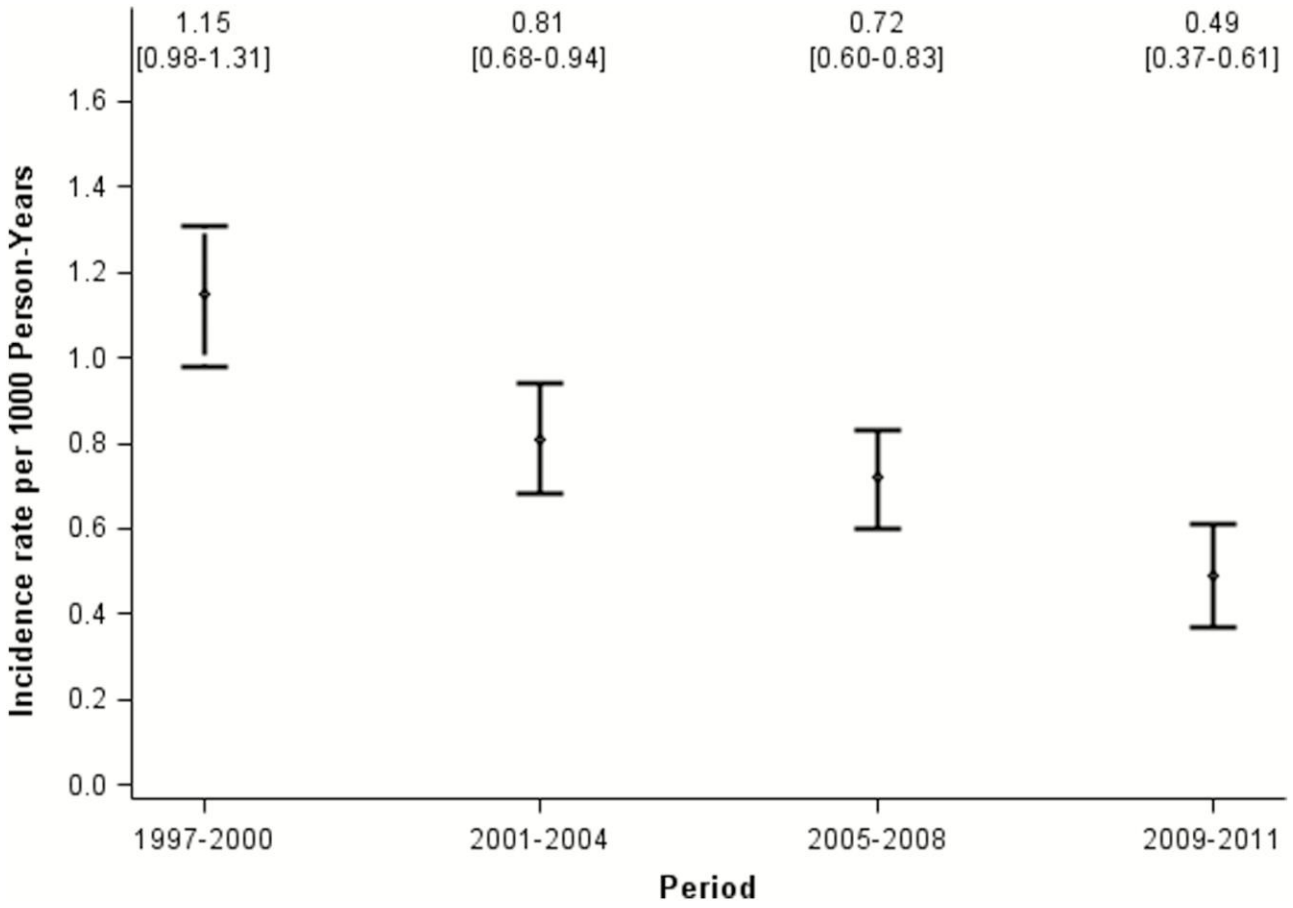
PML incidence in France



Clin Infect Dis. 2018 Jul 2;67(2):275-282

