When to start ART
in patients with opportunistic infections

Ole Kirk

Early ART initiation in patients with opportunistic infections (OIs)?

Pro:

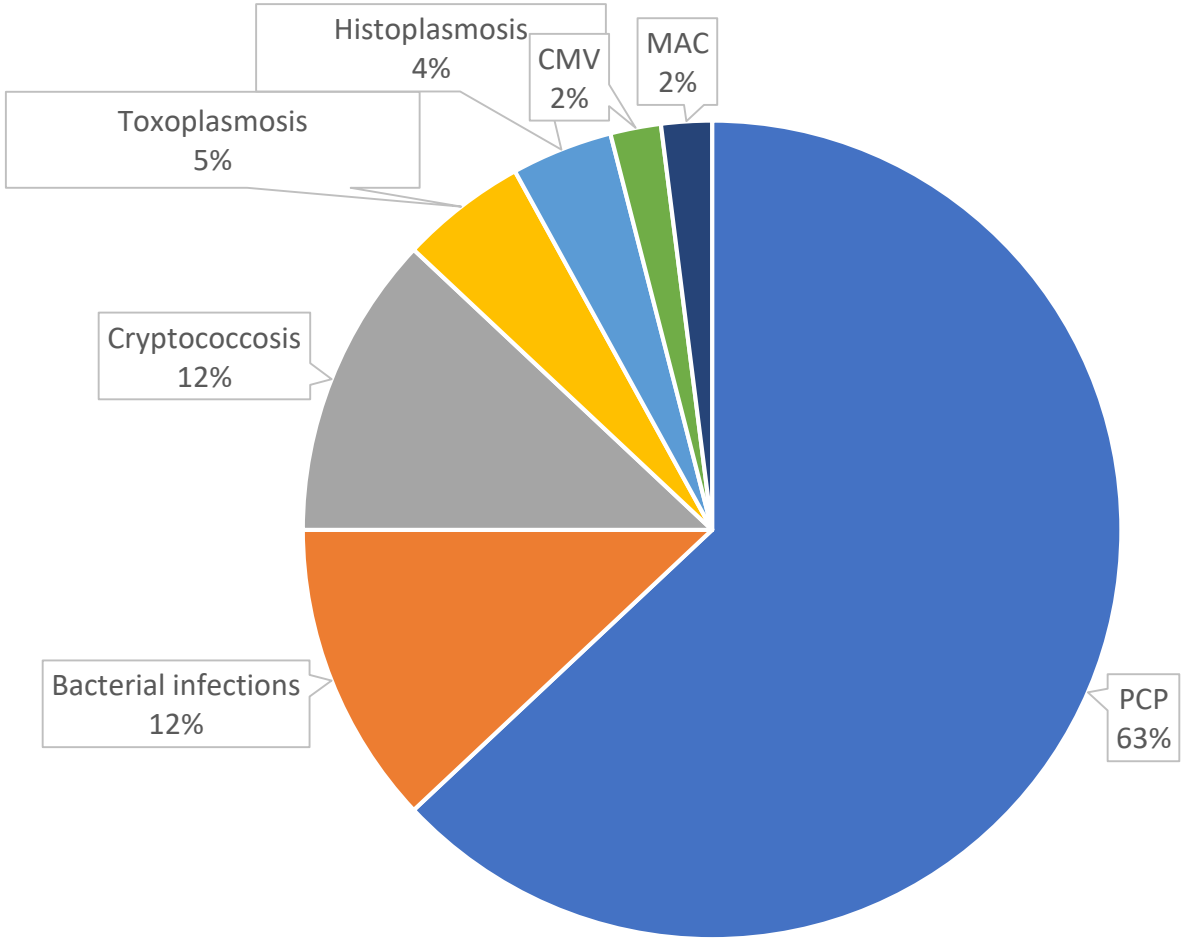
- lower risk of HIV disease progression/death in patients with CD4 <50-100 cells/mm^3

Con:

- risk of immune reconstitution inflammatory syndrome (IRIS)
- PK interactions
- higher pill burden
- overlapping toxicity

