The ART of treating TB in HIV-infected persons

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Fever and confusion in a newly-arrived visitor

- 51 year old man from Kenya
  - 2 weeks of fever, cough, weight loss
  - 1 day of confusion
- Exam: hallucinating, no focal deficits
- T – 38.4, P – 100, BP – 136/74, O2 saturation – 100%
- Mouth – dry mucous membranes, thrush
- Axillary nodes bilaterally

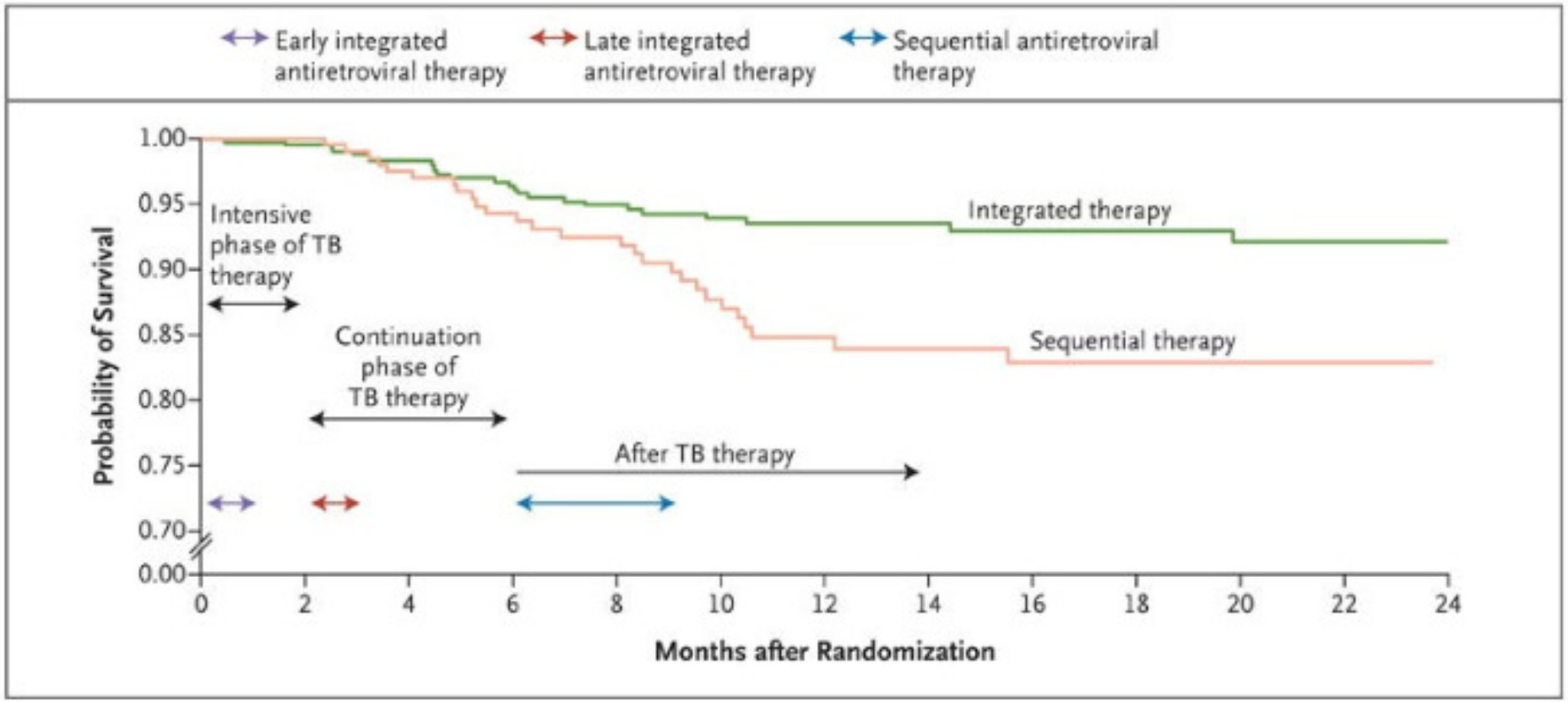
Follow-up

- HIV +, CD4 cell count – 18 (2%)
- Sputum smear: 4+ AFB
- Rapid assay: *M. tuberculosis* positive, no resistance to INH and RIF
- Lumbar puncture - normal
- Good initial clinical response to INH, RIF, PZA, and EMB

ART-related questions

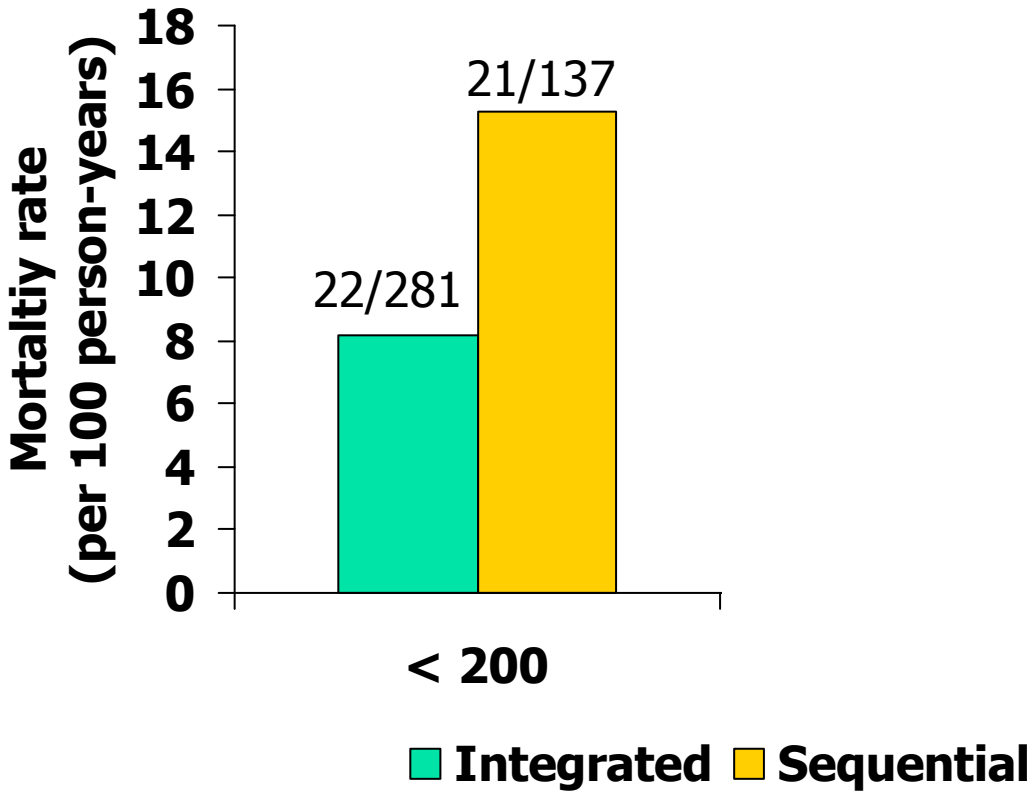
- When should ART be started in a patient being treated for TB?
- How should drug-drug interactions between rifamycins and ART be managed?
- How should immune reconstitution disease (IRD) be diagnosed and treated?
- What are the programmatic challenges of starting ART during TB treatment?