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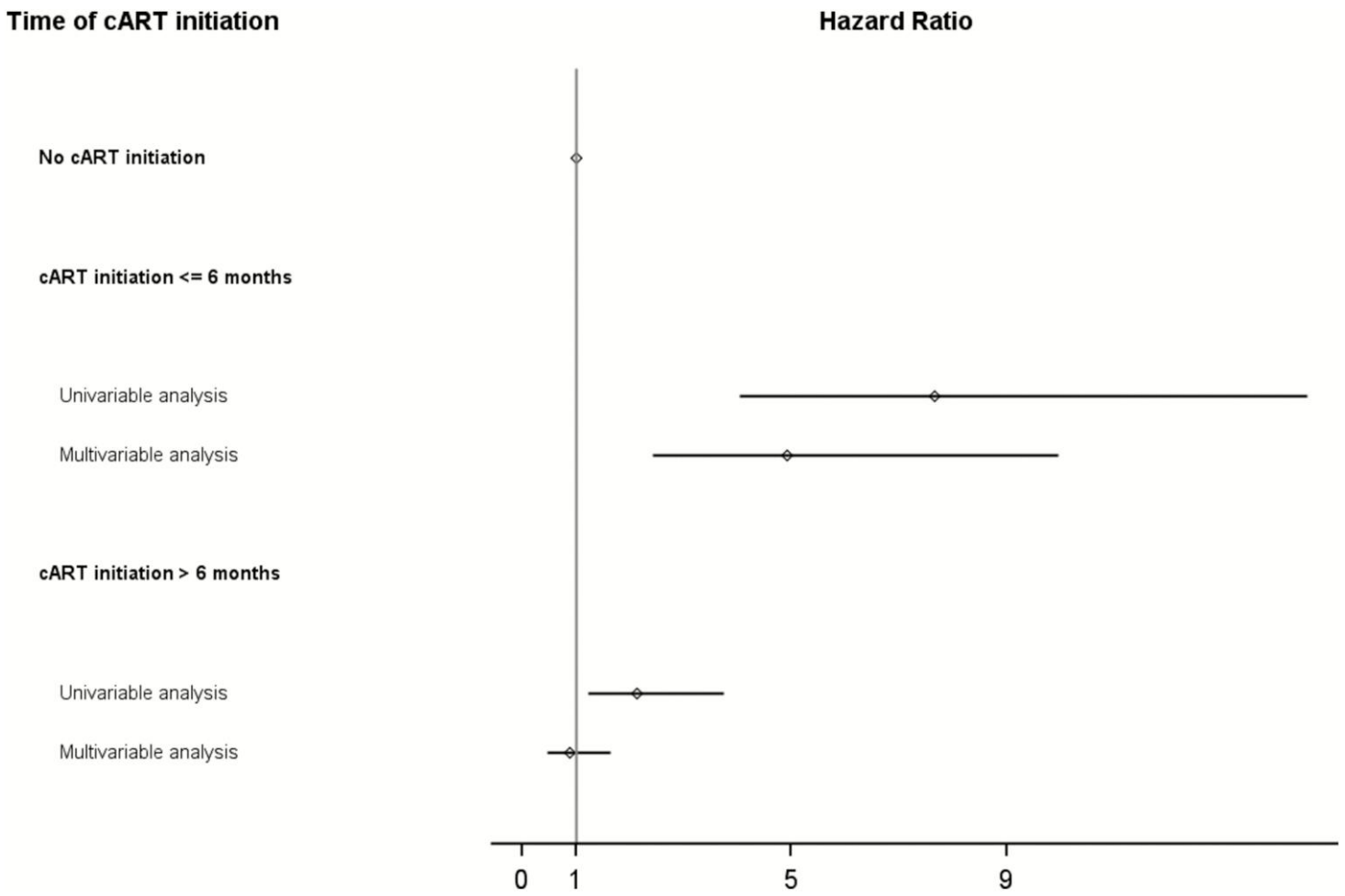
Risk of PML after cART initiation