Early v. deferred ART in patients with OIs

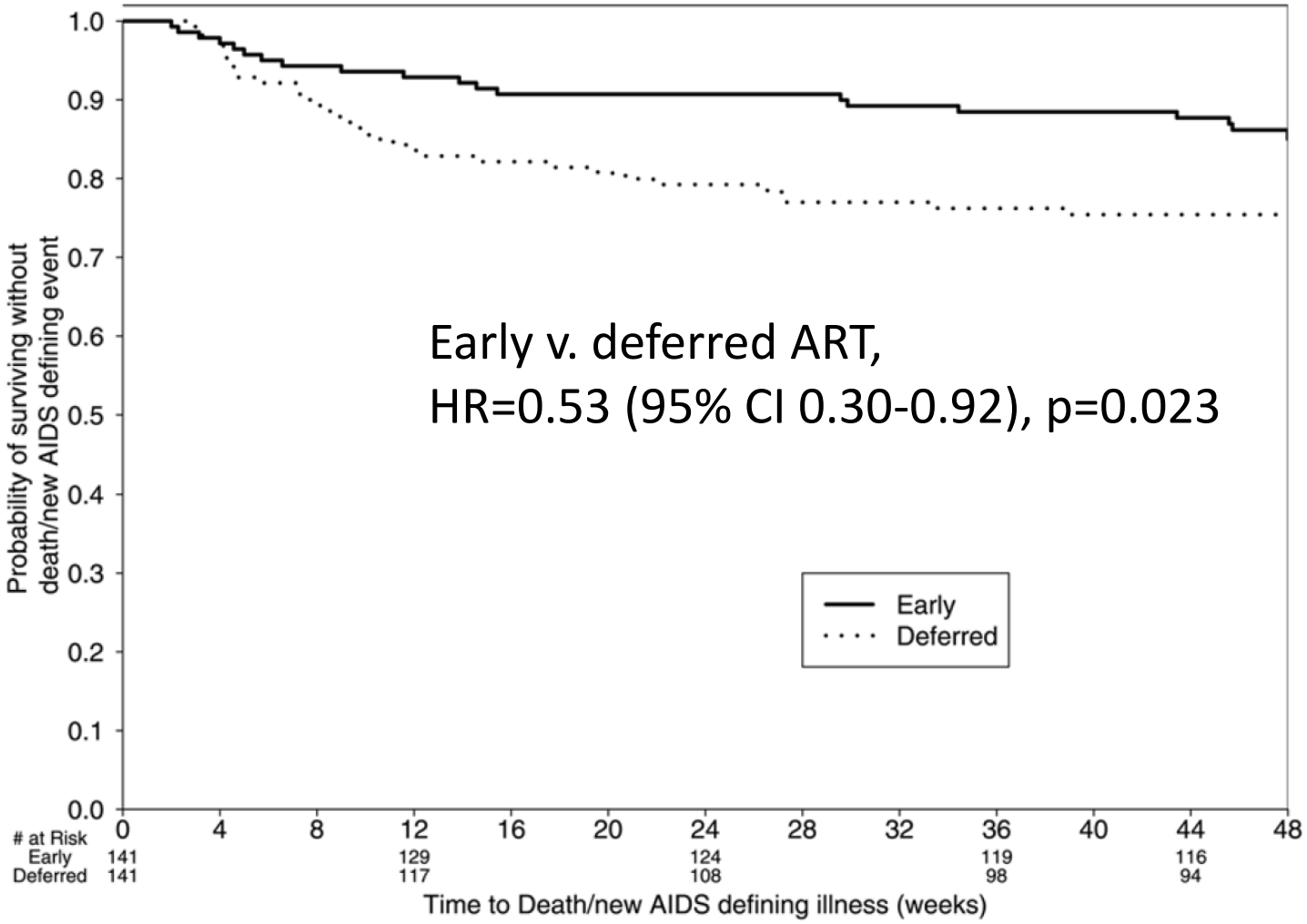
- **Early ART:** given within 14 days of starting acute OI treatment
- **Deferred ART:** given after acute OI treatment is completed
- Median time from initiation of OI treatment to initiation of ART:
  - Early ART: 12 (IQR, 9–13) days
  - Deferred ART: 45 (41–55) days