Initiation of ART **during** vs. **after** TB treatment: SAPIT



Abdool Karim S, et al. New Engl J Med 2010; 362: 697-706

Effects of timing of ART on mortality, by baseline CD4 cell count: SAPIT



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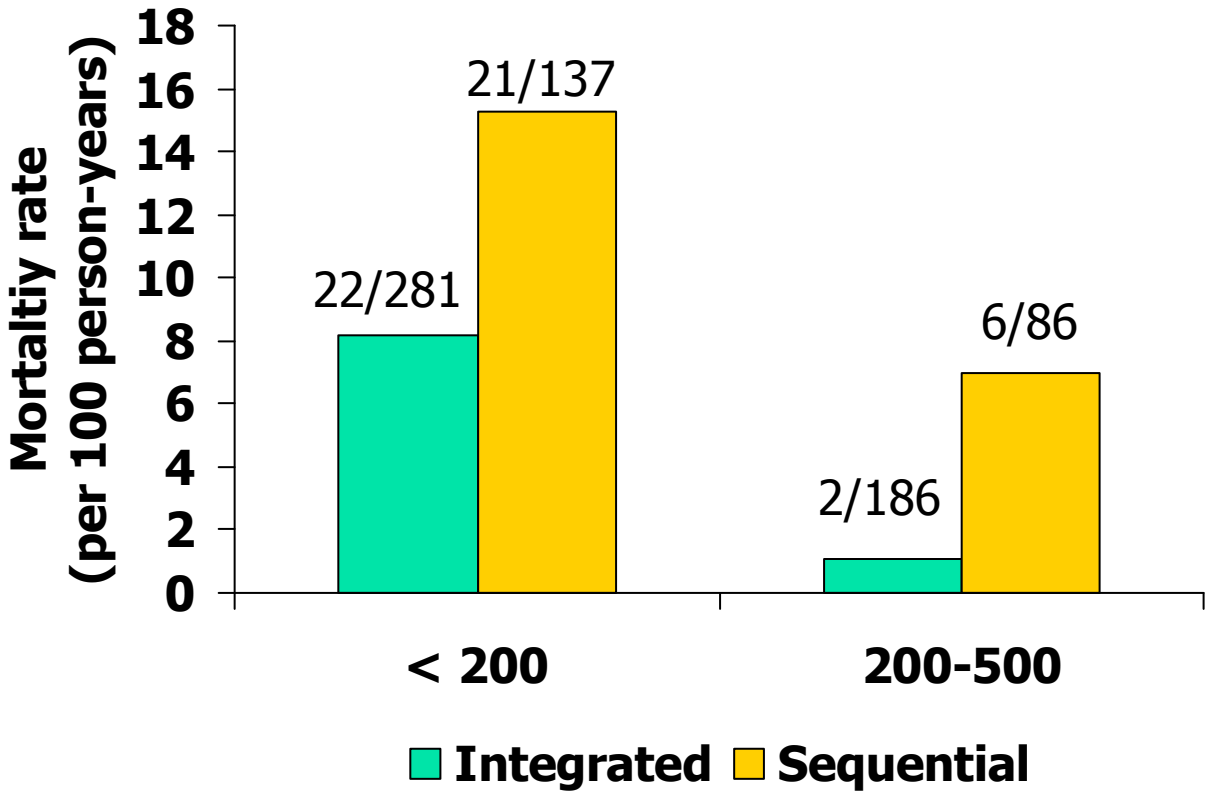

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ART during TB treatment: conclusions of SAPIT

- Starting ART during TB treatment decreases the high case fatality rate of HIV-TB
- Mortality benefit was present across a broad range of CD4 cell counts
- Earlier ART resulted in higher risk of IRD, but these cases were manageable
- WHO and DHHS recommendations: start ART during TB treatment for all patients

Competing risks in the timing of ART **during** TB treatment

Immediate (< 2 wks)

Benefits:
- ↓ risk of other OIs

Risks:
- ↑ adverse effects
- ↑ incidence of IRD

Early (2 months)

Benefiits:
- ↓ risk of IRD

Risks:
- ↑ incidence of OIs
- feasibility

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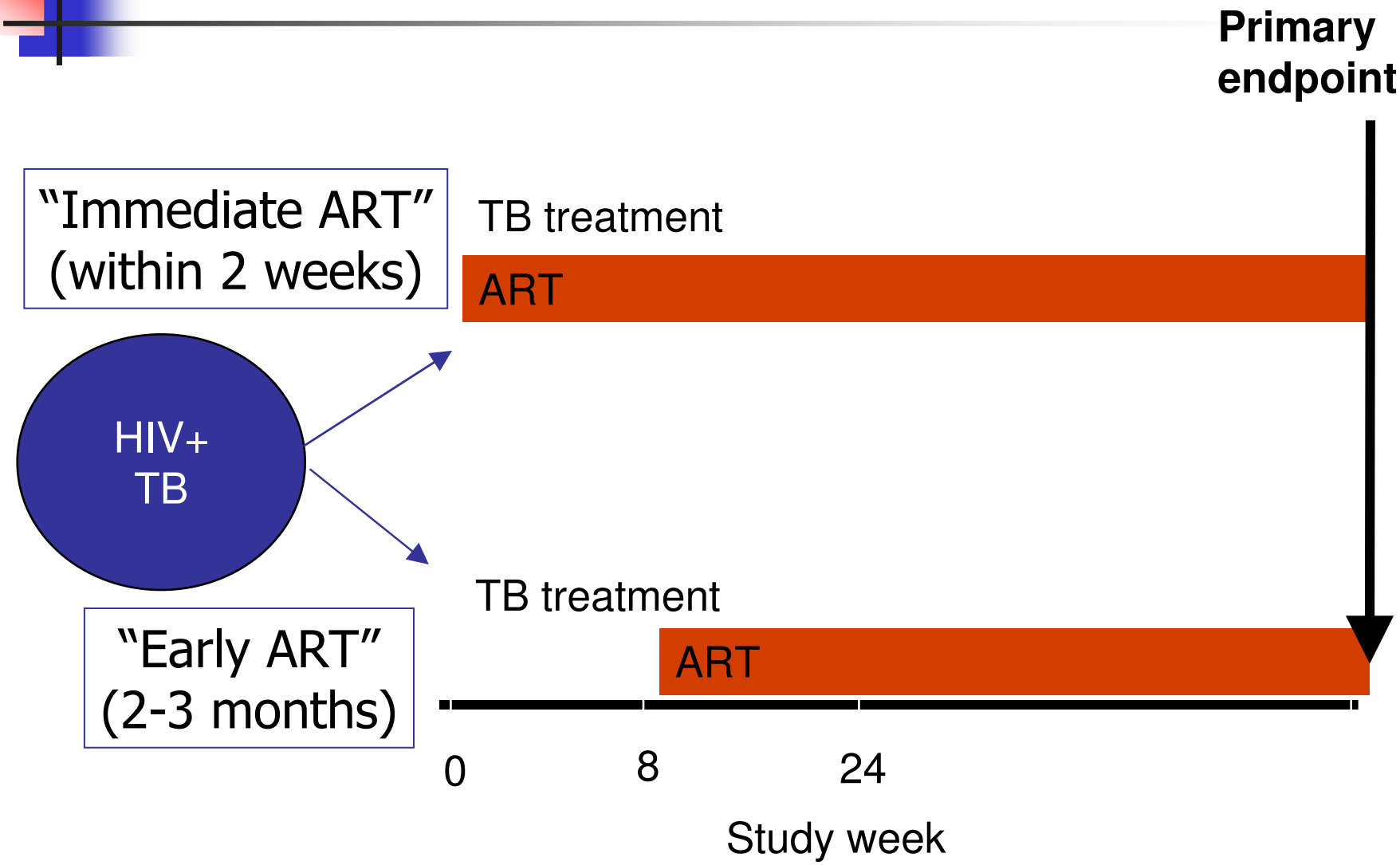
Mortality

