

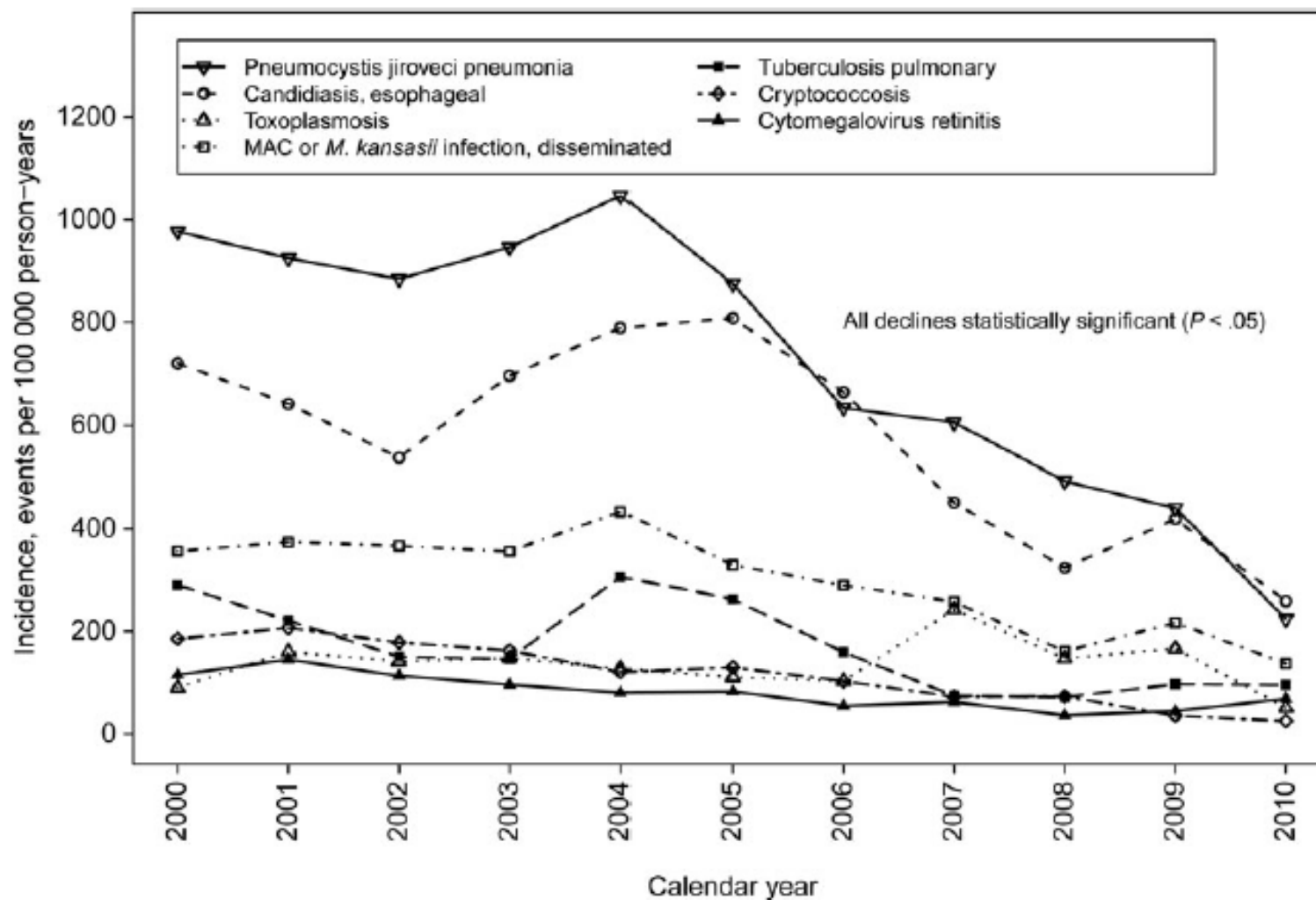
OPPORTUNISTIC INFECTIONS

Sanjay Pujari, MD

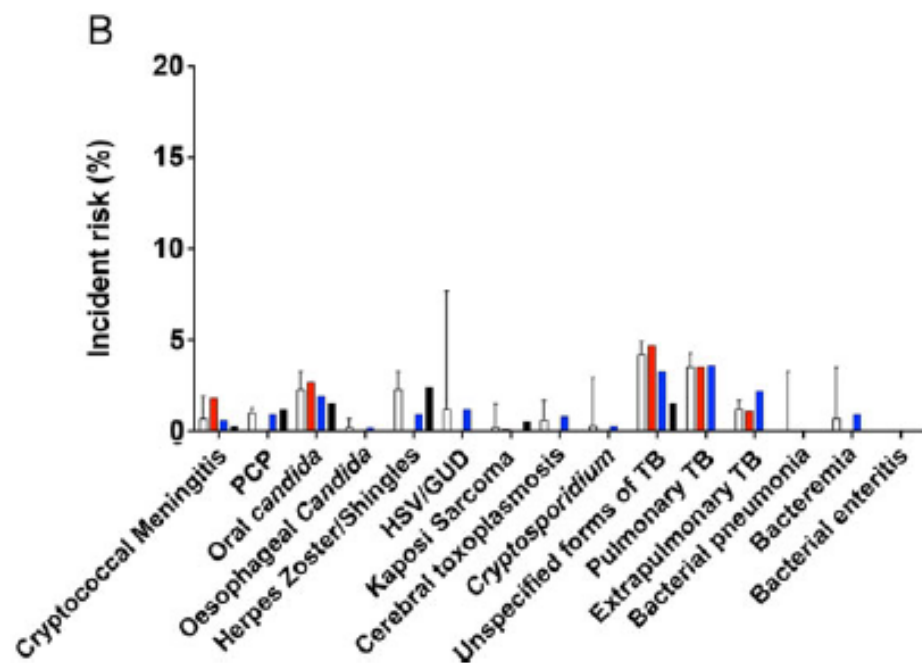
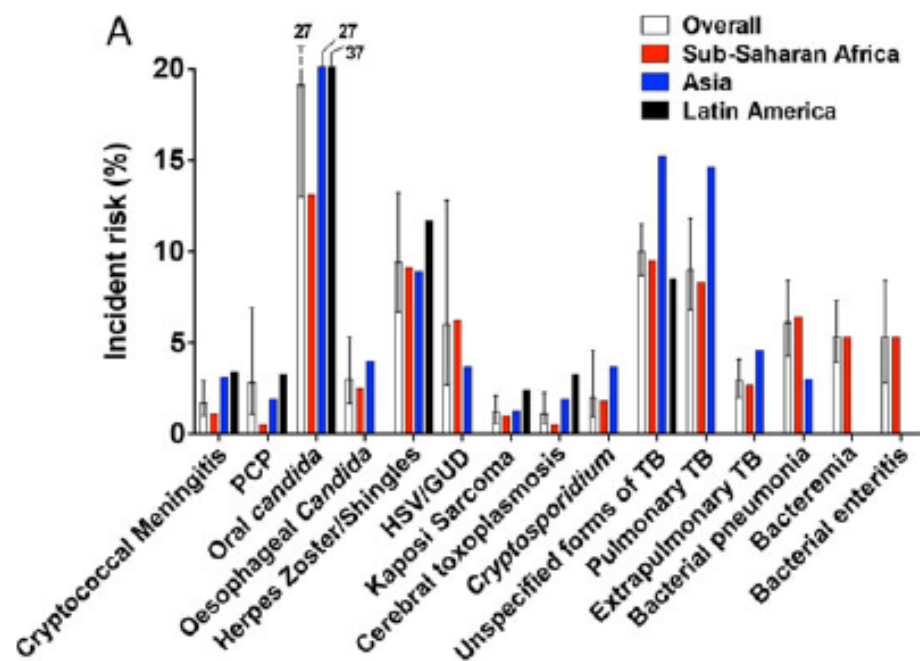
Institute of Infectious Diseases

Pune, India

Declining OI's in NA-ACCORD



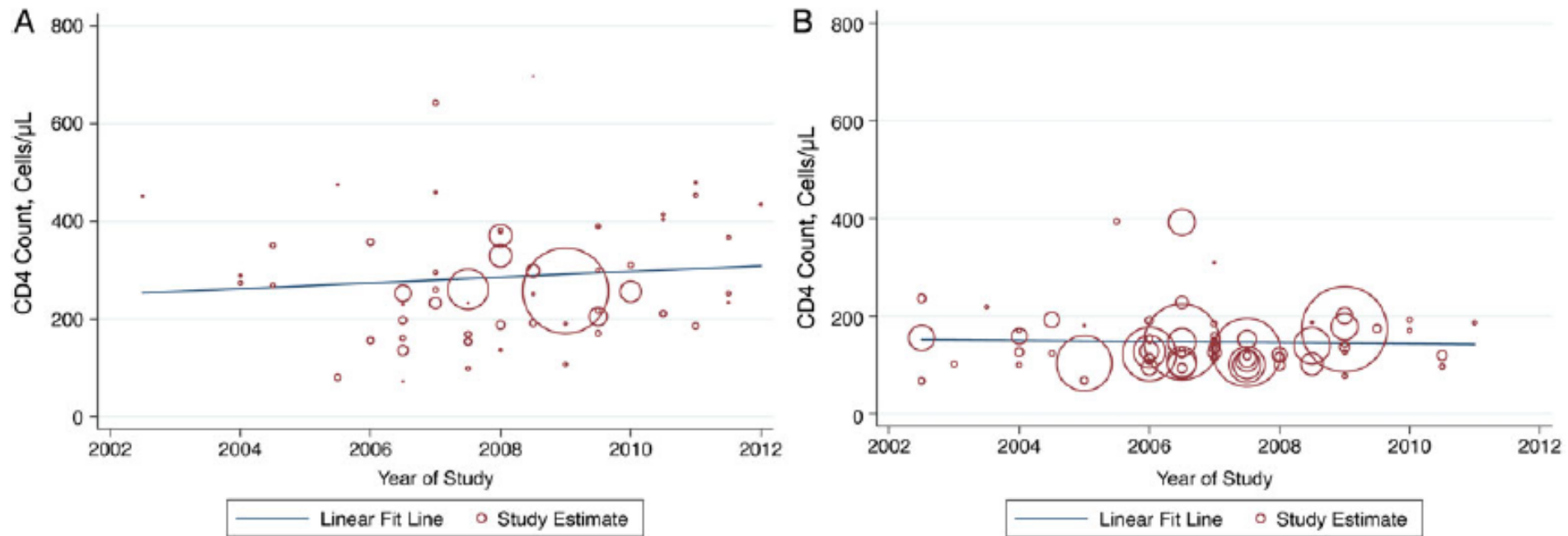
ART: Impact on OI incidence in LMICs



Why do OI's still occur?

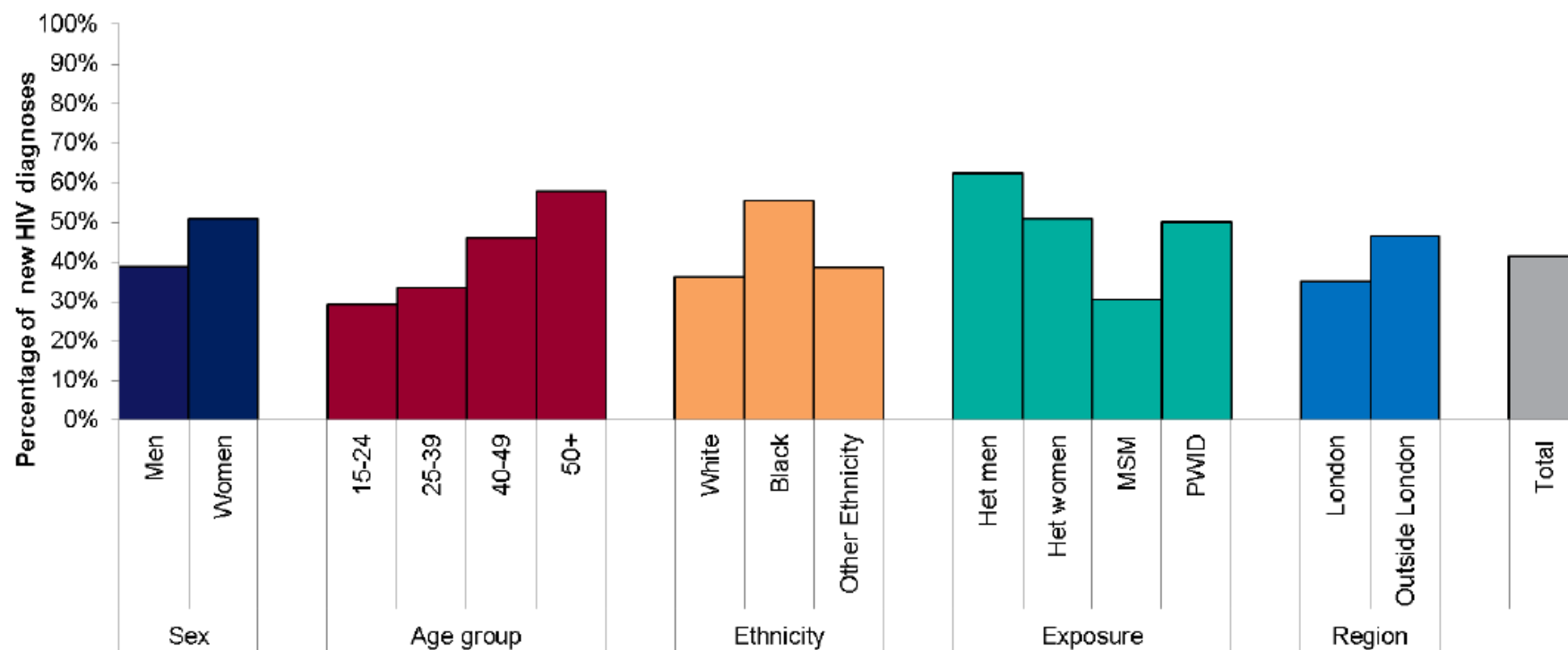
- Late HIV diagnosis, missed presentations (*HIV Med.* 2016 Aug 1 (epub), *BMC Infect Dis.* 2012;12:72-72)
- Sub-optimal adherence
 - HAART (*Curr Opin HIV AIDS.* 2015 Jul;10(4):219-25)
 - Prophylaxis
- Immunologic disconnect (*J Int AIDS Soc.* 2014 Mar 3;17:18651)
- Imperfect functional reconstitution of immune response (*Clin Infect Dis* 2009;48:609–11)
- Is CD4 count a good predictor of OI risk?

CD4 count at presentation and ART: SSA



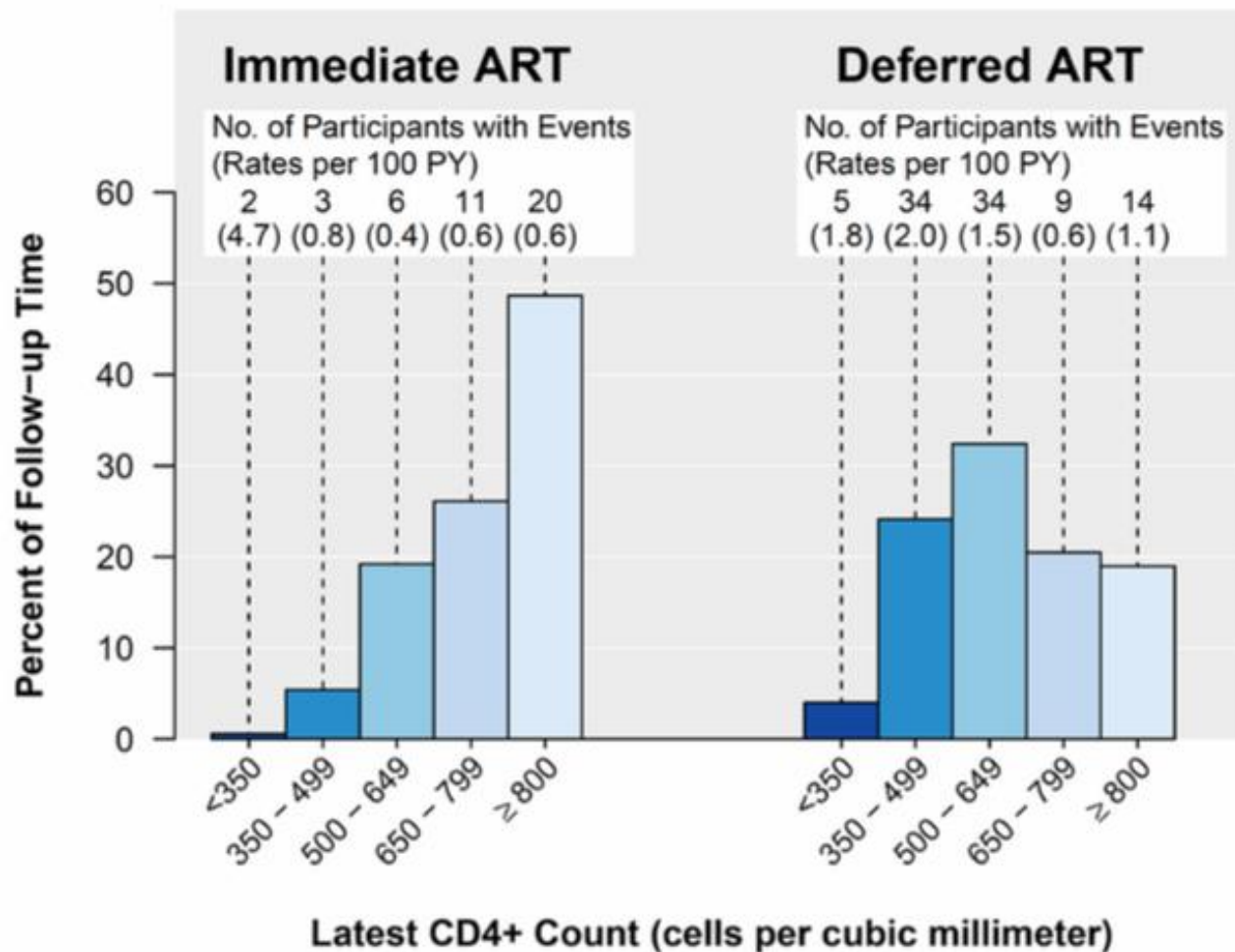
Late diagnosis in UK

Figure 9: Late diagnoses¹: proportion of adults diagnosed with a CD4 count <350 cells/mm³: UK, 2013



¹ CD4<350 cells/mm³ within three months of diagnosis.

