

ART Timing for Selected Opportunistic Infections

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Disclosures

Merck: adjudication work for new HIV test

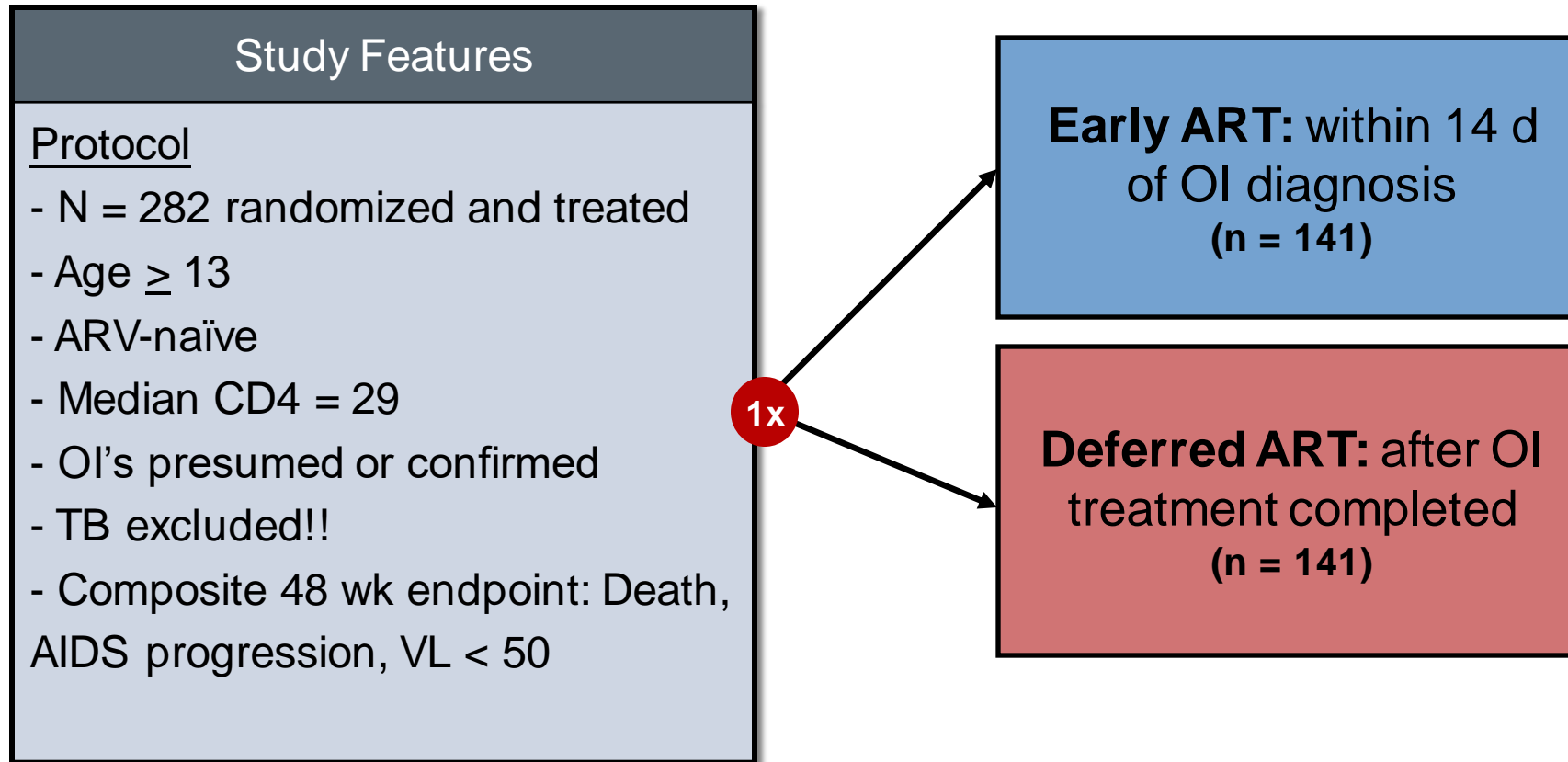
Case 1

What should I do with this patient's ART?

- A 26yo man with HIV, not engaged in care and not on ART presents with cough, dyspnea, and fever. Sputum stains + for PJP.
- Start ART?



ACTG 5164 – ART in setting of Acute OI



- Entry OI's: PJP (63%), Crypto (12%), Bacterial Infection (12%), Toxo (5%), Histo (4%), CMV (2%), MAC (2%), [Multiple 33%]

