AETC AIDS Education & Training Center Program Mountain West

ART Timing for Selected Opportunistic Infections

Bob Harrington
University of Washington

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echo

Disclosures

Merck: adjudication work for new HIV test

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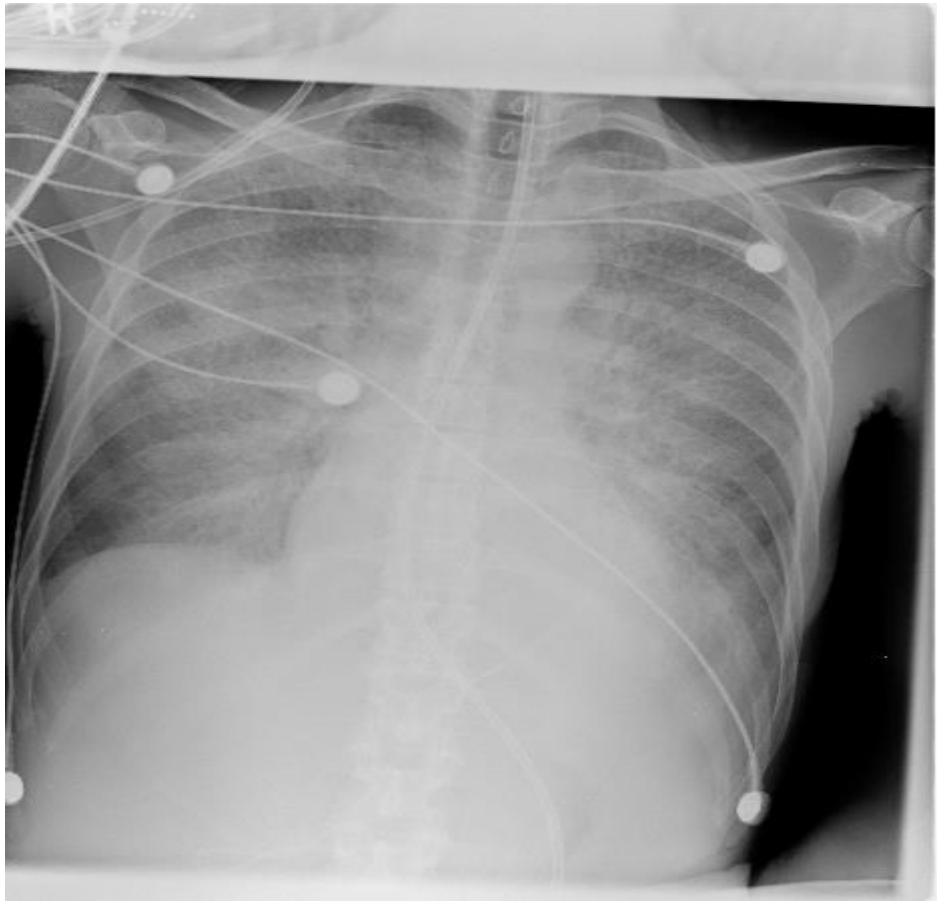
Case 1

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?



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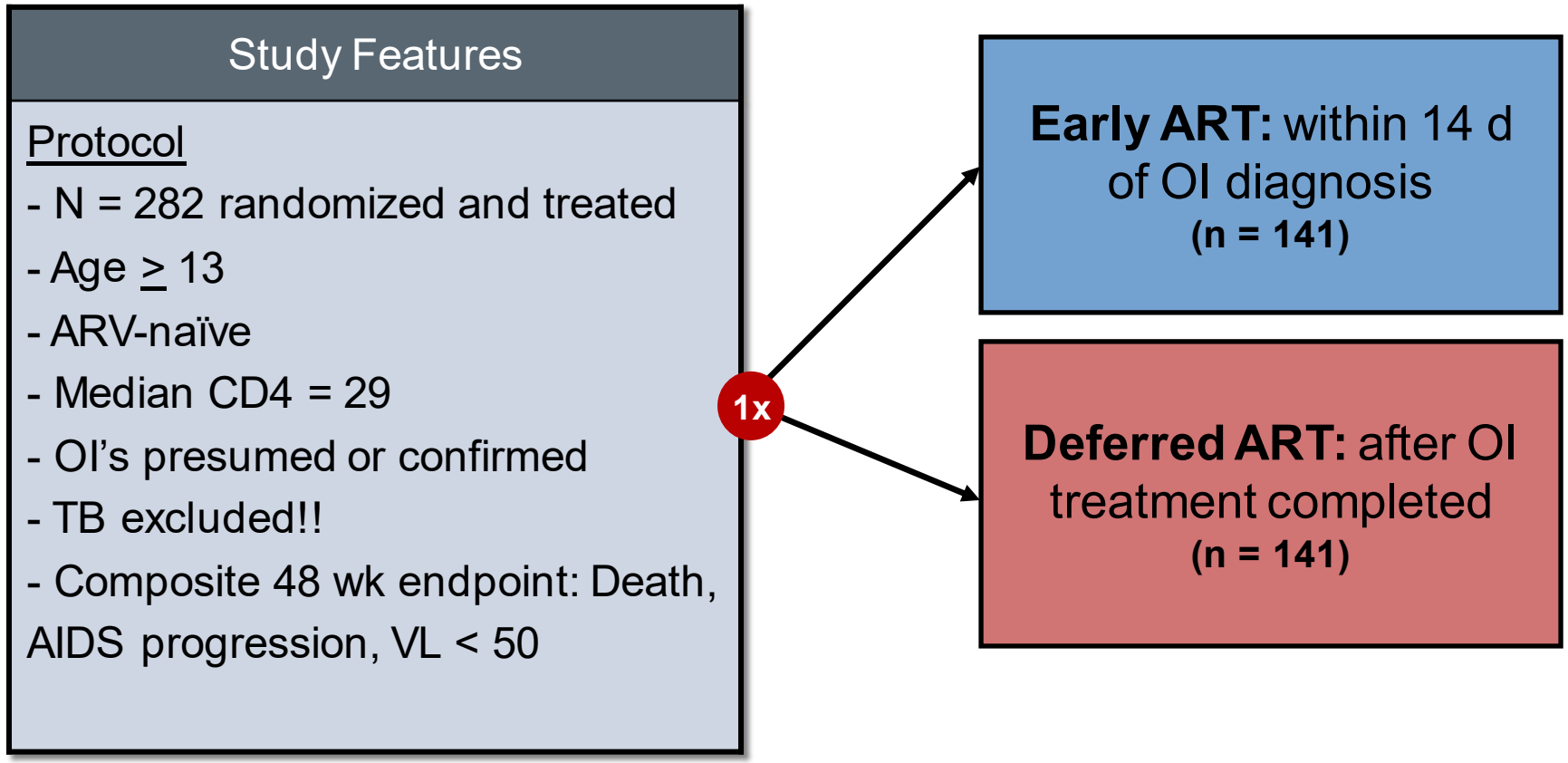
ACTG 5164 – ART in setting of Acute OI



