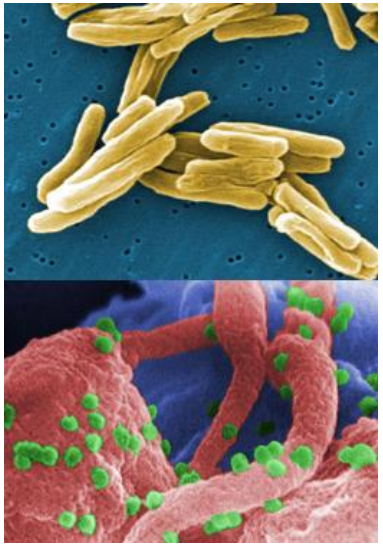
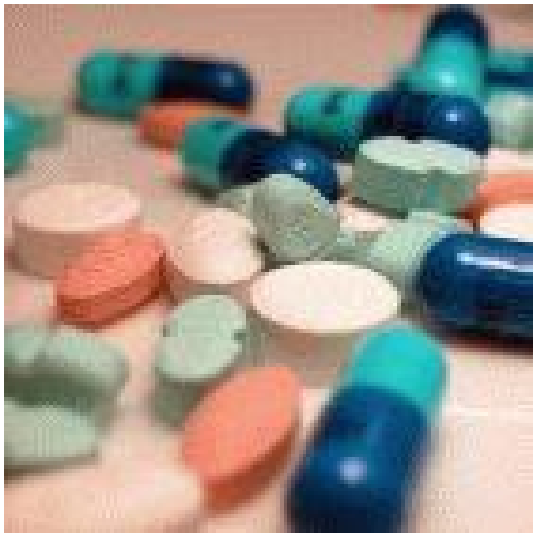
New data in HIV/TB and role of the Working Group

Beijing, November 11, 2011

What is new in …

- Timing of ART start in TB patients
- Use of new ART drugs in TB patients
- Use of ART to prevent TB





Reluctance to start ART in TB patients

1.CD4 high and ART not needed

2. ART needed but not it is not urgent because co-treatment

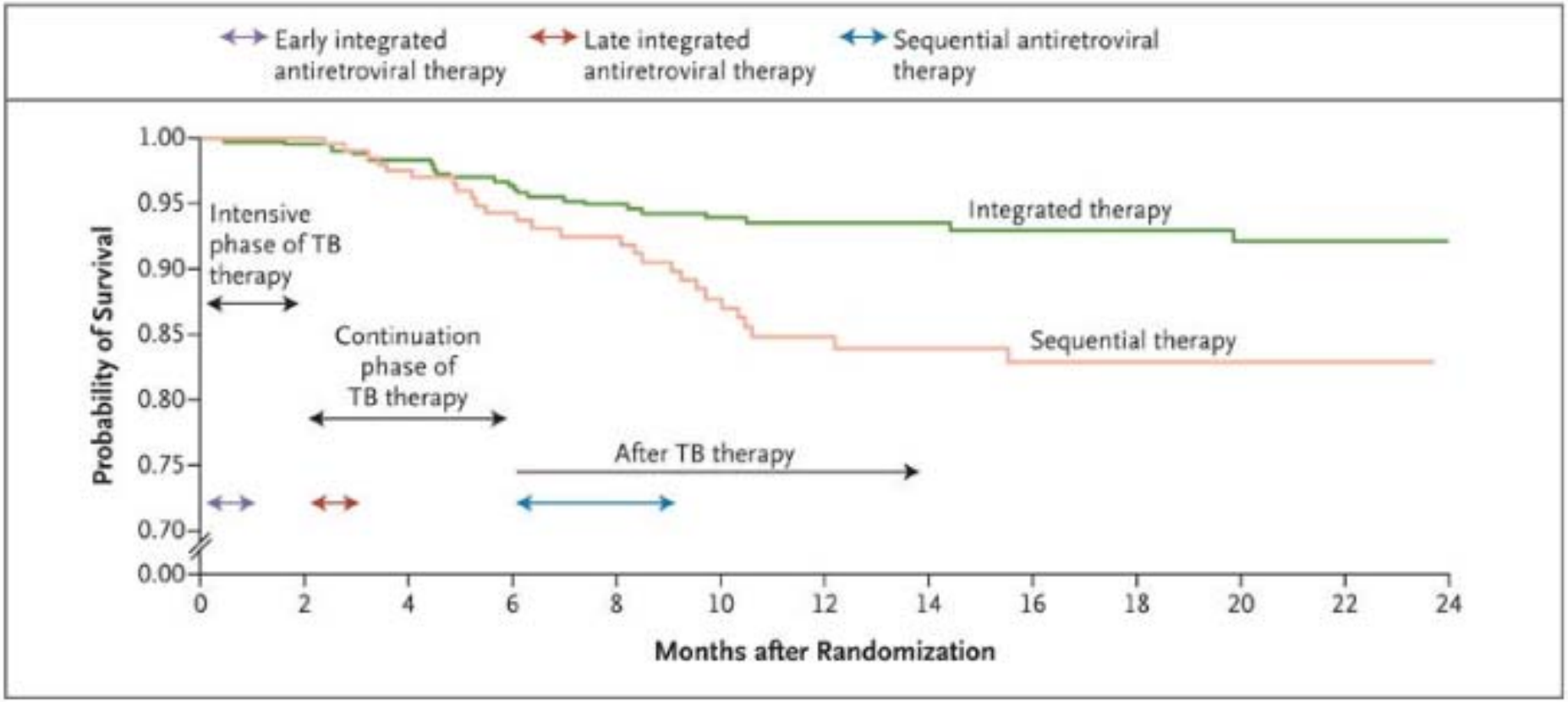
- Increases risk for TB immune reconstitution disease
- Increases drug toxicity from ART and TB
- Could adversely affect adherence for either TB or HIV
- Could reduce ART efficacy because of drug interactions

SAPIT Study

- **642 HIV+ adults in Durban, South Africa**
- **AFB smear + pulmonary TB**
- **CD4 <500**
- **Randomized to**
  - ART during TB therapy at 2 weeks
  - ART during TB therapy after induction
  - ART after TB therapy completion