ACTG 5164 – ART in setting of Acute OI

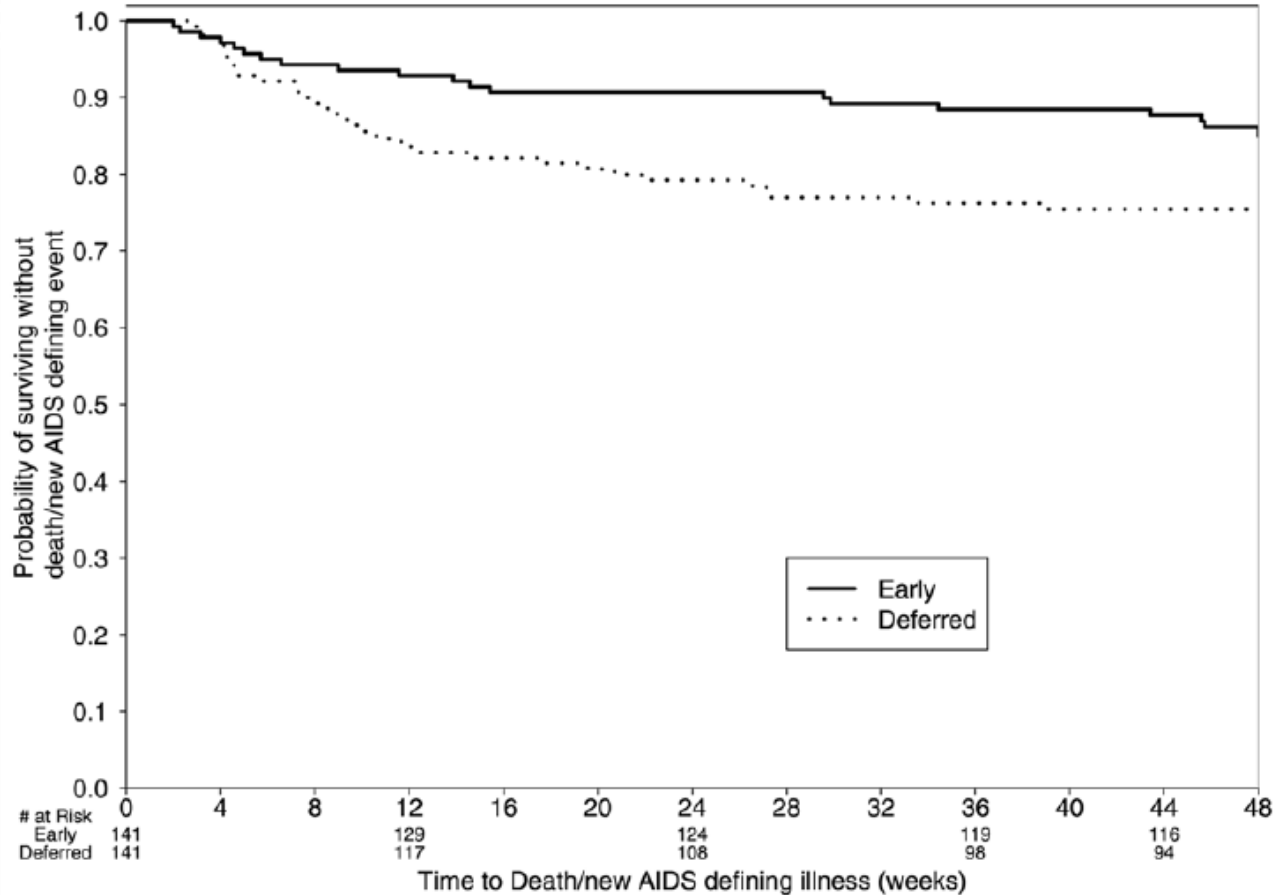
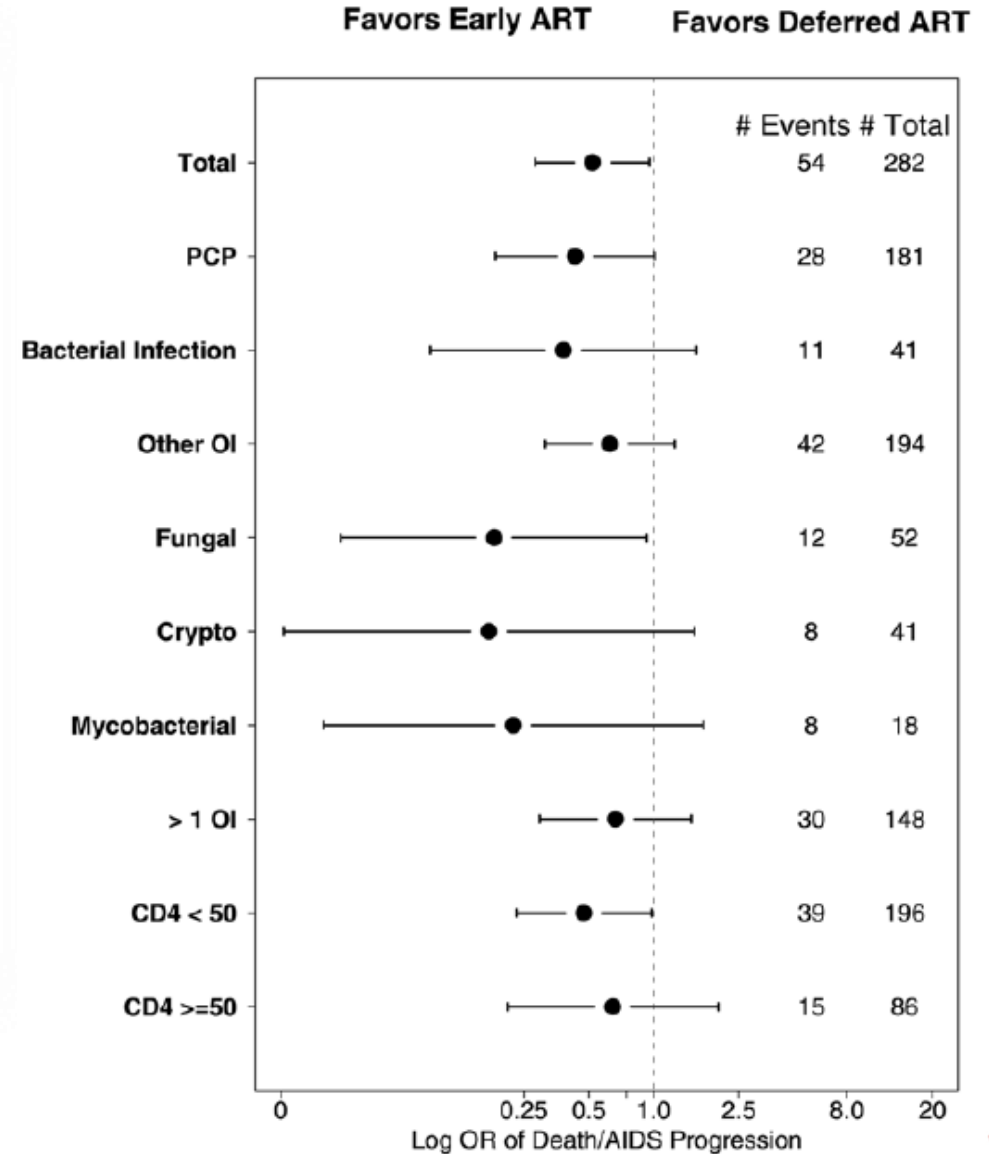