Clin Infect Dis. 2018 Jul 2;67(2):275-282

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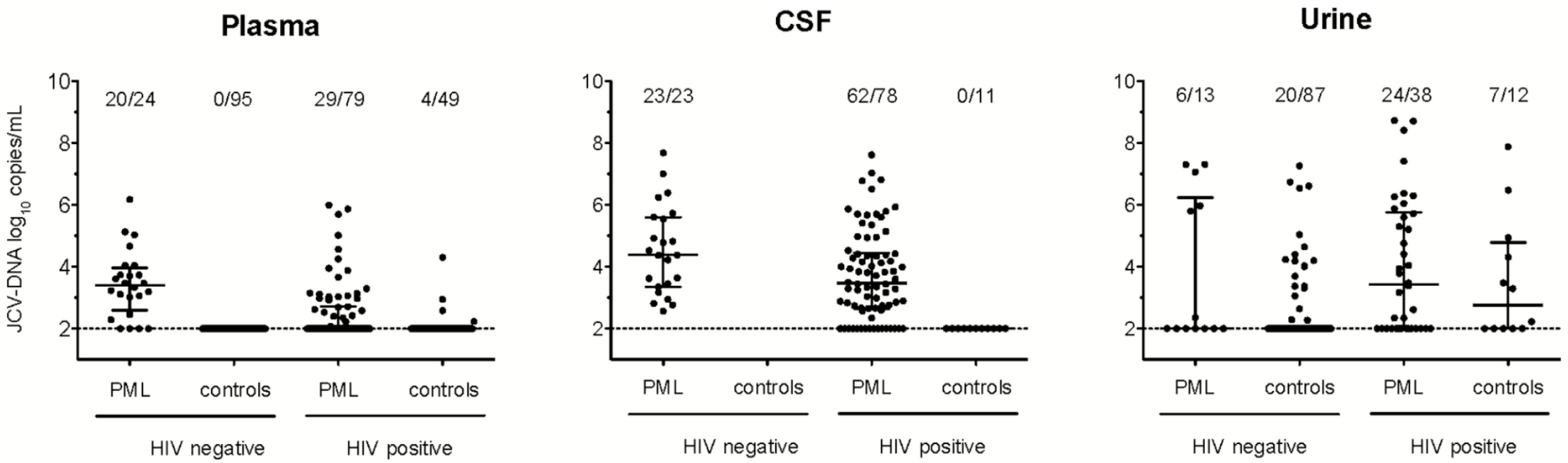
JCV DNA levels and PML