General schema for CAMELIA, STRIDE, and integrated arms of SAPIT

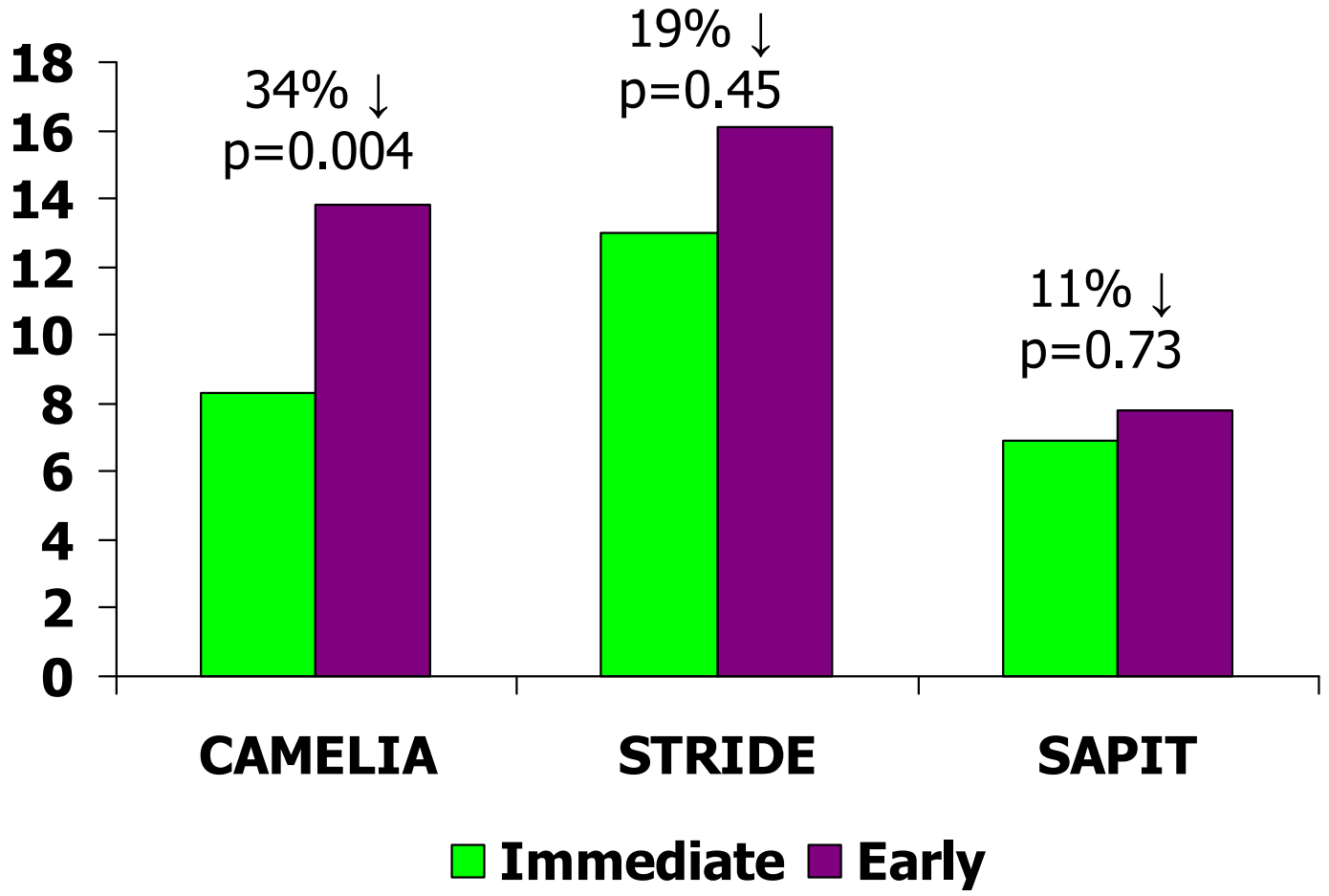


Key characteristics of trials of timing of ART during TB treatment

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

AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

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



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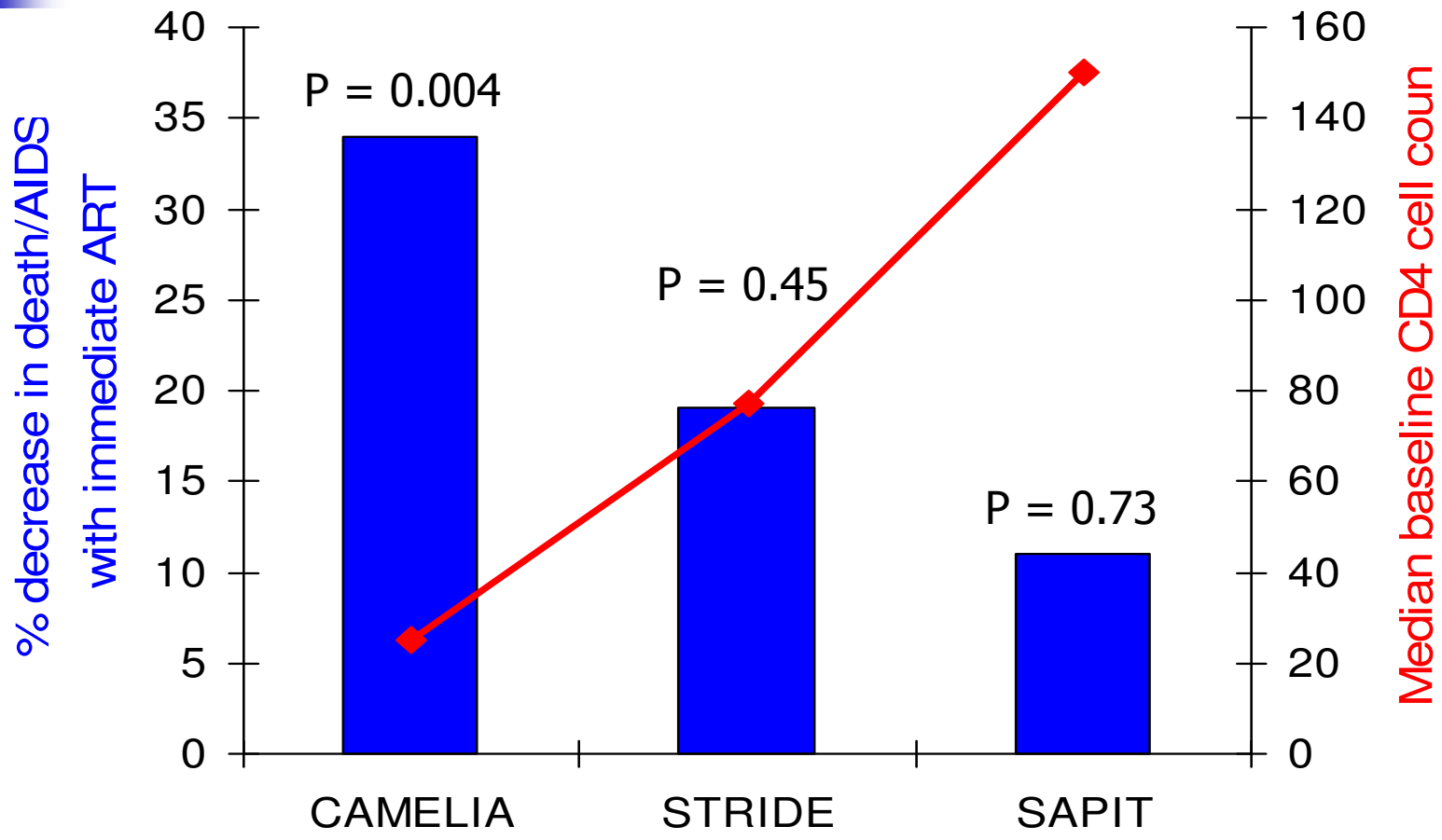
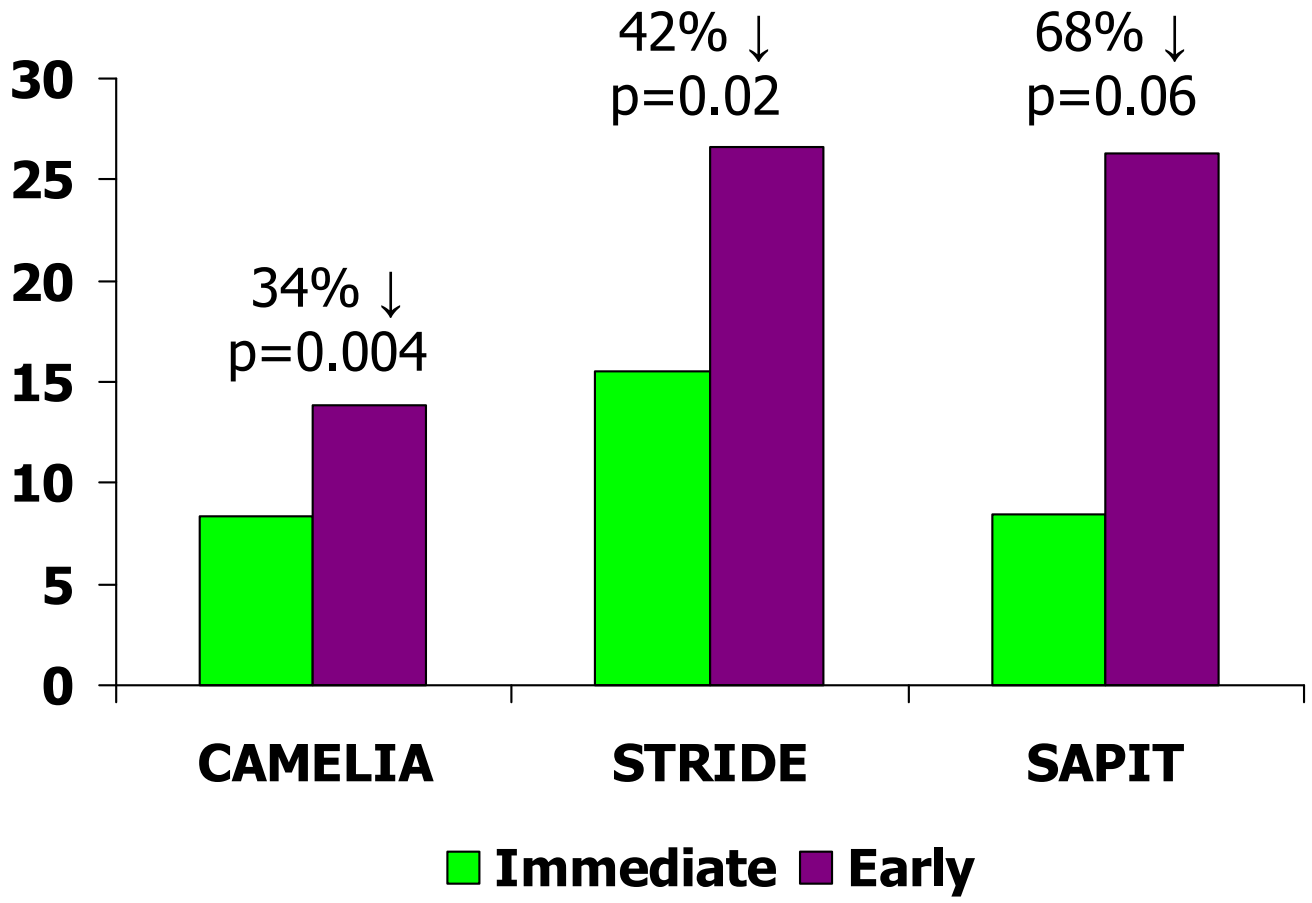
Relationship between median baseline CD4 count and the effect of immediate ART on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)