Figure 3. Time to AIDS progression or death. HR=0.53 Early versus Deferred ART [95%CI 0.30–0.92 p=0.023].

HR 0.53 (95%CI 0.3-0.92) favoring early ART



Case 2

What should I do with this patient's ART?

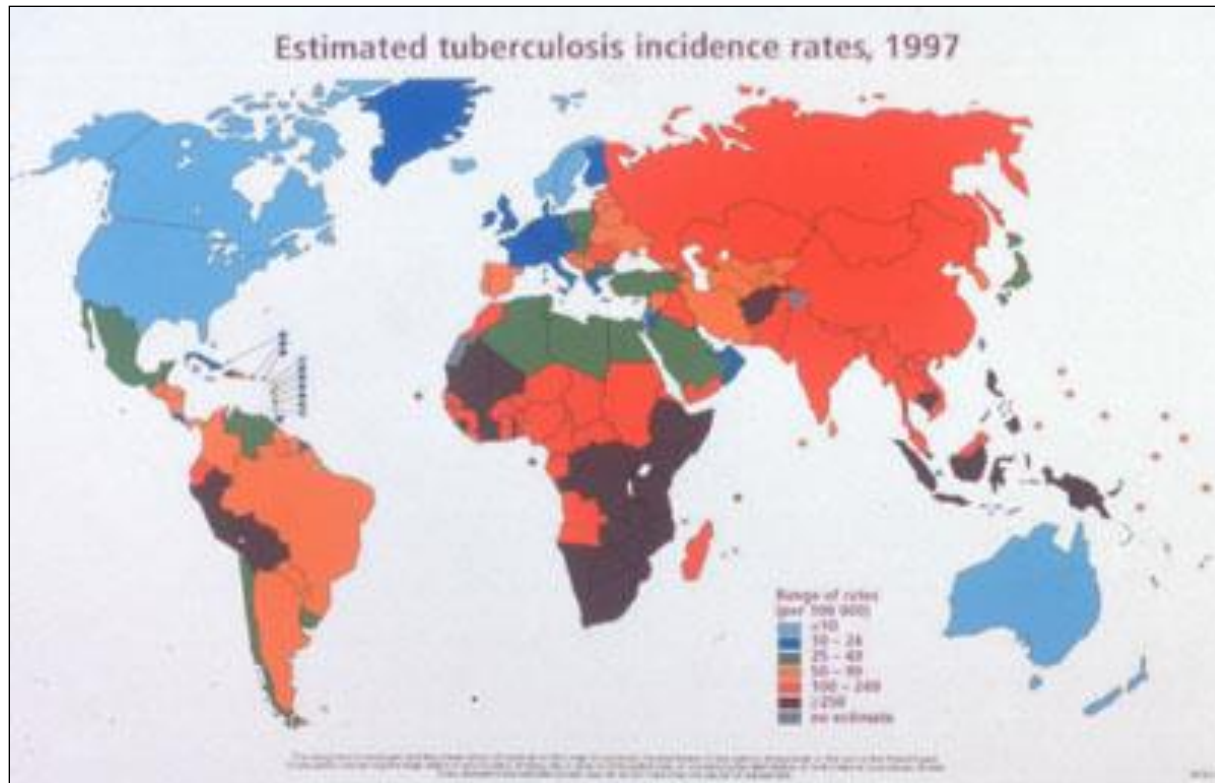
- A 37 yo African man presents with weight loss, cough, and fever. He tests HIV+. His CD4 T-cell count is 26, pVL is 210K. His sputum stains AFB+ and he is started on RIPE.
- Start ART?