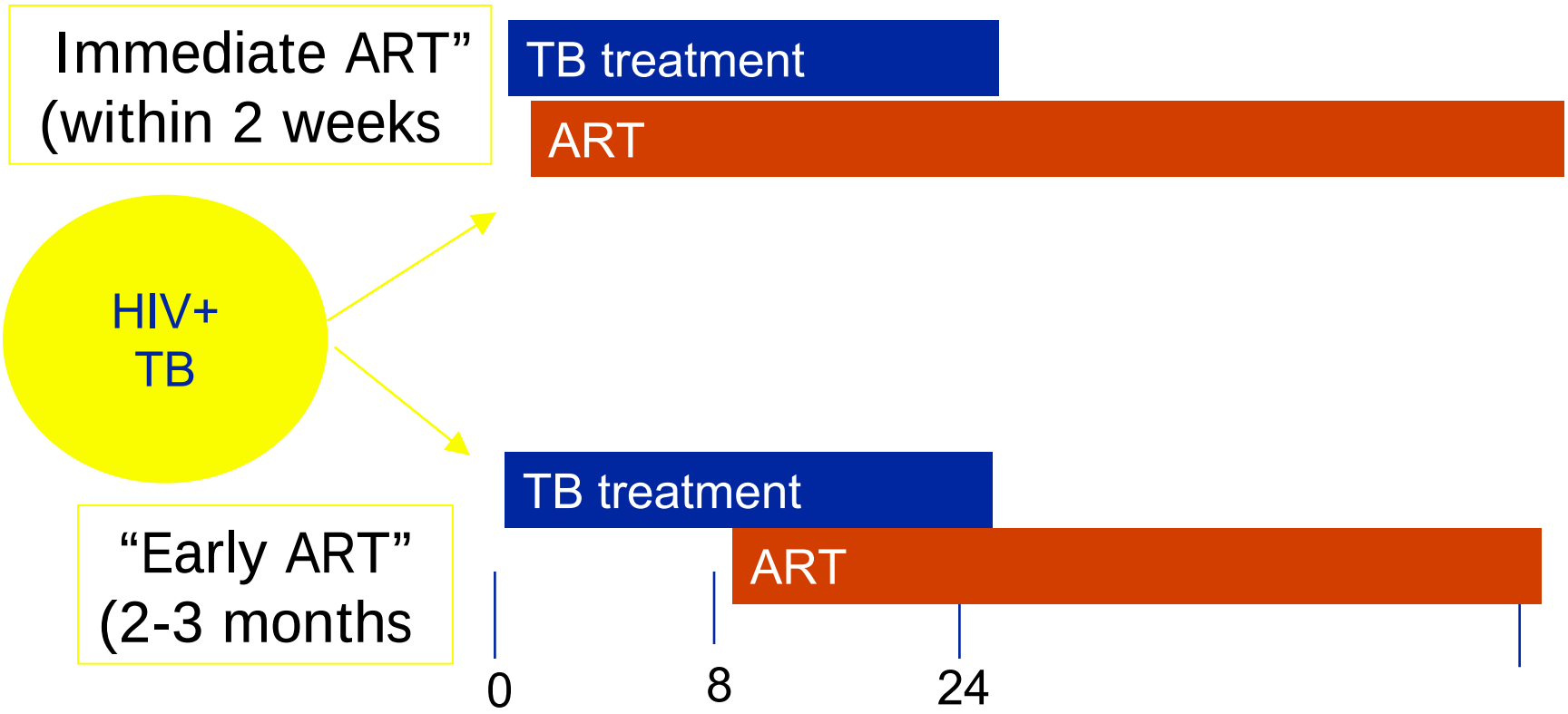
Karim S, et al. New Engl J Med 2010

Mortality reduced when ART started during vs. after TB treatment: SAPIT



Karim S, et al. New Engl J Med 2010

When should ART be started during TB treatment? 3 RCTs-- CAMELIA, STRIDE, and integrated arms of SAPIT



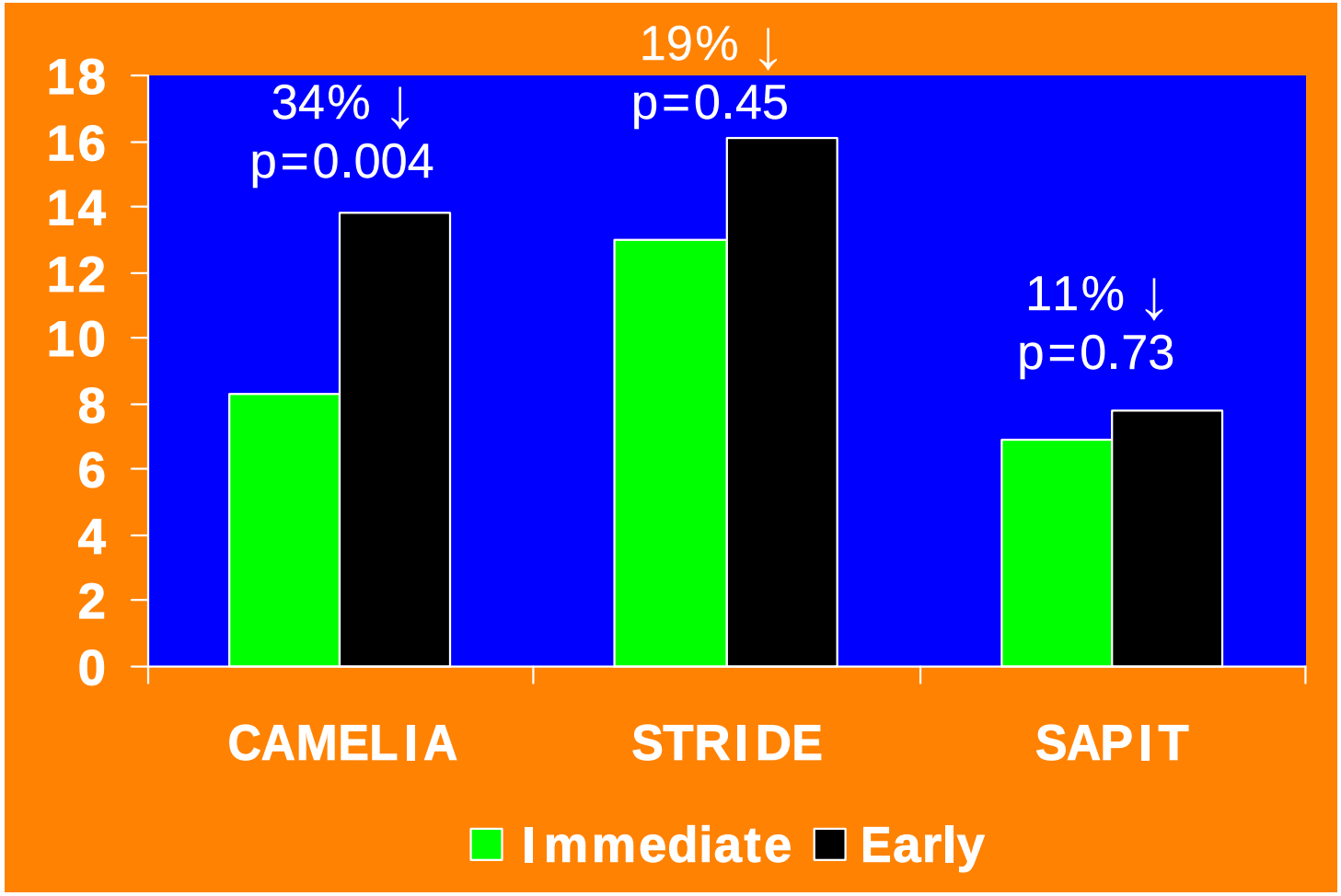
Blanc, Vienna, 2010, Havlir, CROI, 2011, Karim , CROI, 2011

Key characteristics of trials of timing of ART during TB treatment

Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint
CAMELIA	Cambodia	Smear +, CD4 < 200	25 (10 - 56)	Death
STRIDE	Multi-national	Clinical TB, CD4 < 250	77 (36 – 145)	AIDS or death
SAPIT	South Africa	Smear +, CD4 < 500	150 (77 – 254)	AIDS or death