AIDS 2010 abstract THLBB106, CROI 2011 abstract , CROI 2011 abstract

Effects of ART timing on outcomes in CAMELIA and patients with **CD4 < 50** in STRIDE and SAPIT



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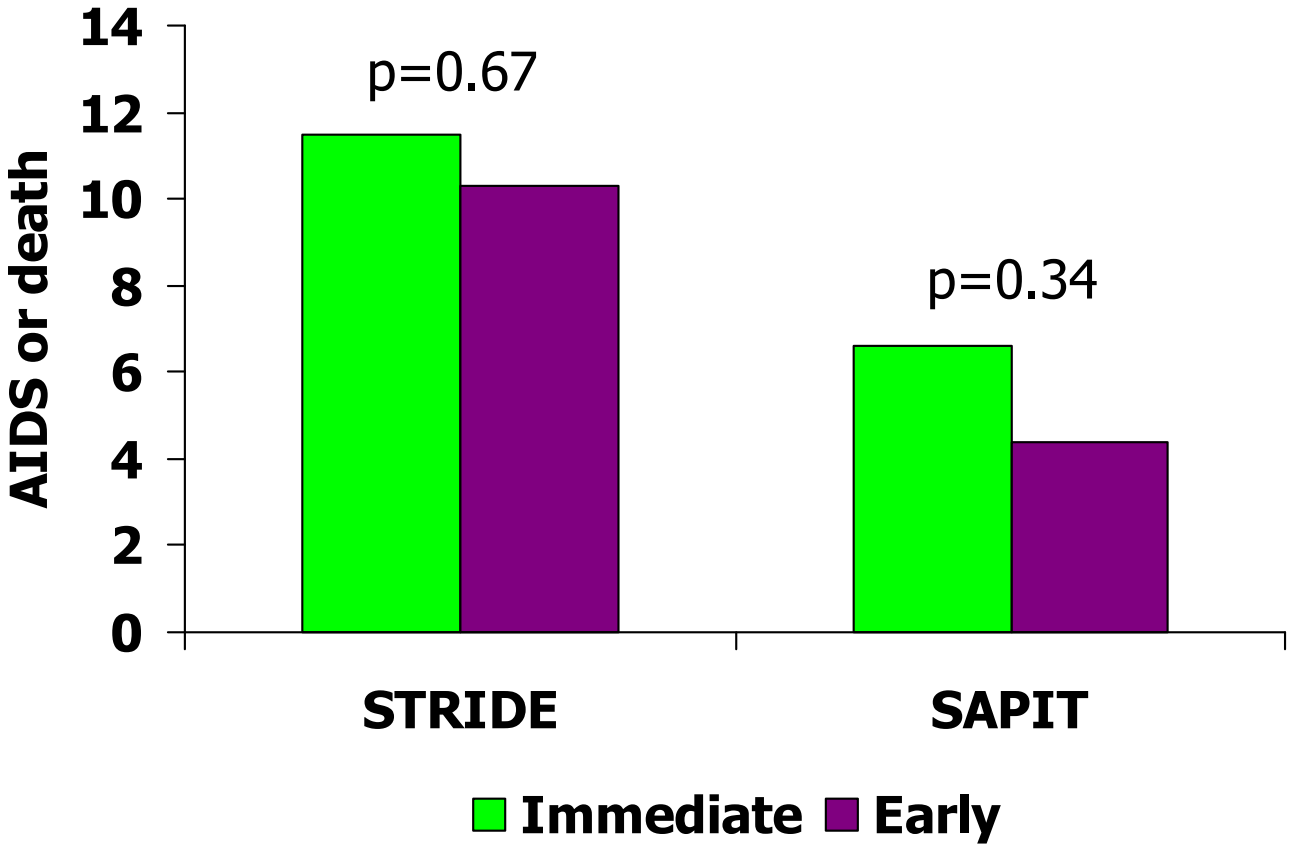
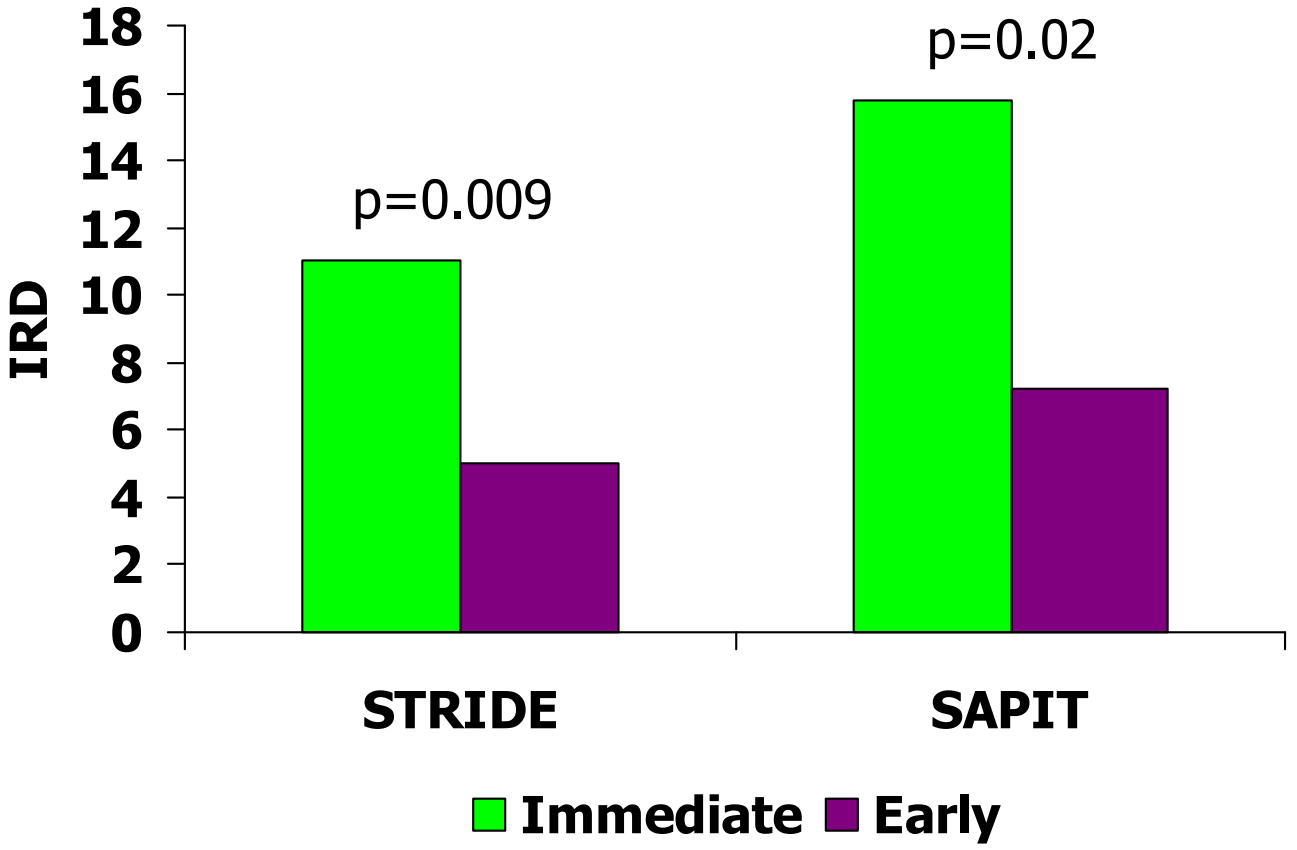
Effects of ART timing on death/AIDS among patients with **CD4 > 50** in STRIDE and SAPIT