Epidemiology

Overlapping Epidemics

At Least 1/3 of all patients with HIV are infected with TB

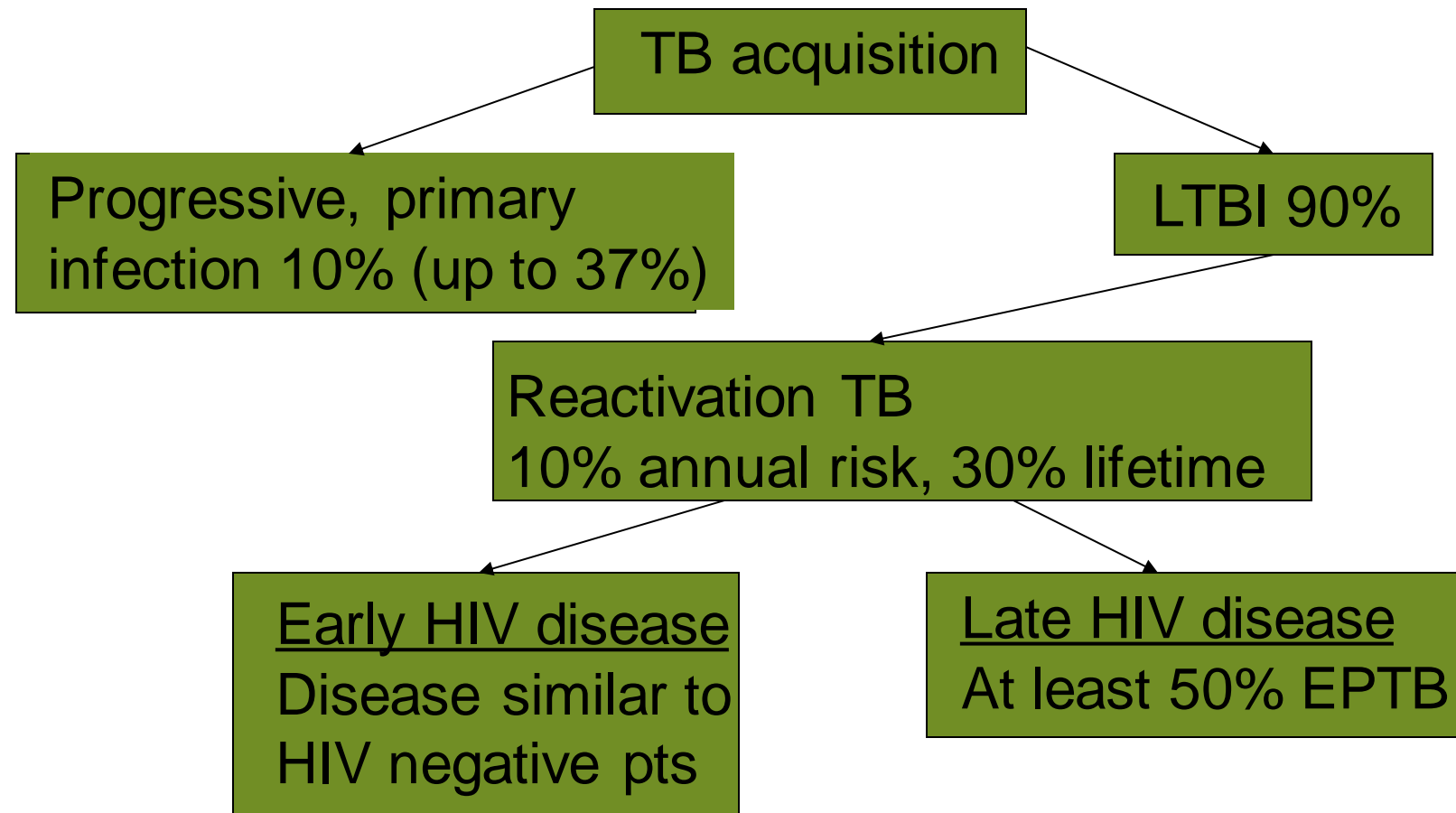


c Estimated HIV prevalence in TB cases, 2003



Pathogenesis and Natural History

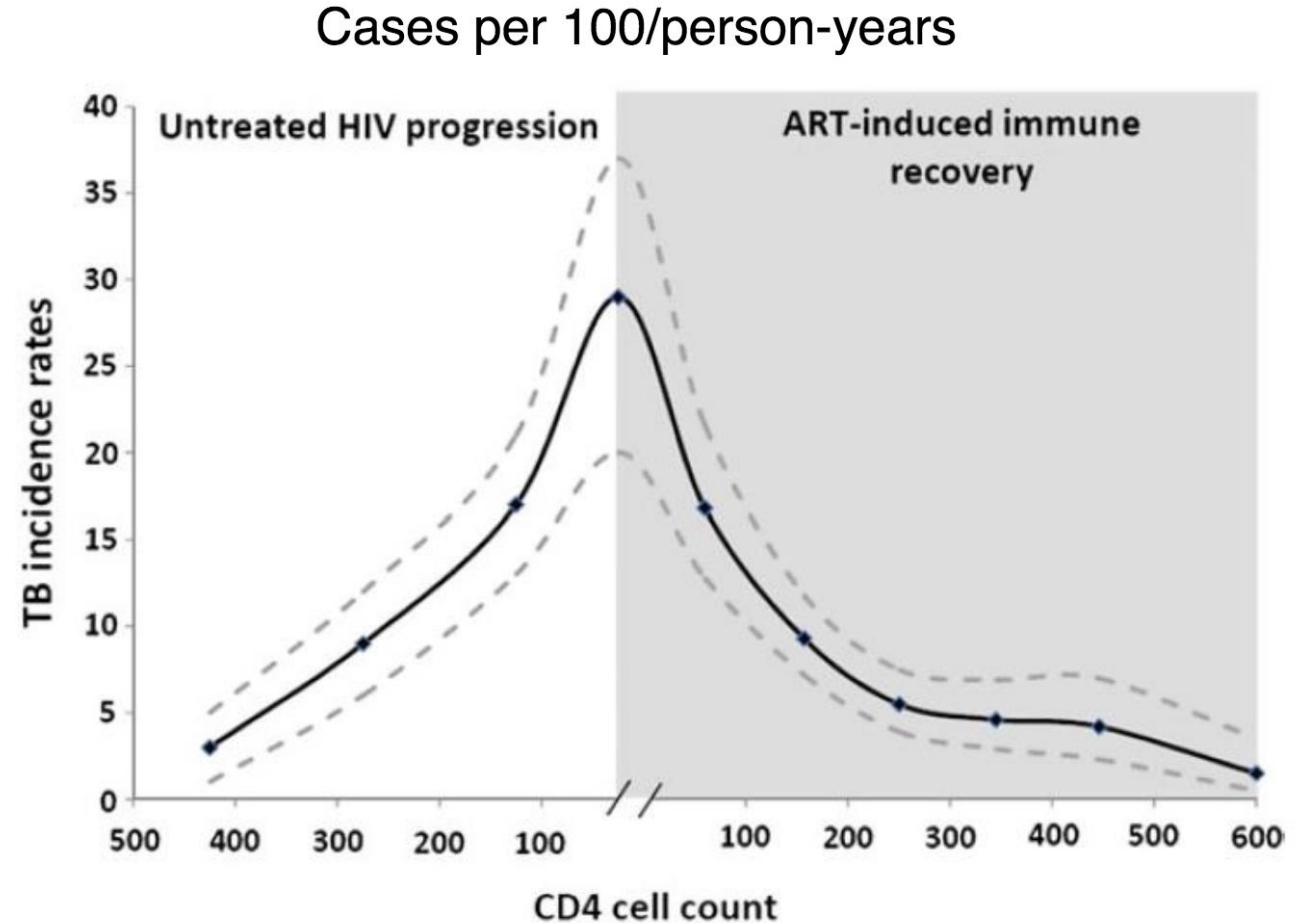
Effect of HIV on TB



Pathogenesis and Natural History

Effect of ART

- Incidence of tuberculosis is decreased by 70 to 90% over time
- ART reduces mortality 64-95%



Lederberger, JAMA, 1999
Girardi, AIDS, 2000
Jones Int J Tuberc Lung Dis, 2000