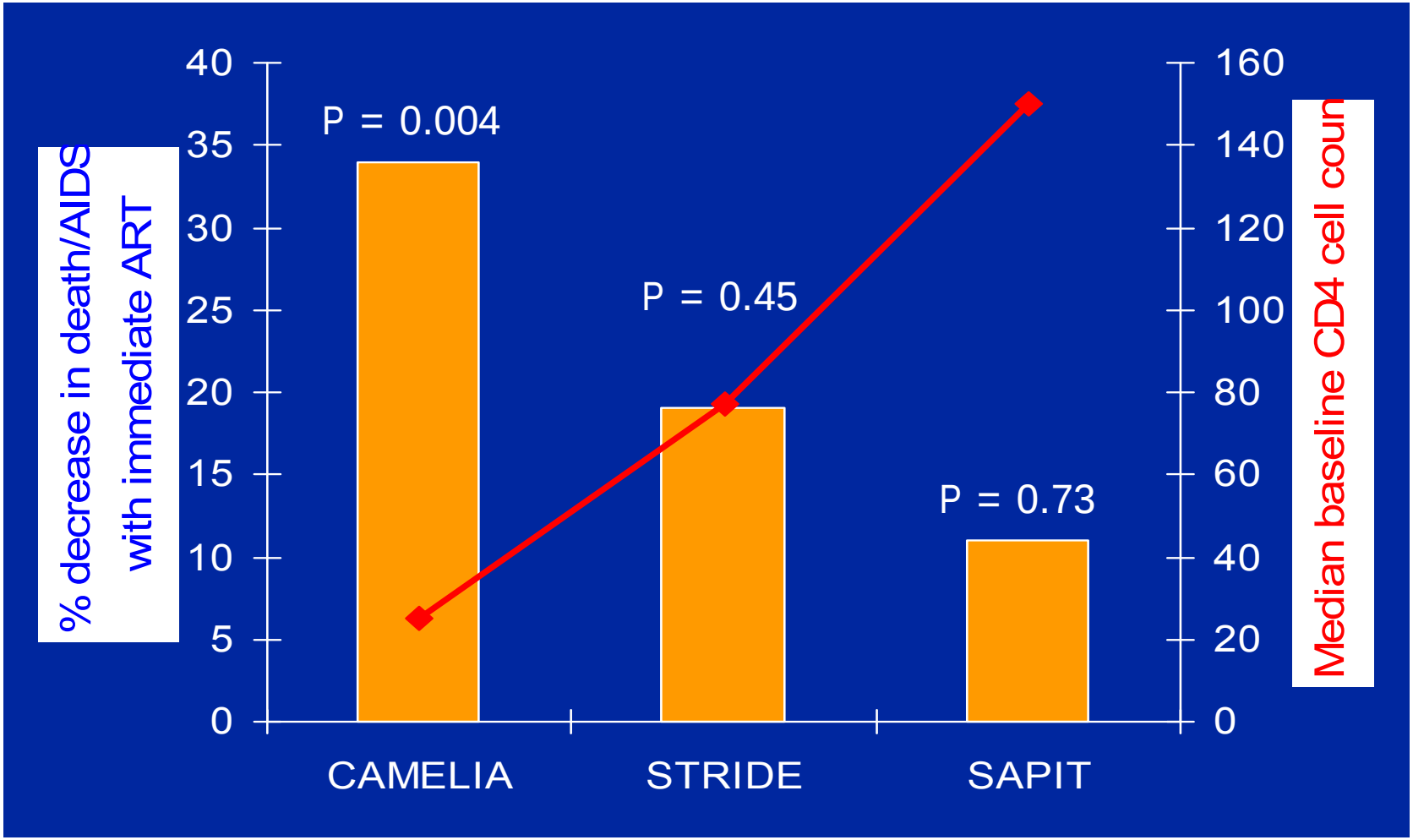
Blanc, Vienna, 2010, Havlir, CROI, 2011, Karim , CROI, 2011

Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)



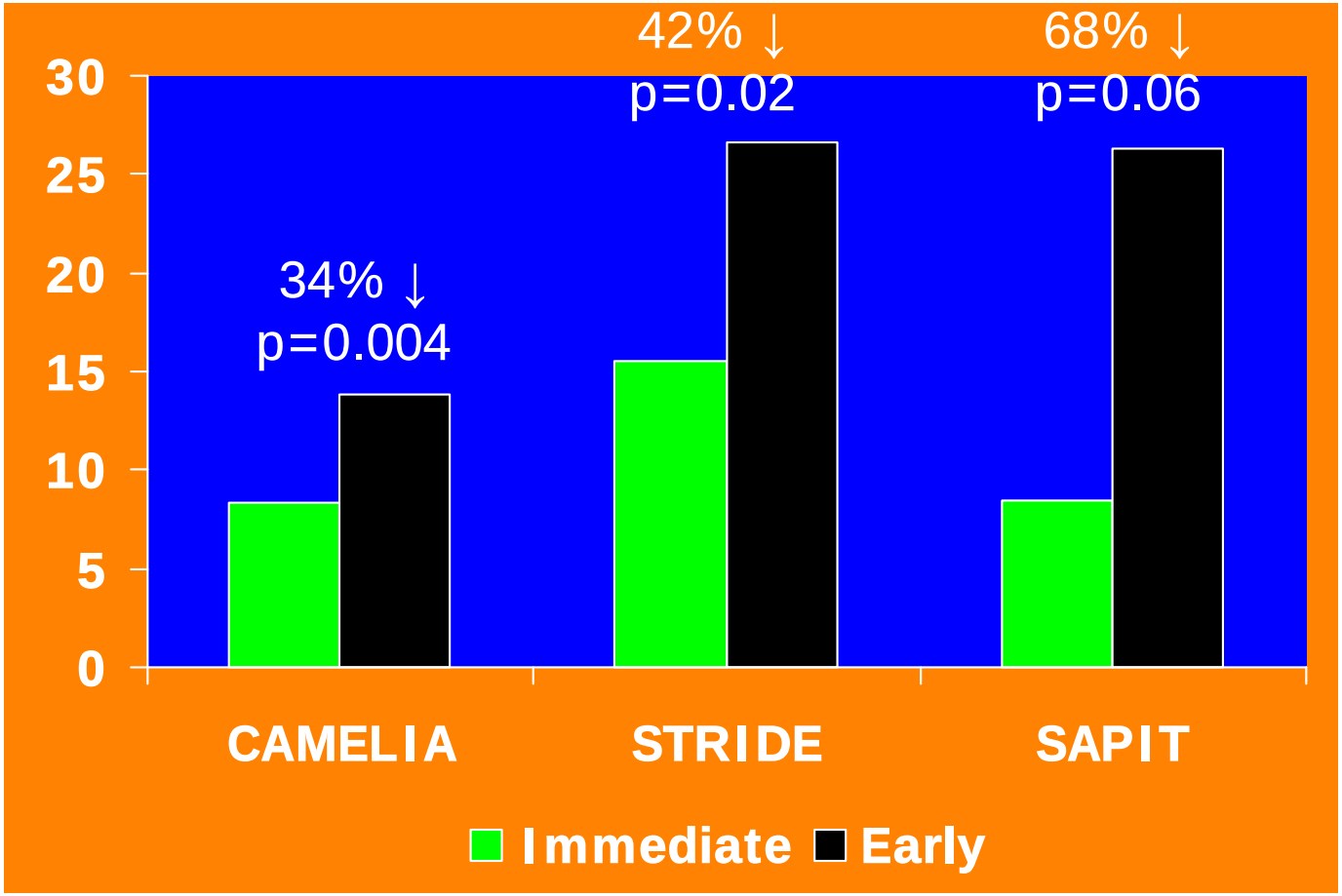
Blanc, Vienna, 2010, Havlir, CROI, 2011, Karim , CROI, 2011