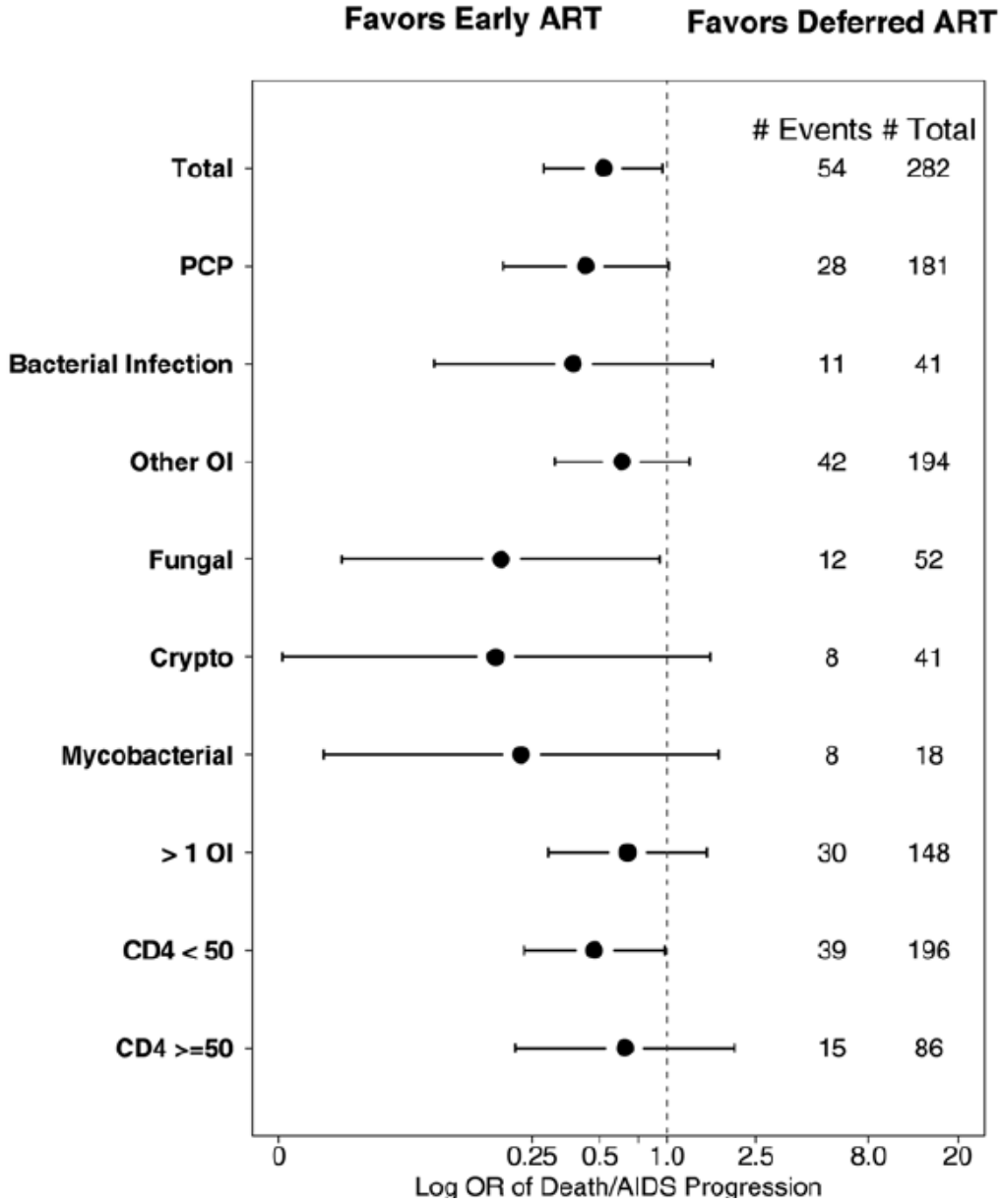


Subjects with/on treatment for TB excluded

Zolopa, *PLoS ONE* 2009

Early v. deferred ART in patients with OIs

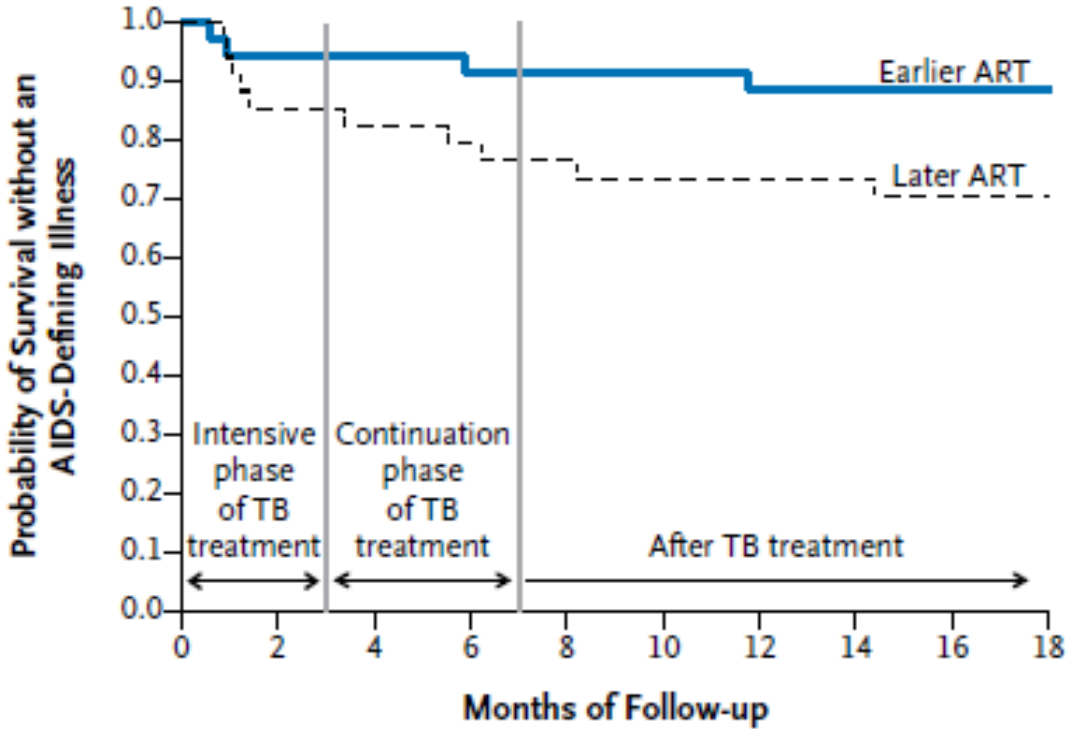




Zolopa, *PLoS ONE* 2009

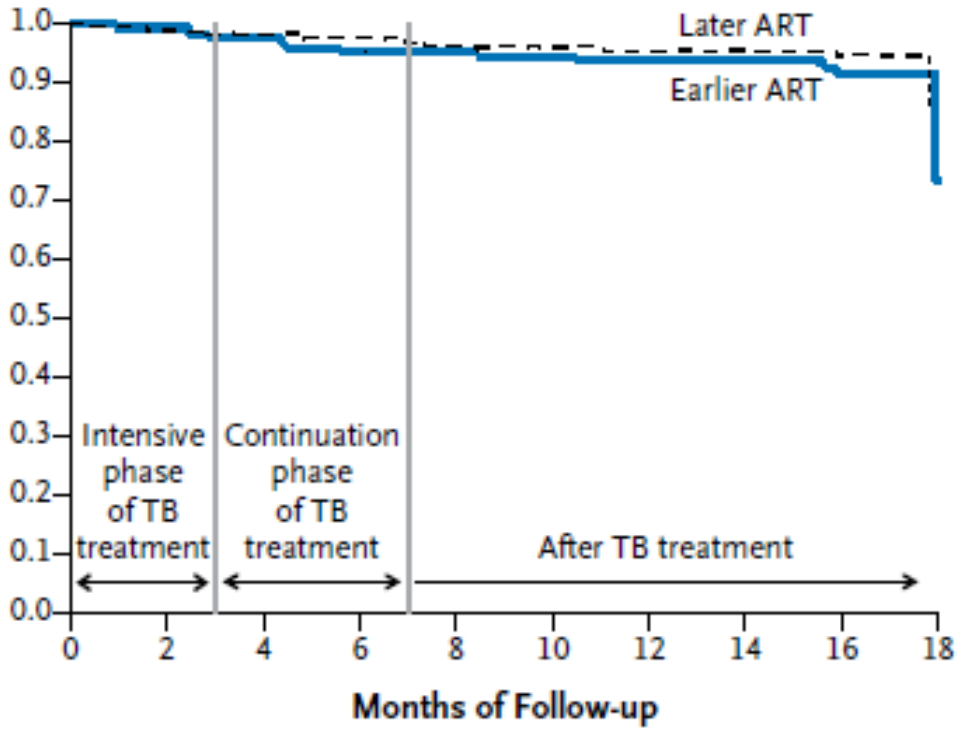
Tuberculosis and ART

CD4 <50 cells/mm^3