Santoro-Lopez, CID, 2002
ARV Rx Cohort Collab, CID, 2005
Lawn, Clin Chest Med, 2009

Lawn, JID, 2011



Tuberculosis and HAART: Timing

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ORIGINAL ARTICLE

Integration of Antiretroviral Therapy with Tuberculosis Treatment

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ORIGINAL ARTICLE

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

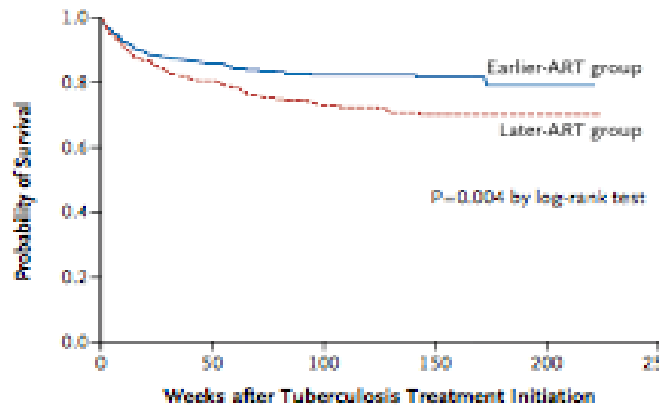
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Tuberculosis and HAART: Timing