Greater reduction in mortality at lower CD4



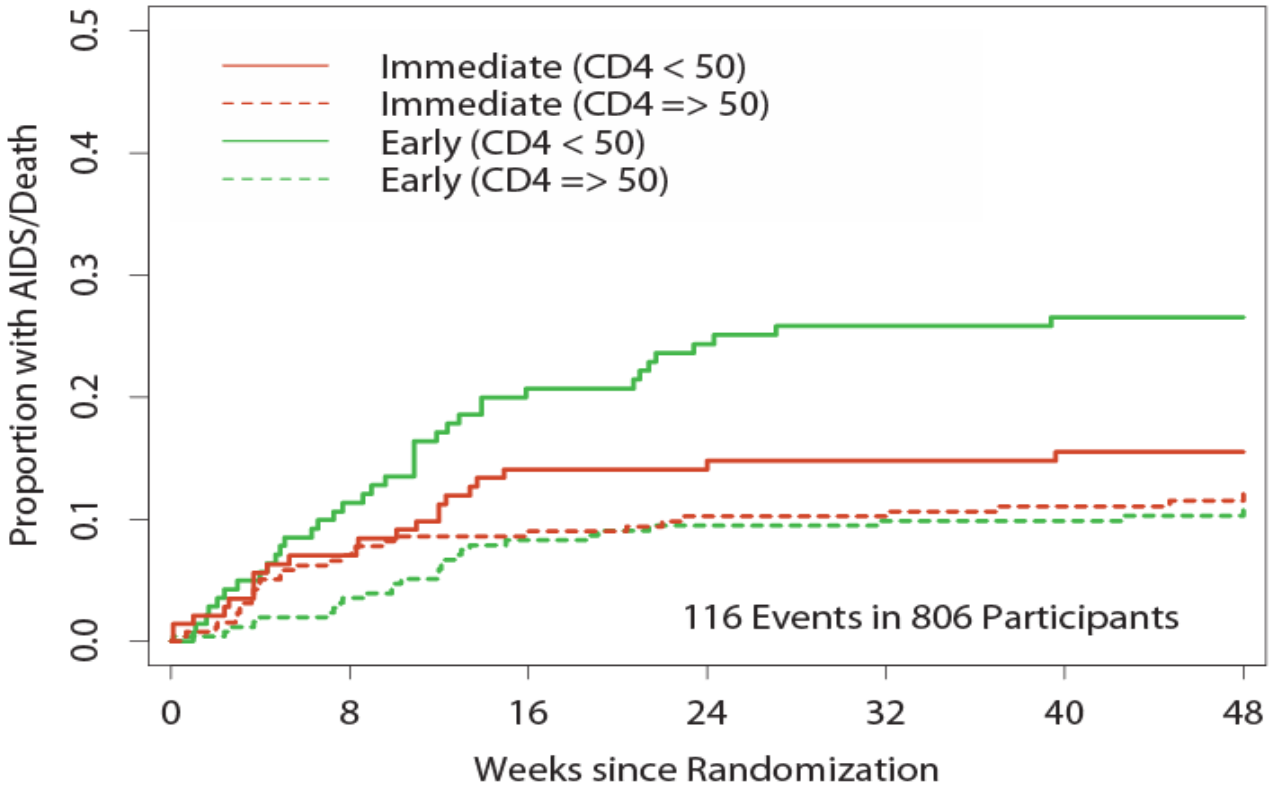
Blanc, Vienna, 2010, Havlir, CROI, 2011, Karim , CROI, 2011

All studies showed significant reduction in death/AIDS among those with CD4 < 50



Blanc, Vienna, 2010, Havlir, CROI, 2011, Karim , CROI, 2011

Timing is everything – why does a 6 week delay in ART matter so much?

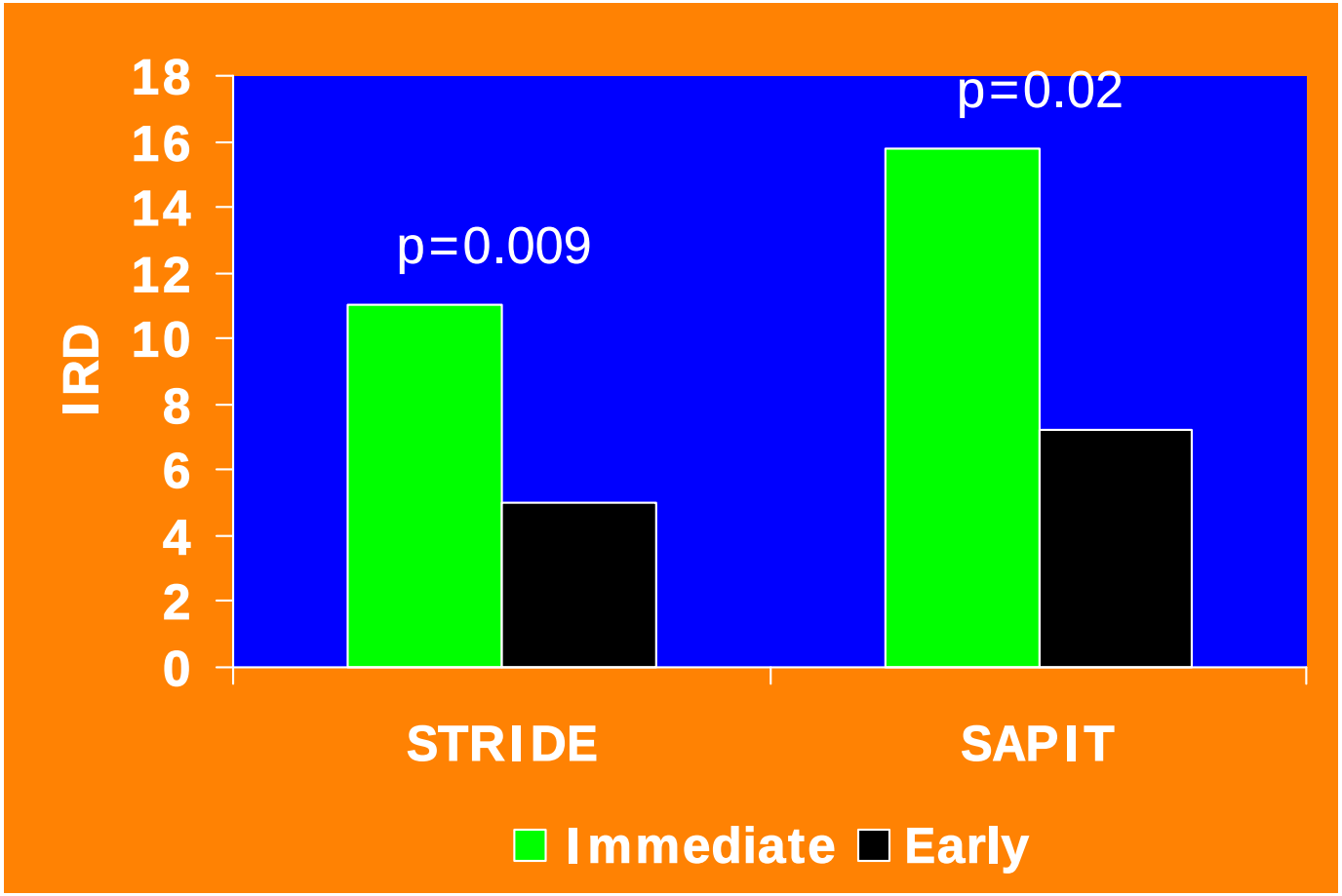


N at risk						
Immed 405	368	346	341	335	324	226
Early 401	371	342	329	325	318	218

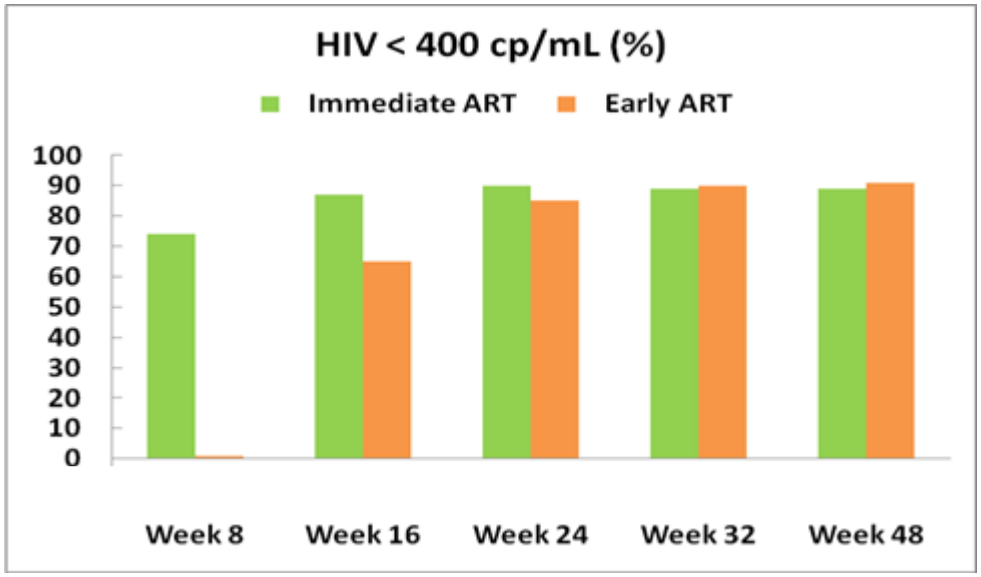
Are there any trade-offs or benefits for starting ART immediately ?