Clin Infect Dis. 2018 Jun 18;67(1):65-72

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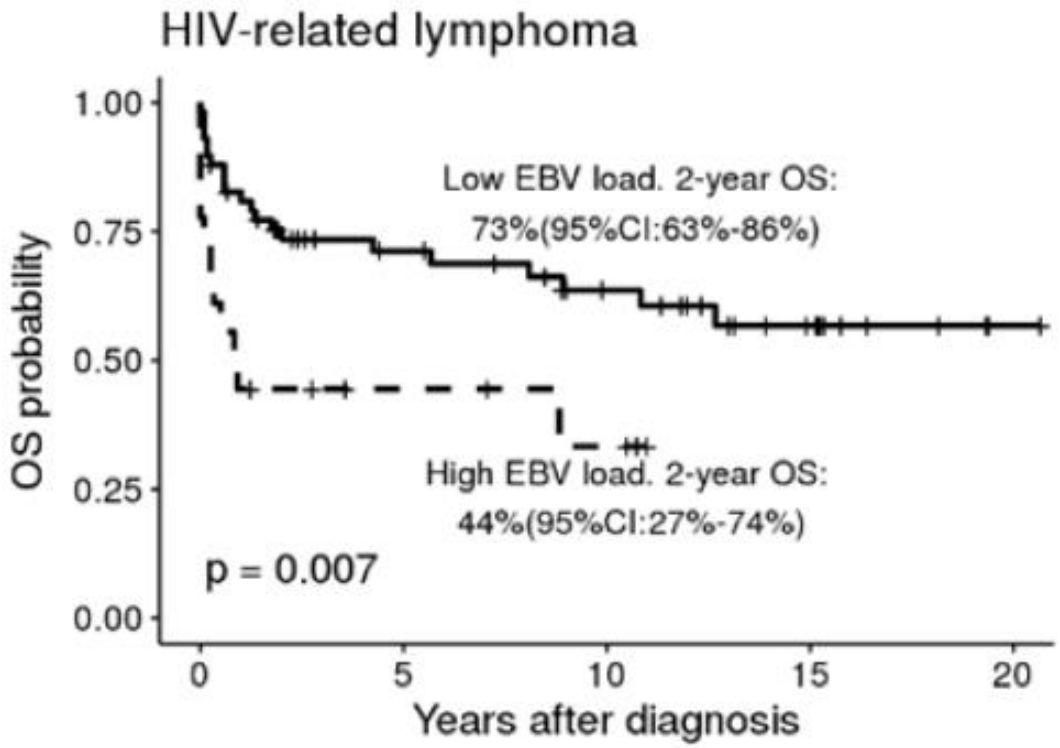
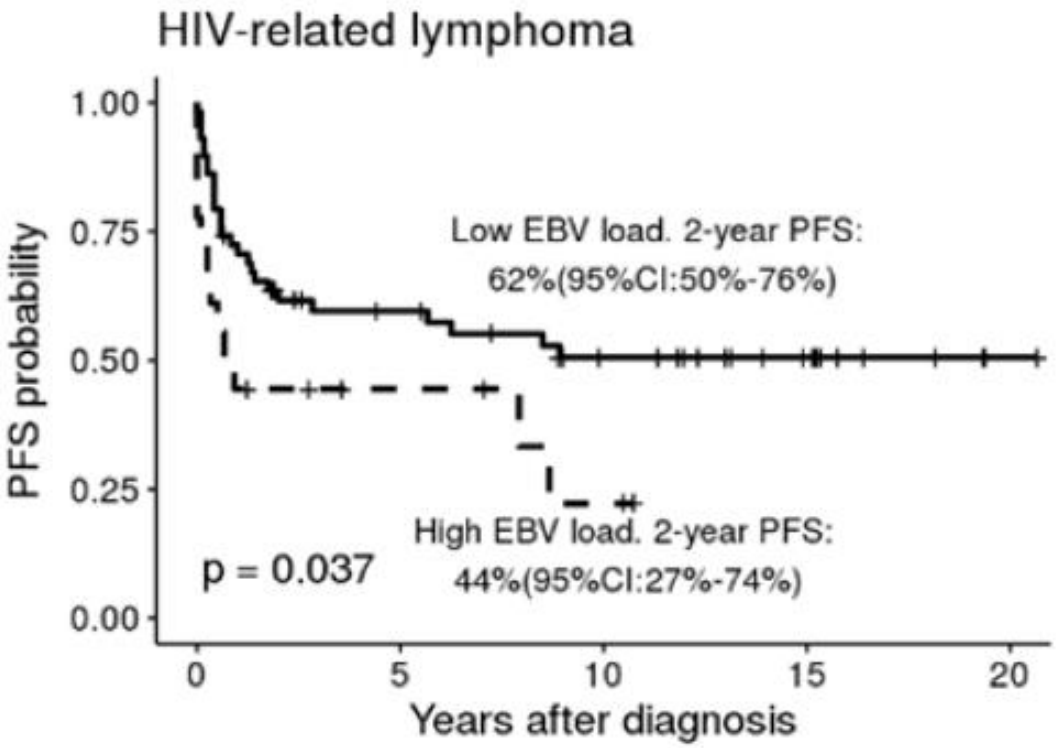
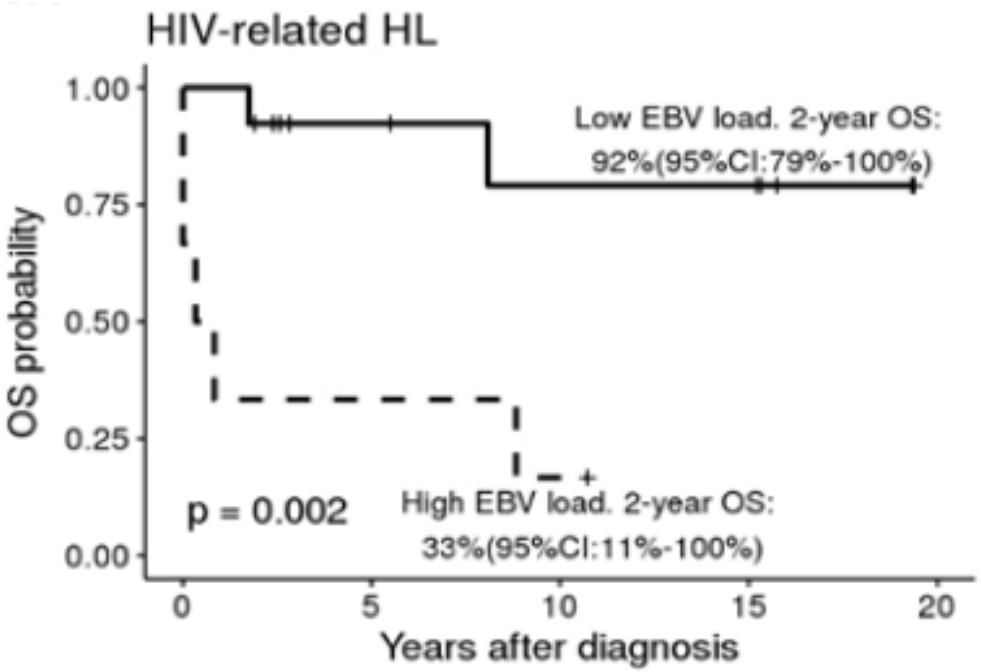
HIV-L: Plasma EBV and survival