CROI 2011 abstract 38, CROI 2011 abstract 39LB

Effects of ART timing on Immune Reconstitution Disease among patients with **CD4 > 50** in STRIDE and SAPIT



CROI 2011 abstract 38, CROI 2011 abstract 39LB

Other outcomes in CAMELIA, STRIDE and SAPIT

- Immune reconstitution disease (IRD)
  - Risk factors: immediate ART, low CD4 cell count, confirmed TB (STRIDE)
  - No deaths attributed to IRD, but excess "TB deaths" (14 vs. 7) in immediate arm or STRIDE
- Viral suppression – no effect of timing of ART on suppression at the end of TB treatment
- ART switches – higher in immediate arm of SAPIT

Comments – randomized trials of when to start ART during TB treatment

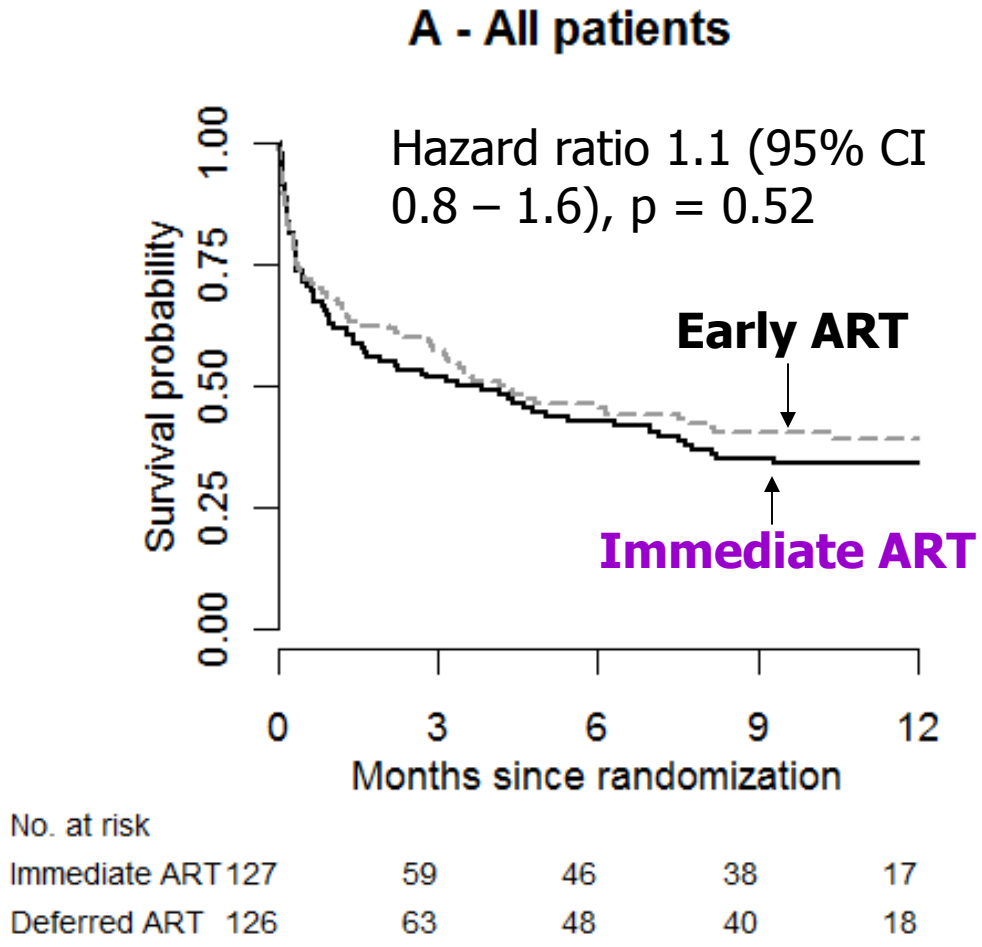
- Mortality is the appropriate endpoint; it captures the competing risks of HIV disease progression and severe IRD
  - Attempts to attribute causation to events (TB, IRD, OI, toxicity) are very problematic and ultimately not helpful
- 3 trials should combine data in a meta-analysis, using death as the endpoint
  - Formal statistical test for heterogeneity by baseline CD4 count should be done

Effect of ART timing on survival of patients with TB meningitis

- Median CD4 ~ 40 (16 – 100)
- 60% + CSF culture

- KM survival estimates at 9 months
  - 35.2% in immediate arm
  - 40.3% in deferred arm