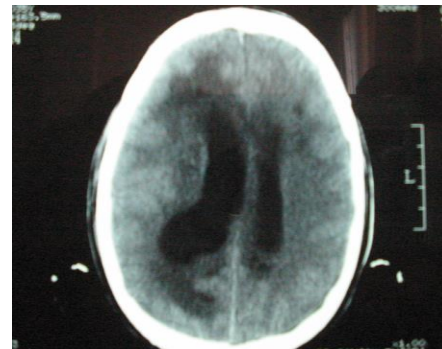
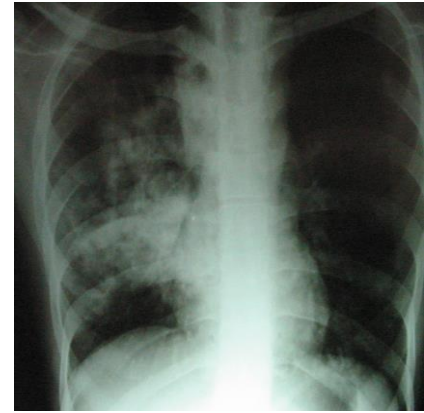
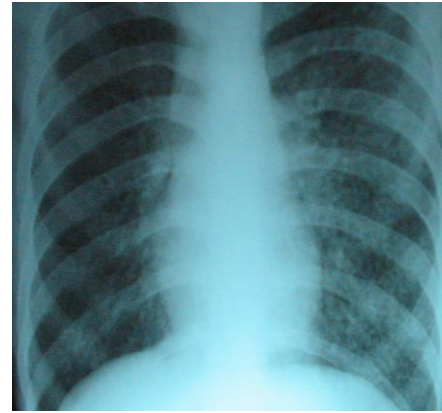
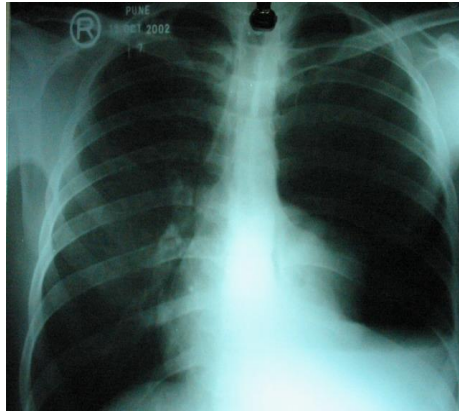
START: Results (1)



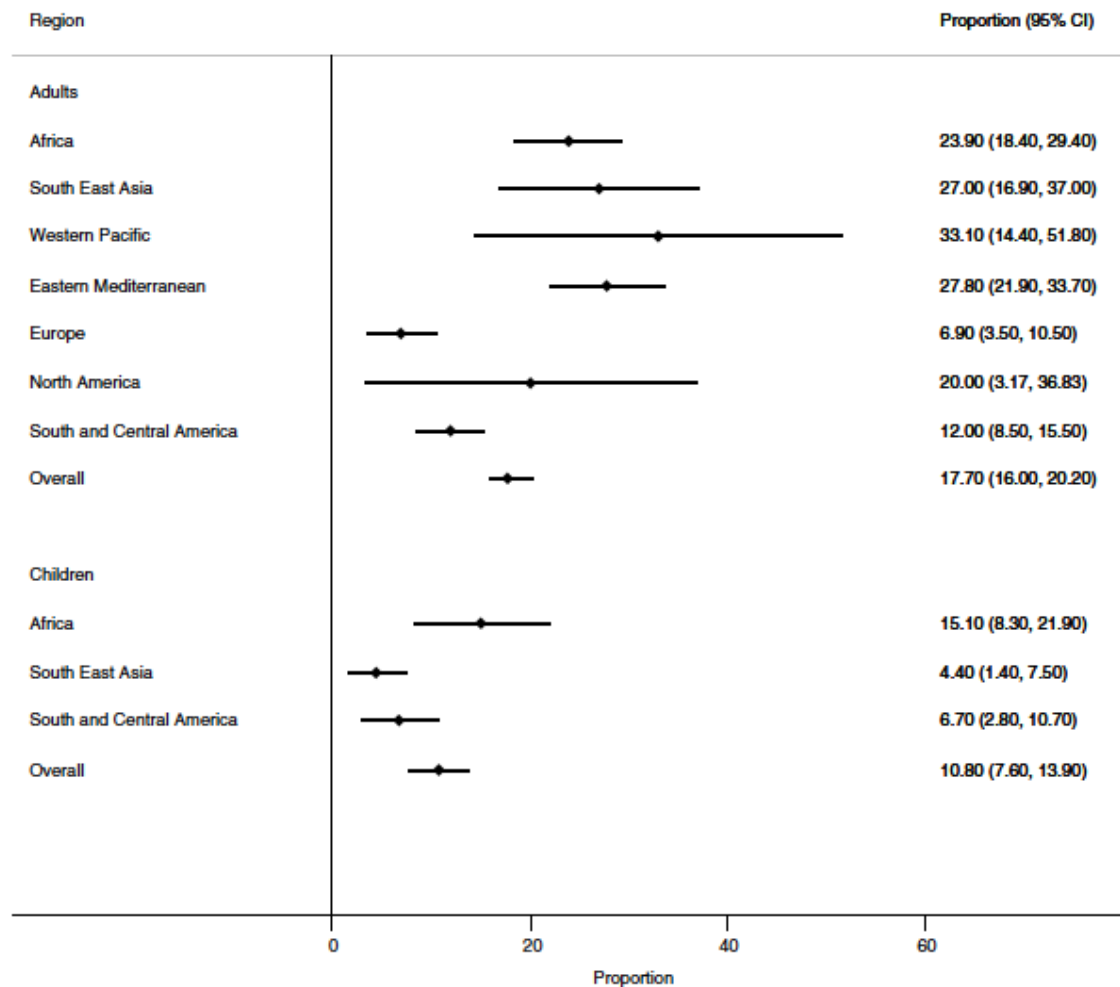
START: Results (2)

Endpoint	Immediate ART (n = 2326)		Deferred ART (n = 2359)		HR (95% CI)	P Value
	N	Rate/100 PY	N	Rate/100 PY		
Serious AIDS-related event	14	0.20	50	0.72	0.28 (0.15-0.50)	< .001
Serious non-AIDS-related event	29	0.42	47	0.67	0.61 (0.38-0.97)	.04
All-cause death	12	0.17	21	0.30	0.58 (0.28-1.17)	.13
Tuberculosis	6	0.09	20	0.28	0.29 (0.12-0.73)	.008
Kaposi's sarcoma	1	0.01	11	0.16	0.09 (0.01-0.71)	.02
Malignant lymphoma	3	0.04	10	0.14	0.30 (0.08-1.10)	.07
Non-AIDS-defining cancer	9	0.13	18	0.26	0.50 (0.22-1.11)	.09
CVD	12	0.17	14	0.20	0.84 (0.39-1.81)	.65