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

Zolopa A, *et al* PLoS One 2009; 4(5): 5575

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ACTG 5164 – ART in setting of Acute OI

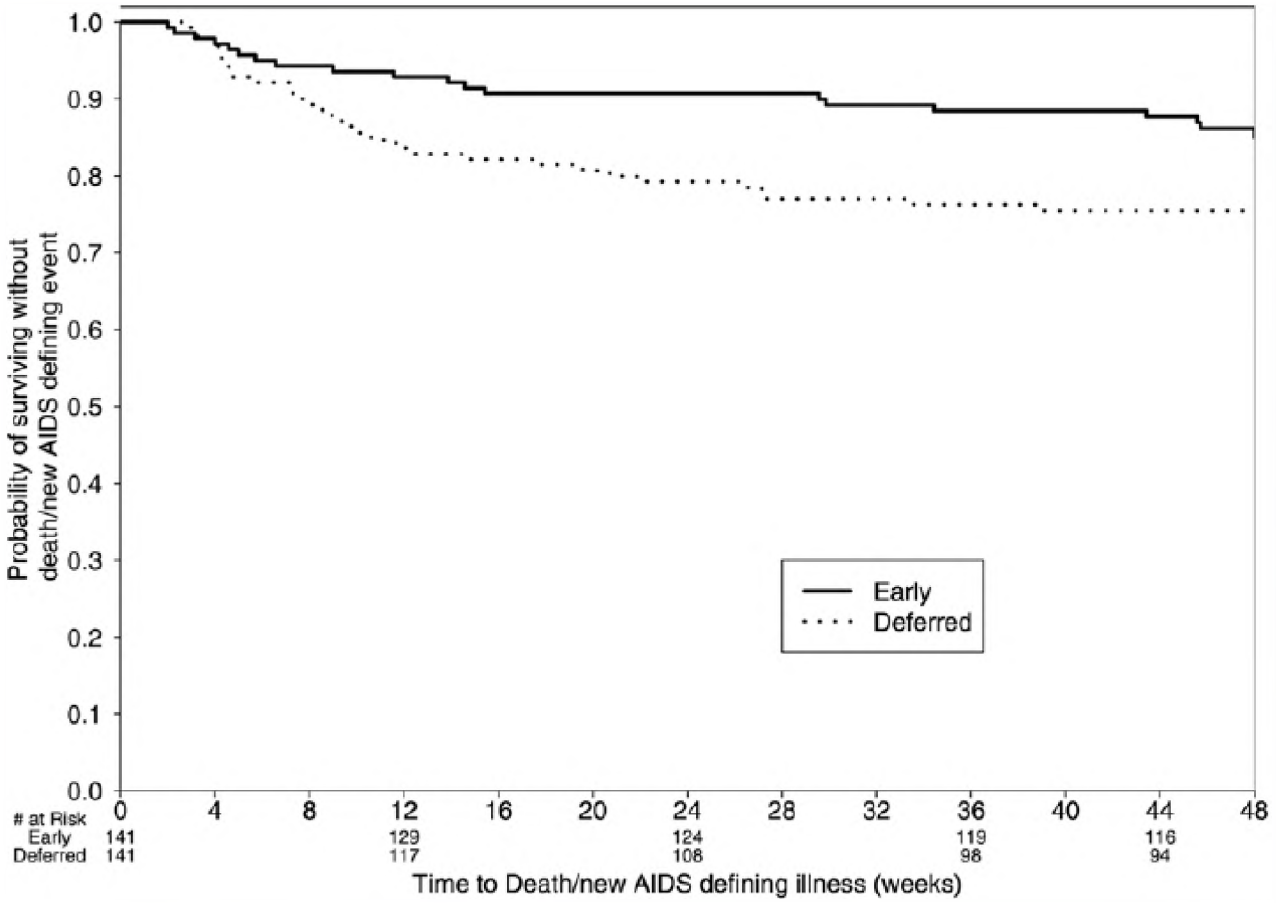
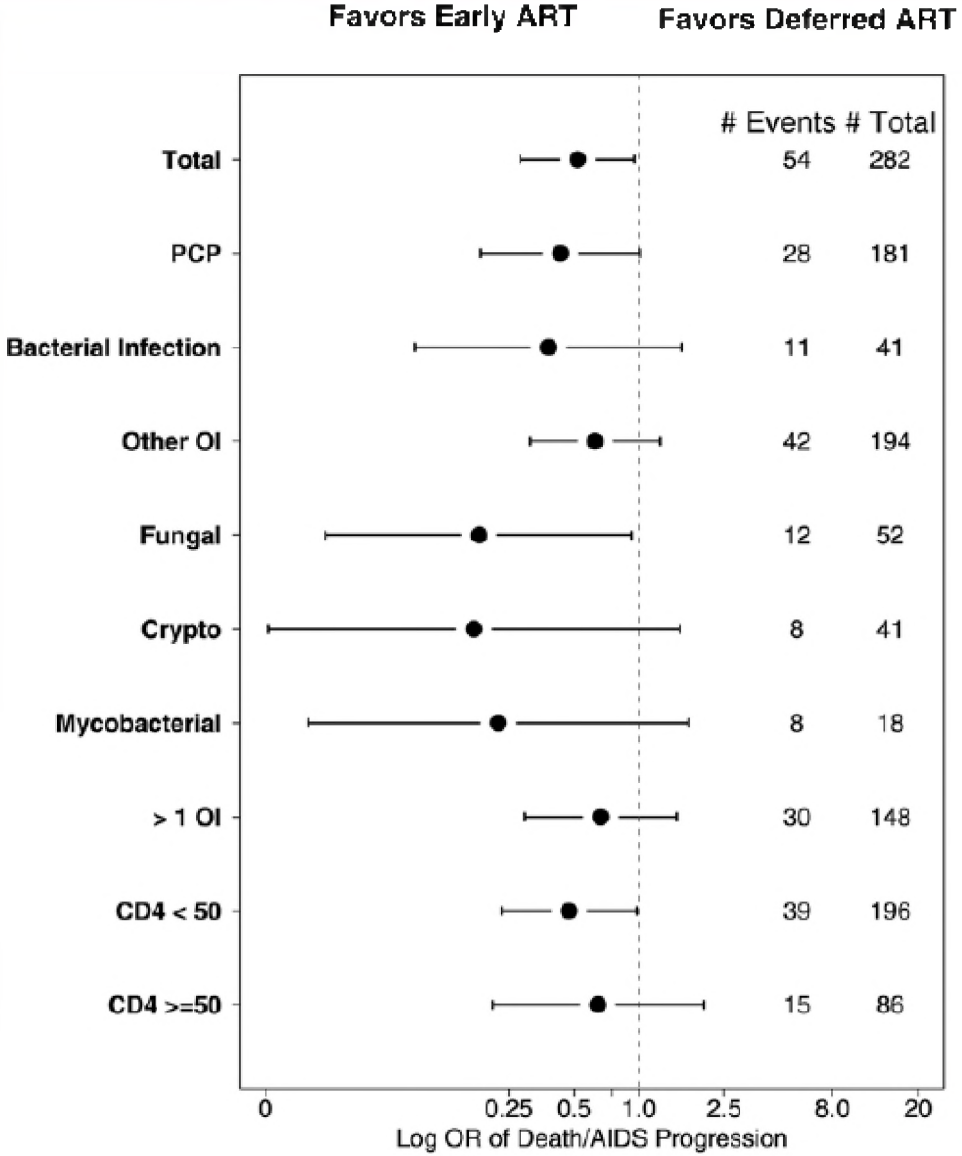