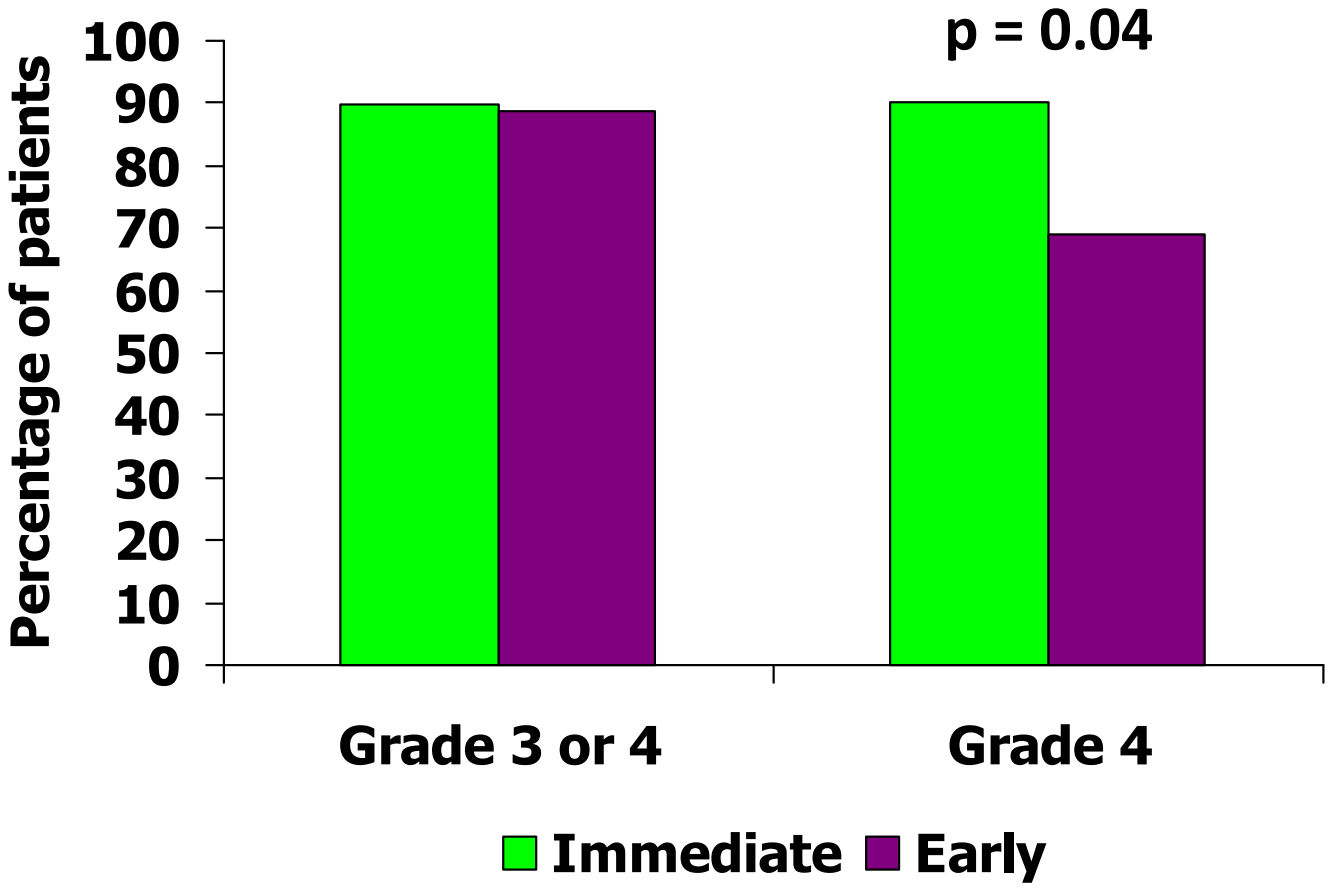
- Similar in per protocol analysis



UNIVERSITY OF CAMBRIDGE

Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

Effect of ART timing on risk of adverse events in patients with TB meningits



UNIVERSITY OF CAMBRIDGE

Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

Timing of ART in patients with TB

- Advanced AIDS (CD4 < 50): immediate ART (within 2 weeks) improves survival
  - Markedly increased risk of IRD, including fatal IRD events
  - Overall survival benefit despite IRD
- CD4 > 50: early ART (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRD
- Caveats
  - CNS involvement – no benefit to immediate therapy, and there may be increased risk
  - Programmatic complexities of early ART

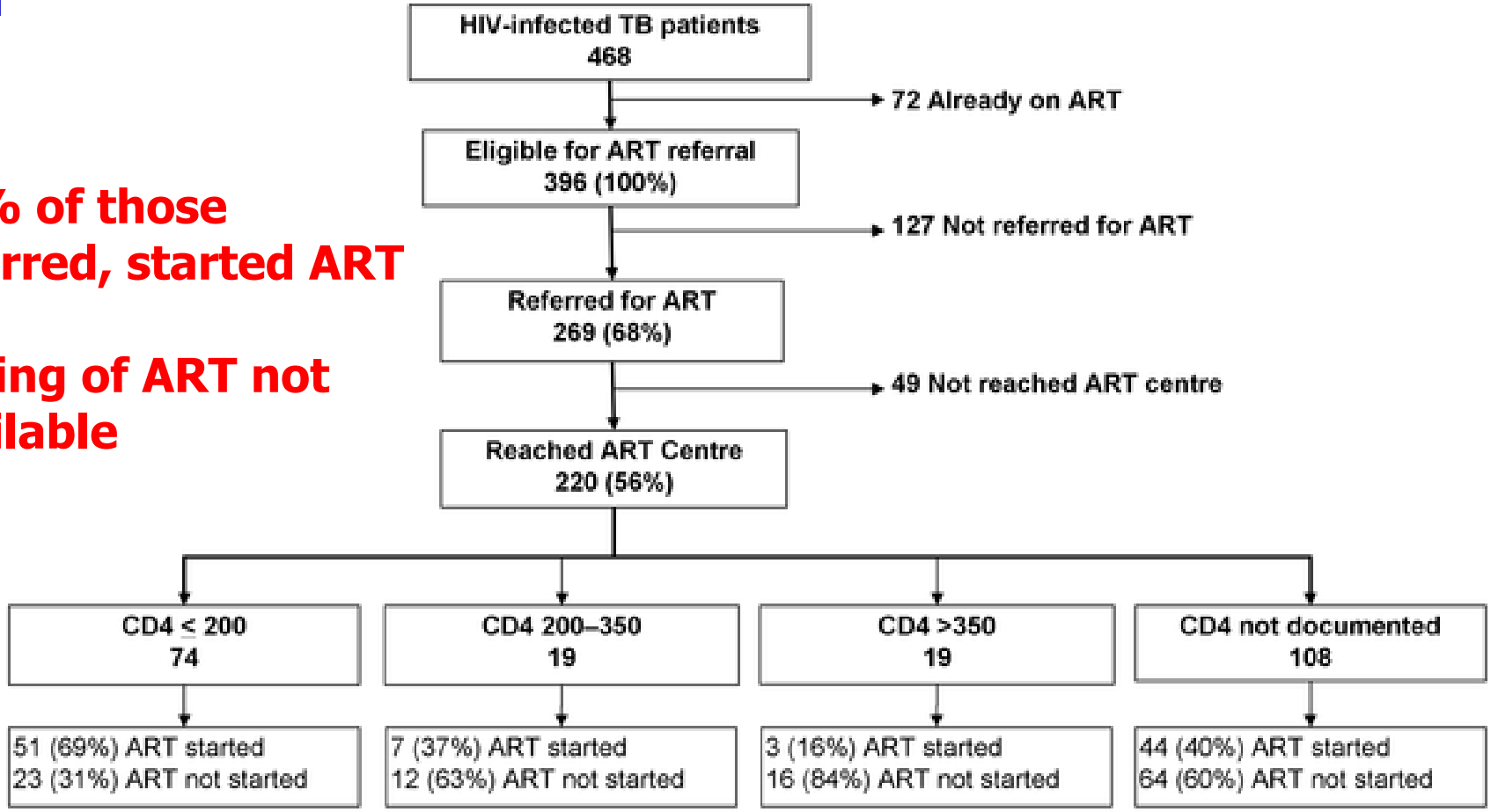
Programmatic challenges of immediate ART during TB treatment

- Rapid HIV diagnosis
- Rapid provisional diagnosis of TB
- Widespread availability of a way to identify those in need of immediate ART: CD4 cell count, BMI, hemoglobin, clinical/radiographic score
- ART available in settings where TB is diagnosed (hospital or clinic)
- Training in diagnosis and management of IRD events

Starting ART among patients with HIV-TB in India

26% of those referred, started ART

Timing of ART not available



Vijay S, et al. PLoS One 2009; 4: 2 7989

Initiation of ART in patients with HIV-TB (London, 1998-2007)

- British recommendations
  - CD4 < 100 – within 2 weeks
  - CD4 100-200 – at 2 months
  - CD4 > 200 – after completion of TB treatment
- 83 pacients eligible to start ART
  - 20 pacients (**24%**) started per the recommendations