Tuberculosis

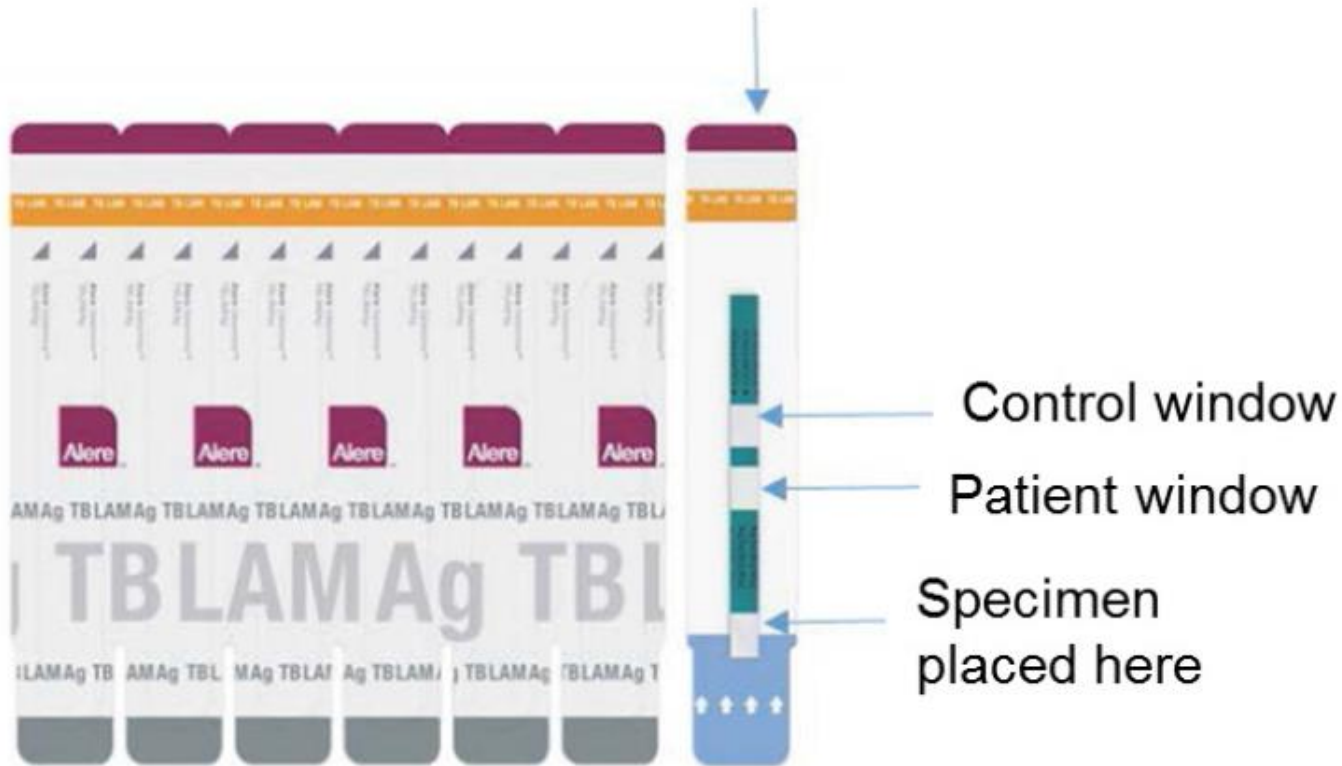


TB amongst hospitalized PLHIV

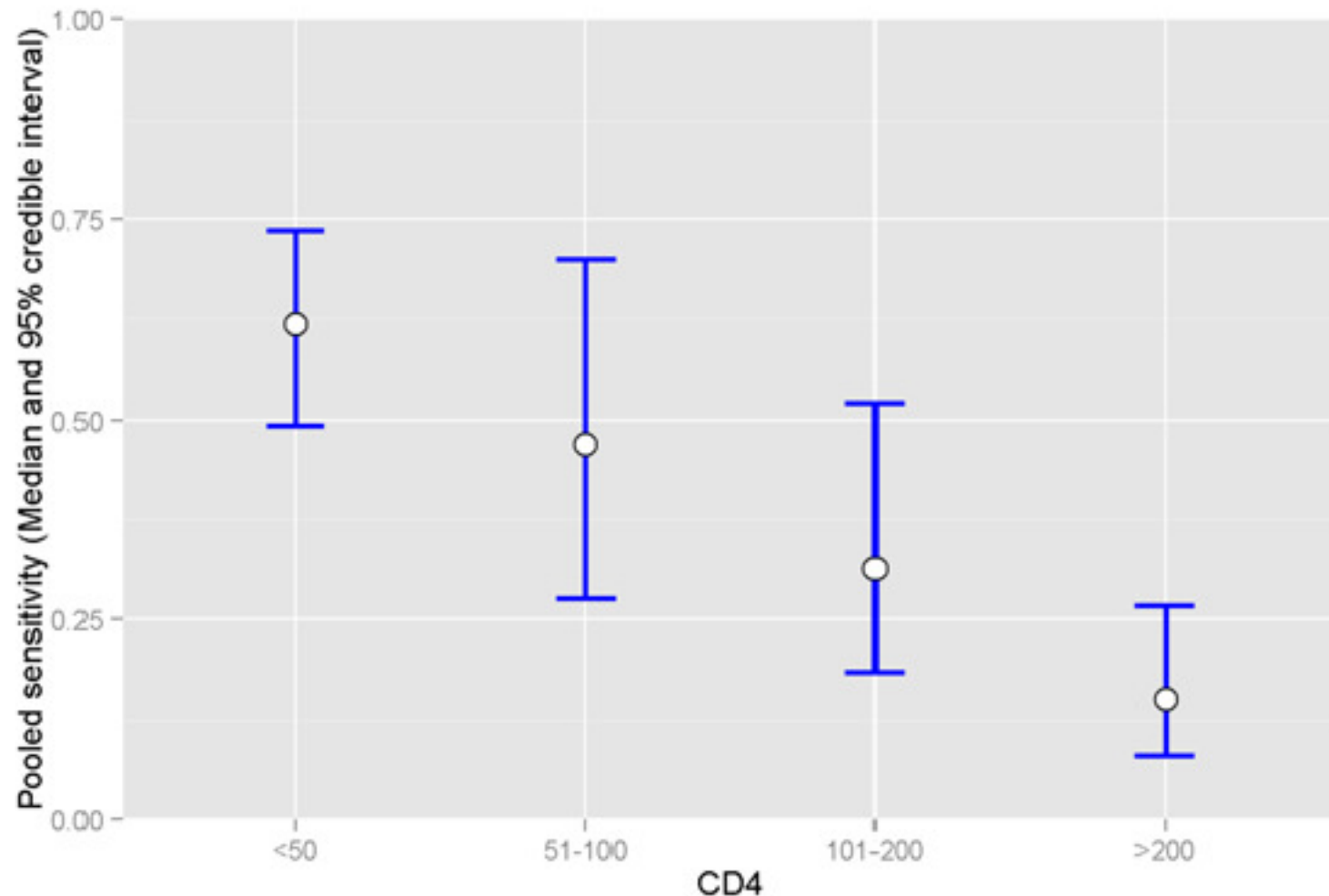


LF-LAM

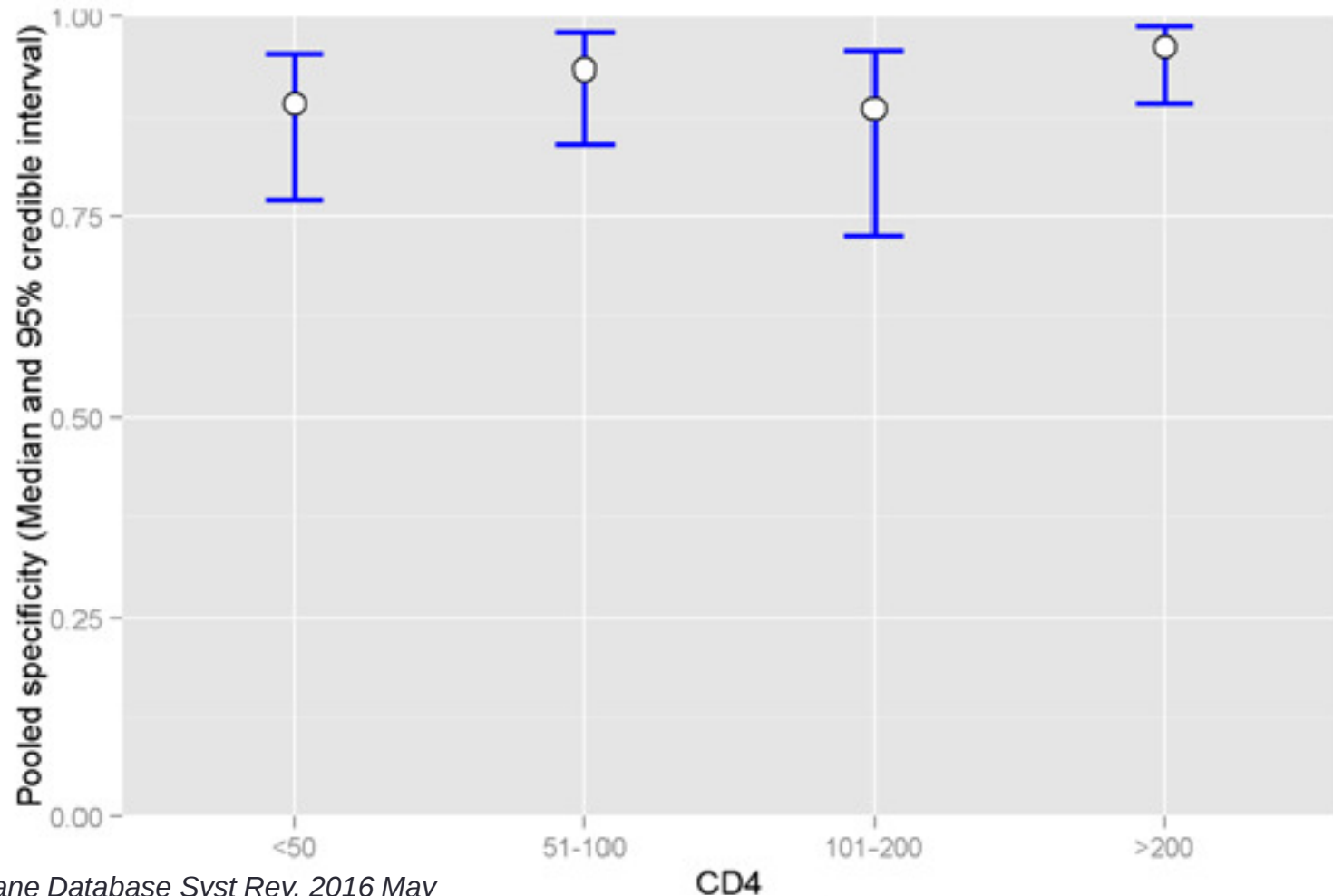
Individual LF-LAM strip



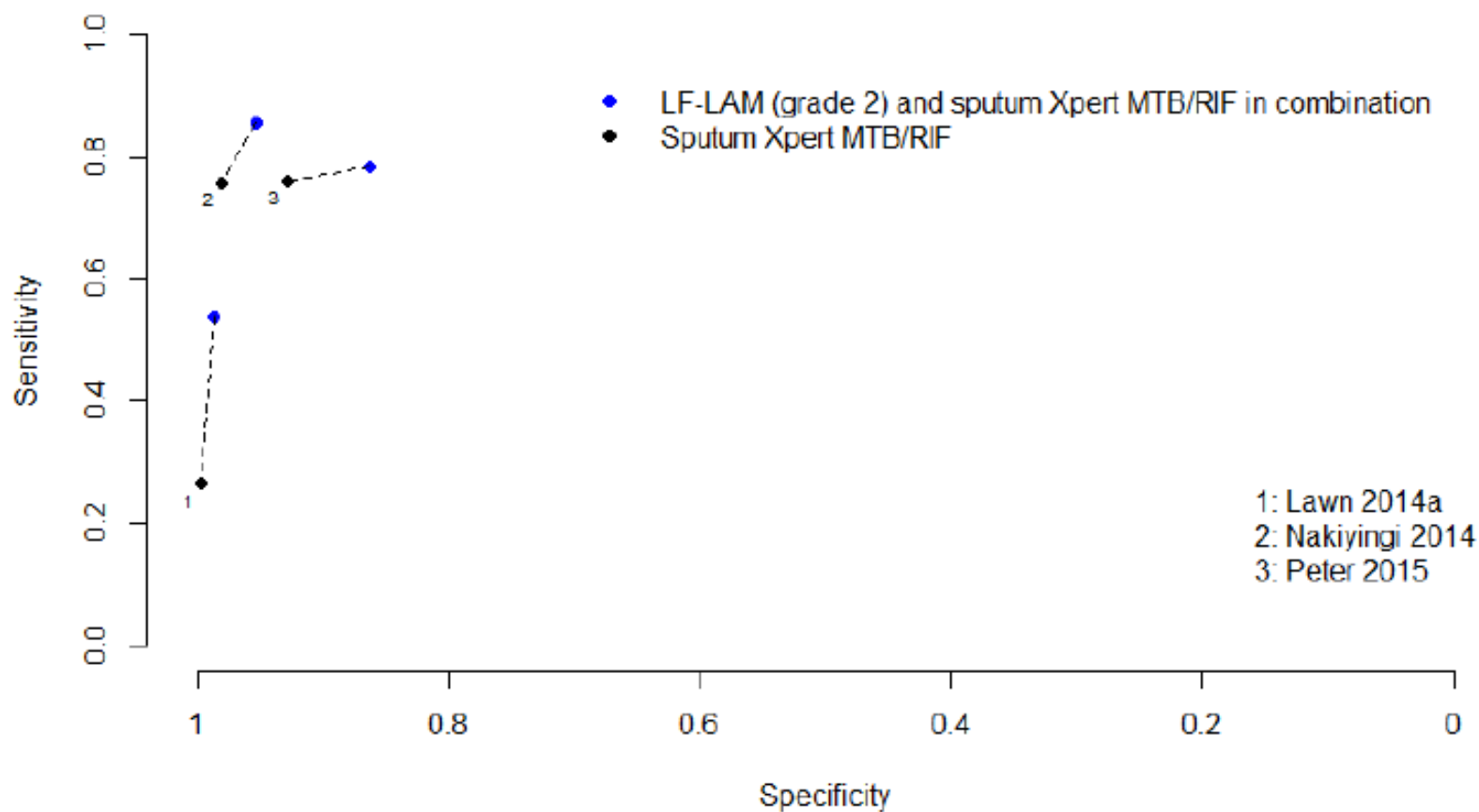
LF-LAM: sensitivity at CD4 levels



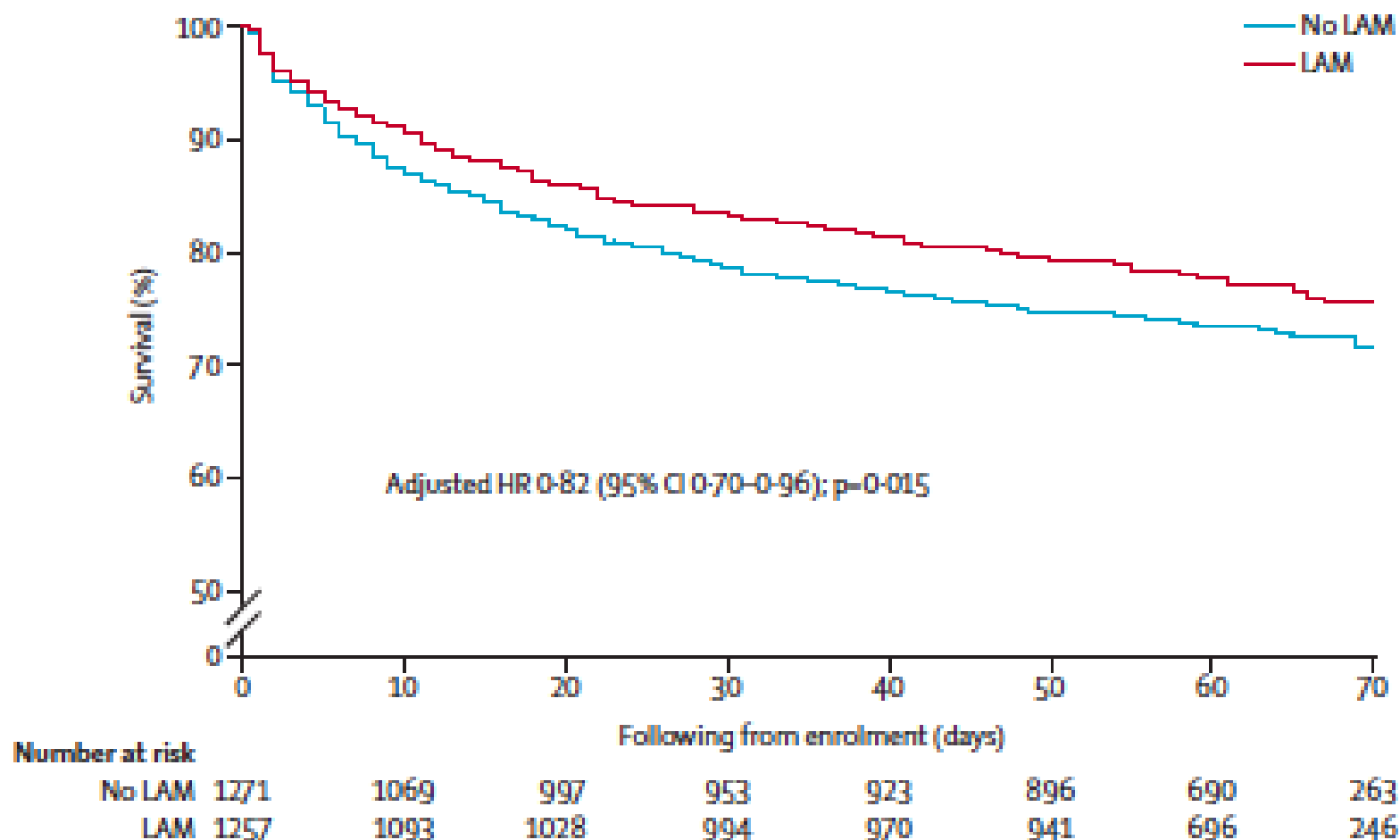
LF-LAM: Specificity at CD4 levels



LF-LAM+Xpert MTB/Rif



LF-LAM: Mortality benefit in inpatients



LF-LAM in Out-patients

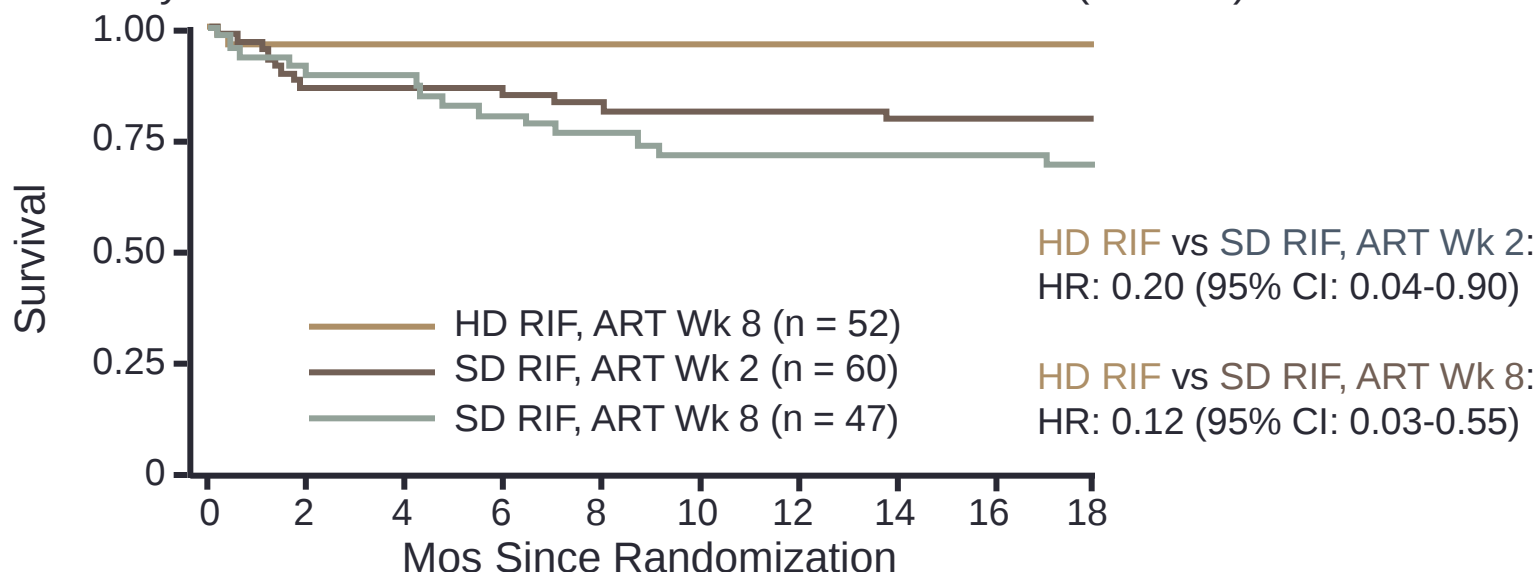
	Prevalence of TB		Prevalence of positive LAM			Sensitivity	Specificity	
Gold standard = confirmed* and clinical† TB	n/N	%	n/N	%	n/ N	% (95% CI)	n/N	% (95% CI)
Grade 1[‡] cut-off	56/ 424	13.2%	24/ 424	5.7%	8/ 56	14.3% (6.4, 26.2)	352/ 368	95.7% (93.0, 97.5)
CD4 <100	35/ 187	18.7%	12/ 187	6.4%	6/ 35	17.1% (6.6, 33.6)	146/ 152	96.1% (91.6, 98.5)
CD4 ≥100	21/ 237	8.9%	12/ 237	5.1%	2/ 21	9.5% (1.2, 30.4)	206/ 216	95.4% (91.7, 97.8)
Grade 2[§] cut-off	56/ 424	13.2%	8/ 424	1.9%	3/ 56	5.4% (1.1, 14.9)	363/ 368	98.6% (96.9, 99.6)

RAFA: High dose RMP in HIV-TB

- Overall survival not improved, but high-dose rifampicin may benefit severely immunocompromised pts

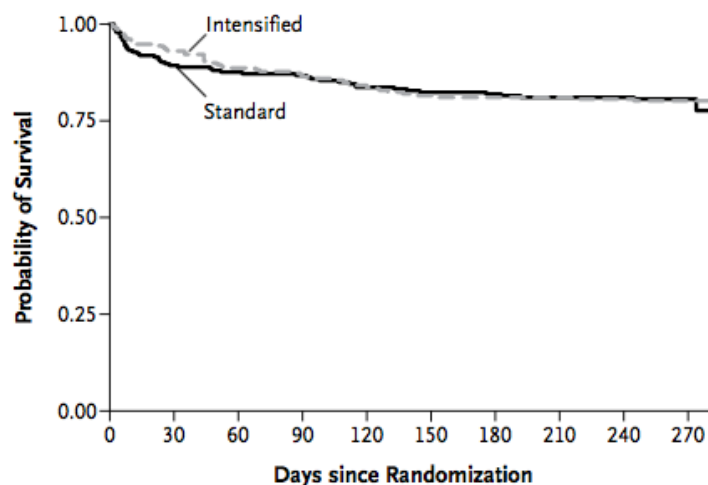
Overall Survival, %	HD RIF, ART Wk 8 (n = 249)	SD RIF, ART Wk 8 (n = 247)	SD RIF, ART Wk 2 (n = 251)
12 mos	90	86	89
18 mos	90	85	88

Mortality for Pts With CD4+ Cell Count < 100 cells/mm³ (n = 159)



HIV-TB: high dose RMP + Lfx in TBM

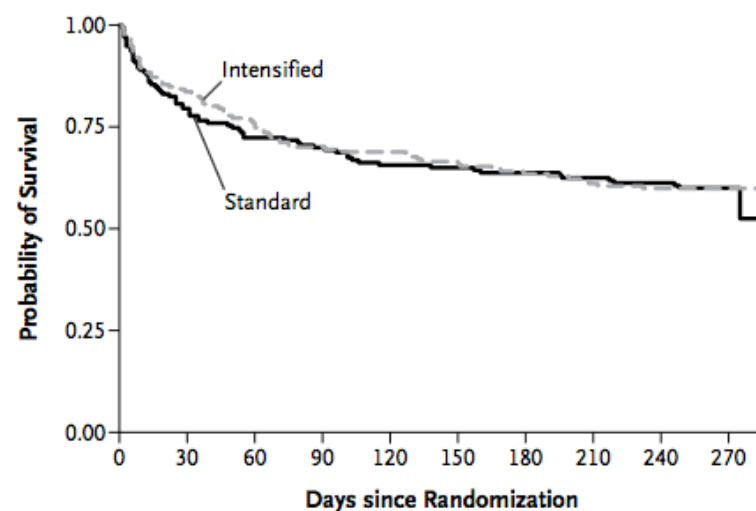
B HIV-Uninfected Patients



No. at Risk

Standard	235	208	202	200	192	189	188	186	186	151
Intensified	233	211	200	195	189	183	182	181	179	148

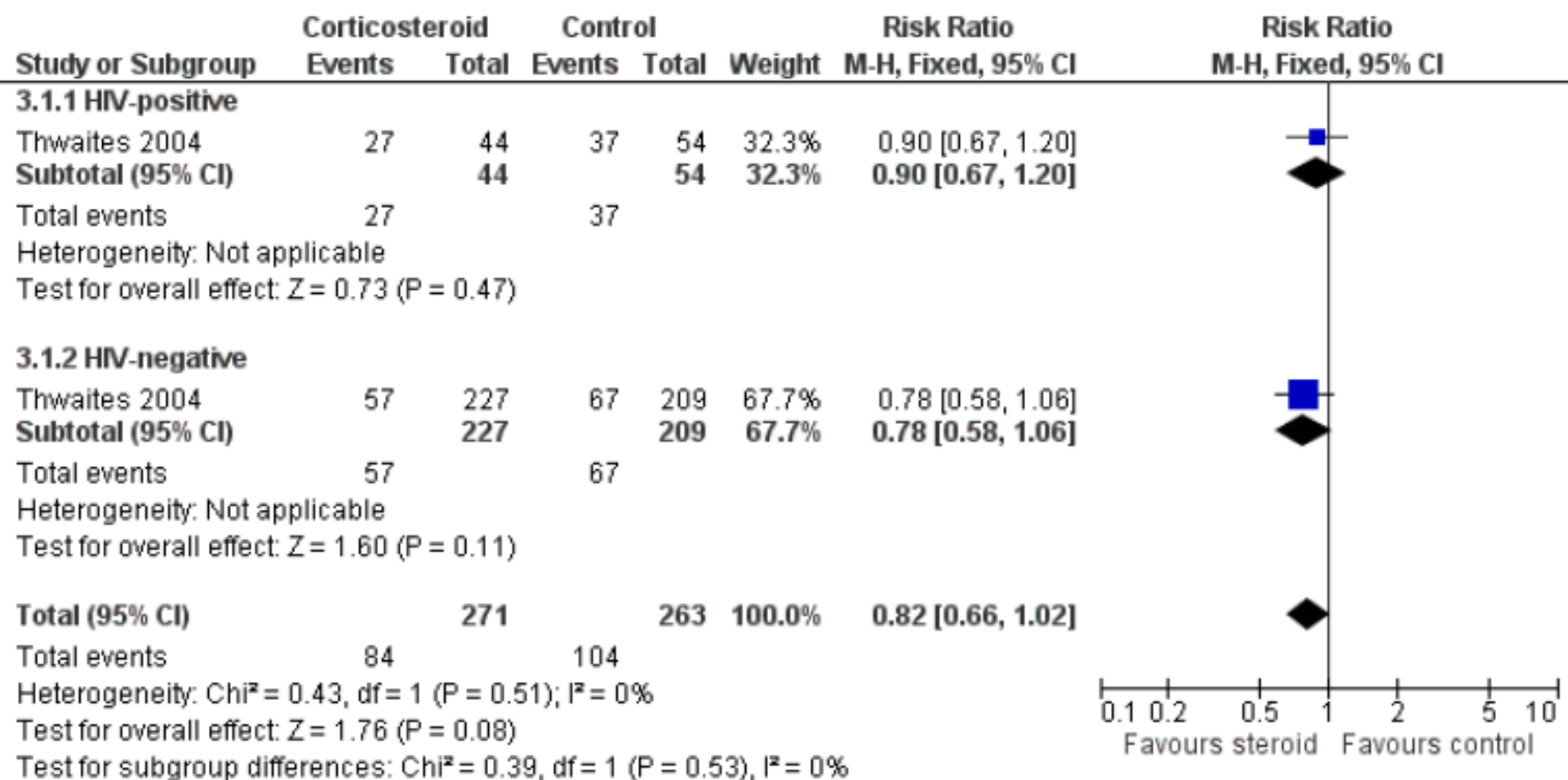
C HIV-Infected Patients



No. at Risk

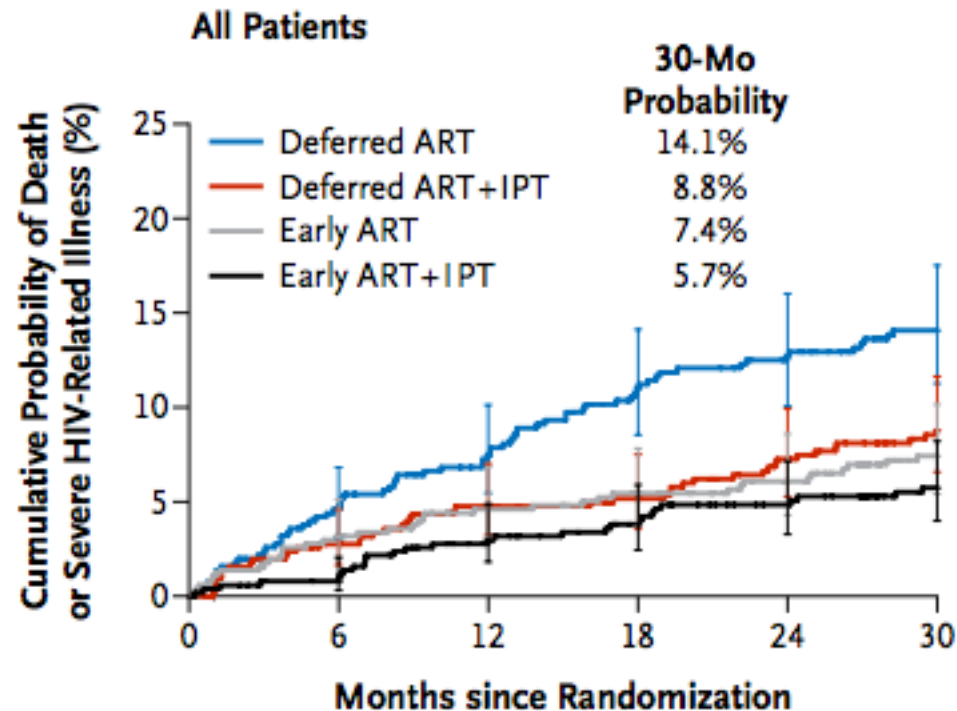
Standard	174	134	120	115	106	104	102	100	98	71
Intensified	175	142	128	118	116	112	106	102	100	77

Steroids for TBM in PLHIV



TEMPRANO: ART+ INH (1)