Figure 3. Time to AIDS progression or death. HR=0.53 Early versus Deferred ART [95%CI 0.30–0.92 p=0.023].



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

Zolopa A, *et al* PLoS One 2009; 4(5): 5575

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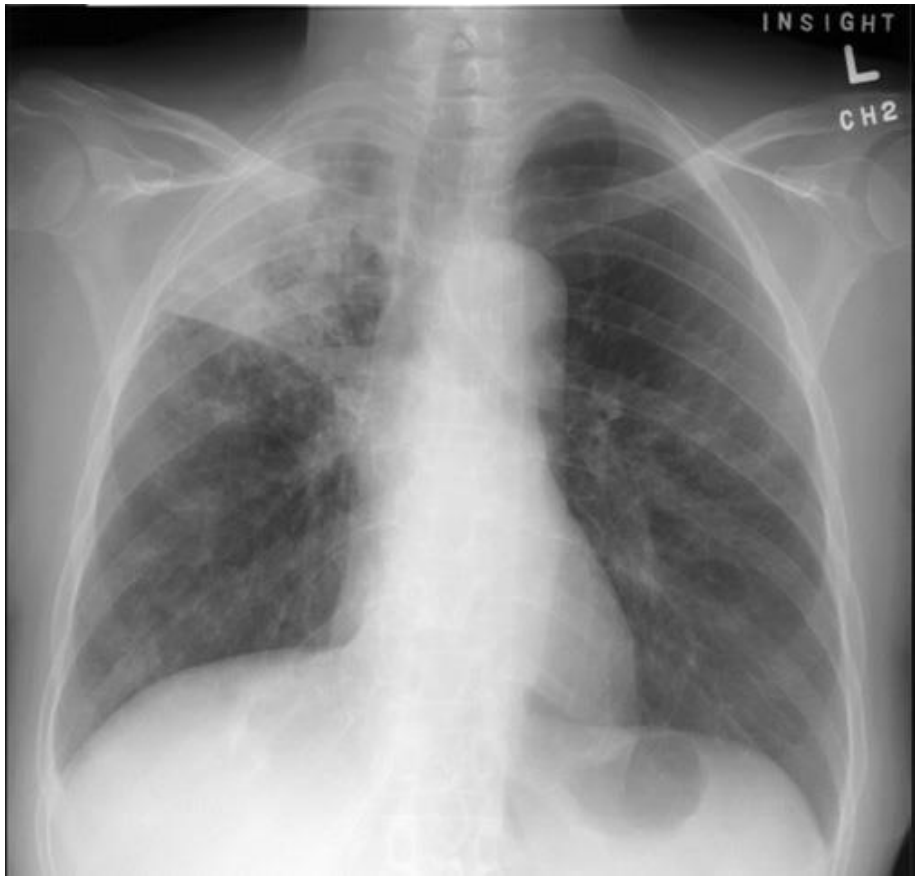
Case 2

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?