Thorax 2008;63:935

Reasons for delayed ART among patients with CD4 < 100

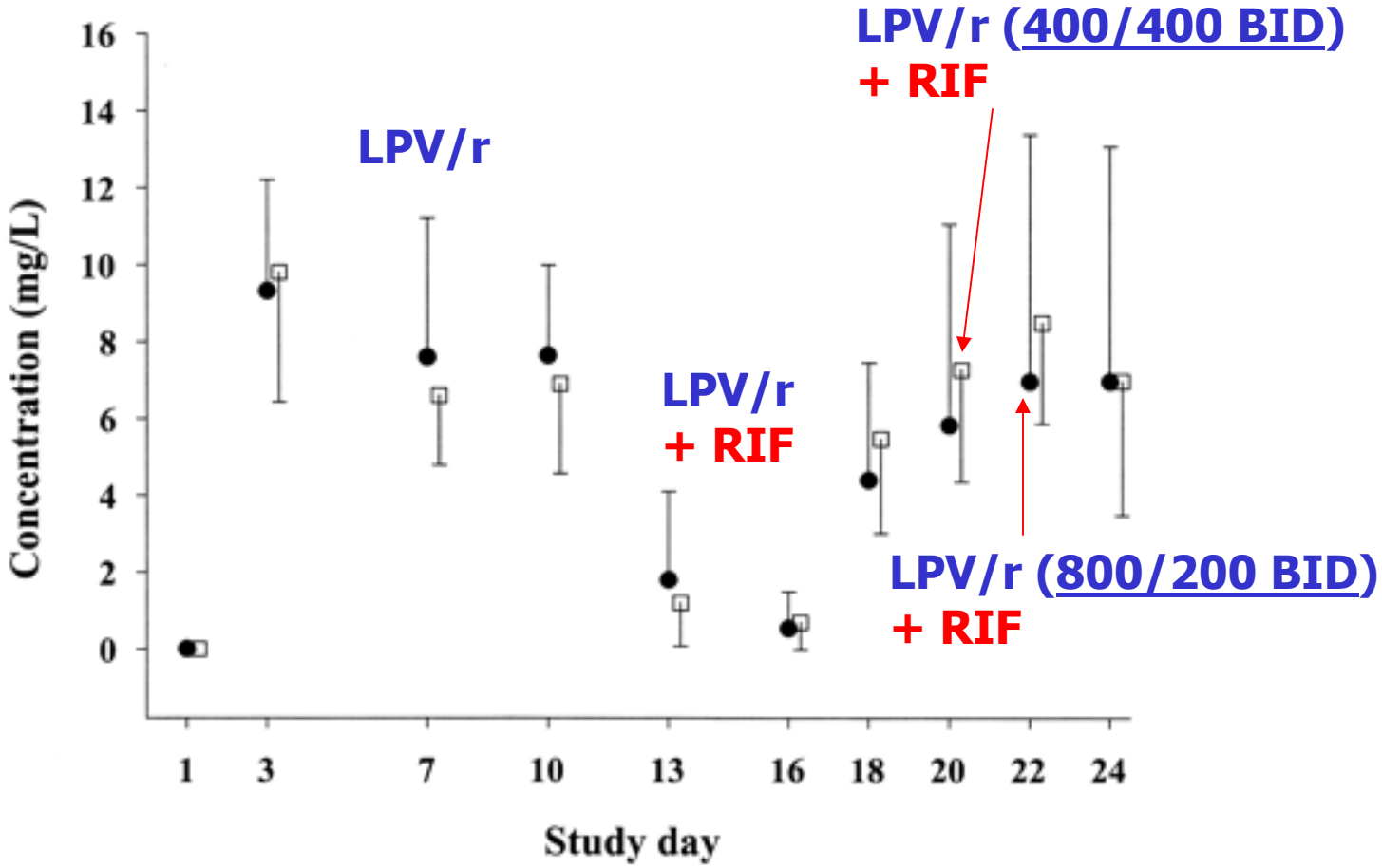
	# (%)
Delays by the patient:	
Refusal to start ART	7 (21%)
Concern about side effects	2 (6%)
Poor adherence	3 (9%)
Delays by the doctor:	
Serious side effect of TB treatment	8 (24%)
Concern about side effects / IRD	6 (18%)
Presence of another illness	4 (12%)
Severity of the manifestations of TB	5 (15%)

Thorax 2008;63:935

Remaining questions: ART during TB treatment

- Optimal treatment of patients who cannot take efavirenz-based ART
  - Problems of giving boosted PIs with rifampin
  - Uncertainty about dose of rifabutin with boosted PIs
- Optimal diagnosis and management of IRD
- Prevention of IRD among subgroups with very high risk
  - 30-45% with immediate ART among patients with CD4 count < 50