A Primary Outcome

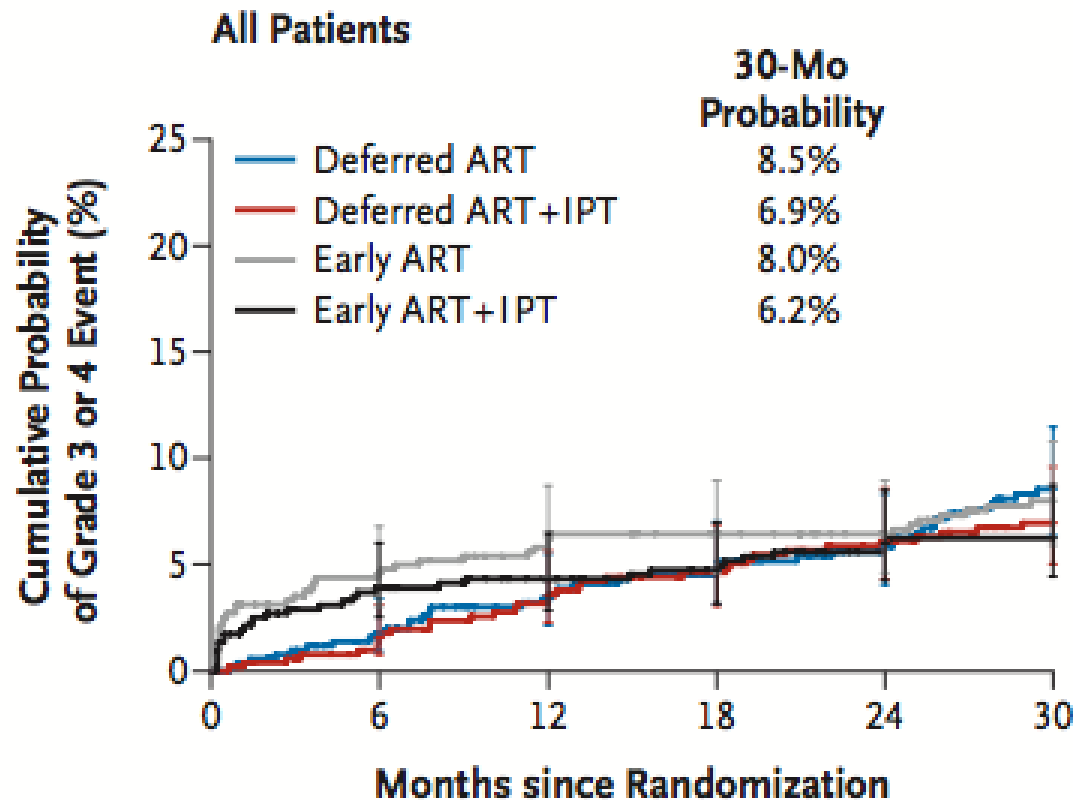


No. at Risk

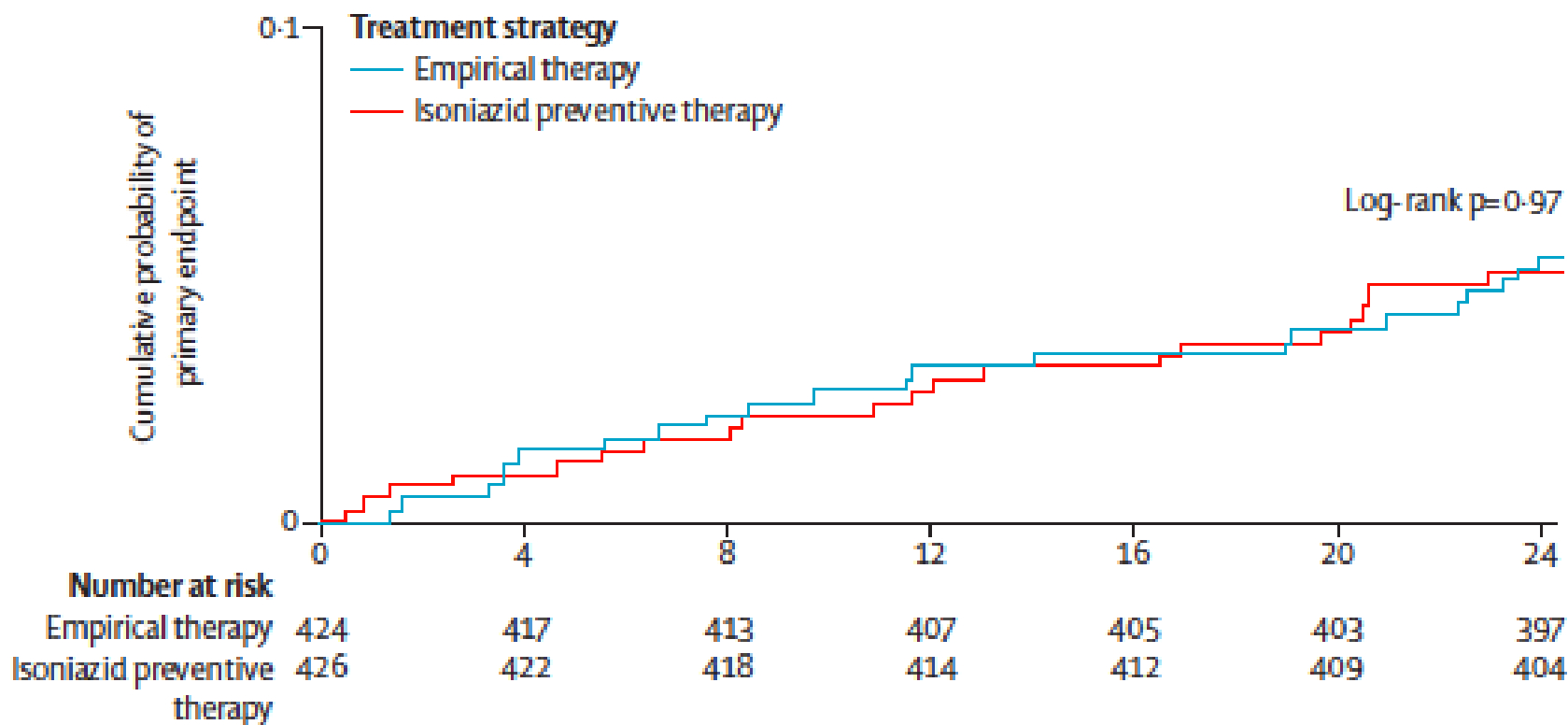
Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

TEMPRANO: ART+ INH (2)

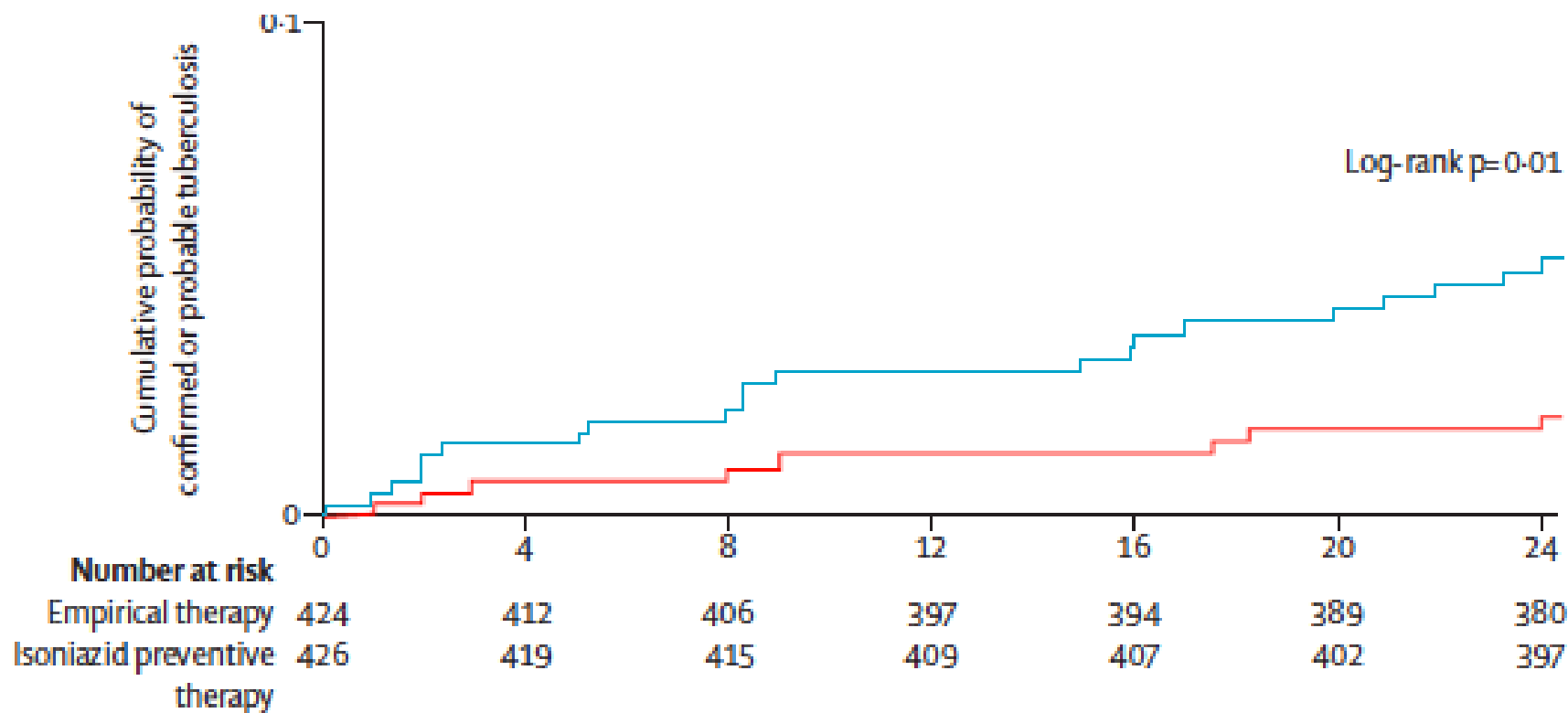
B Main Secondary Outcome



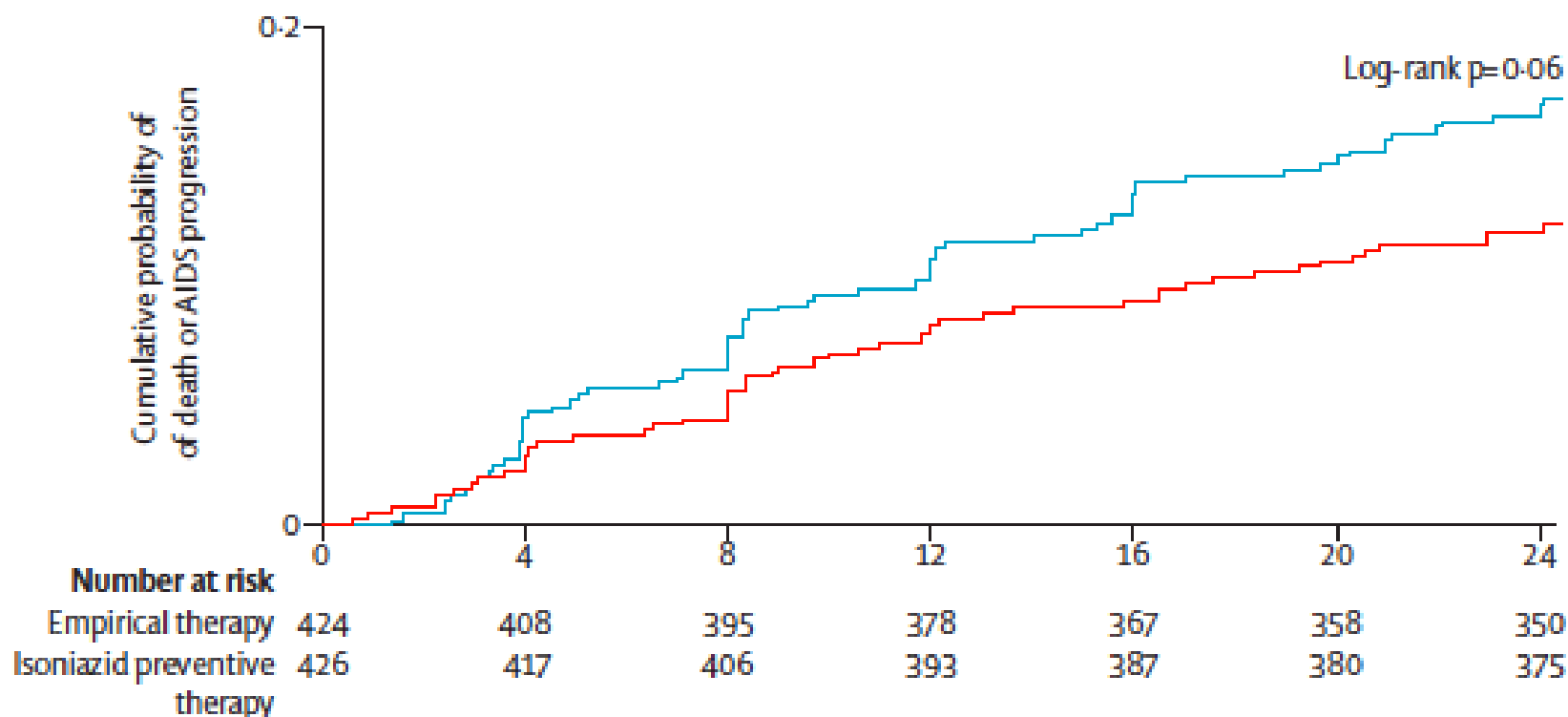
Empirical ATT vs IPT in advanced HIV



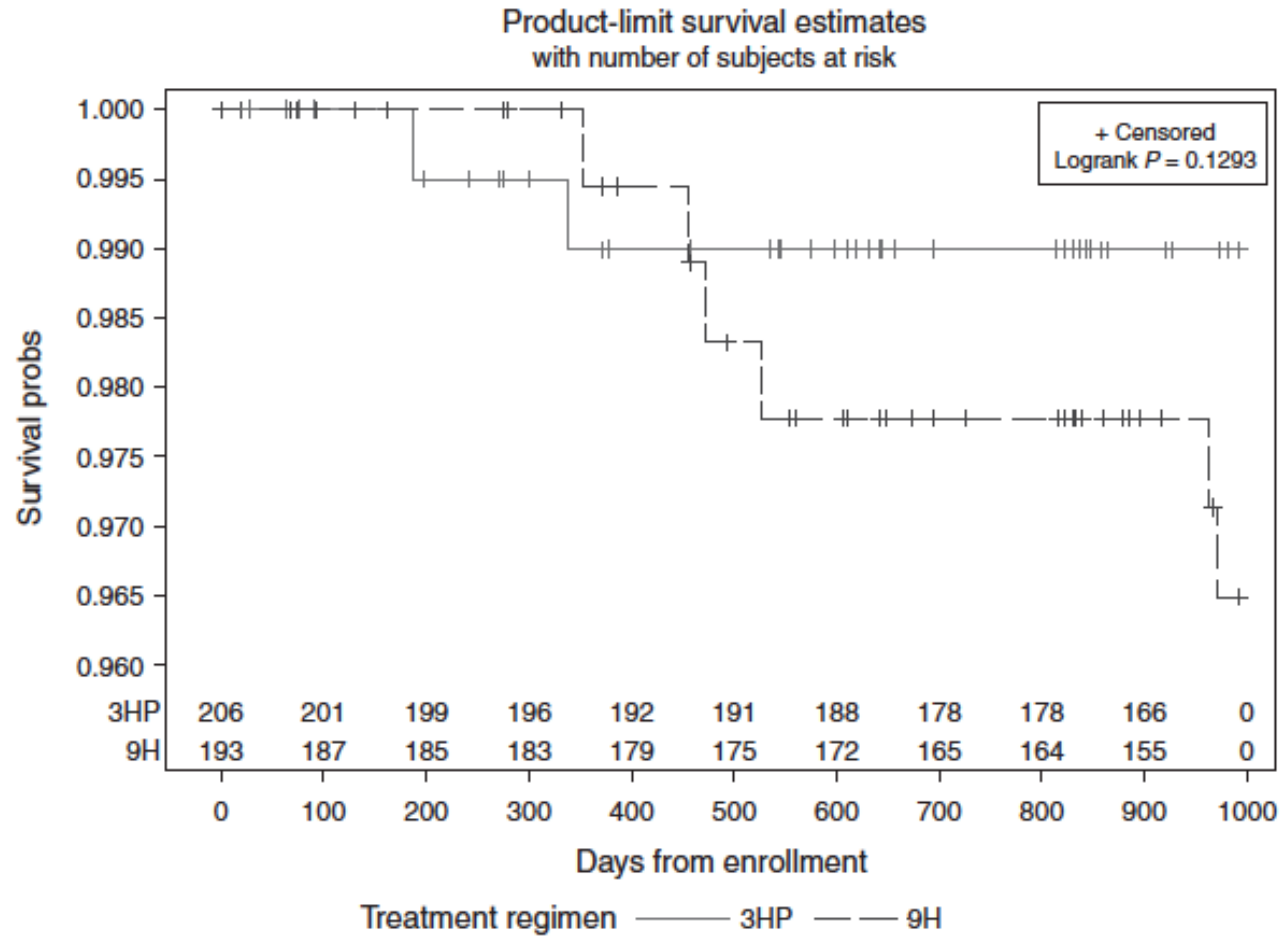
Empirical ATT vs IPT in advanced HIV



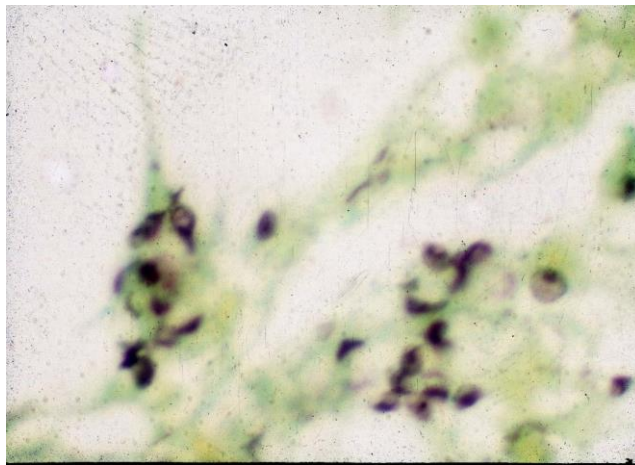
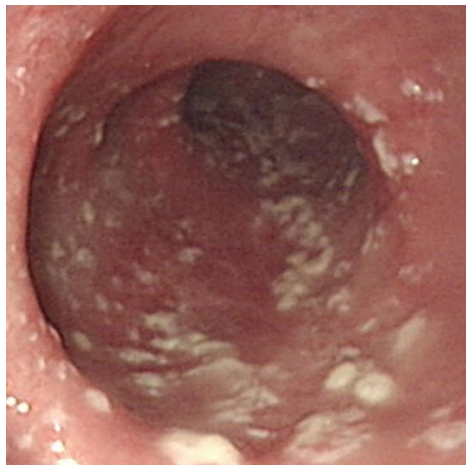
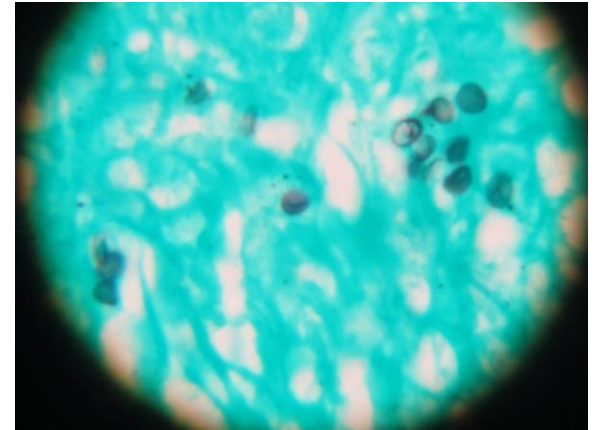
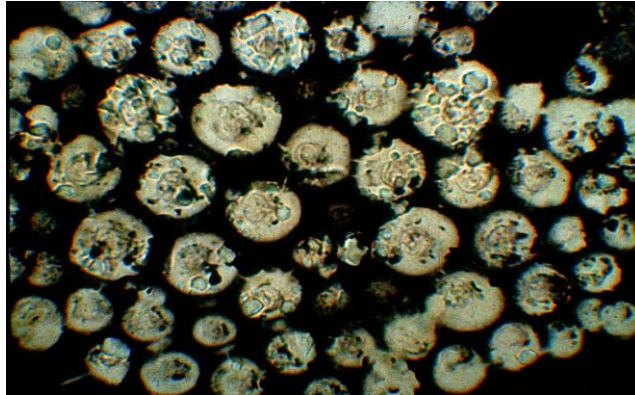
Empirical ATT vs IPT in advanced HIV