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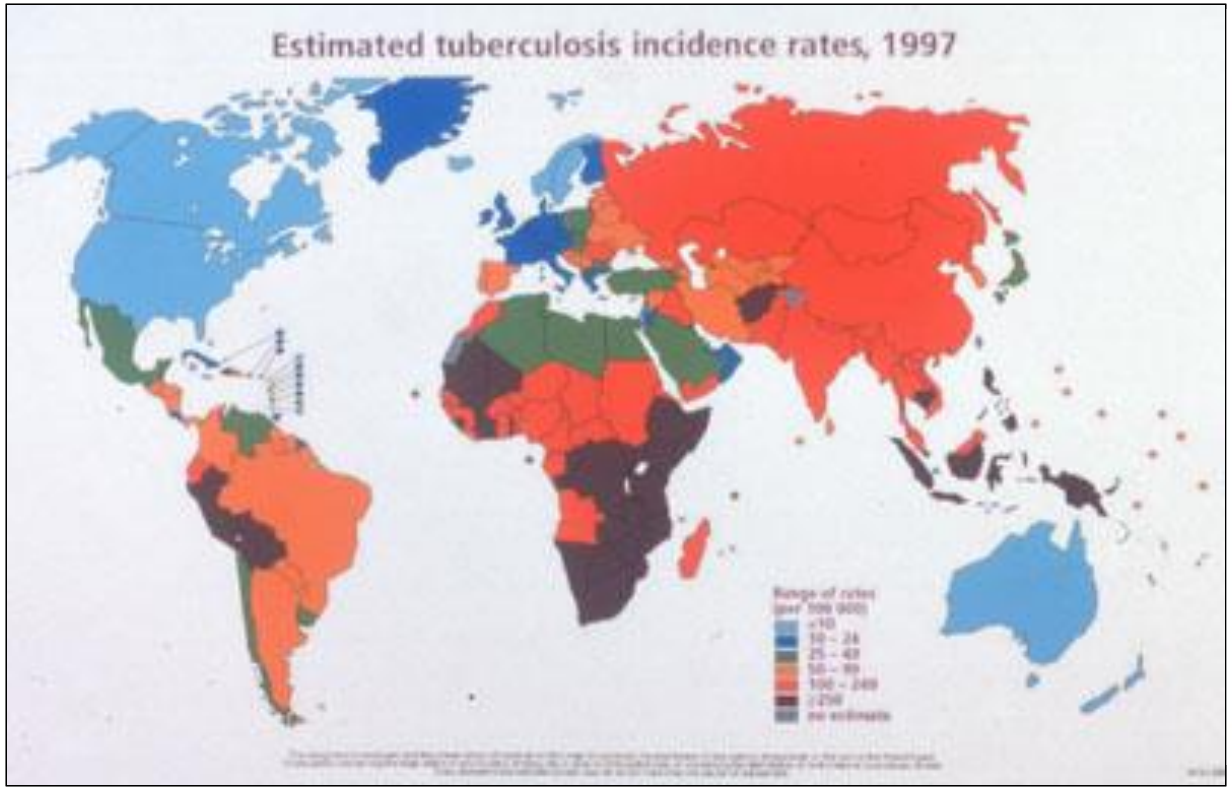
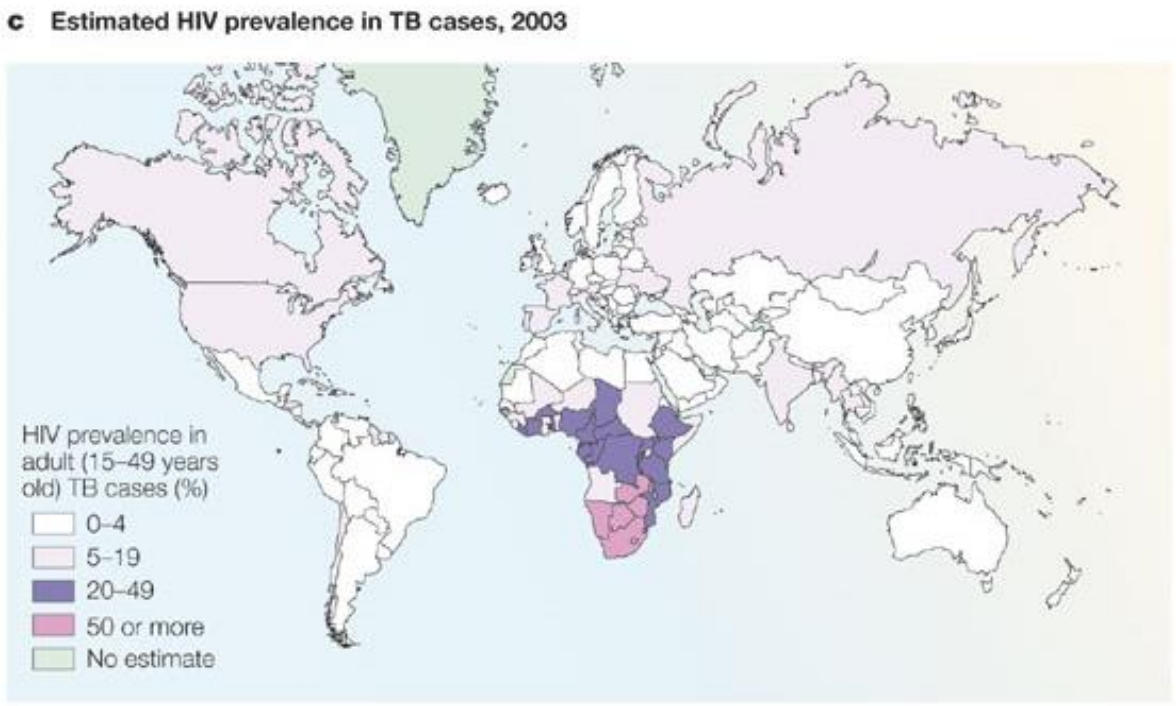
Epidemiology