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/mm^3

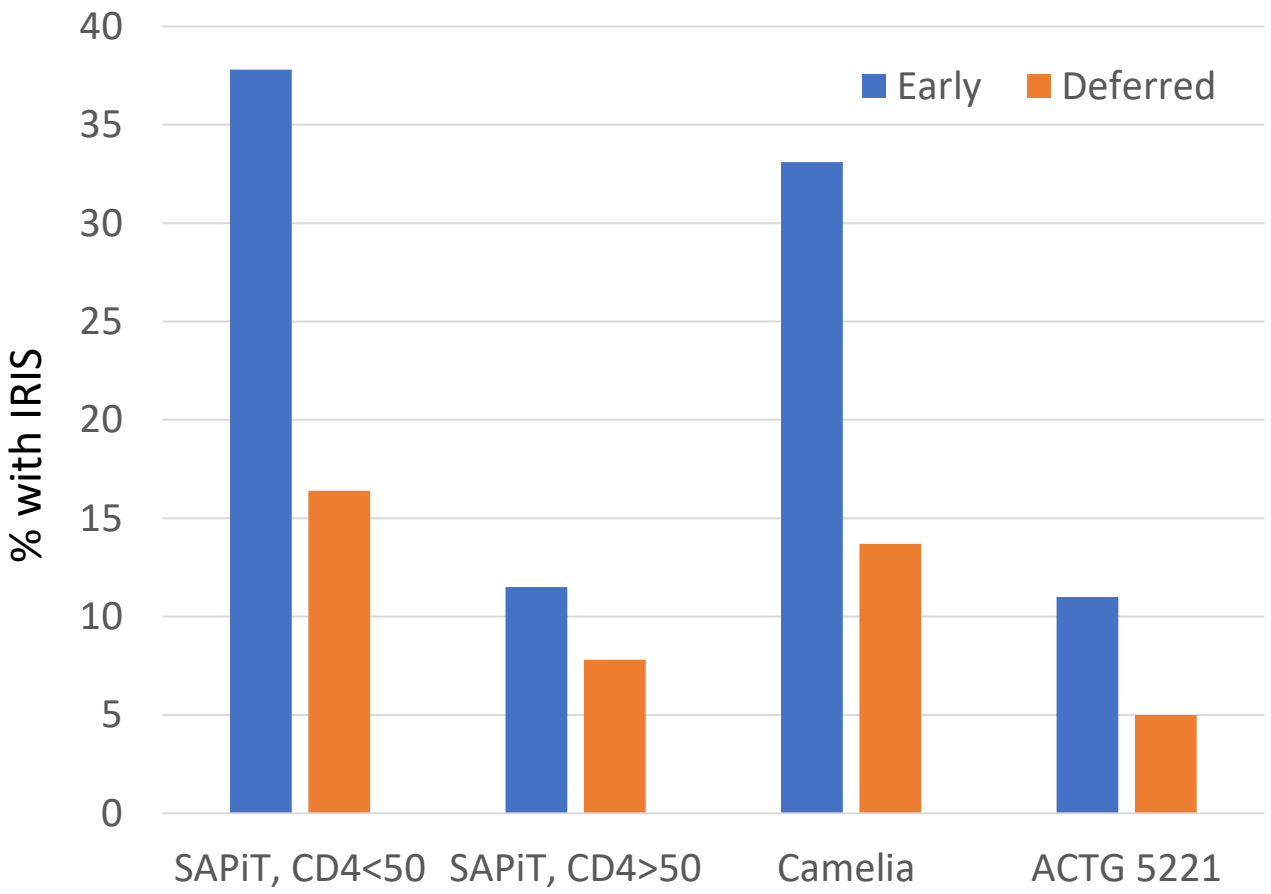


Earlier ART	177	166	159	149	145	140	137	133	125	121
Later ART	180	164	153	148	138	134	129	126	124	119

Significant interaction between therapy group and CD4 cells; p=0.03

Abdool Karim, *NEJM* 2011, Havlir *NEJM* 2011 & Blanc *NEJM* 2011

TB-IRIS – role of early initiation of ART



- SAPiT:
  - CD4 <50 cells/mm^3:
    - HR=4.71 (1.48-19.64), p=0.01
  - CD4 ≥50 cells/mm^3:
    - HR=2.18 (1.12-4.47), p=0.02
  - 2 deaths in the early-ART group
- Camelia:
  - HR=2.51 (1.78-3.59), p<0.001
  - 6 TB-IRIS-associated deaths in early-ART group
- ATCG:
  - no deaths