Study	Patients	ARV timing	IRIS	Outcome
Blanc (Cambodia)	N = 661 Median CD4 = 25	2 weeks Vs 8 weeks	HR 2.51 (for early ARVs)	HR for death 0.62 (for early ARVs)
Havir (Africa, Asia, NA, SA)	N = 809 Median CD4 = 77	Median of 10 Vs 70 days	Early 11% Late 5%	Death rate: Overall 12.9% Vs 16.1% (NS) CD4 < 50: 15.5% Vs 26.6% (P=0.02)
Karim (S. Africa)	N = 642 Median CD4 = 150	Median of 21 Vs 97 days	HR of 2.62 (for early ARVs)	AIDS or Death: Overall: No difference CD4 < 50: 8.5 Vs 26.3 per 100 py (P=0.06)

Tuberculosis and HAART: Timing

Blanc, Cambodia



Havir, Africa, Asia, NA, SA

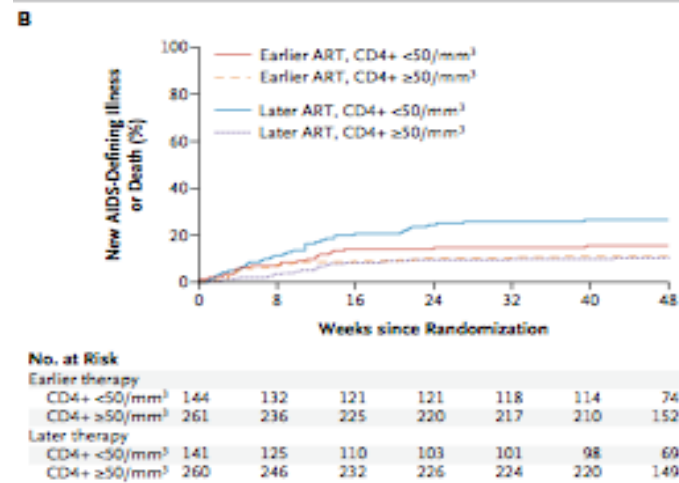
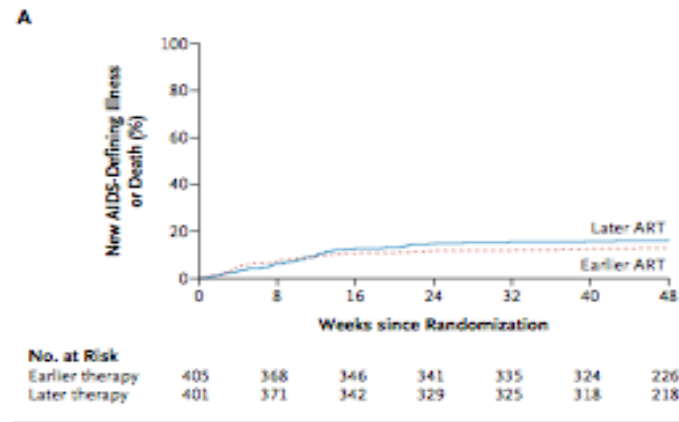


Figure 2. Time to New AIDS-Defining Illness or Death.

Shown are the times to the end point of a new AIDS-defining illness or death for the entire study population (Panel A) and for the study population according to CD4+ T-cell count (Panel B).

Karim, South Africa

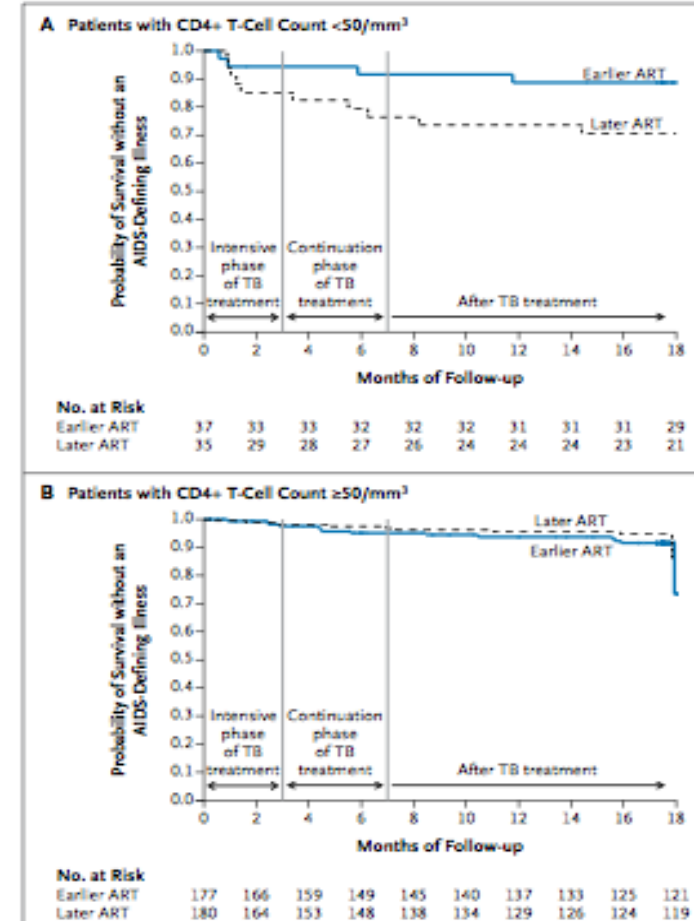


Figure 2. Kaplan-Meier Curves for Survival without an AIDS-Defining Illness.