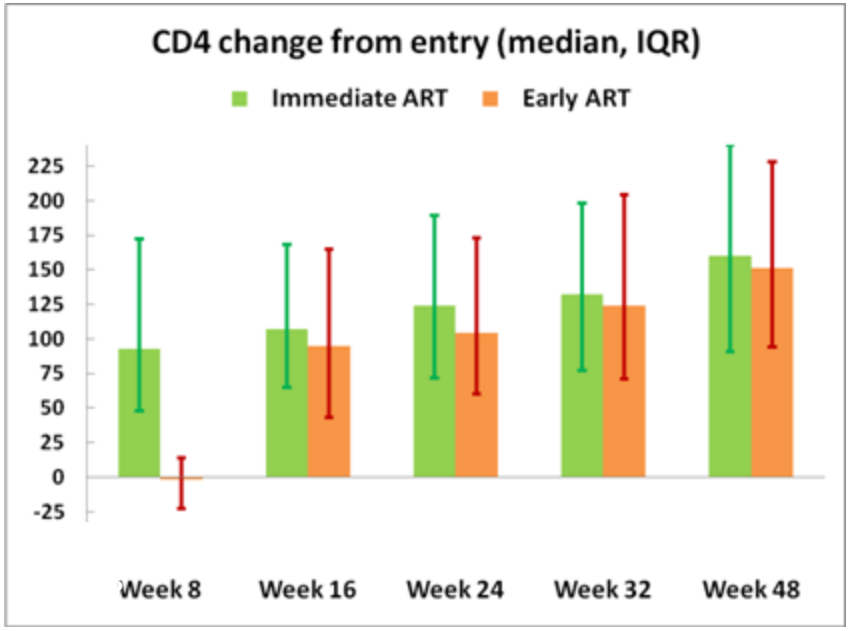
- Rates of Immune Reconstitution
- ART response
- Drug toxicity
- TB response

TB IRIS Greater in Immediate vs Early Arms



HIV RNA and CD4 Responses Similar at 48 weeks





HIV RNA suppression 74% at 48 weeks
No difference between arms

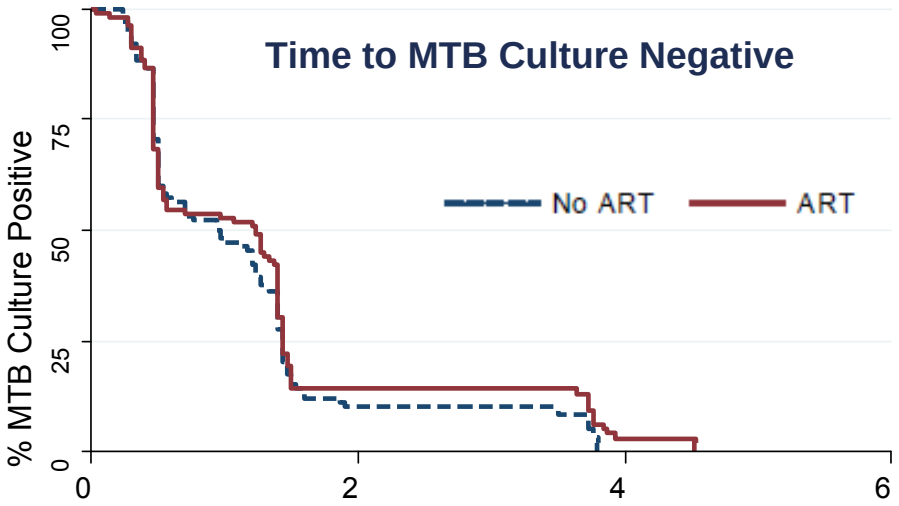
CD4 change from entry 156 cells/mm^3
No difference between arms

Toxicity similar between immediate and early arms

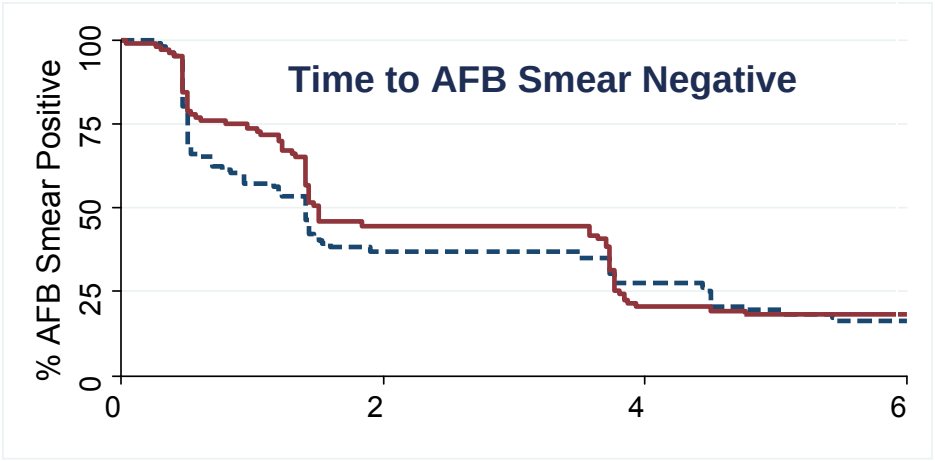
Event (%)	Immediate	Early	Total
Constitutional	8	8	8
Respiratory	4	4	4
Cardiac/Circulatory	3	2	2
Gastrointestinal	4	5	5
Skin	3	3	3
Neurological	5	7	6
ANC < 750/mm^3 *	9	17	13
Hemoglobin	7	5	6
Platelets	<1	3	2
Liver transaminase > 5x UNL	6	10	8
ANY	44	47	46

*P<0.05

Does immediate ART enhance clearance of TB?



No difference in time to TB culture negative



No difference to AFB smear negativity

Chamie, CID, 2010

What about other populations?