Abdool Karim, *NEJM* 2011, Havlir *NEJM* 2011 & Blanc *NEJM* 2011

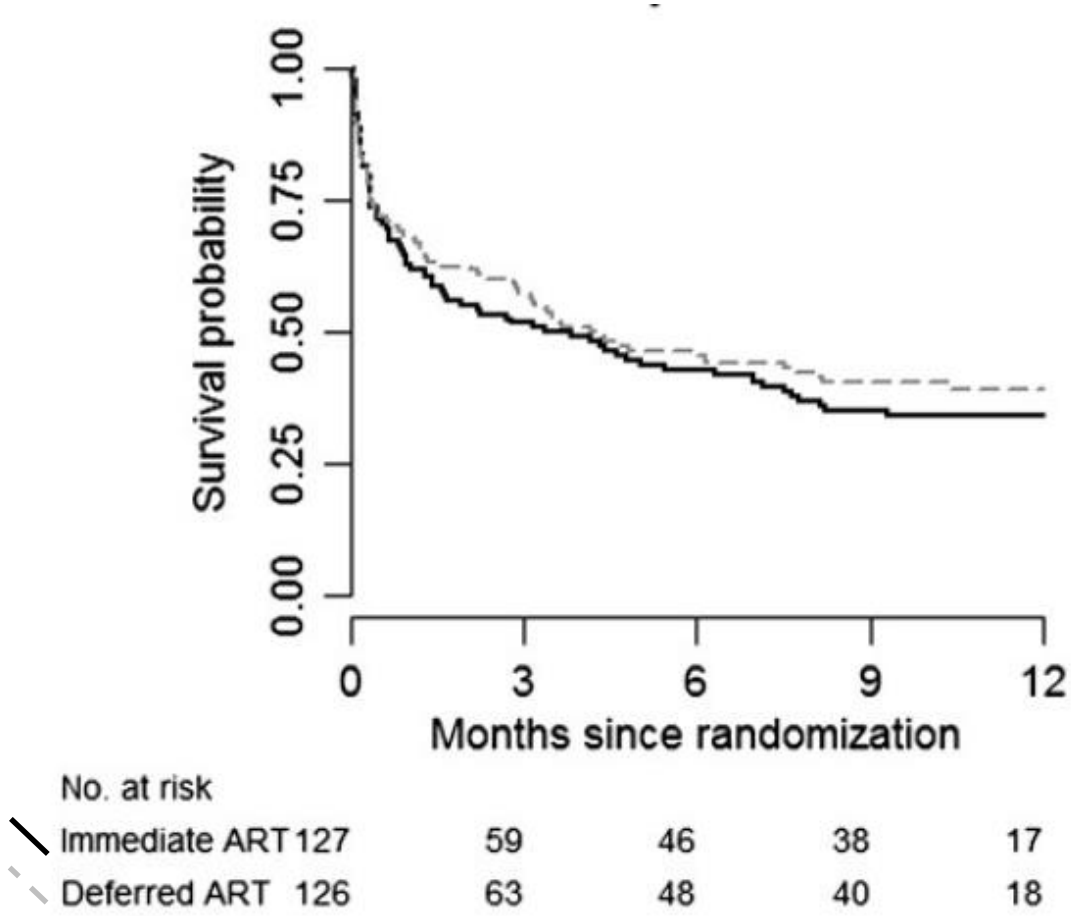
TB meningitis and ART

- 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%

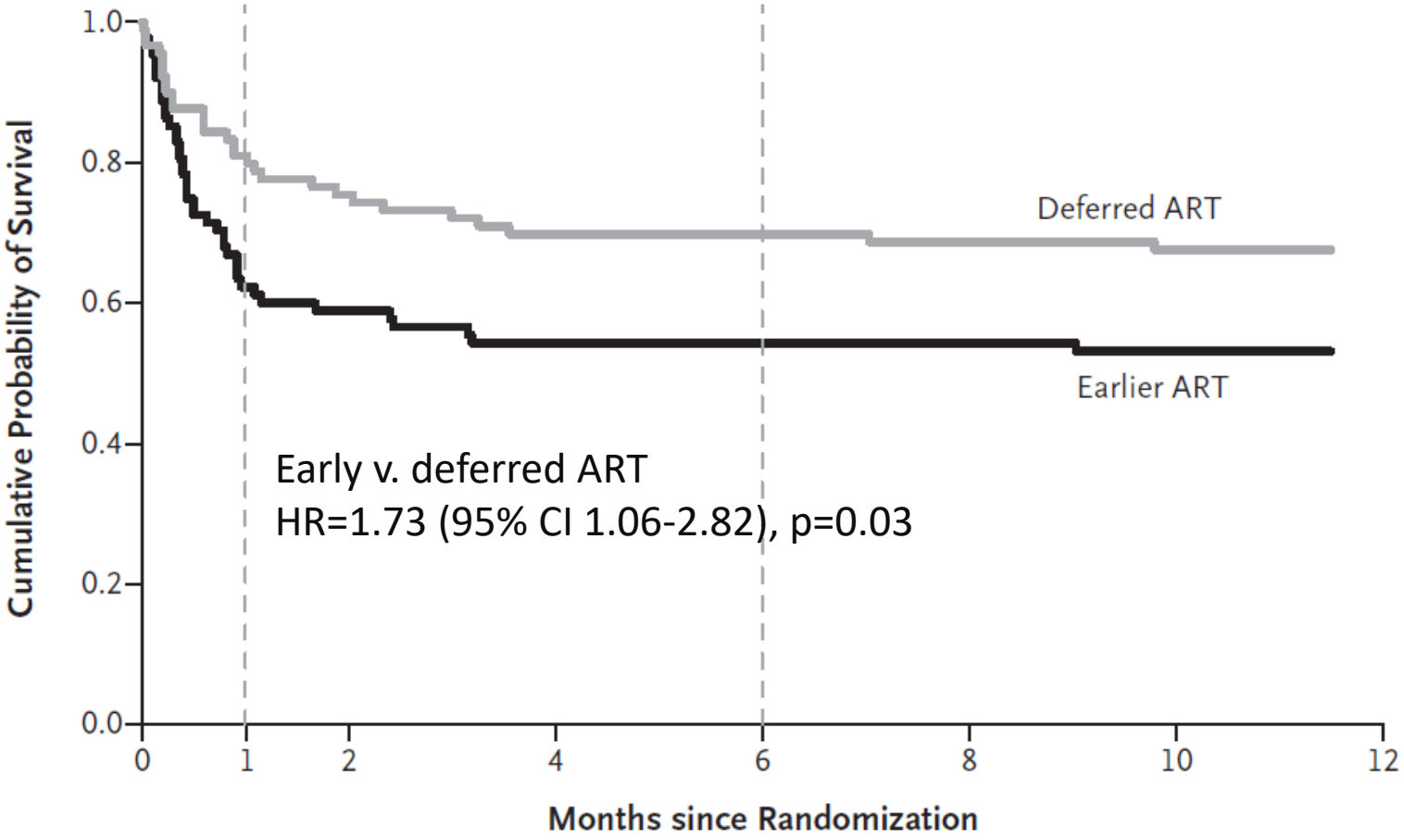
Grade 4 adverse events:
- Immediate: 80.3%
- Deferred: 69.0%

- p=0.04, but no difference in neurological events



Török, *CID* 2011

Cryptococcal meningitis and ART



No. at Risk							
Earlier ART	88	54	51	47	47	46	42
Deferred ART	89	72	67	62	62	61	59

- Randomization after a median of 8 days of amphotericin B + fluconazol treatment:
- - earlier ART initiation (1-2 weeks after diagnosis)
- - deferred ART initiation (5 weeks after diagnosis)