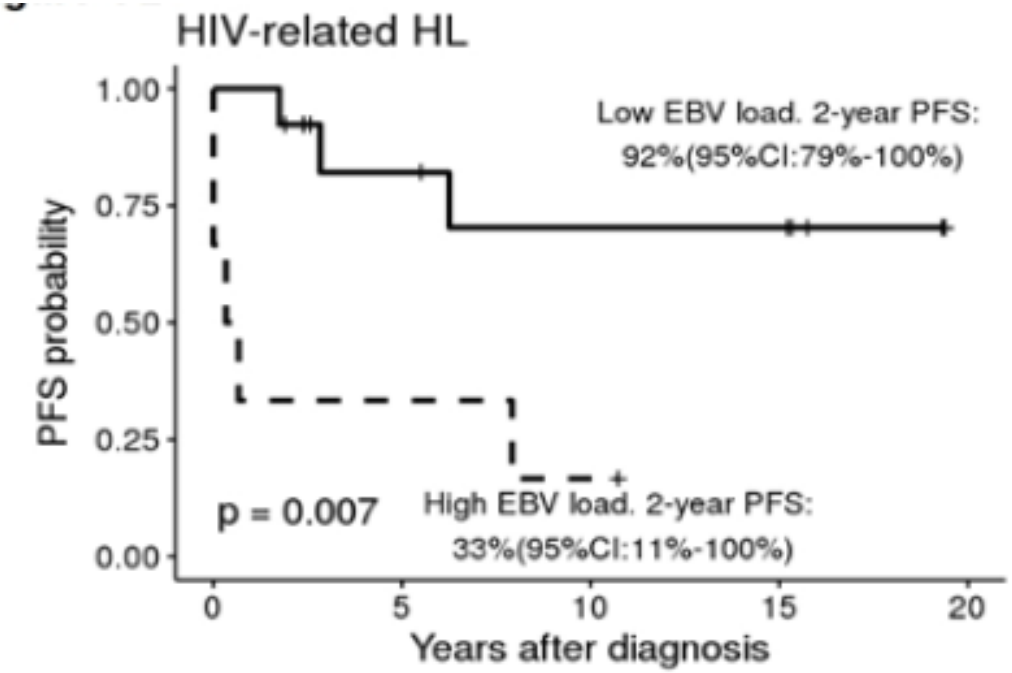




Clin Infect Dis. 2018 Jun 29

HIV-L: Plasma EBV and survival





Clin Infect Dis. 2018 Jun 29

qHPV vaccine efficacy in G/WLHIV

	Unvaccinated Historical WLWH (Canadian Women's HIV Study)	Vaccinated WLWH (Present study)
Endpoint	**Rate per 100 person-years (95% CI)**	**Rate per 100 person-years (95% CI)**
Persistent qHPV	6.0 (4.6-7.7)	2.3 (1.1-4.1)
Genital warts	2.9 (2.1-3.9)	2.3 (1.2-4.1)
CIN2+	1.0 (0.5-1.9)	0 (0.0-0.9)

Clin Infect Dis. 2018 Jul 7. [Epub ahead of print]