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





Nunn, Nature Reviews, 2005
Harries, Int J Tuberc Lung Dis 2006;10:1306-11

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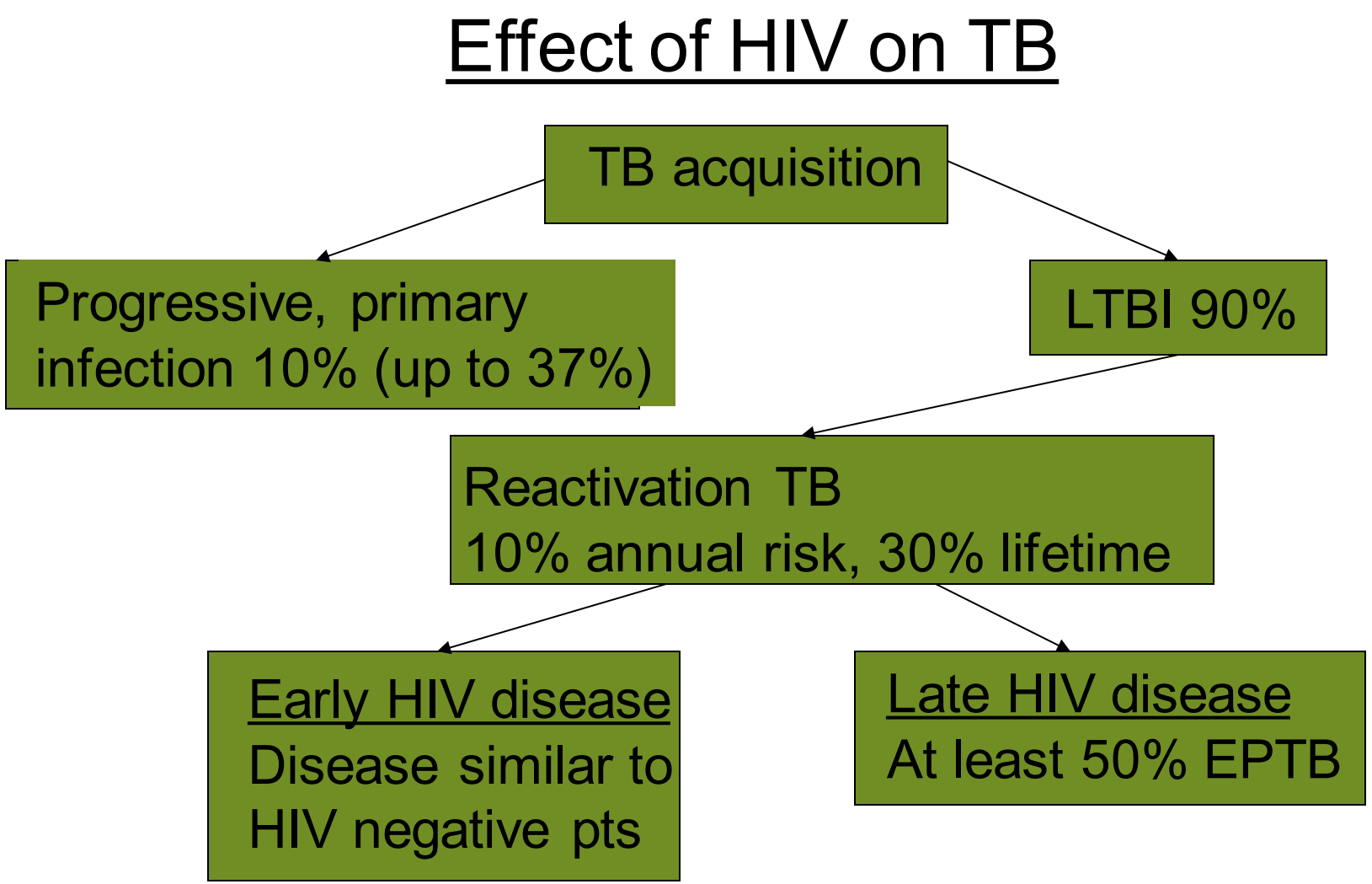
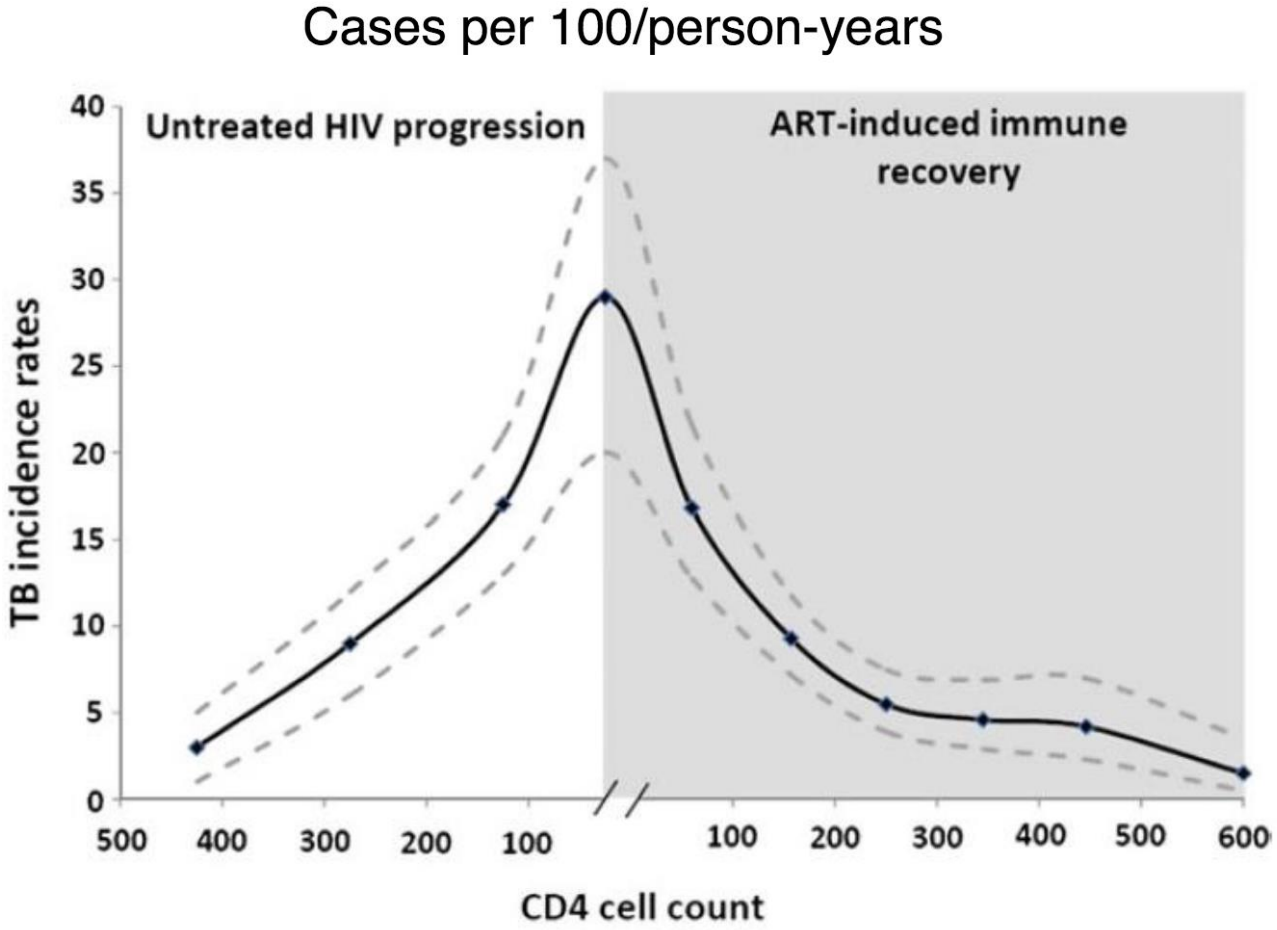
Pathogenesis and Natural History