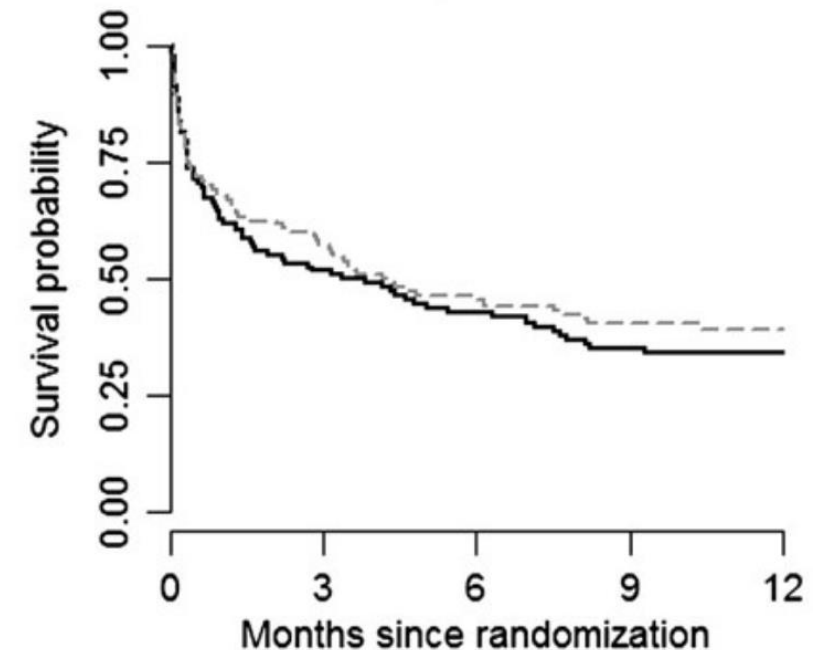
Panel A shows the data for patients with a CD4+ T-cell count of less than 50 per cubic millimeter, and Panel B shows the data for patients with higher CD4+ T-cell counts. TB denotes tuberculosis.

TB Meningitis and HAART – Be Careful

- R, DB, PC trial of 253 pts with TB meningitis
- All received RIPE + Dex
- ART (3TC/AZT/EFV) was given either
 - Immediately (~ 1 week)
 - After 2 months of TB Rx
- *Results*
 - *No difference in mortality or new AIDS dx between groups*
 - *More grade 4 AE in the immediate group*
 - *No difference in neurological events between groups*

Survival

A - All patients



No. at risk	0	3	6	9	12
Immediate ART	127	59	46	38	17
Deferred ART	126	63	48	40	18

Principles of Treatment: It's All About Rifampin

	Rifampin	Rifabutin
TAF	TAF AUC decreased 55%, but intracellular concentration of TFV-DP less affected (decreased by 36%) – still not recommended	Not tested
NNRTI Efavirenz Nevirapine Etravirine Rilpivirine Doravirine	EVF decreased 28% - OK NVP decreased by 20-58% - No Decreased ETR - No RLP decreased by 80% - No DOR decreased 88% - No	OK Not tested Not tested Not tested Not tested
Protease inhibitors	Decreased PI by 75% - No	OK with r-boosted PI but reduce rifabutin dose to 150 per day
Integrase inhibitors Raltegravir c/Elvitegravir Dolutegravir Bictegravir	RAL decreased 40%, dose: 800 bid Significant decrease in ELV – No DTG decreased - dose DTG 50 bid BIC decreased 75% - No	RAL AUC increased 70% - OK DTG – probably OK ELV – No BIC - No

Tuberculosis and ART

- ART improves the outcomes of HIV/TB co-infected persons
- In those with CD4 < 50 – start ART within 2 weeks of TB therapy
- In those with CD4 > 50 – start ART within 2 months of TB therapy
- In those with TB meningitis – be careful with early ART start: there are more grade 4 AEs (but no change in mortality)
- ART choices in patients on TB therapy: EFV or DTG or RAL + 2NRTIs is preferred. Avoid TAF and PIs.

Case 3

What should I do with this patient's ART?

- A 46 yo man with HIV presents with confusion and fever. His CD4 is 68. Lumbar puncture reveals an opening pressure of 300, 15 WBC (all lymphocytes), protein of 110 , glucose 40, CrAg + 1:128. He is started on L-Ampho and 5-FC.
- Start ART?