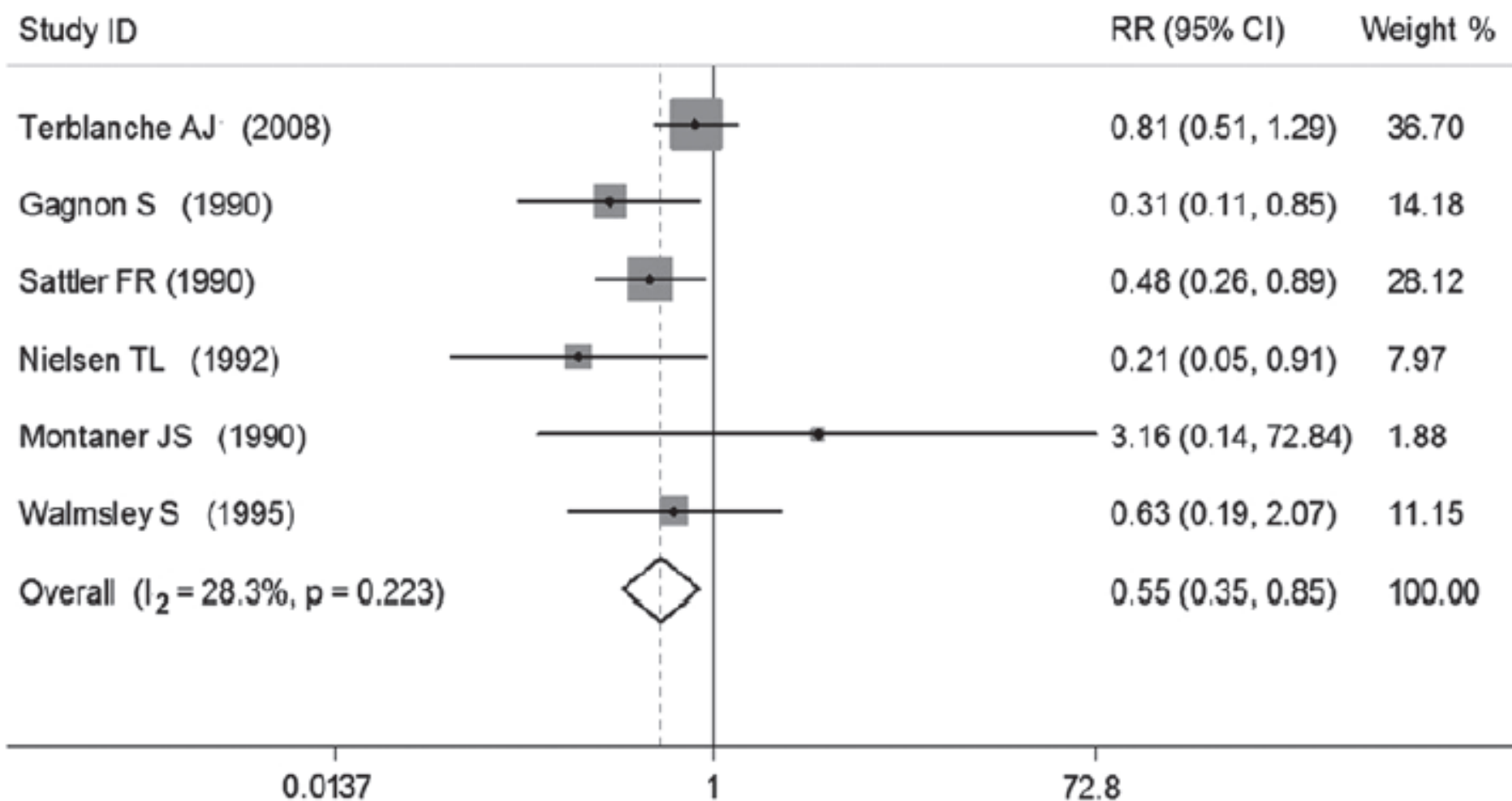
Preventing TB : 3HP in PLHIV CD4>500



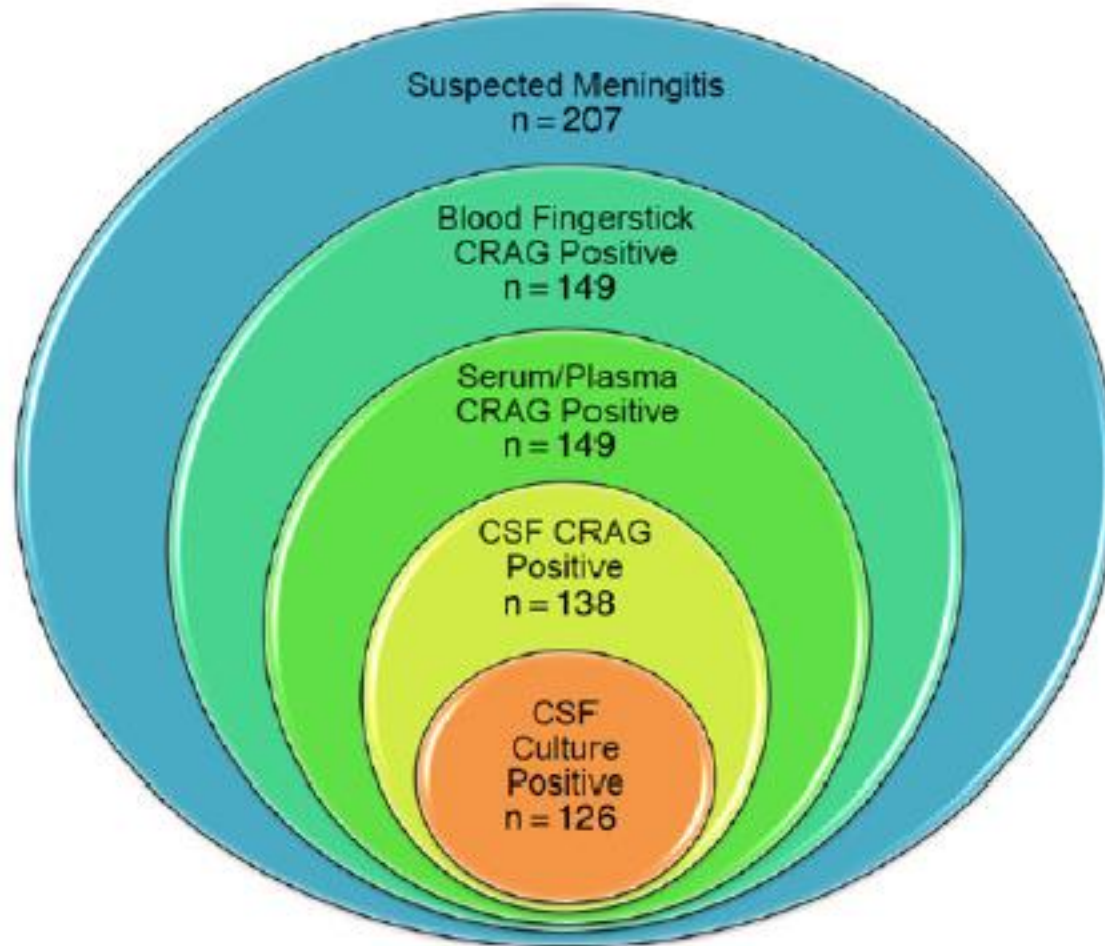
Fungal infections



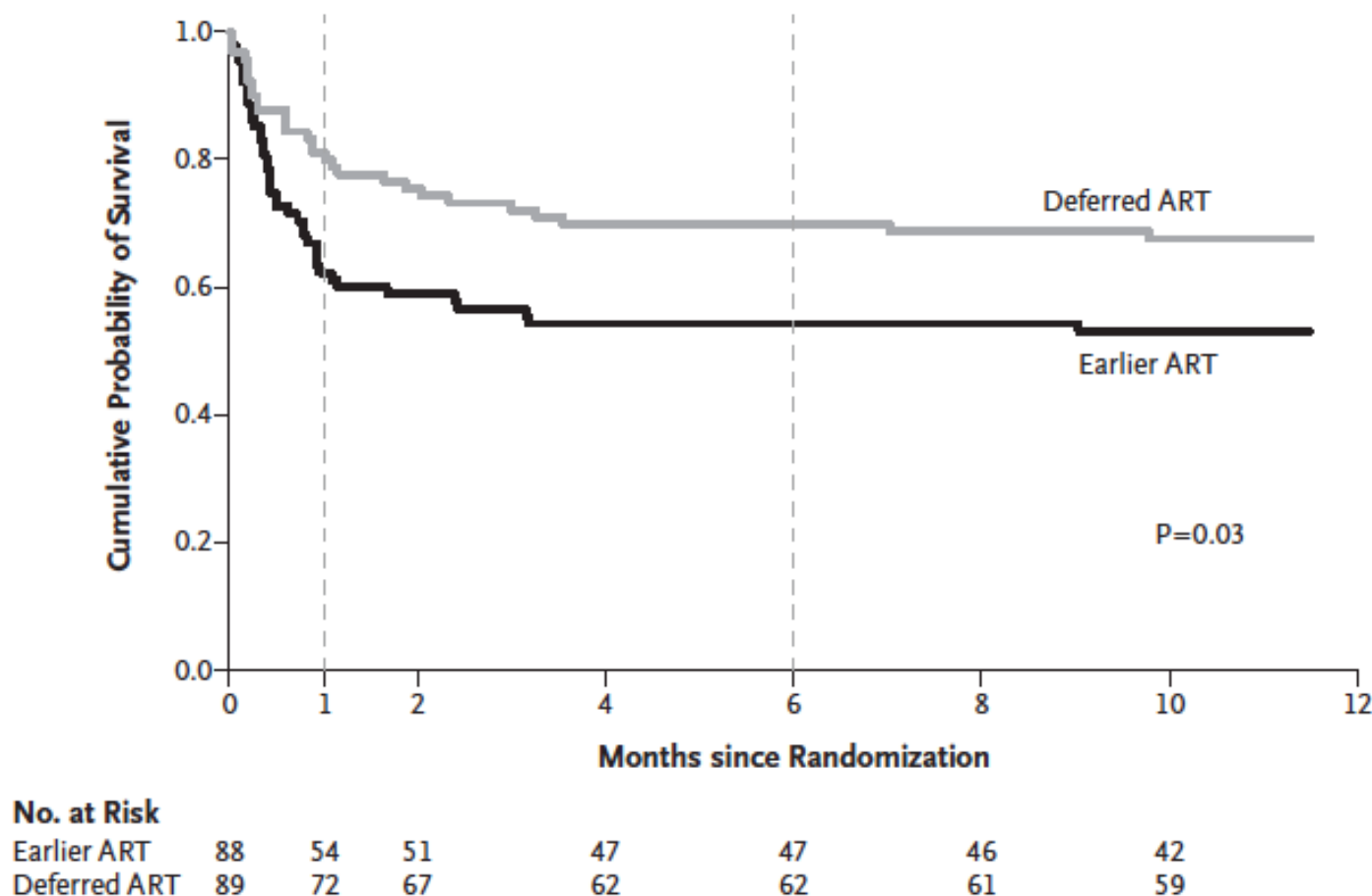
Steroids in PCP



Cryptococcosis: LFA fingerstick

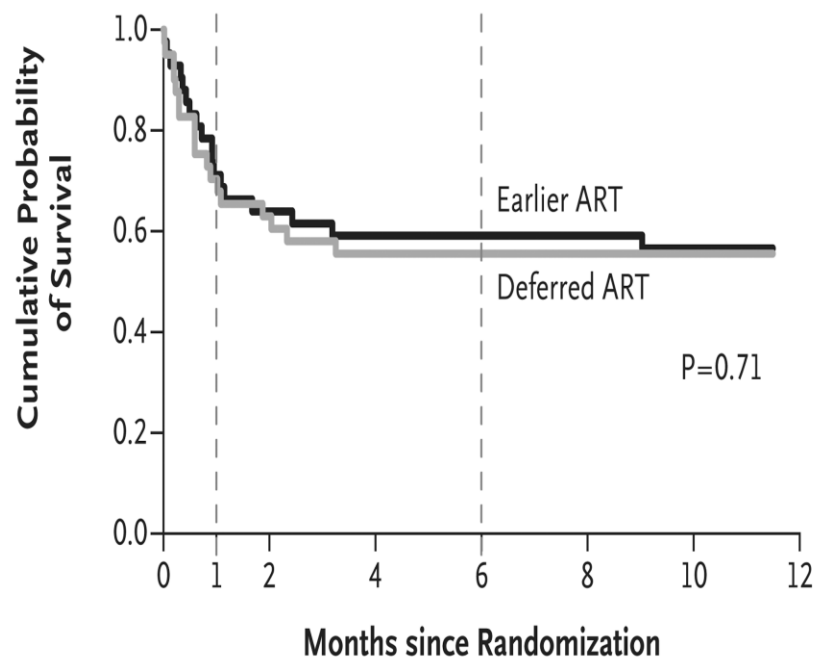


Cryptococcal meningitis: ART timing



Cryptococcal meningitis: ART timing

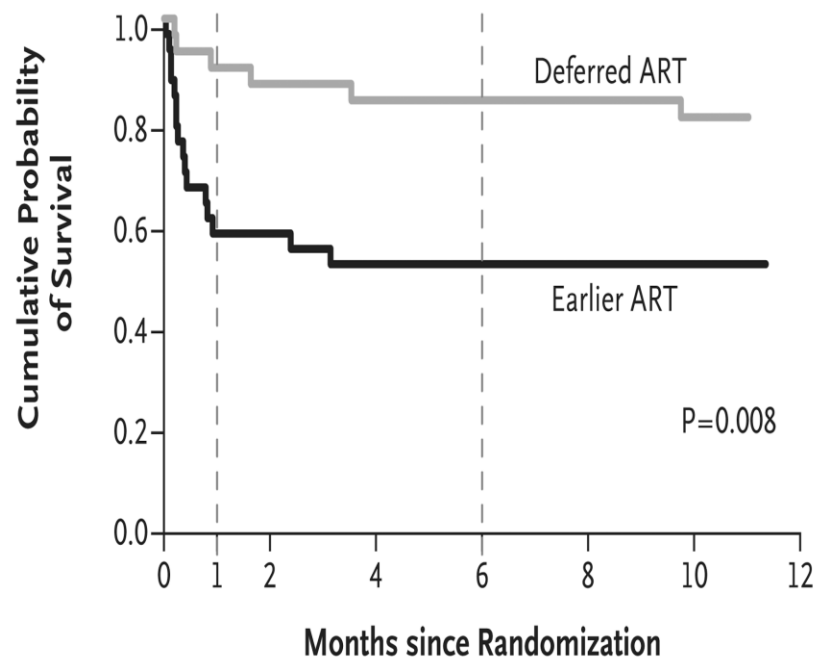
B Survival in Those with CSF White-Cell Count ≥ 5 Cells per mm^3 at Randomization



No. at Risk

Earlier ART	42	29	26	24	24	23	21
Deferred ART	40	28	25	22	22	22	22

C Survival in Those with CSF White-Cell Count < 5 Cells per mm^3 at Randomization