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

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Tuberculosis and HAART: Timing

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2011 VOL. 365 NO. 16

Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

François-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., Claire Rekacewicz, M.D., Eric Nerrienet, Ph.D., Yoann Madec, Ph.D., Olivier Marcy, M.D., Sarin Chan, M.D., Narom Prak, M.D., Chindamony Kim, M.D., Khemarin Kim Lak, M.D., Chanroeurn Hak, M.D., Bunnet Dim, M.D., Chhun Im Sin, M.D., Sath Sun, M.D., Bertrand Guillard, M.D., Borann Sar, M.D., Ph.D., Sirenda Vong, M.D., Marcelo Fernandez, M.D., Lawrence Fox, M.D., Ph.D., Jean-François Delfraissy, M.D., Ph.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team*

ORIGINAL ARTICLE

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew L. Gray, M.Sc.(Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S.(Epi.), Santhanalakshmi Gengiah, M.A.(Res.Psych.), Anushka Naidoo, M.Med.Sci.(Pharm.), Niraksha Jithoo, M.B., Ch.B., Gonasagrie Nair, M.B., Ch.B., M.P.H., Wafaa M. El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

ORIGINAL ARTICLE

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

Diane V. Havlir, M.D., Michelle A. Kendall, M.S., Prudence Ive, M.D., Johnstone Kumwenda, M.B., B.S., Susan Swindells, M.B., B.S., Sarojini S. Qasba, M.D., Anne F. Luetkemeyer, M.D., Evelyn Hogg, B.A., James F. Rooney, M.D., Xingye Wu, M.S., Mina C. Hosseinipour, M.D., Umesh Lalloo, M.B., Ch.B., Valdilea G. Veloso, M.D., Fatuma F. Some, M.B., Ch.B., N. Kumarasamy, M.D., Nesri Padayatchi, M.D., Breno R. Santos, M.D., Stewart Reid, M.D., James Hakim, M.B., Ch.B., Lerato Mohapi, M.D., Peter Mugyenyi, M.D., Jorge Sanchez, M.D., Javier R. Lama, M.D., Jean W. Pape, M.D., Alejandro Sanchez, M.D., Aida Asmelash, M.D., Evans Moko, M.B., Ch.B., Fred Sawe, M.B., Ch.B., Janet Andersen, Sc.D., and Ian Sanne, M.D., for the AIDS Clinical Trials Group Study A5221*

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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)
Havlir (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)

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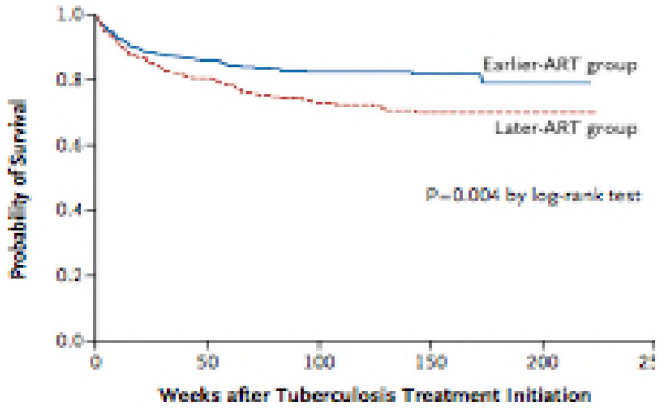
Tuberculosis and HAART: Timing