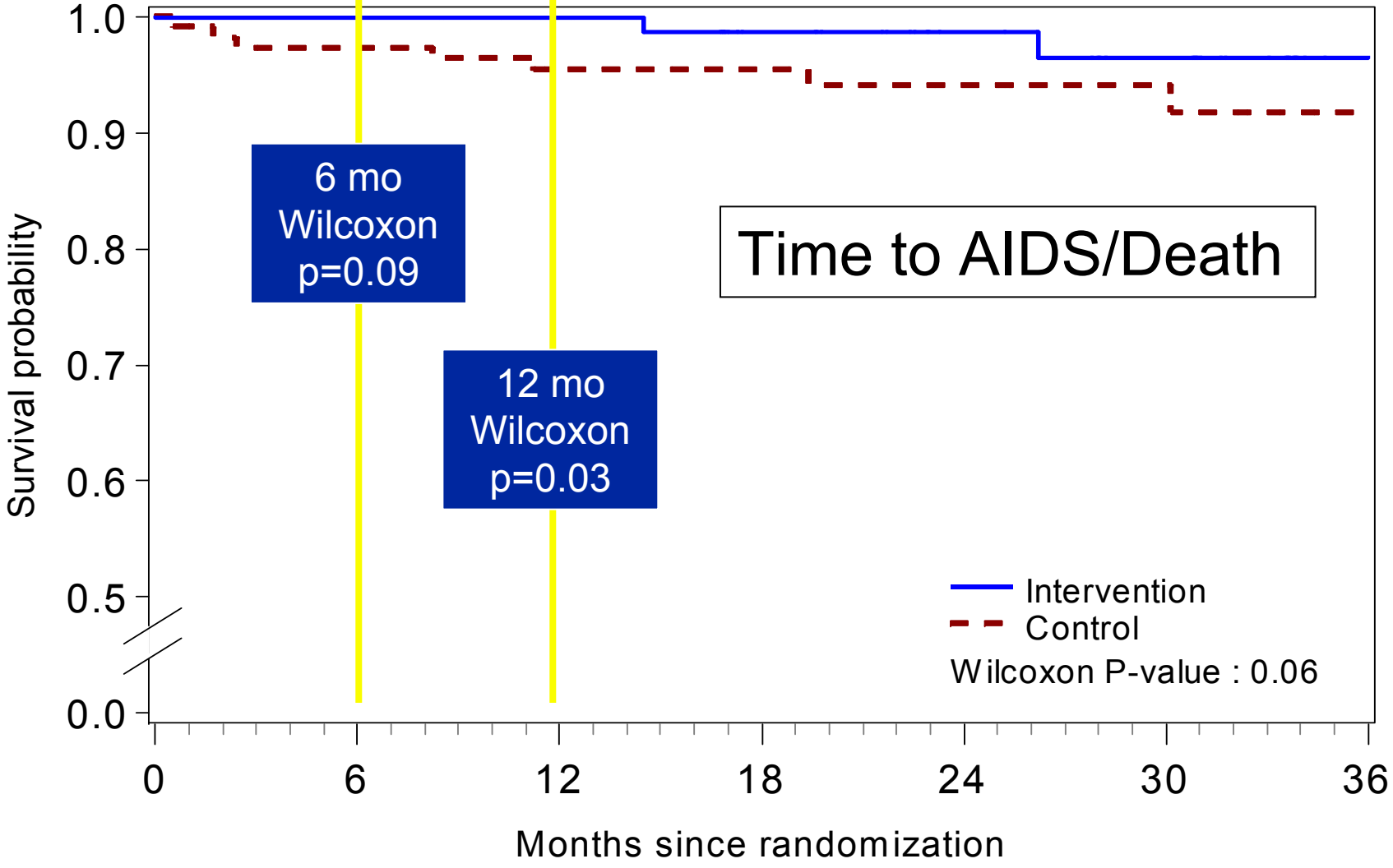
- High CD4 populations– PART study
- TB Meningitis– Viet Nam study
- Children– No data

PART Study– CD4>350 population

- **232 HIV+ adults in Kampala, Uganda**
- **Confirmed (AFB smear + or culture) TB**
- **CD4>350**
- **Randomized to ART (abacavir/3TC/zidovudine)**
  - Immediately for 6 months
  - Start when CD4 reaches 250

Nanteza, M, et al, JID, 2011

Time to clinical event slower with immediate ART start



Nanteza, M, et al, JID, 2011

TB Meningitis – Viet Nam study

Study Design

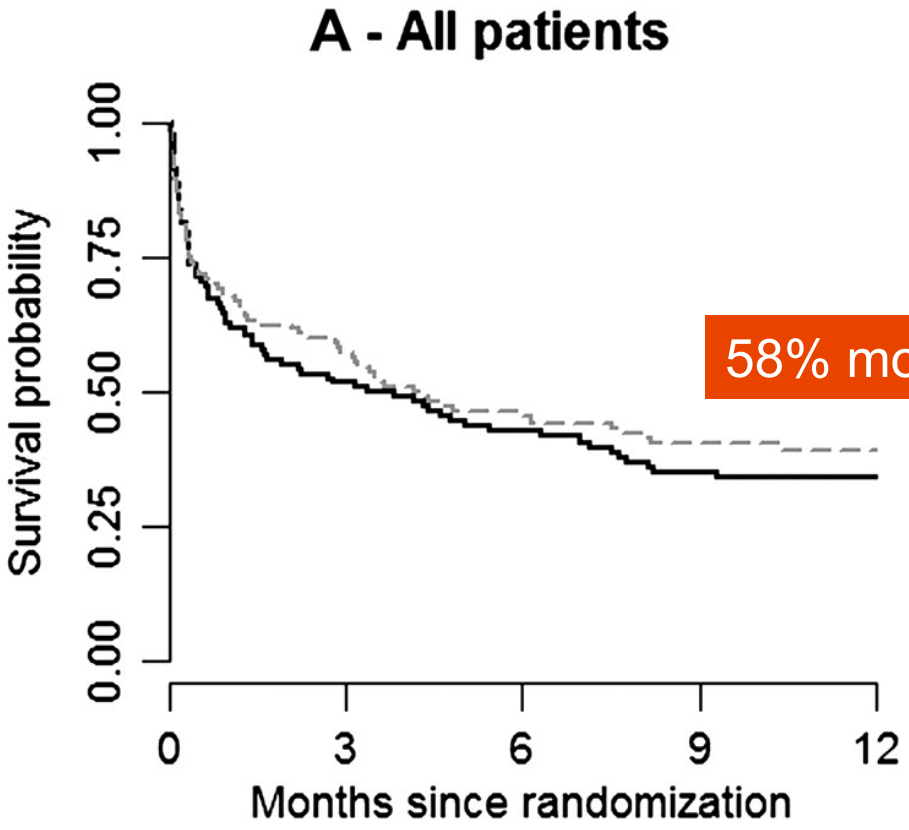
- **253 HIV+ adults**
- **TB meningitis**
- **Immediate or early (2 months) ART**
- **Adjunctive steroids**
- **Primary endpoint: mortality at 9 months**

Population

- **CD4 44 (16-84)**
- **TB cx + 60%**
- **TB MDR 5%**

Torok, CID, 2011

TB meningitis: No benefit to immediate vs. early ART



58% mortality at 9 months

Török M E et al. Clin Infect Dis. 2011;52:1374-1383

Torok, CID, 2011

Summary– Timing of ART

- **HIV and TB co-treatment reduces AIDS/mortality at all CD4**
- **It is safe to start ART at onset of TB**
- **There is mortality benefit to start ART at 2 (vs 8) weeks in 1 study when CD4 at start of TB < 200**
- **AIDS/Mortality benefit to start ART at 2 (vs 8 to 12) weeks only when CD4 at start of TB <50 in 2 other studies**
- **Immune reconstitution higher when CD4 lower and when ART is started earlier**
- **1 study showed no benefit of starting ART at 2 vs 8 weeks in HIV infected patients with TB meningitis**