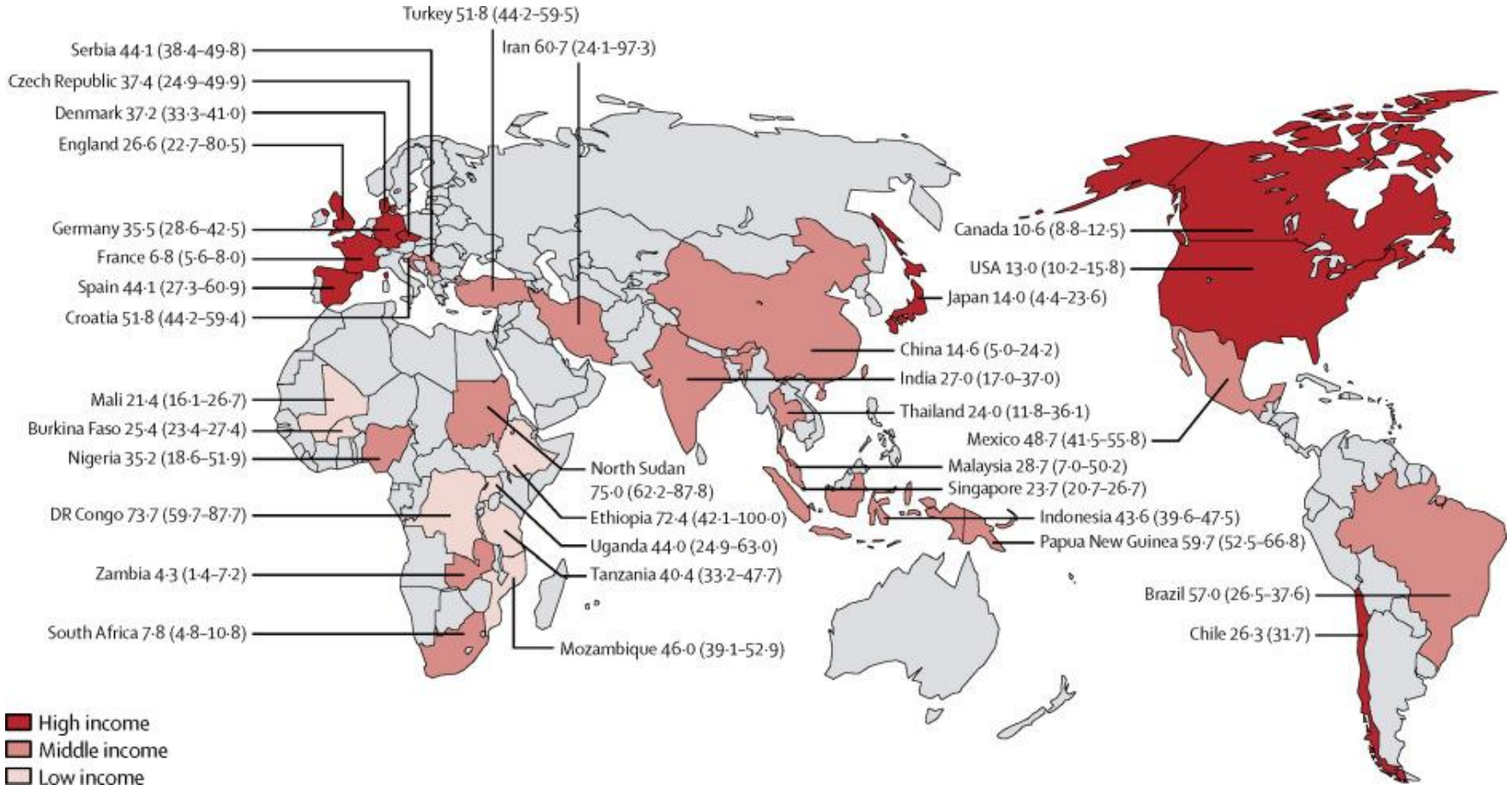
HIV/Viral: Research ideas

- Role of neurotropic viruses like HCV in PML onset
- Strategies to diagnose and manage PML IRIS
- Efficacy of HZ/su or ZV amongst elderly PLHIV
- Efficacy of nine-valent HPV vaccine in WHIV
- Use of EBV VL in prognostic scores for HIV- Lymphoma