Blanc, Cambodia



Havlir, Africa, Asia, NA, SA

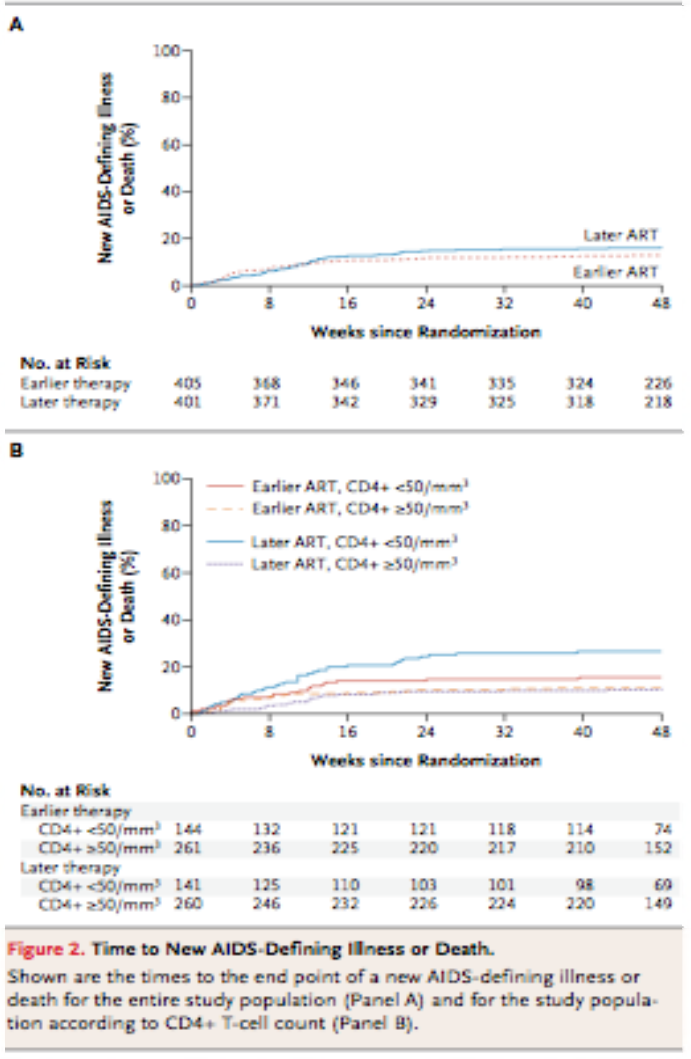


Figure 2. Time to New AIDS-Defining Illness or Death.
Shown are the times to the end point of a new AIDS-defining illness or death for the entire study population (Panel A) and for the study population according to CD4+ T-cell count (Panel B).

Karim, South Africa

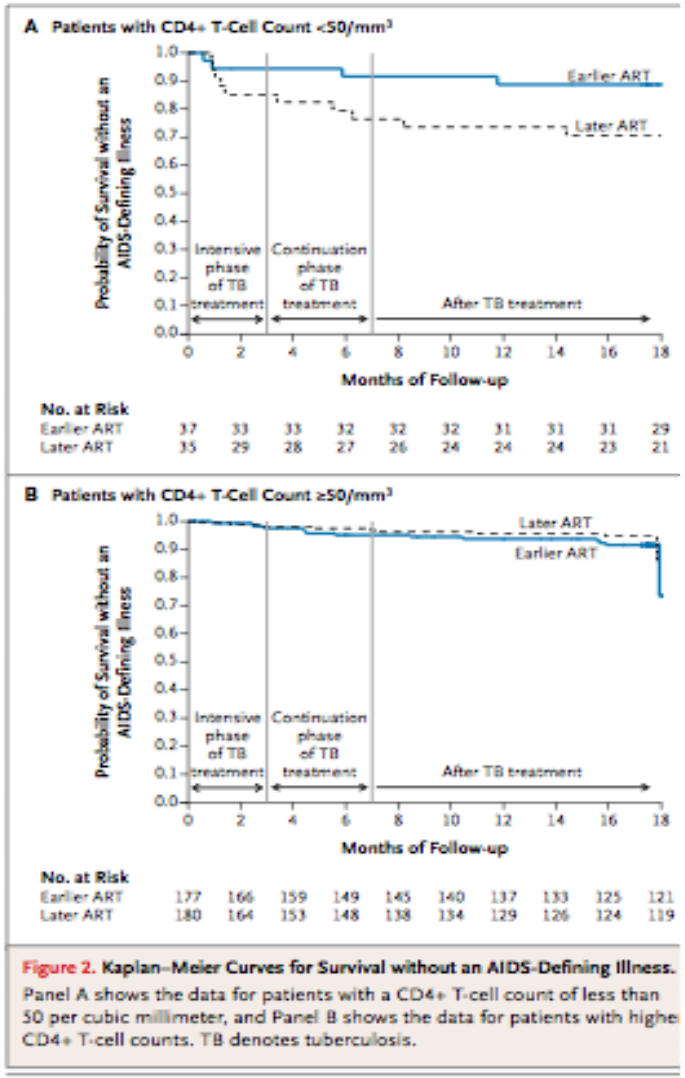


Figure 2. Kaplan–Meier Curves for Survival without an AIDS-Defining Illness.
Panel A shows the data for patients with a CD4+ T-cell count of less than 50 per cubic millimeter, and Panel B shows the data for patients with higher CD4+ T-cell counts. TB denotes tuberculosis.