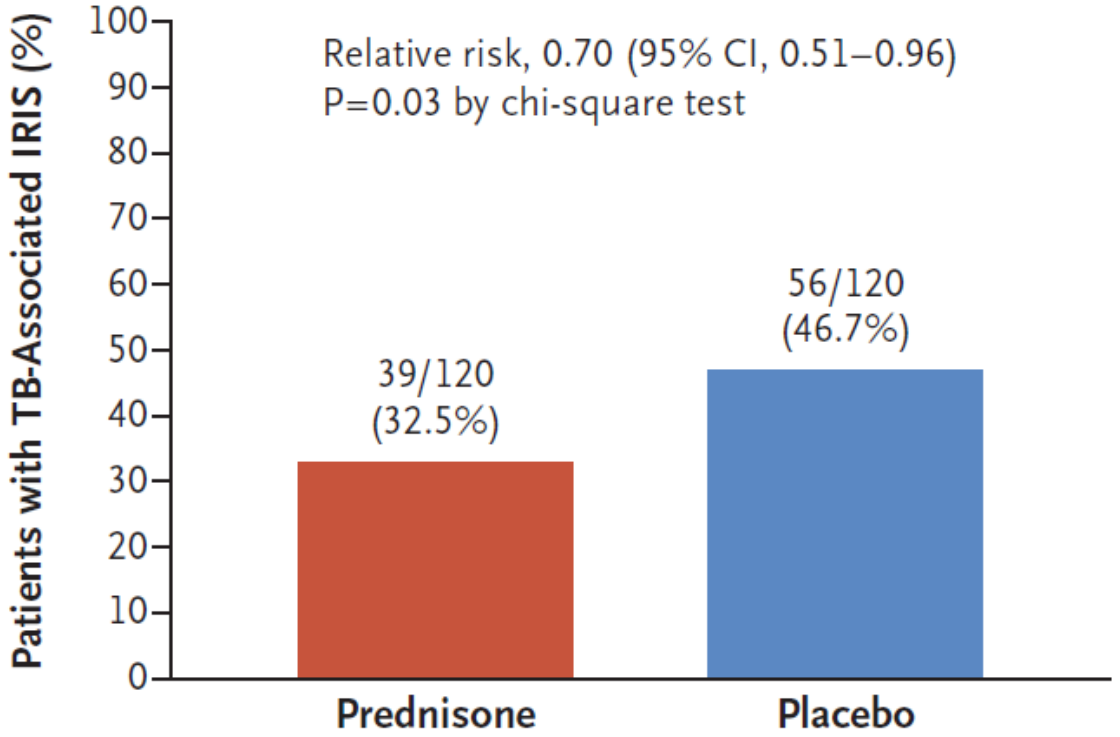
- Median time from diagnosis of CM to ART-initiation:
  - early: 9 (IQR: 8-9) days
  - deferred: 36 (IQR: 34-38) days

- No significant difference in IRIS and adverse events

Boulware, *NEJM* 2016, Makadzange *CID* 2010

IRIS and early ART

- Role of steroid as preventive therapy?
  - TB ✓
- Components of ART regimen?
  - Integrase inhibitors ✓



Meintjes NEJM 2018; Kityo *PLOS Medicine* 2018

Drug-drug-interactions and overlapping toxicity – influence of early ART

- **Drug-drug interactions (DDIs)**
  - Most DDIs present in relation to both early-ART and deferred ART
  - Rifampicin!
  - Tenofovir-TAF, dolutegravir etc

- **Overlapping toxicity?**
- Not a clinically important issue
- In general, no difference in incidences of adverse events between early and late ART

Havlir *NEJM* 2011, Blanc *NEJM* 2011, Cerrone CROI 1018 abstract 28LB, Dooley CROI 2018 abstract 33

EACS Guidelines - when to start ART?

	CD4 count	Initiation of ART	Comments
General	Any	As soon as possible and within 2 weeks after starting treatment for the opportunistic infection	
TB	<50 cells/mm^3	As soon as possible and within 2 weeks after starting TB treatment	Threshold of 100 cells/mm^3?
	≥50 cells/mm^3	As soon as possible, but can be delayed until 8-12 weeks after starting TB treatment	CD4 thresholds also apply for TB meningitis
Cryptococcal meningitis		Defer initiation of ART for at least 4 weeks (6-10 weeks in severe meningitis?)	
CMV end organ disease	Any	A delay of ART up to 2 weeks can be considered	Chorioretinitis and encephalitis due to risk of IRIS

Package of care interventions for Advanced HIV Disease, WHO recommendations 03/2018

AREAS FOR THE PACKAGE	INTERVENTION	CD4 CELL COUNT	ADULTS AND ADOLESCENTS	CHILDREN
Screening and Diagnosis	Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients	Any	Yes	Yes
	Urine LF-LAM* for TB diagnosis in patients with symptoms and signs of TB	≤100 cells/mm3 Or at any CD4 cell count value if seriously ill	Yes	Yes**
	Cryptococcal antigen (CrAg) screening***	≤100 cells/mm3 ****	Yes	No
		≤200 cells/mm3****	Yes	No
Prophylaxis and pre-emptive Treatment	Co-trimoxazole prophylaxis	≤350 cells/mm3 or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial Infections	Yes	No
	TB preventive treatment §	Any	Yes	Yes
	Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis	≤200 cells/mm3****	Yes	Not applicable (Screening not advised)
ART initiation	Rapid ART initiation	Any	Yes	Yes
	Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis	Any	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to advance disease care package, including home visits if feasible	< 200 cells/mm3	Yes	Yes

https://apps.who.int/iris/bitstream/handle/10665/260446/WHO-CDS-HIV-18.3-eng.pdf?sequence=1&isAllowed=y