Outline

- Why do OI's still occur?
- Mycobacterial
- Fungal
- Viral
- Protozoal

T. gondii infection in PLHIV worldwide



*Lancet **HIV**. 2017 Apr;4(4):e177-e188*

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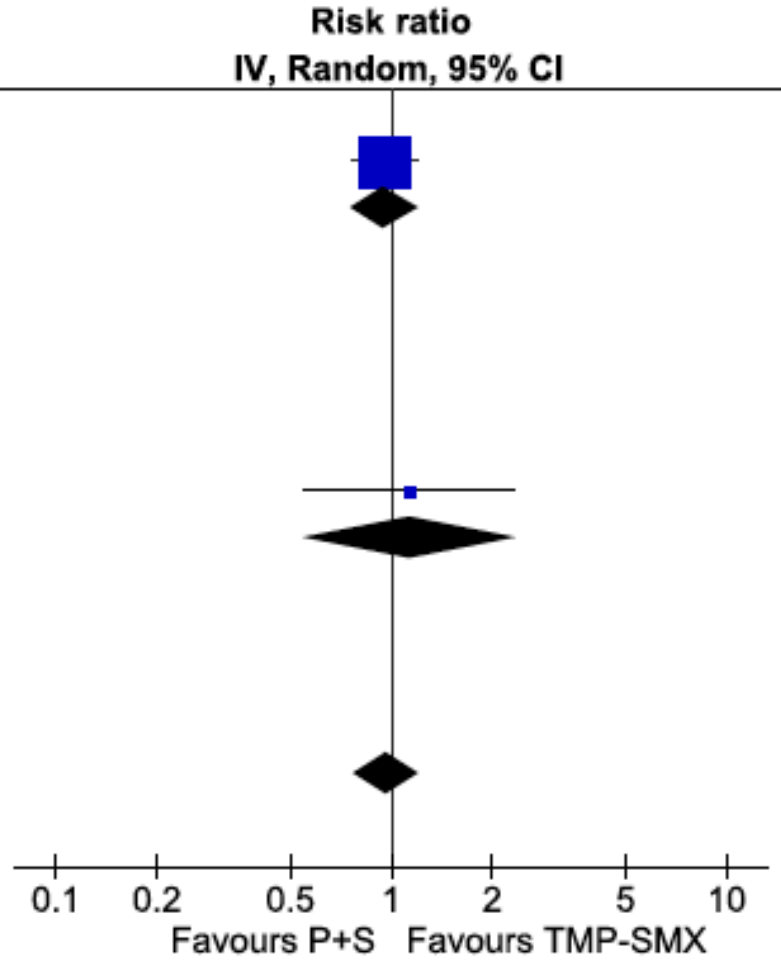
Cerebral toxoplasmosis: Treatment

(b)

Study or subgroup	TMP-SMX Events	TMP-SMX Total	P+S Events	P+S Total	Weight	Risk ratio IV, Random, 95% CI
2.1.1 RCT						
Torre 1998	31	40	30	37	91.1%	0.96 [0.76, 1.20]
Subtotal (95% CI)		**40**		**37**	**91.1%**	**0.96 [0.76, 1.20]**
Total events	31		30			
Heterogeneity: not applicable						
Test for overall effect: $Z = 0.39$ ($P = 0.70$)						
2.1.2 Cohort						
Arens 2007	11	25	7	18	8.9%	1.13 [0.55, 2.34]
Subtotal (95% CI)		**25**		**18**	**8.9%**	**1.13 [0.55, 2.34]**
Total events	11		7			
Heterogeneity: not applicable						
Test for overall effect: $Z = 0.33$ ($P = 0.74$)						
Total (95% CI)		**65**		**55**	**100.0%**	**0.97 [0.78, 1.21]**
Total events	42		37			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.19$, df = 1 ($P = 0.67$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.27$ ($P = 0.79$)						
Test for subgroup differences: $\chi^2 = 0.19$, df = 1 ($P = 0.67$), $I^2 = 0\%$						



HIV Med. 2017 Feb;18(2):115-124

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Summary

- OI's: Going, Going, not gone
- Improving screening and diagnosis of TB: key to control TB in PLHIV
- Evidence for use of RAL/DTG with RMP: Encouraging and evolving
- Urgent access to flucytosine in LMICs needed
- Vaccine uptake needs to improve: reduce residual morbidity