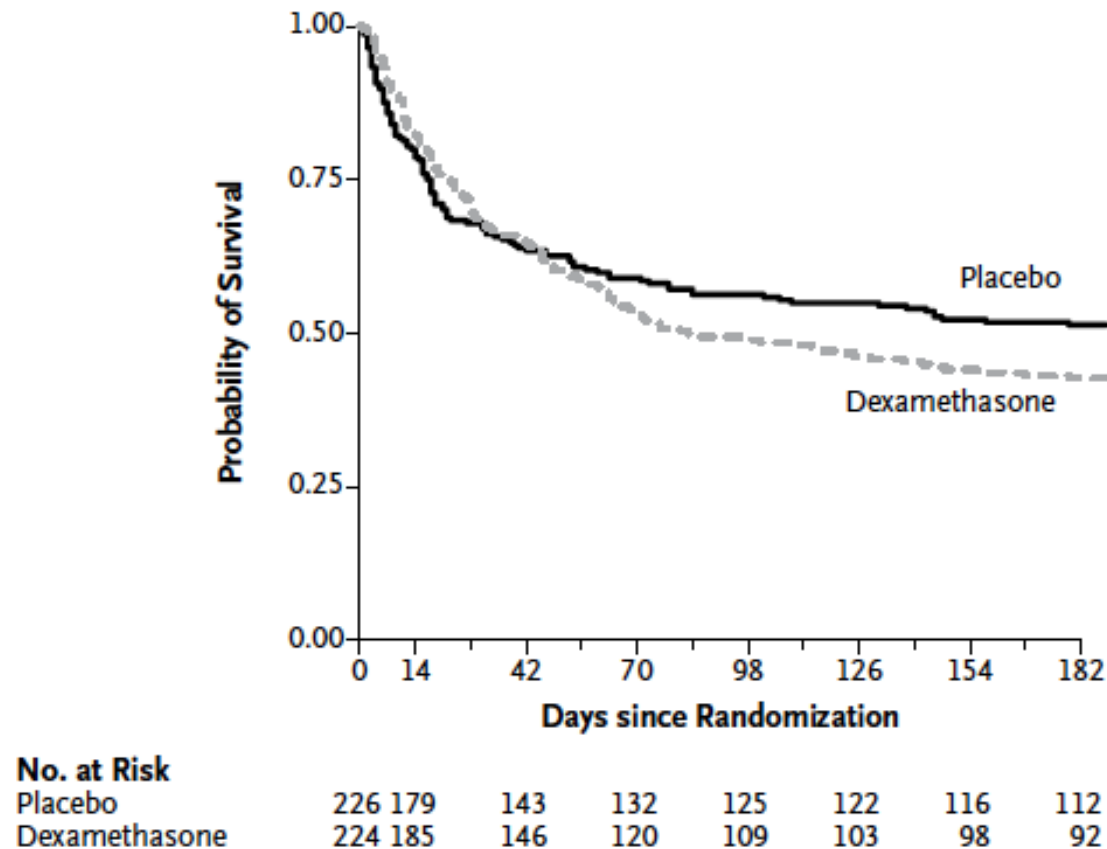


No. at Risk

Earlier ART	33	19	19	17	17	17	16
Deferred ART	31	28	27	26	26	26	24

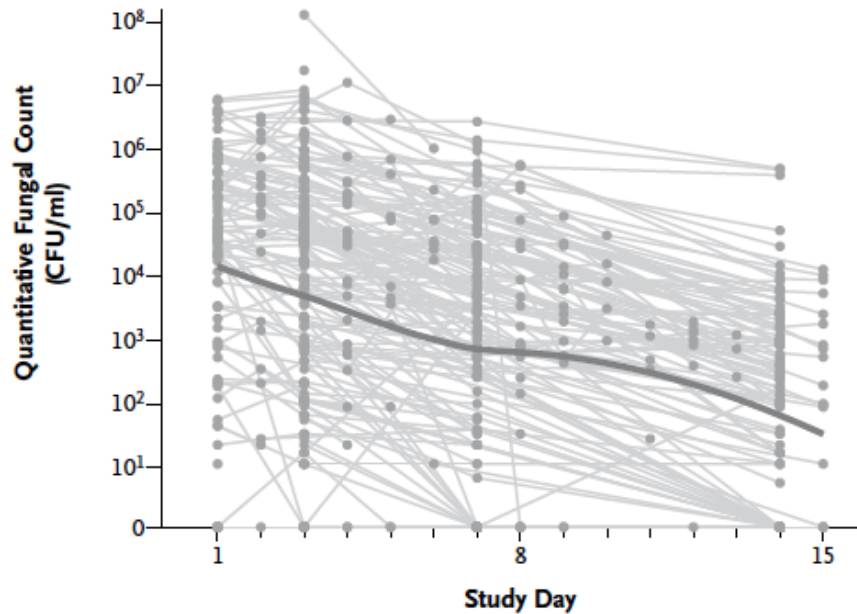
Cryptococcosis: role of steroids

A All Patients

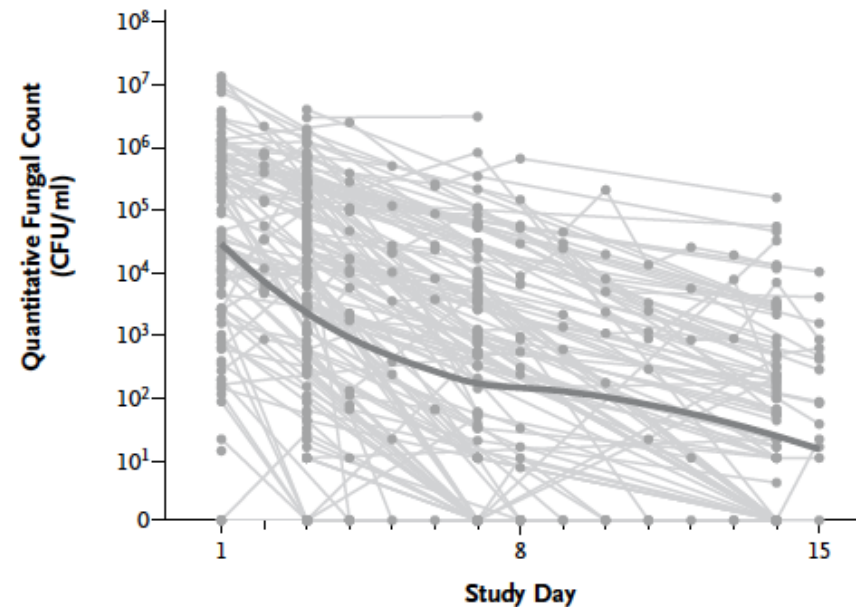


Cryptococcosis: role of steroids

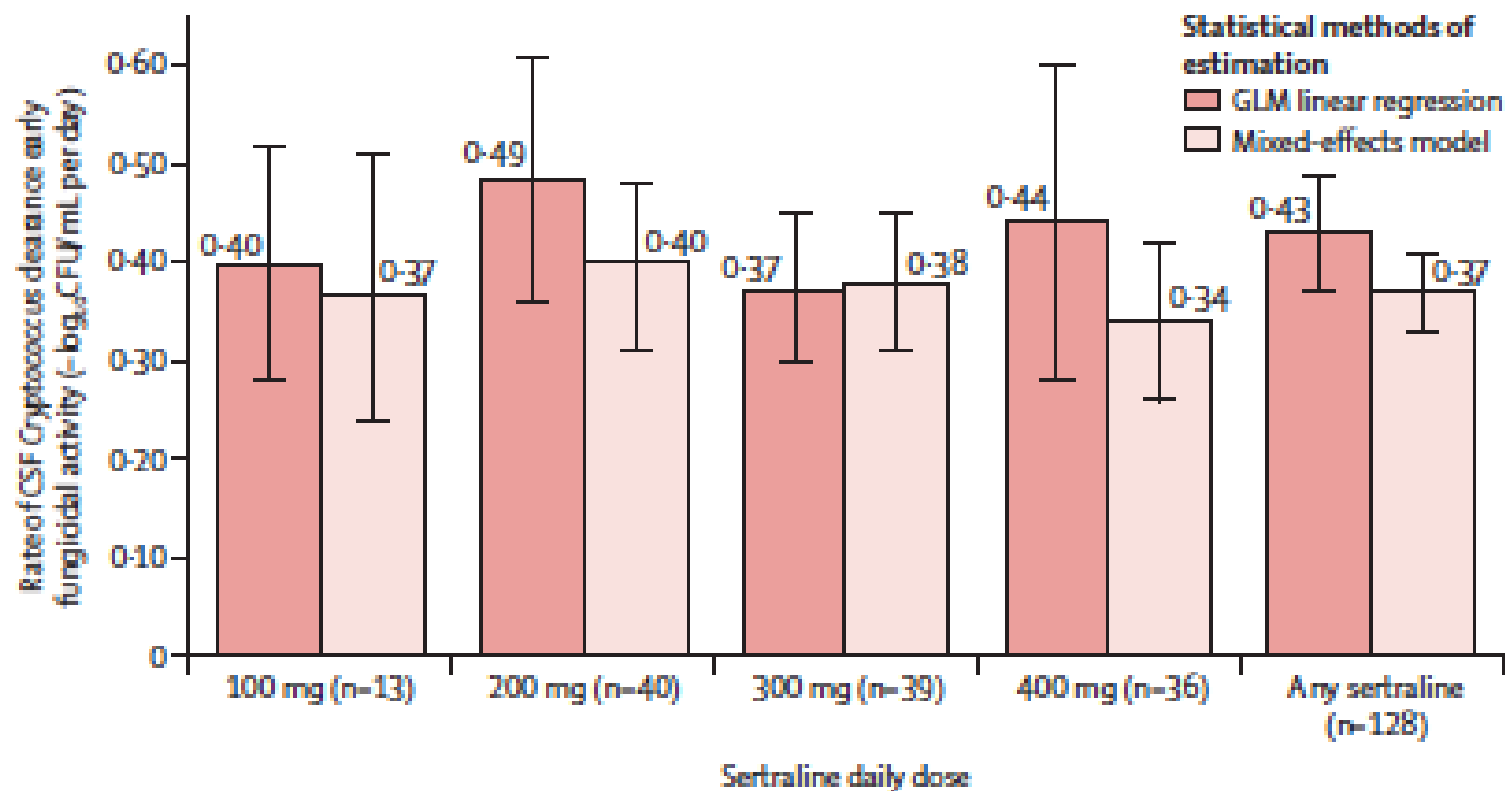
A Dexamethasone



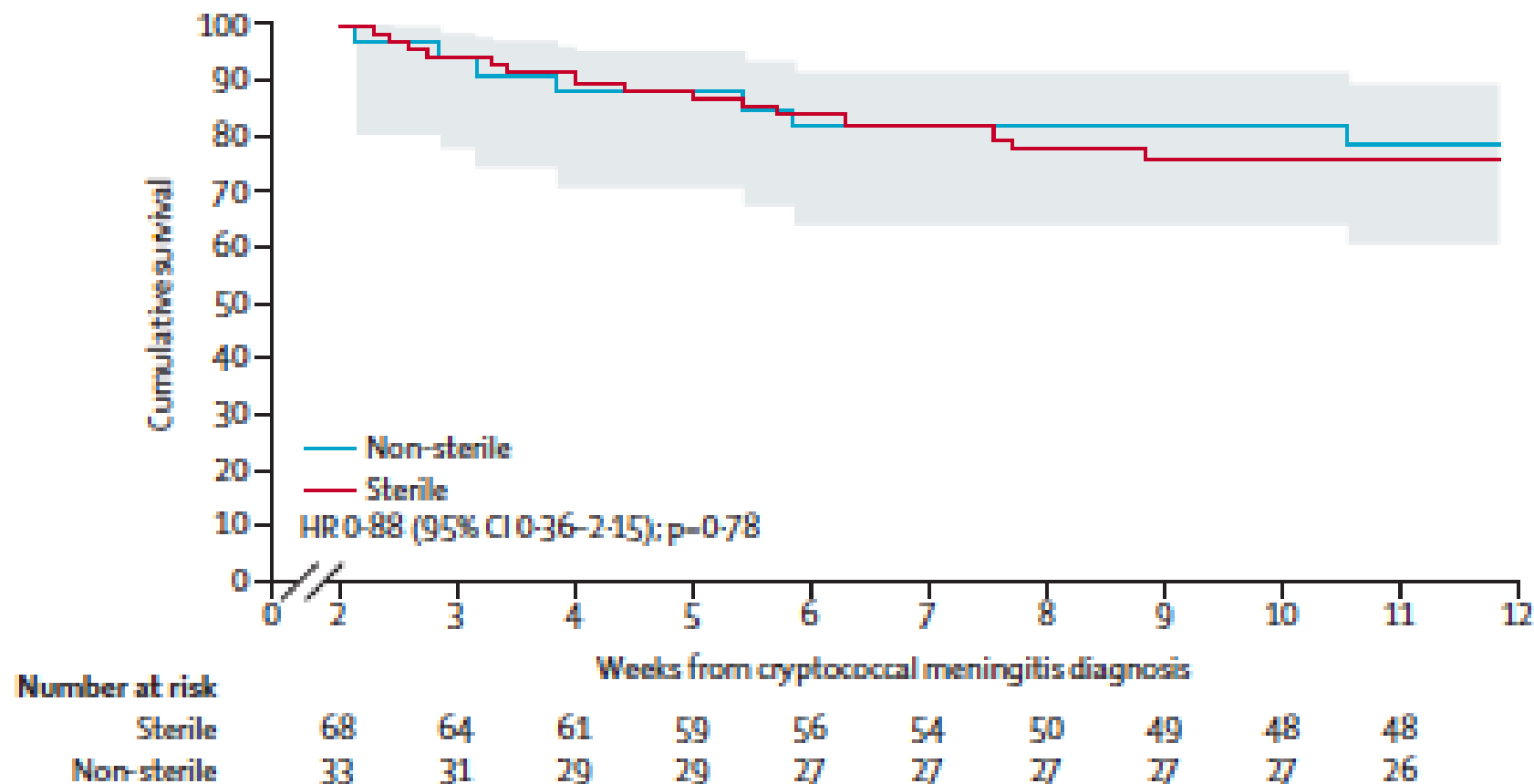
B Placebo



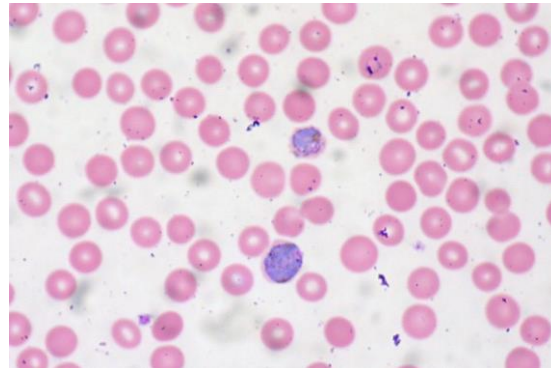
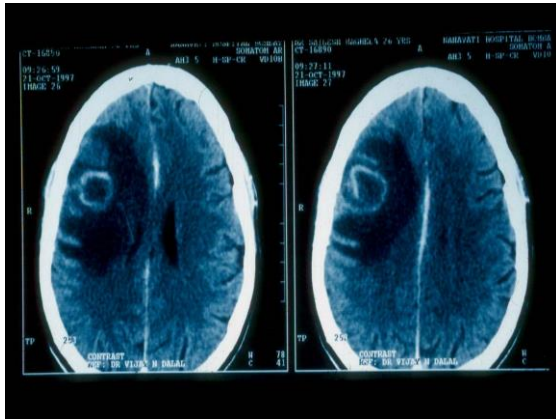
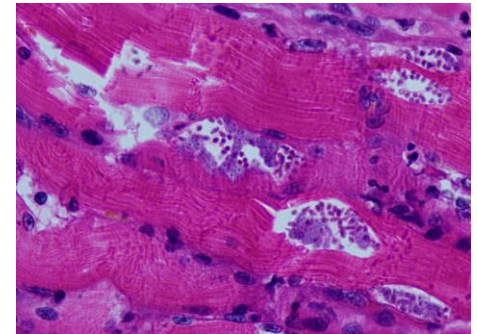
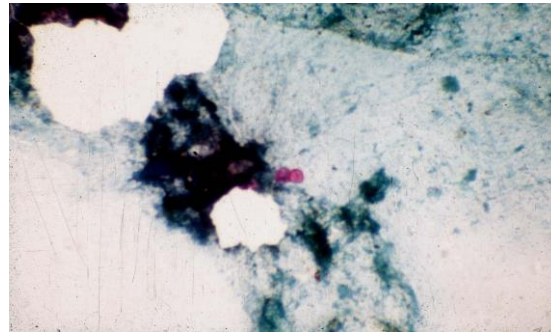
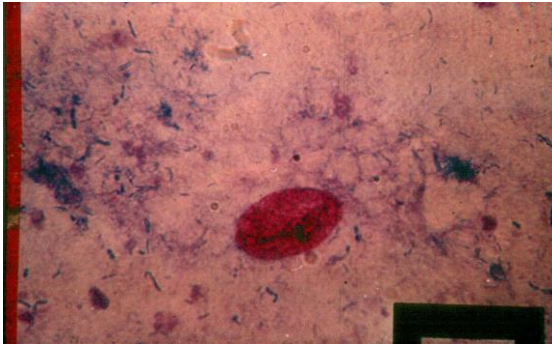
Cryptococcal meningitis : Sertraline as adjunct



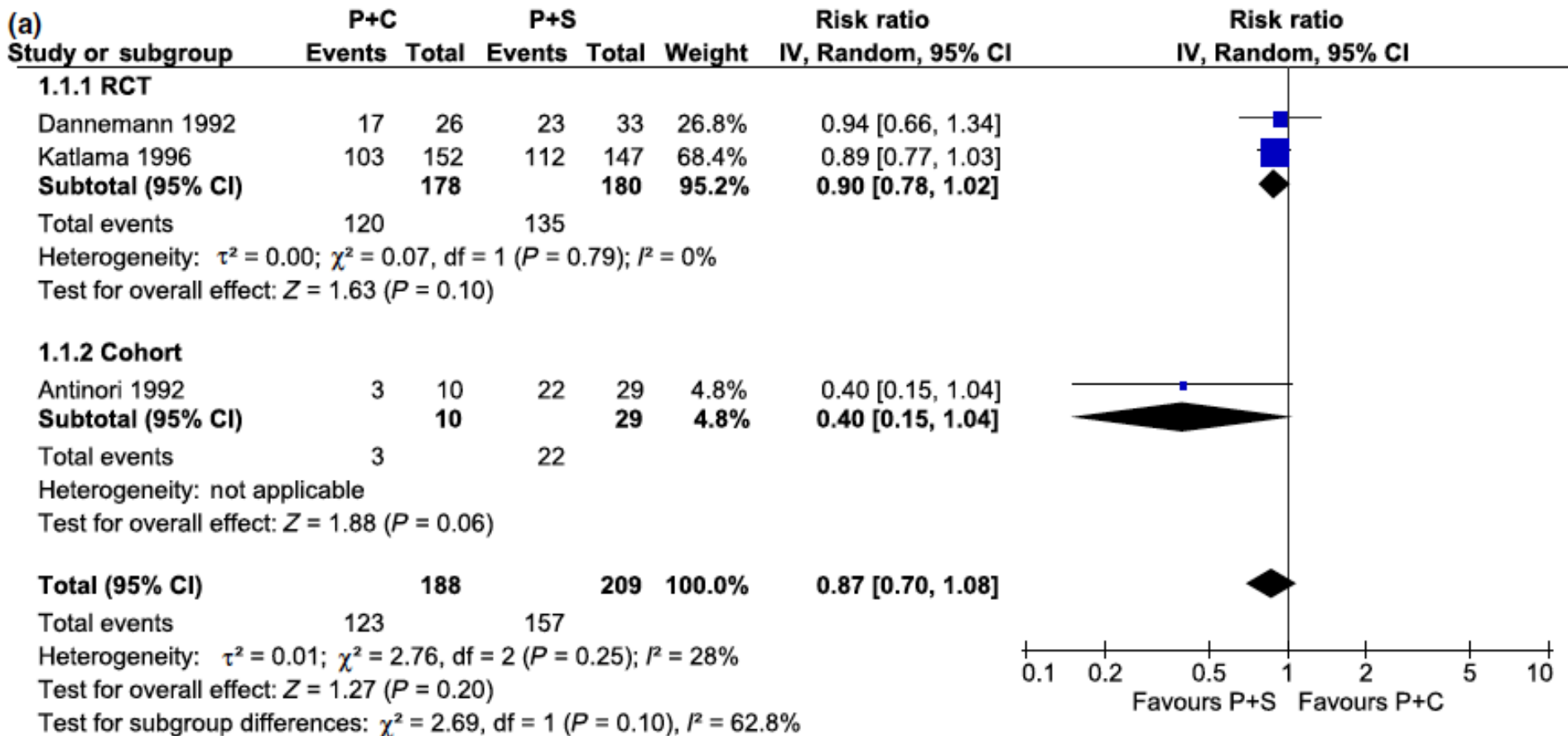
Cryptococcal meningitis : Sertraline as adjunct