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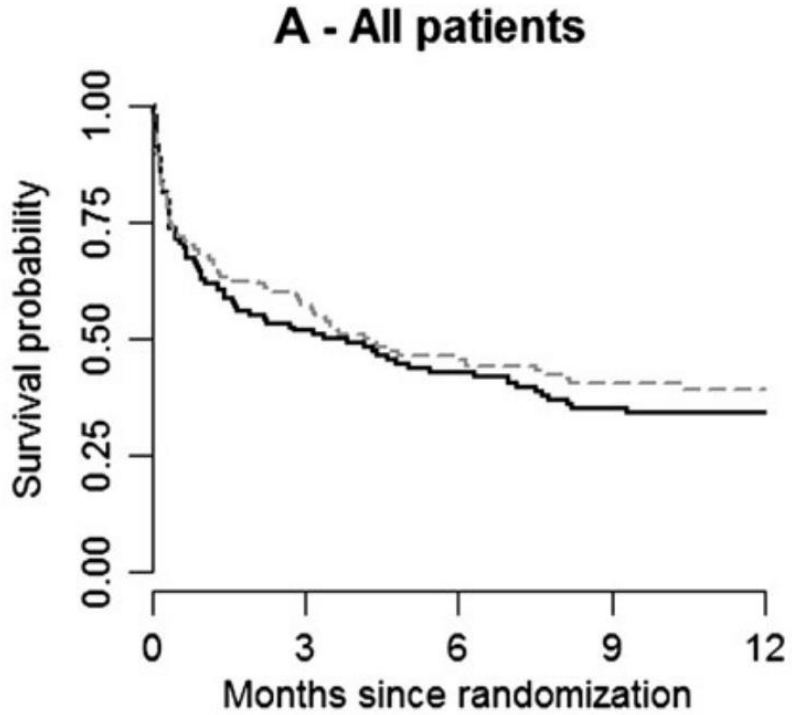
TB Meningitis and HAART – Be Careful

- 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



Torok, CID, 2011

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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	EVF decreased 28% - OK	OK
Nevirapine	NVP decreased by 20-58% - No	Not tested
Etravirine	Decreased ETR - No	Not tested
Rilpivirine	RLP decreased by 80% - No	Not tested
Doravirine	DOR decreased 88% - No	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	RAL decreased 40%, dose: 800 bid	RAL AUC increased 70% - OK
c/Elvitegravir	Significant decrease in ELV – No	DTG – probably OK
Dolutegravir	DTG decreased - dose DTG 50 bid	ELV – No
Bictegravir	BIC decreased 75% - No	BIC - No

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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.

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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 (≥4 weeks)
  - Goal: 250 participants in each arm
  - Primary endpoint: 6-month survival
  - Stratified by MS (GCS 15 vs. <15) and CSF WBC (≥ 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)]

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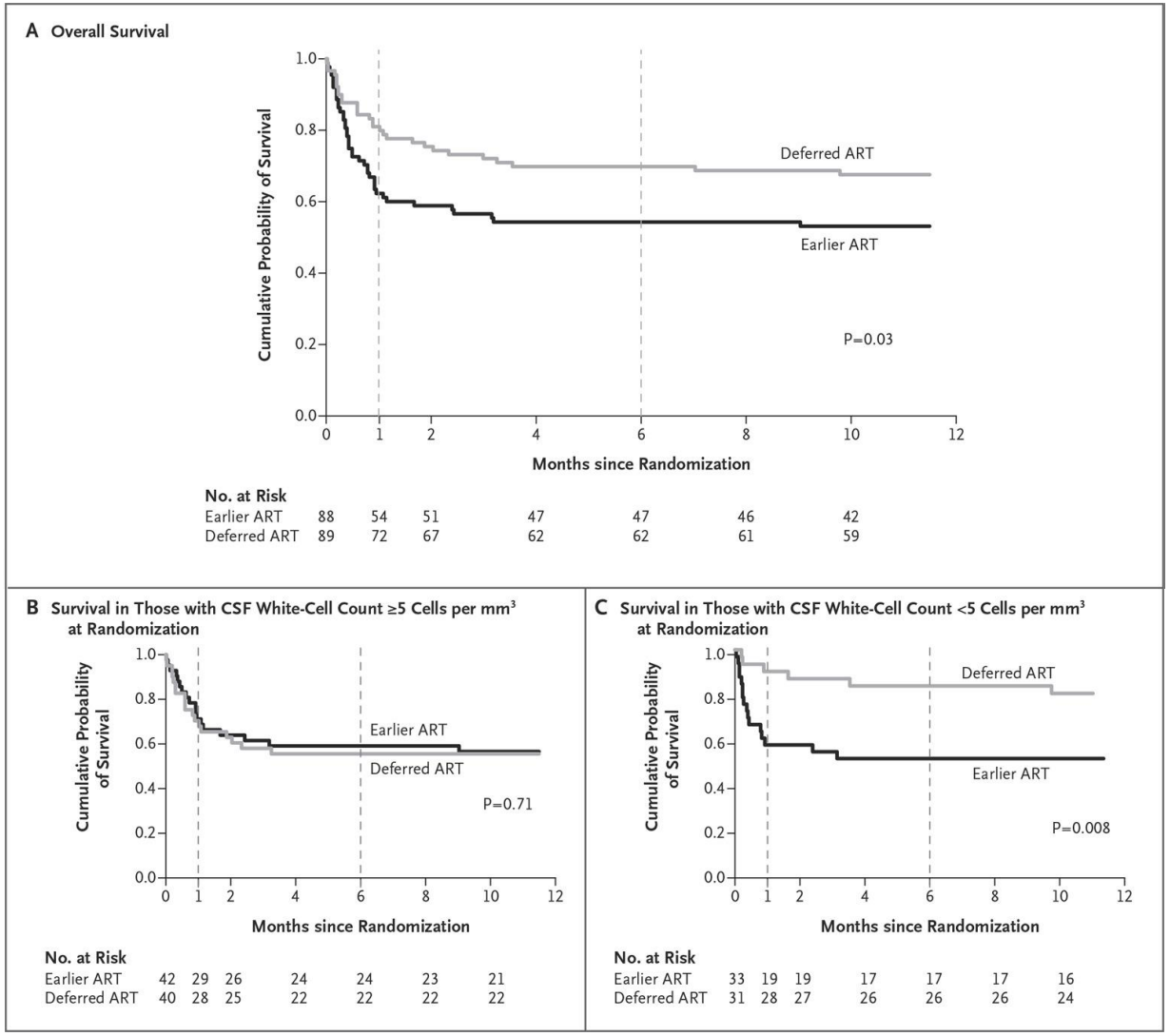
COAT: Cryptococcal Optimal ART *Timing*



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

Boulware D et al, NEJM, 2014

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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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