ART and TB Drug Interactions– General Principles

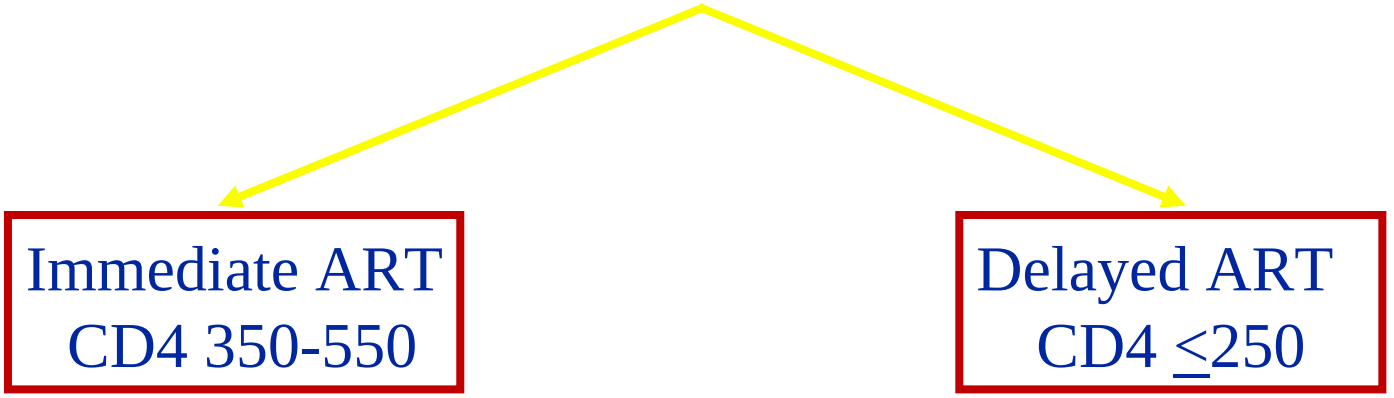
- Rifampin potent inducer of CYP3A4 and interacts with a number of ART drugs
- Rifabutin is a less potent inducer of CYP3A4 than rifampin and preferred TB rifamycin agent when rifampin cannot be used
- Using rifabutin complicates TB management because not co-formulated
- ART+ TB treatment regimens may call for adjustment of ART dose, rifabutin dose or both
- Data covering all possible drug interactions are incomplete

Dose Adjustments with ART and TB Medications

	Rifampin	Rifabutin
Efavirenz		Increase rifabutin
Nevirapine	No NVP lead in	
Etravirine		
Rilpivirine		Increase RPV
DRV/r or ATZ/r		Decrease rifabutin
Lopinavir/r	Increase LPV/r	Decrease rifabuin
Raltegravir	Increase RTG	
Maraviroc	Increase MVC	
Enfurvitide		