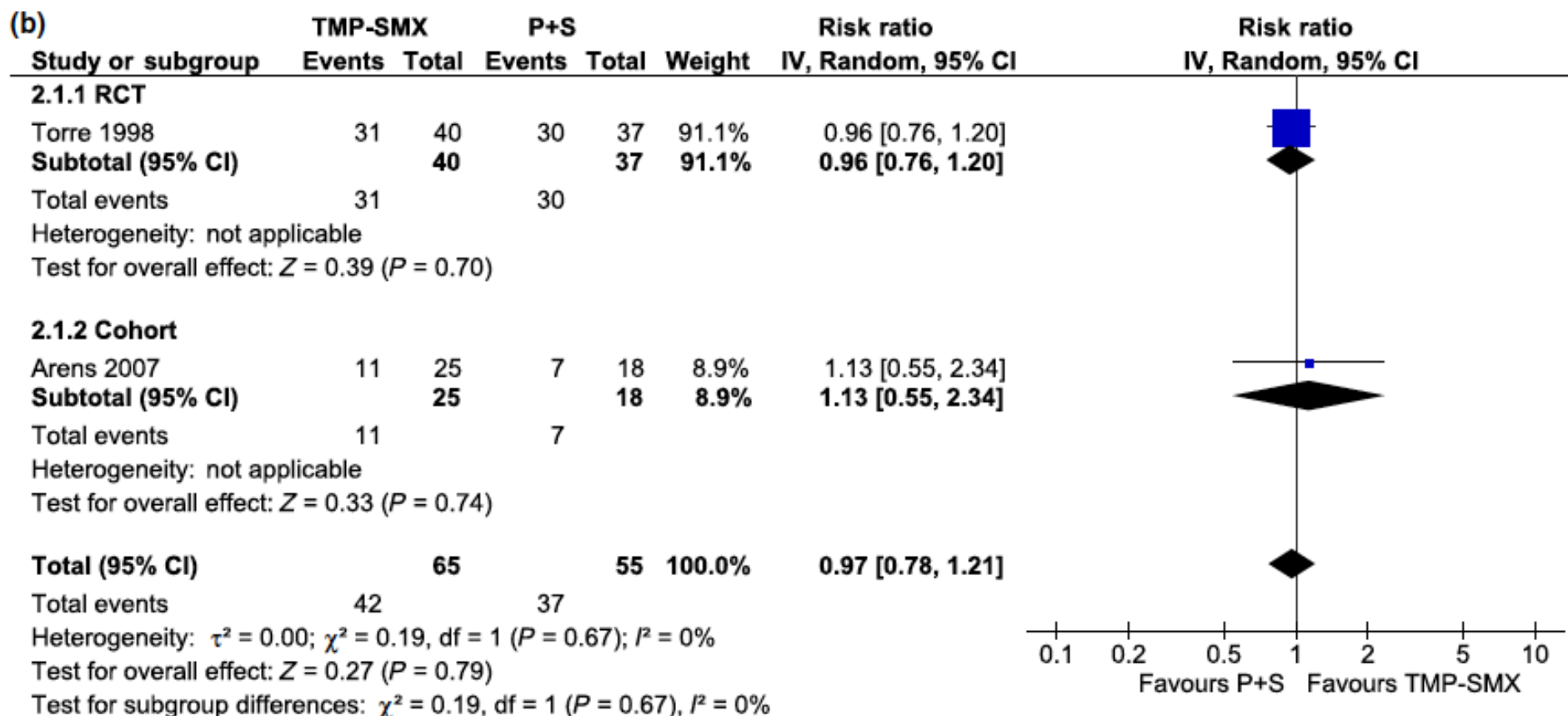
Protozoal OIs



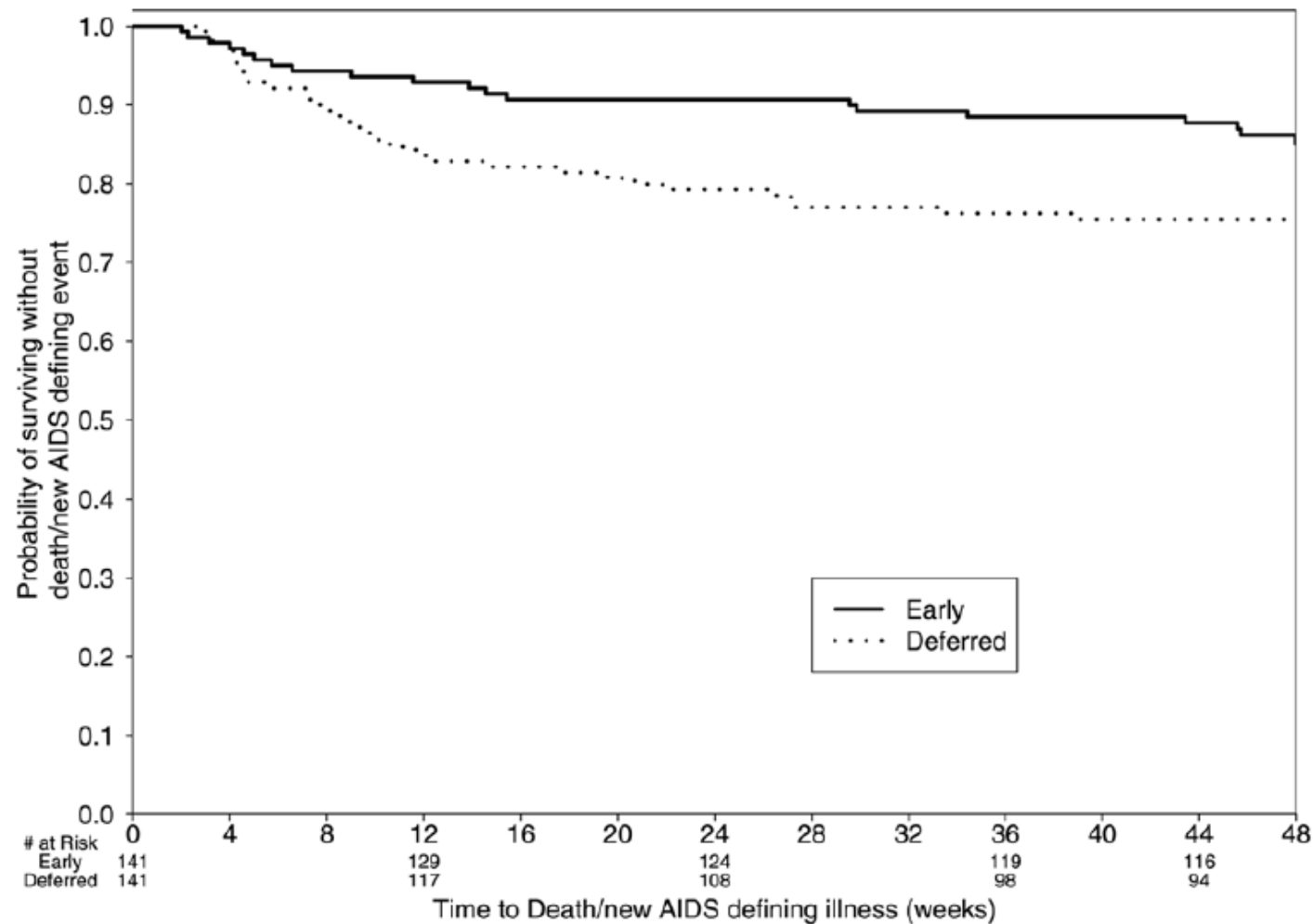
Cerebral toxoplasmosis: Treatment



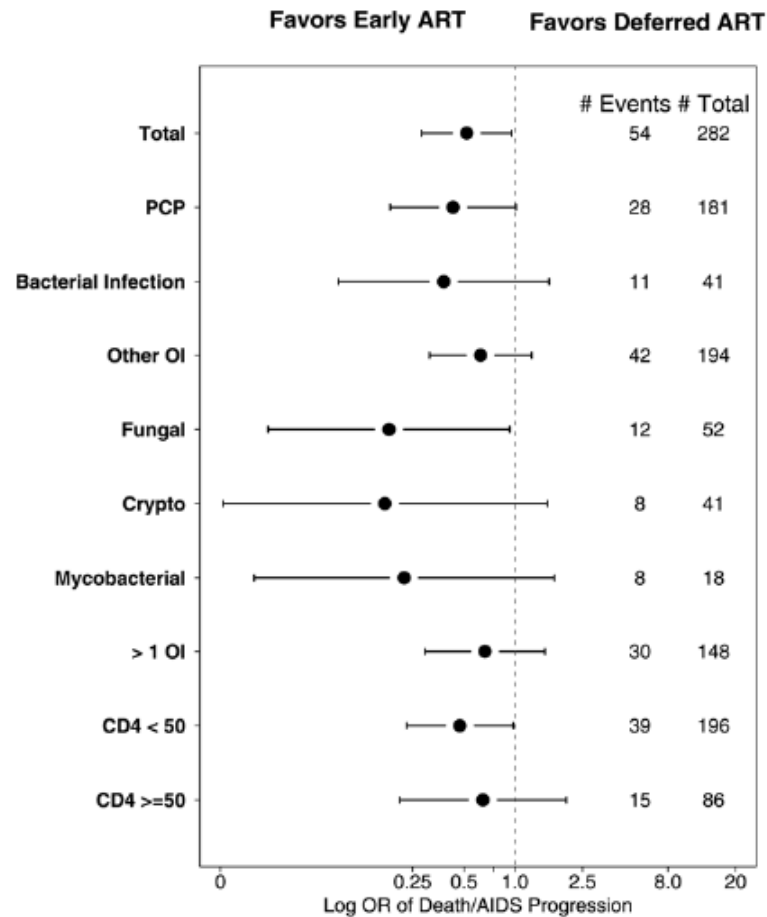
Cerebral toxoplasmosis: Treatment



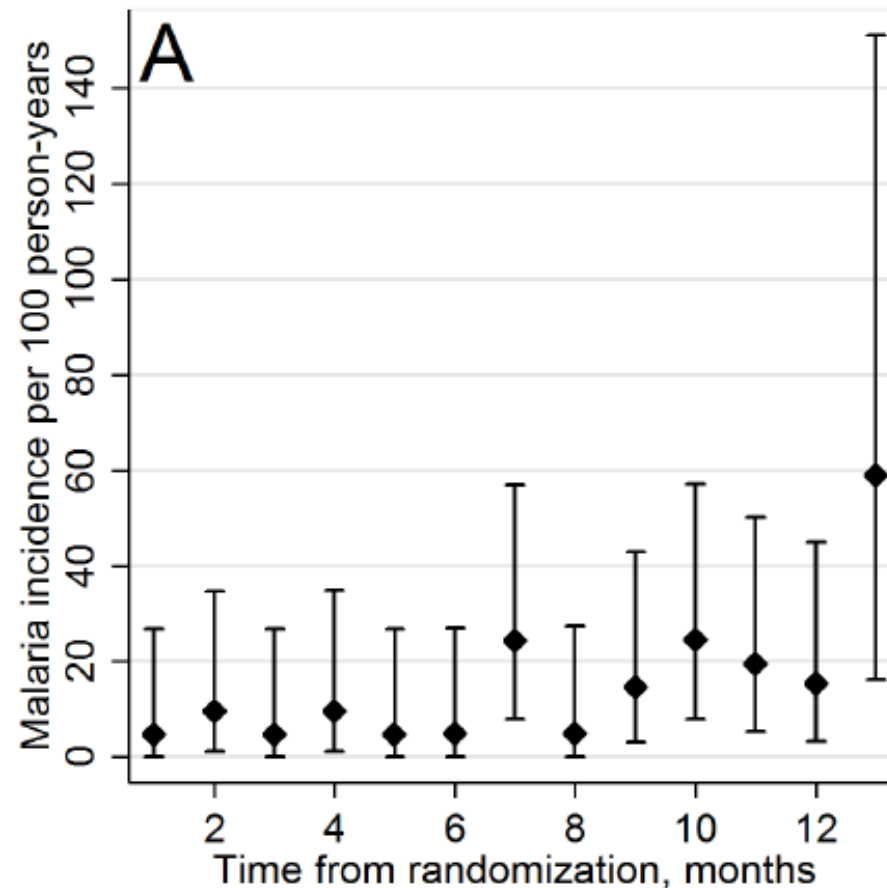
Acute OI: ART timing



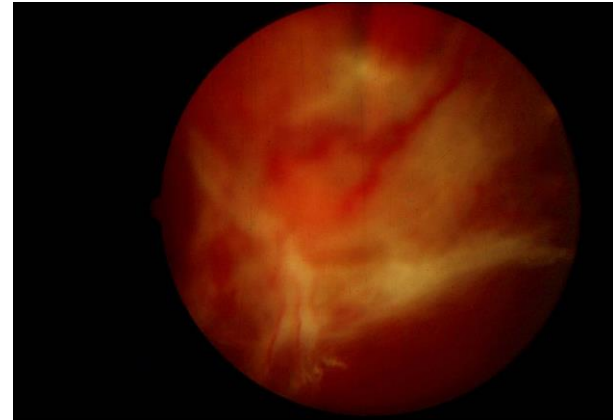
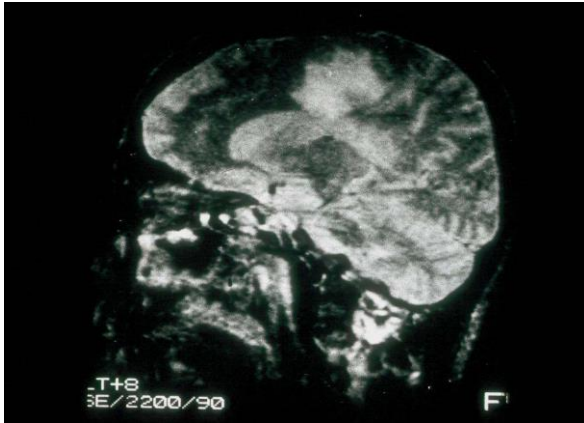
Acute OI: ART timing



TMP-SMX discontinuation and malaria



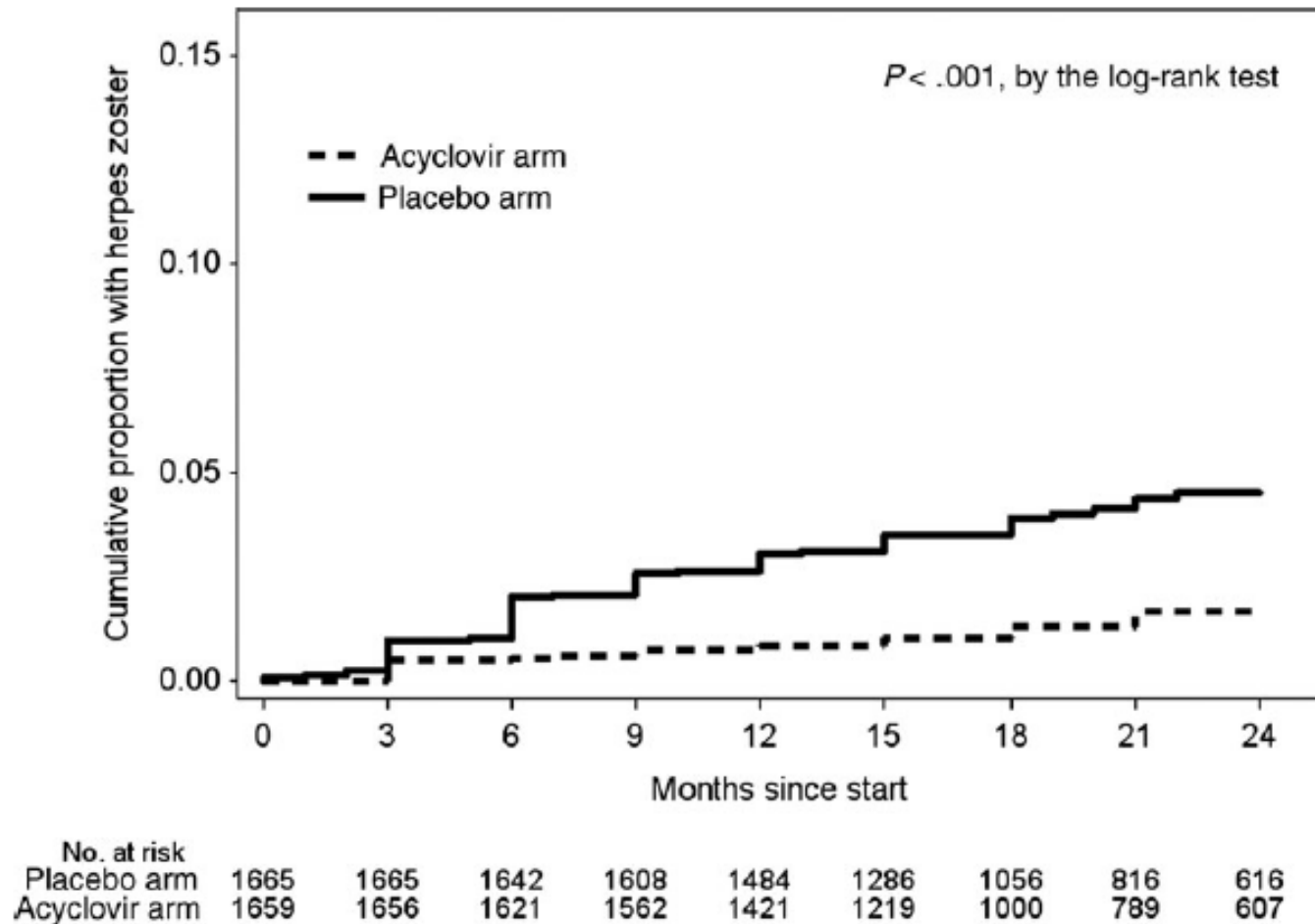
Viral infections (1)



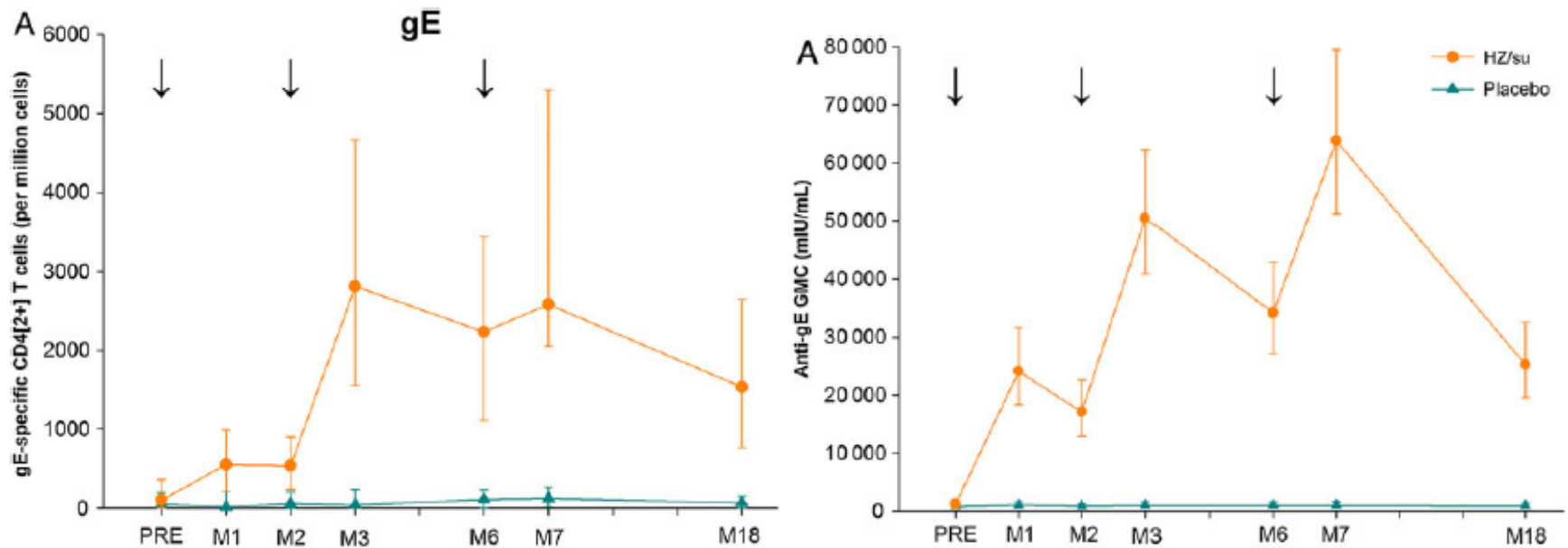
Viral infections (2)



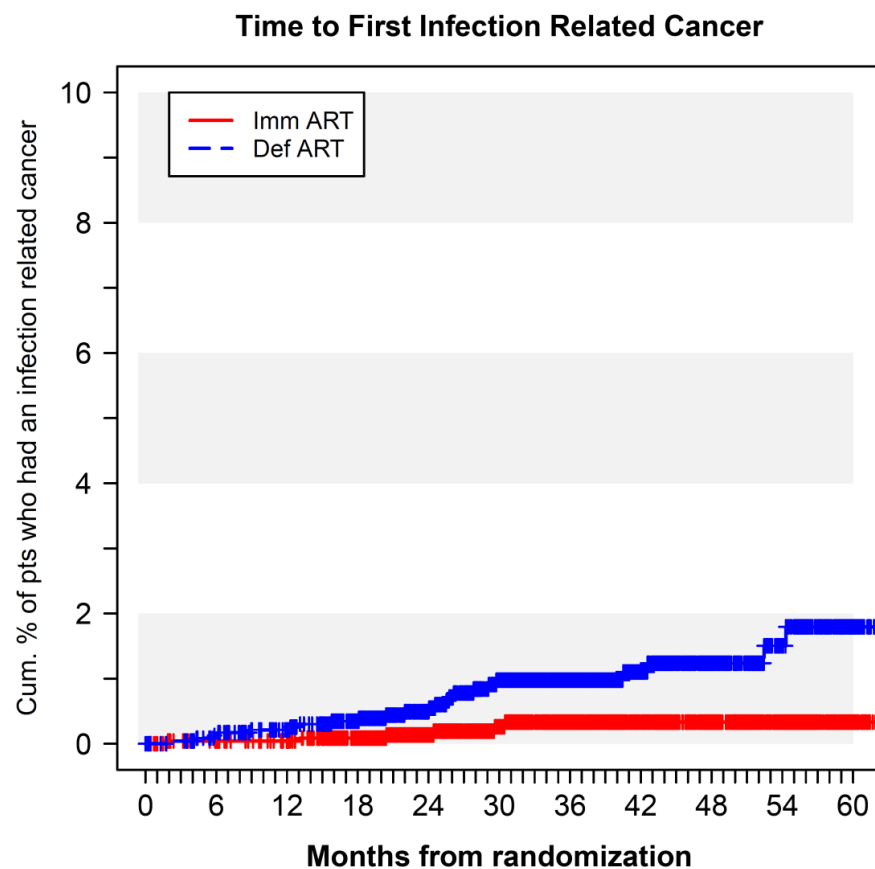
Acylovir prophylaxis for HZ



Subunit HZ(E) vaccine in PLHIV



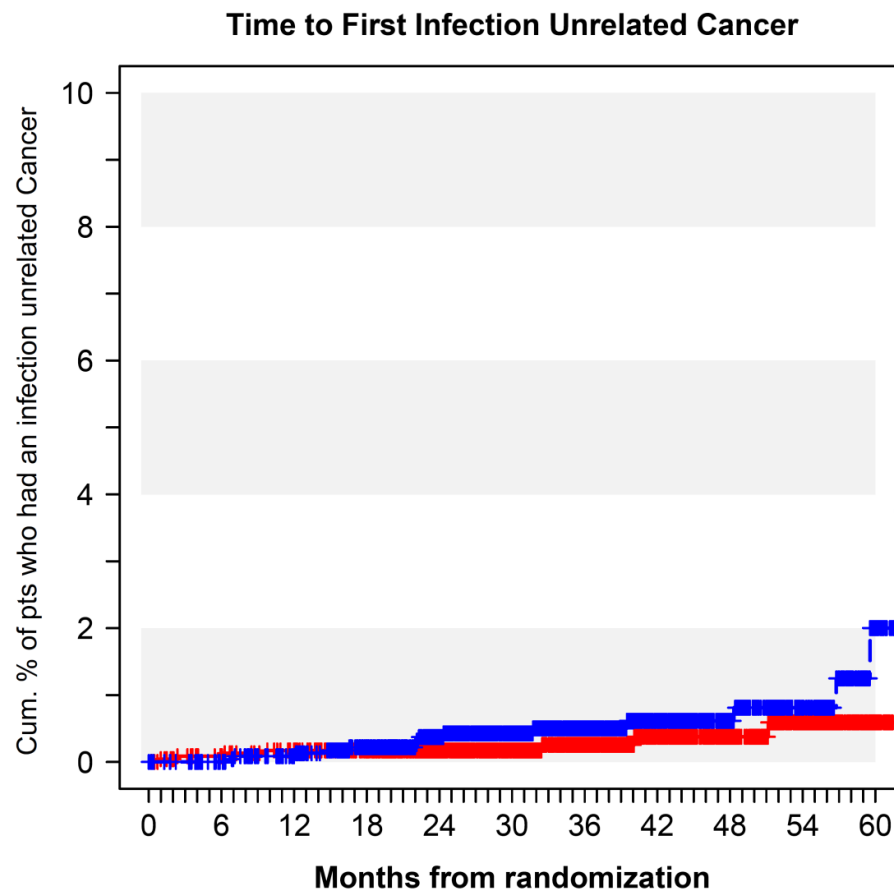
START: ART and infection-related cancer



No. at risk:

Imm	2326	2302	2282	2168	1805	1441	1035	762	546	338	111
Def	2359	2333	2296	2152	1822	1437	1040	743	532	343	106

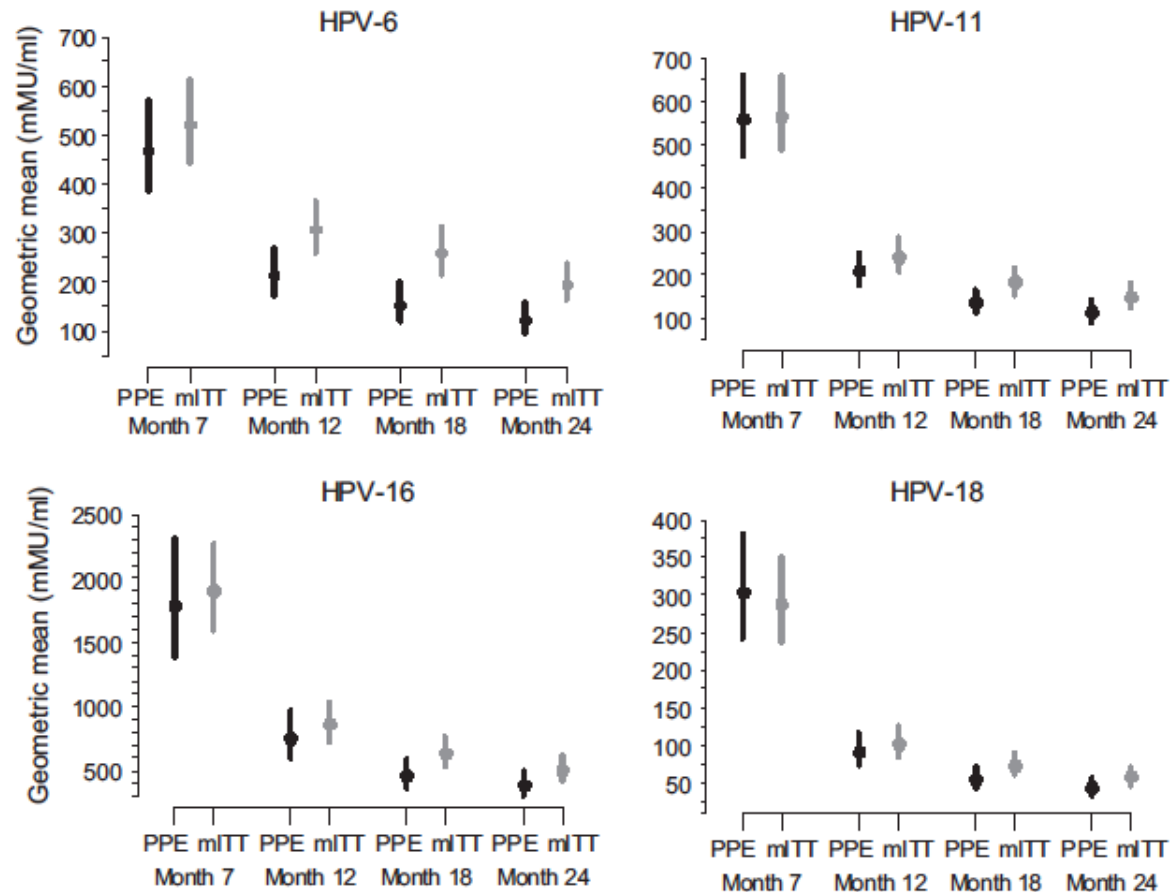
START: ART and infection-unrelated cancer



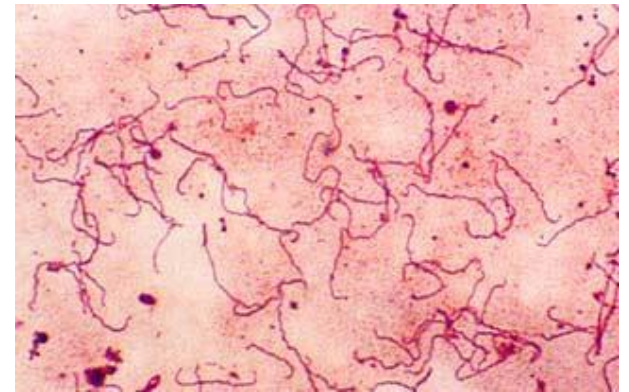
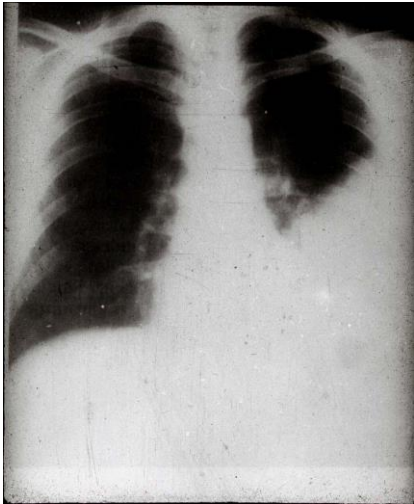
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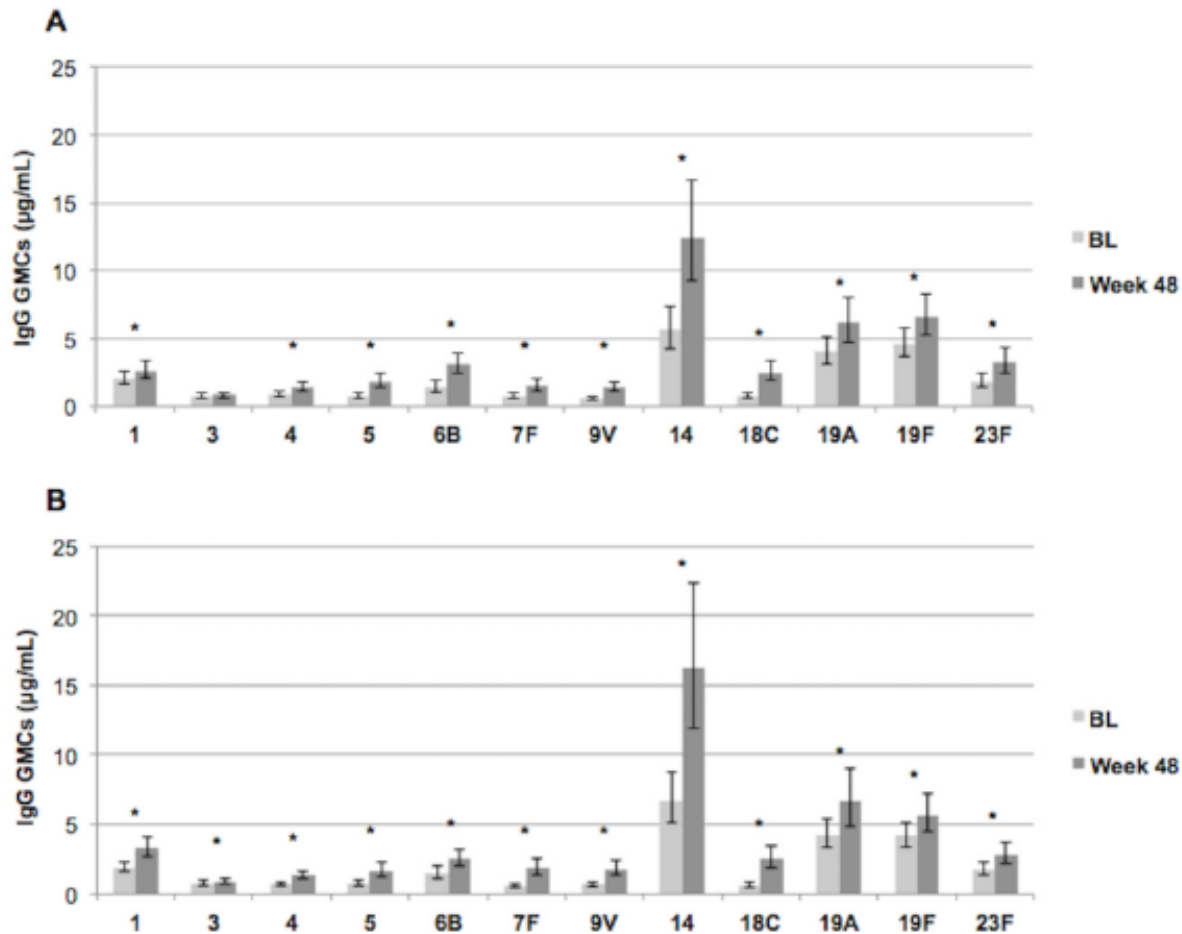
qHPV response in WLHIV



Bacterial infections



PCV-13 vs PPV-23 in PLHIV



REALITY: Mortality Benefit With Enhanced OI Prophylaxis for Pts Initiating ART

Deaths, % ^[1]	Enhanced Prophylaxis (n = 906)	Standard Prophylaxis (n = 899)	HR (95% CI)	P Value
Wk 24*	8.9	12.2	0.73 (0.54-0.97)	.03
Wk 48	11.0	14.4	0.75 (0.58-0.98)	.04

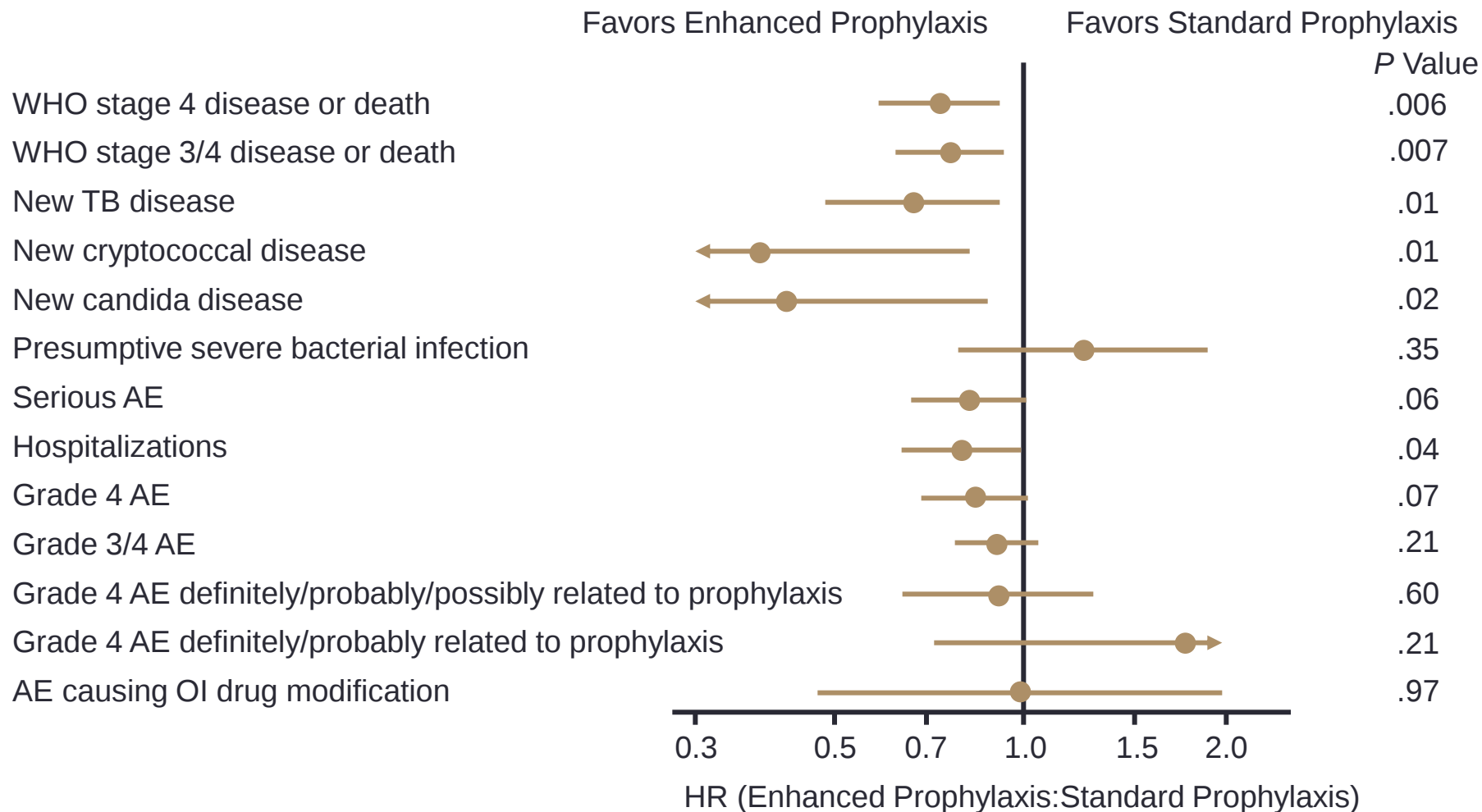
*Primary endpoint.

- 3.3 lives saved for every 100 treated with enhanced prophylaxis^[1]
- Additional REALITY factorial randomization assessed mortality for ART initiation with 2 NRTIs + NNRTI + RAL vs 2 NRTIs + NNRTI^[2]
 - Addition of RAL to standard 3-drug ART did not affect all-cause mortality at 24 or 48 wks

1. Hakim J, et al. AIDS 2016. Abstract FRAB0101LB.

2. Kityo C, et al. AIDS 2016. Abstract FRAB0102LB.

REALITY: Additional Outcomes Favor Enhanced OI Prophylaxis



Hakim J, et al. AIDS 2016. Abstract FRAB0101LB.
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Summary

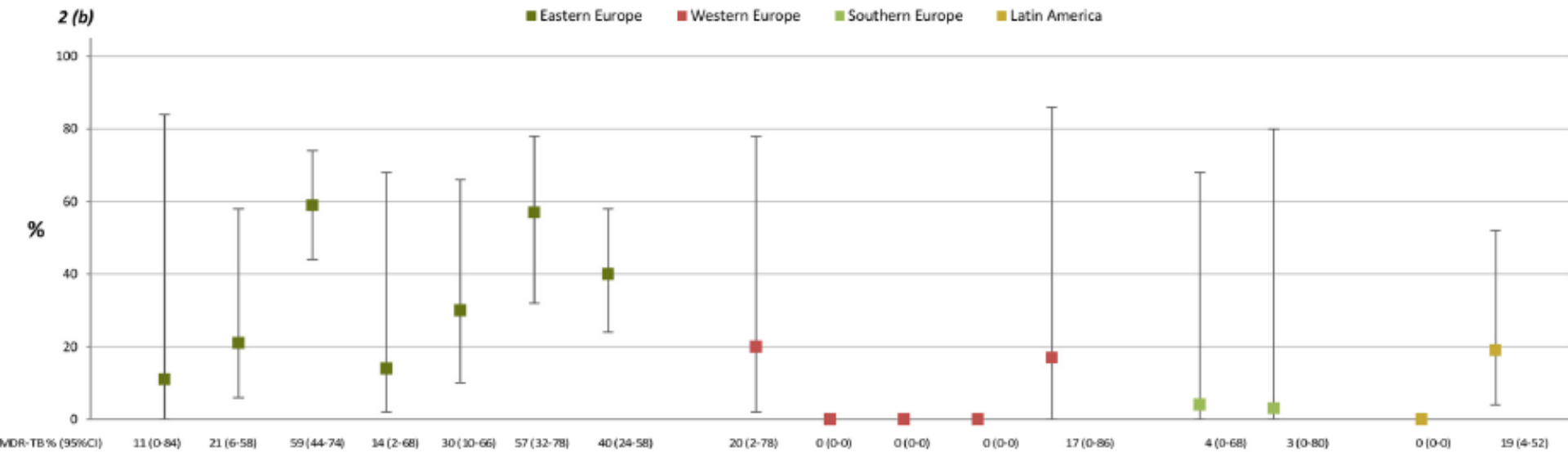
- OI's: Going, Going, but not gone
- Widespread testing for HIV, linkage to care and ART initiation key to reduce burden of OI's
- Preventive strategies e.g. vaccination, screening for cancers need to be implemented
- Clinicians must remain knowledgeable about optimal management and prevention of OI's to provide high quality care



Differential impact of ART on OI incidence

	Tuberculosis	MAC	CMV retinitis	PML	Herpes Simplex	Kaposi Sarcoma	Non Hodgkin Lymphoma	Cryptococcosis	Candidiasis
Overall rate	2.3	0.4	0.3	0.3	1.6	1.9	1.2	0.4	1.4
CD4 count, cells/mm³									
<50	6.0	5.8	3.2	1.6	4.6	4.4	1.9	3.9	4.2
50 - 100	4.8	1.4	1.0	1.1	3.1	2.9	2.3	1.6	3.4
100 - 200	3.7	0.6	0.3	0.6	1.8	1.7	1.8	0.5	1.9
200 - 350	2.6	0.2	0.2	0.2	1.4	1.9	1.3	0.2	1.2
350 - 500	1.7	0.1	0.1	0.2	1.4	1.8	1.1	0.1	1.1
>500	1.5	0.1	0.0	0.1	1.4	1.8	1.0	0.1	1.1
HIV-RNA, copies/mL									
<10,000	1.6	0.1	0.1	0.1	1.5	0.9	0.8	0.1	0.7
10,000 - 100,000	2.3	0.3	0.2	0.2	1.5	2.0	1.3	0.3	1.3
>100,000	3.1	1.1	0.6	0.6	1.9	3.0	1.8	0.7	2.3
Age, years									
< 35	2.2	0.2	0.1	0.1	1.1	1.5	0.8	0.2	1.3
35 - 50	2.3	0.6	0.3	0.4	1.9	2.2	1.4	0.5	1.4
>50	2.7	0.5	0.5	0.5	2.3	2.6	2.2	0.5	1.6
Hazard Ratio	0.48 (0.36,0.64)	0.51 (0.27,0.95)	0.24 (0.09,0.66)	0.41 (0.15,1.09)	0.76 (0.58,1.00)	0.22 (0.15-0.32)	0.51 (0.36,0.73)	0.13 (0.05,0.38)	0.18 (0.12,0.26)

Prevalence of MDRTB across Europe



Empiric RHZ therapy across Europe