COAT: Cryptococcal Optimal ART Timing

COAT Study

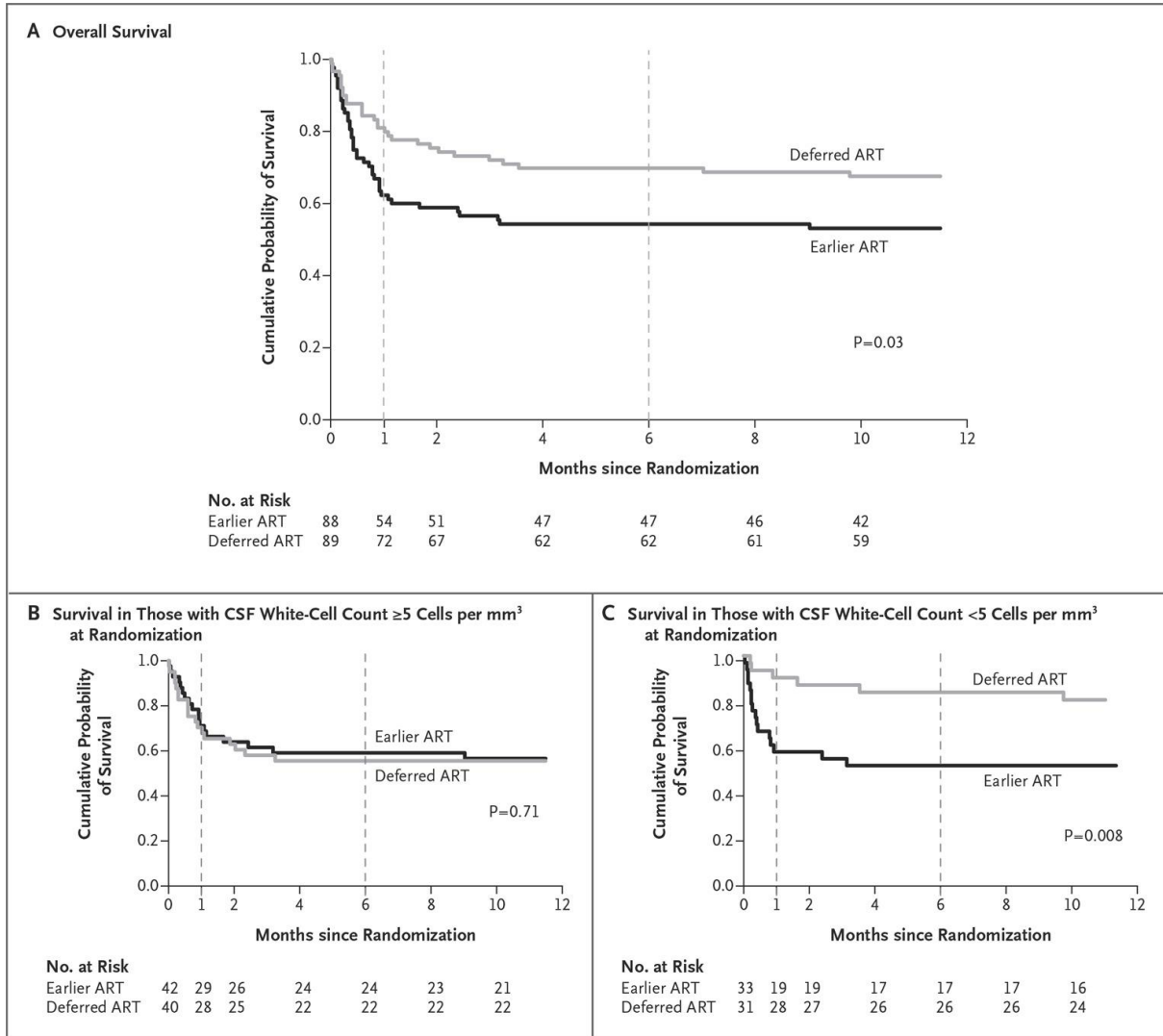
- Design:

- Early ART (<14 days) vs. late (\geq 4 weeks)
- Goal: 250 participants in each arm
- Primary endpoint: 6-month survival
- Stratified by MS (GCS 15 vs. <15) and CSF WBC (\geq or < 5)
- Induction: amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg

- Results:

- Halted by DSMB after 177 randomized
- 6-month survival: early ART- 48/88 (55%), delayed ART- 62/89 (70%) [HR 1.7 (95% CI 1.1-2.8, p=0.03)]

COAT: Cryptococcal Optimal ART Timing



Overall survival better in the deferred group

Especially in those with few CSF WBCs

No increase incidence of IRIS in the early treatment group – But the definition of IRIS required initial improvement – so many early deaths may have been due to misclassified IRIS

Cryptococcal Meningitis and ART

- Worse outcomes in patients starting ART within 2 weeks of initiating cryptococcal therapy
- Delay ART start for at least 4 weeks, monitor for IRIS and manage increased ICP aggressively
 - Repeated lumbar punctures for symptoms – target CSF pressures < 20 (or remove 20-25 mls)
 - Avoid steroids to manage increased ICP early in disease (associated with increased mortality)
 - Later, if dealing with IRIS (and when CSF cultures are sterile) can consider steroids to manage IRIS

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