Overcoming rifampin's effect on lopinavir trough concentrations

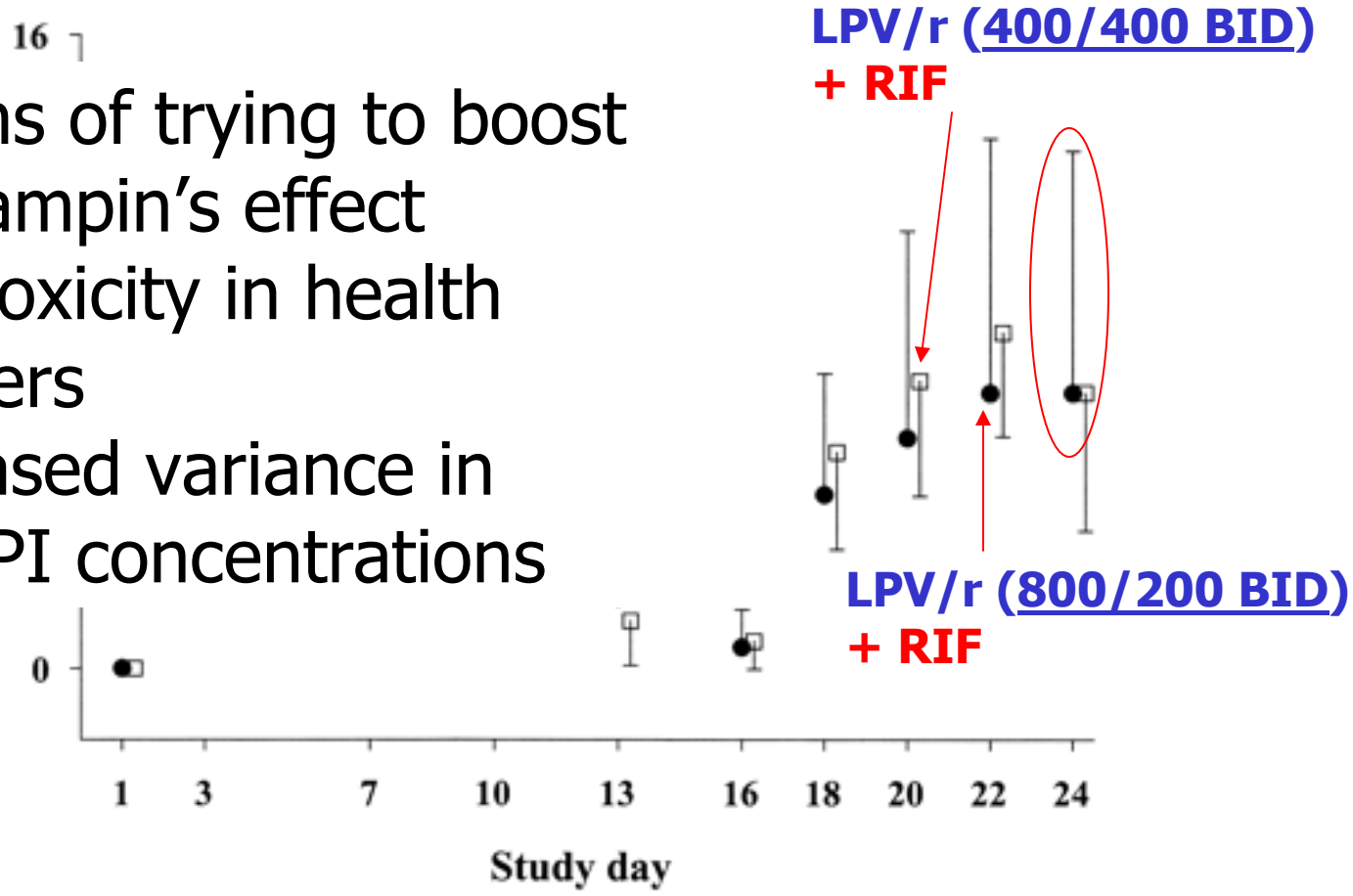


La Porte CJL, et al. Antimicrob Agents Chemother 2004; 48: 1553-60

Overcoming rifampin's effect on lopinavir trough concentrations

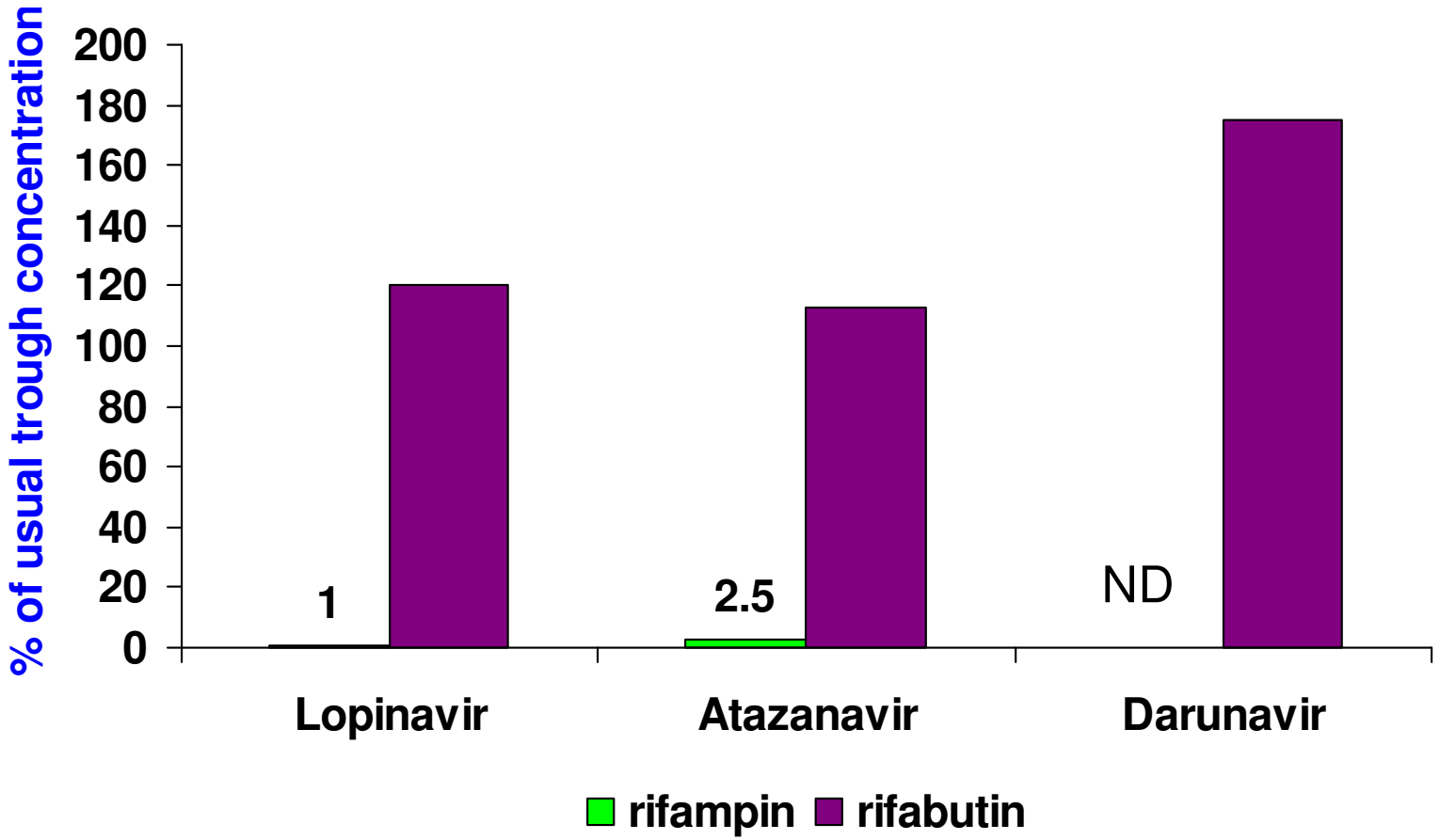
Problems of trying to boost past rifampin's effect

- Hepatoxicity in health volunteers
- Increased variance in trough PI concentrations



La Porte CJL, et al. Antimicrob Agents Chemother 2004; 48: 1553-60

Comparison of the effects of RIF vs. rifabutin on trough concentrations of boosted PIs



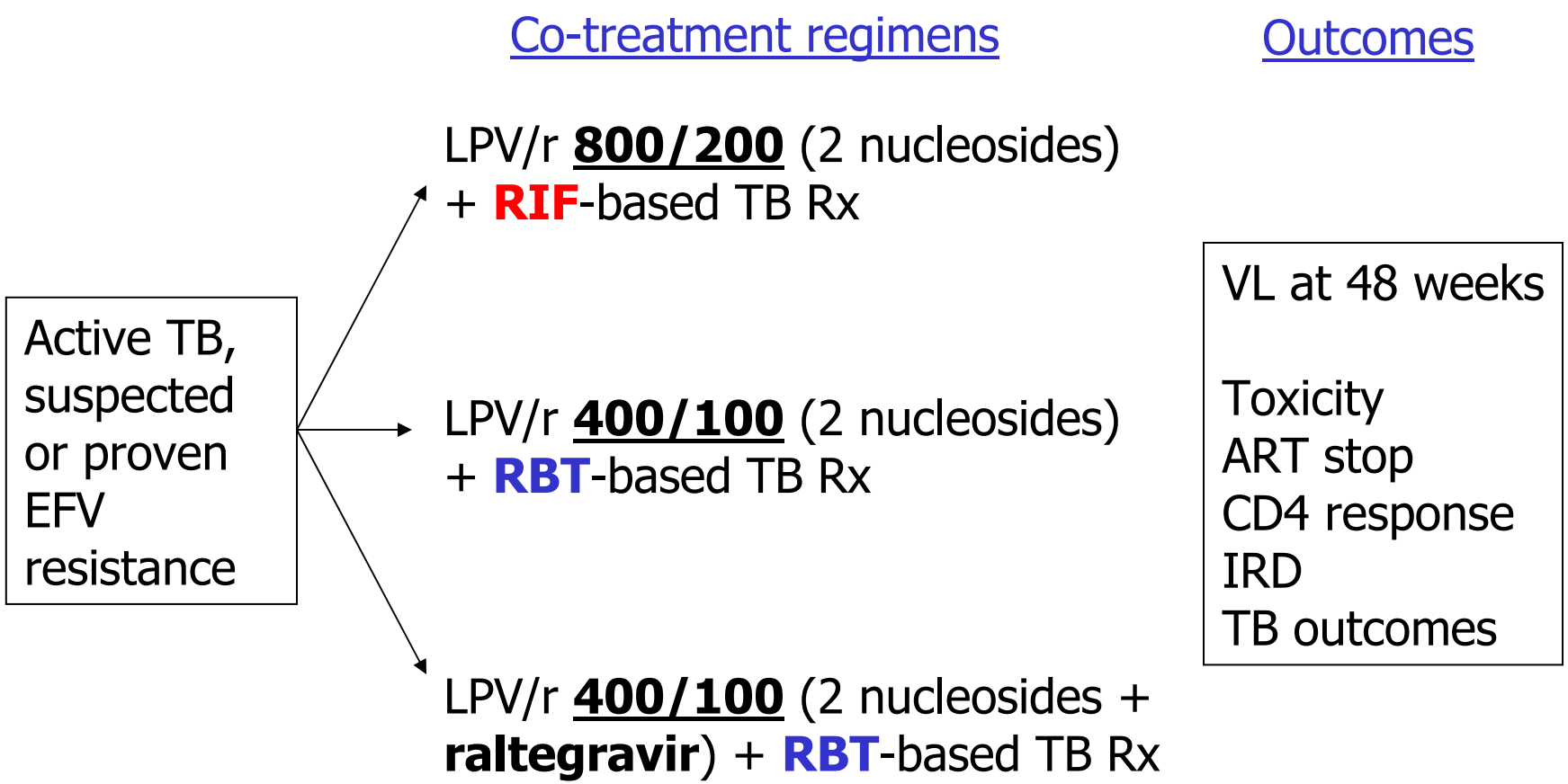
AAC 2204;48:1553-60, AAC 2006; 50:3336-42, AAC 2010;54:4440-5

Rifabutin PK with lopinavir/R in TB patients (n = 16)

PK parameter	RBT 300 mg/day	RBT 150 mg **QOD** + LPV/r	RBT 150 mg/**day**+ LPV/r
Median AUC (exposure)	3026	2307	5010
Median Cmax (peak)	297	168	311

Naiker S, et al. 2011 CROI, abstract 650

ACTG 5290: randomized trial of options for treating HIV-TB in patients who cannot use efavirenz (EFV)



The ART of treating patients with HIV-TB

- "Co-treatment" – both infections must be treated
- Much progress on timing of ART initiation
  - CD4 < 50: immediate (2 weeks)
  - CD4 > 50: early (2-3 months)
- Research needed
  - Co-treatment when EFV/RIF can't be used
  - Diagnosis, treatment, prevention of severe IRD
  - Programmatic issues in early co-treatment

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