Efficacy and Safety of ART in HIV+: HPTN 052

HIV-infected subjects with CD4 350 to 550 cells/mm^3
Serodiscordant couples

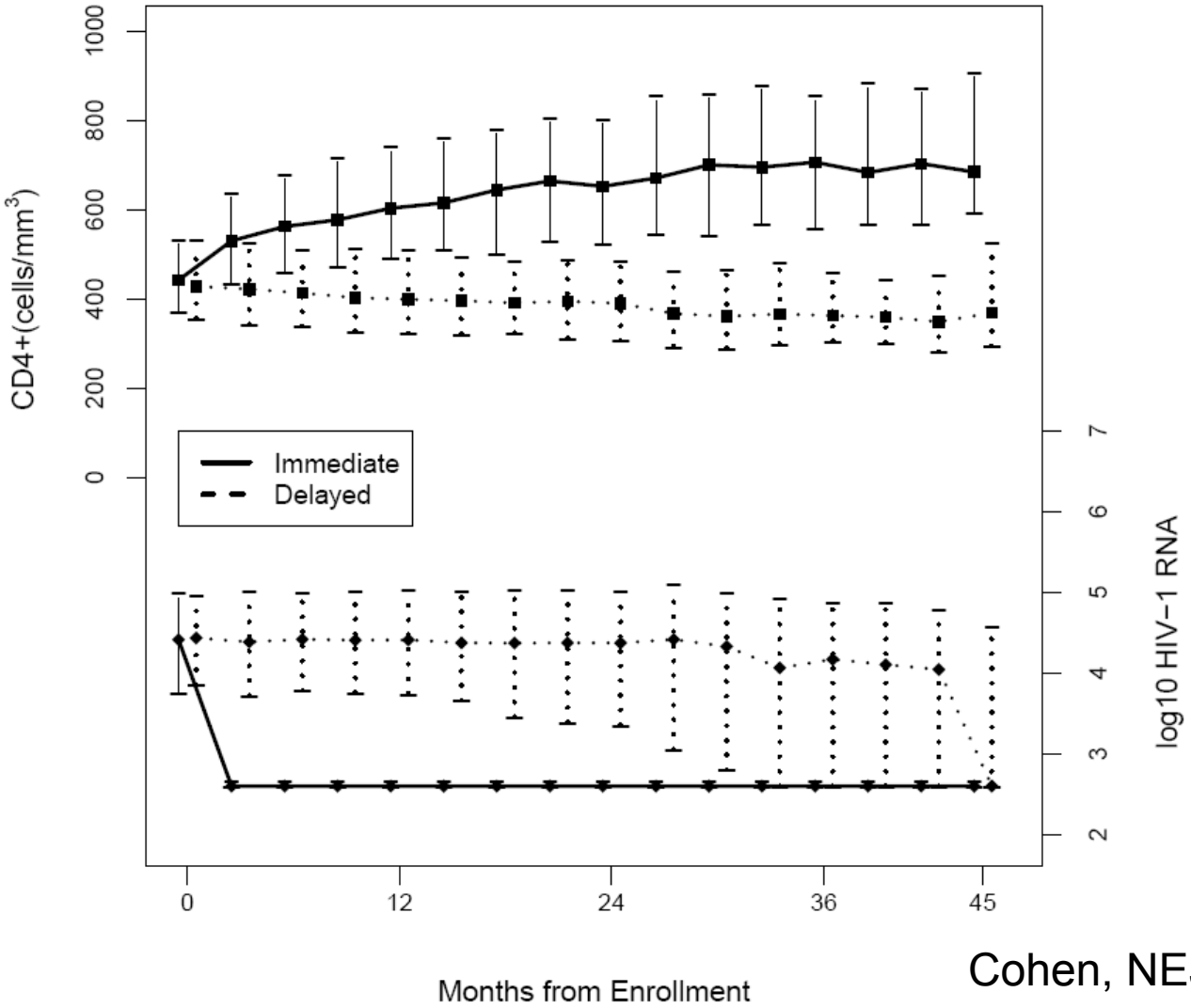


Primary Clinical Endpoint

WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

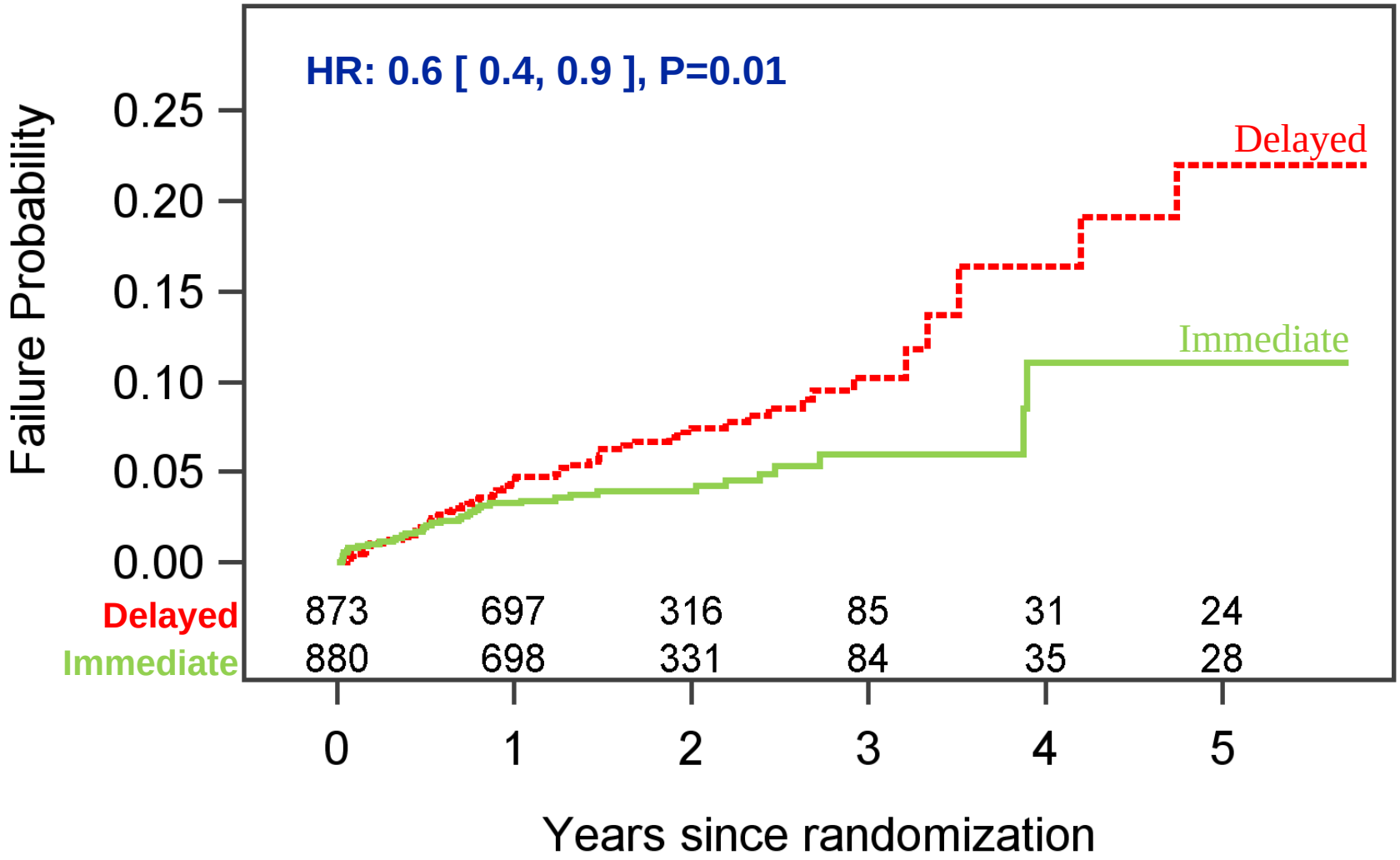
Cohen, NEJM, 2011

HIV-1 RNA and CD4 Over Time in HPTN 052 study



Cohen, NEJM, 2011

Probability of Death, AIDS or TB



Cohen, NEJM, 2011

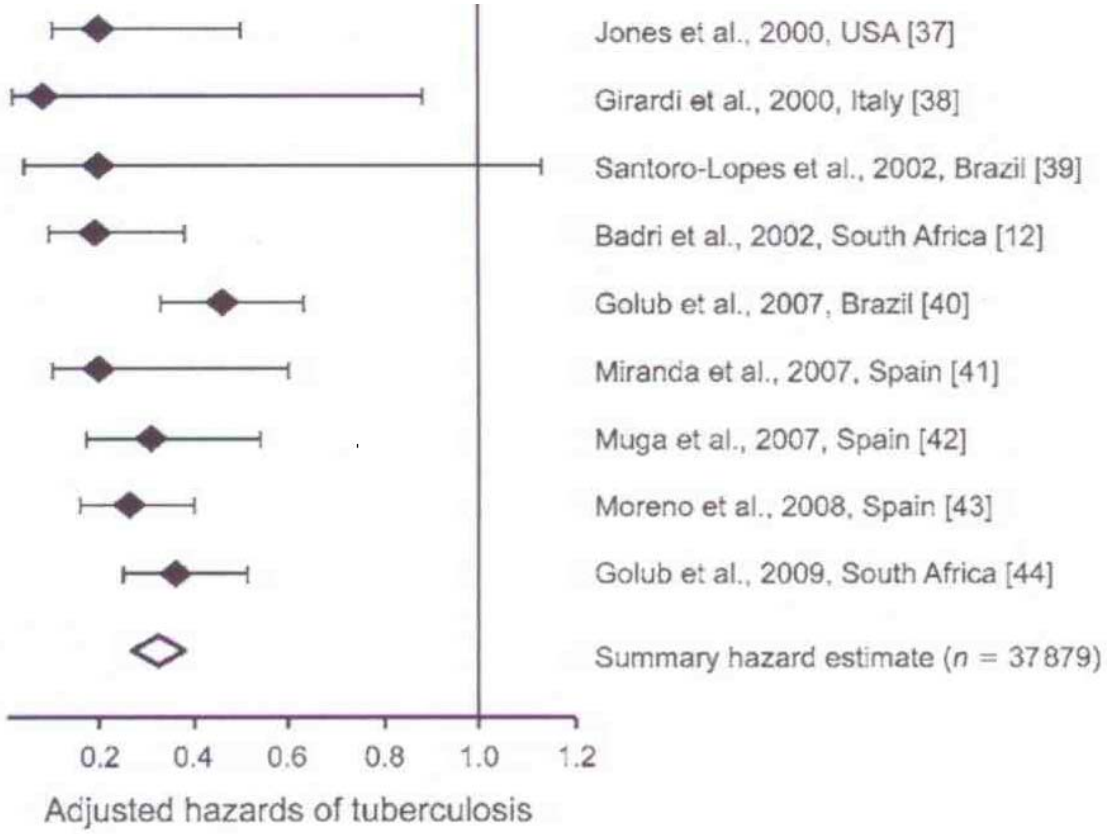
What were clinical events and at what CD4 did they occur?

	Immediate		Delayed	
	N	Median CD4	N	Median CD4
Total (N=129)	53	**506 (409 - 625)**	76	**340 (283 – 418)**
Tuberculosis	17	**518**	33	**316**
Severe bacterial infection	16	**551**	11	**337**
Death	10	**476**	13	**372**
Chronic herpes simplex	3	**753**	7	**413**
Bacterial pneumonia (recurrent)	2	**445**	2	**220**
esophageal candidiasis	2	**301**	2	**256**
Cervical carcinoma	0	**--**	2	**445**
Kaposi's sarcoma	1	**459**	1	**364**
Wasting syndrome	0	**--**	2	**366**
Other	2	**488**	3	**217**

Tuberculosis

	Immediate		Delayed	
	N [incidence]	Median CD4	N [incidence]	Median CD4
Total	**17** [1 /100PY]	**518**	**33** [1.9 /100PY]	**316**
Pulmonary TB	**14** [0.8 /100PY]	**521**	**16** [0.9 /100PY]	**295**
Extrapulmonary TB	**3** [0.2 /100PY]	**443**	**17** [1 /100PY]	**342**
Peripheral Lymph Nodes	2	432	4	492
Abdominal	0	--	8	324
Pleural	1	443	3	316
Skeletal	0	--	1	417
Meningeal	0	--	1	302

Many other cohort studies correlate ART with reduced TB rates



Lawn, 2011

Conclusions

- New studies shed light into the optimal timing of ART
- Optimal timing of ART is a key approach to reducing TB mortality in HIV patients
- Implementation of these findings must be a major focus and will require country policy change and programmatic adaptations with attention to HIV-TB drug interactions and management of TB IRIS
- ART is the most powerful tool for TB prevention and early ART should be supported as part of HIV-TB policy