NORTHWEST AIDS EDUCATION AND TRAINING CENTER

TB and HIV Co-infection, 2012

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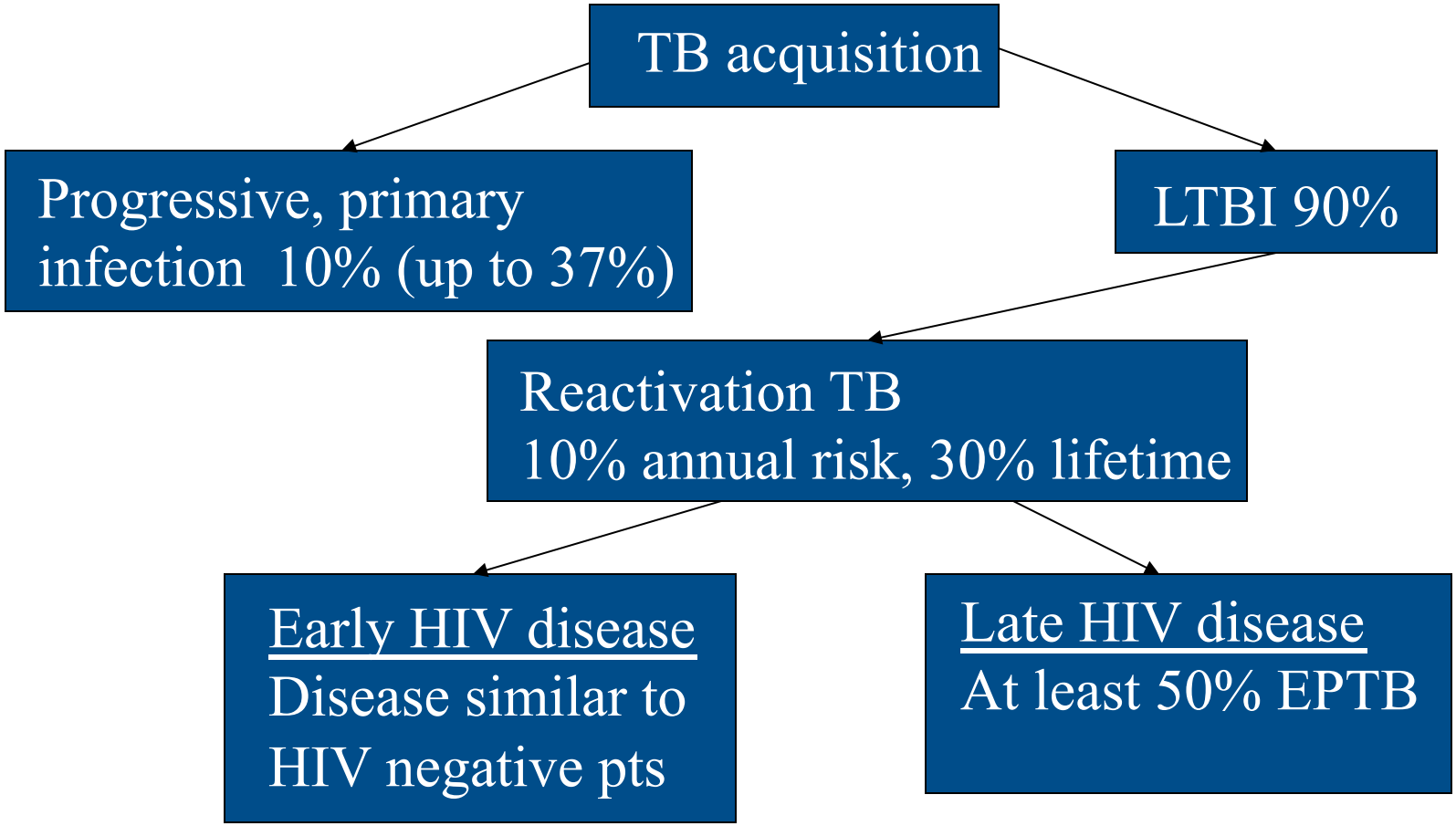
Epidemiology, Pathogenesis and Presentation

TB and HIV Facts , 2012

- At least 1/3 of all HIV infected patients are infected with TB
- 2008
  - 9.4 million incident cases of TB
  - 1.4 million were among HIV+
- 2010
  - 1.1 million cases of TB among 34 million HIV+
  - 350,000 deaths

(WHO Global TB Control 2009 and 2011)

Pathogenesis and Natural History



Clinical Presentation

	Late HIV (CD4 < 200)	Early HIV
PTB:EPTB	50:50	80:20
Presentation	Resembles primary TB	Resembles reactivation
CXR		
LNs	Common	Rare
Lower lobes	Common	Rare
Cavitation	Rare	Common
Anergy	Common	Rare
Smear +	Less common	Common
Adverse drug reactions	Common	Rare
Relapse	Common	Rare

Timing of ART

Case Presentation

- A 38 yo African man with HIV is admitted with fever, weight loss, diffuse adenopathy, a RUL infiltrate & AFB + sputum smear. He is started on RIPE therapy, TMP-SMX and Rx for CAP.
- After a week his constitutional symptoms improve. His CD4 T-cell count measures 15 cells/uL.
- When should ART be started?
  - A. Within the week
  - B. At the completion of the intensive phase of TB treatment (2 months)
  - C. After the completion of TB treatment (6 months)

Tuberculosis and HAART

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)

(Blanc, NEJM; 2011, Havlir, NEJM, 2011, Karim, NEJM, 2011)

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TB Meningitis and HAART

R, DB, PC trial of 253 pts with TB meningitis

All received RIPE + Dex

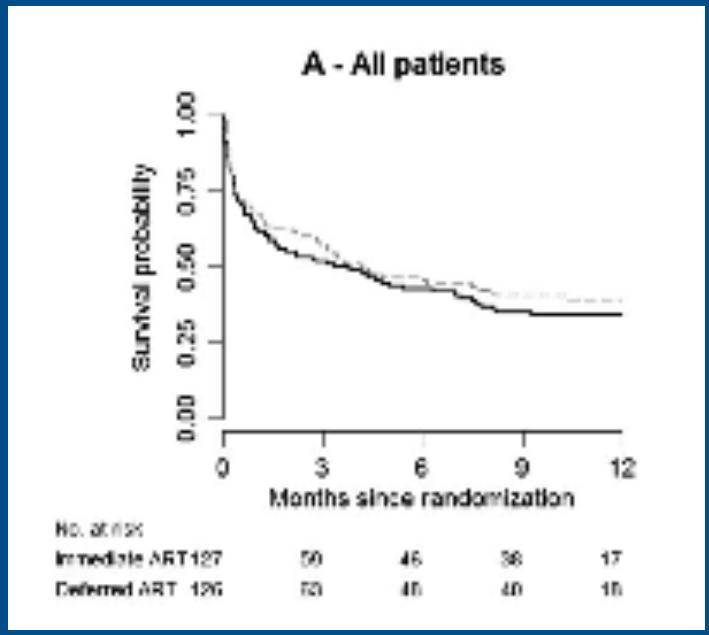
ART (3TC/AZT/EFV) was given either

- Immediately (~ 1 week)
- After 2 months of TB Rx

Results

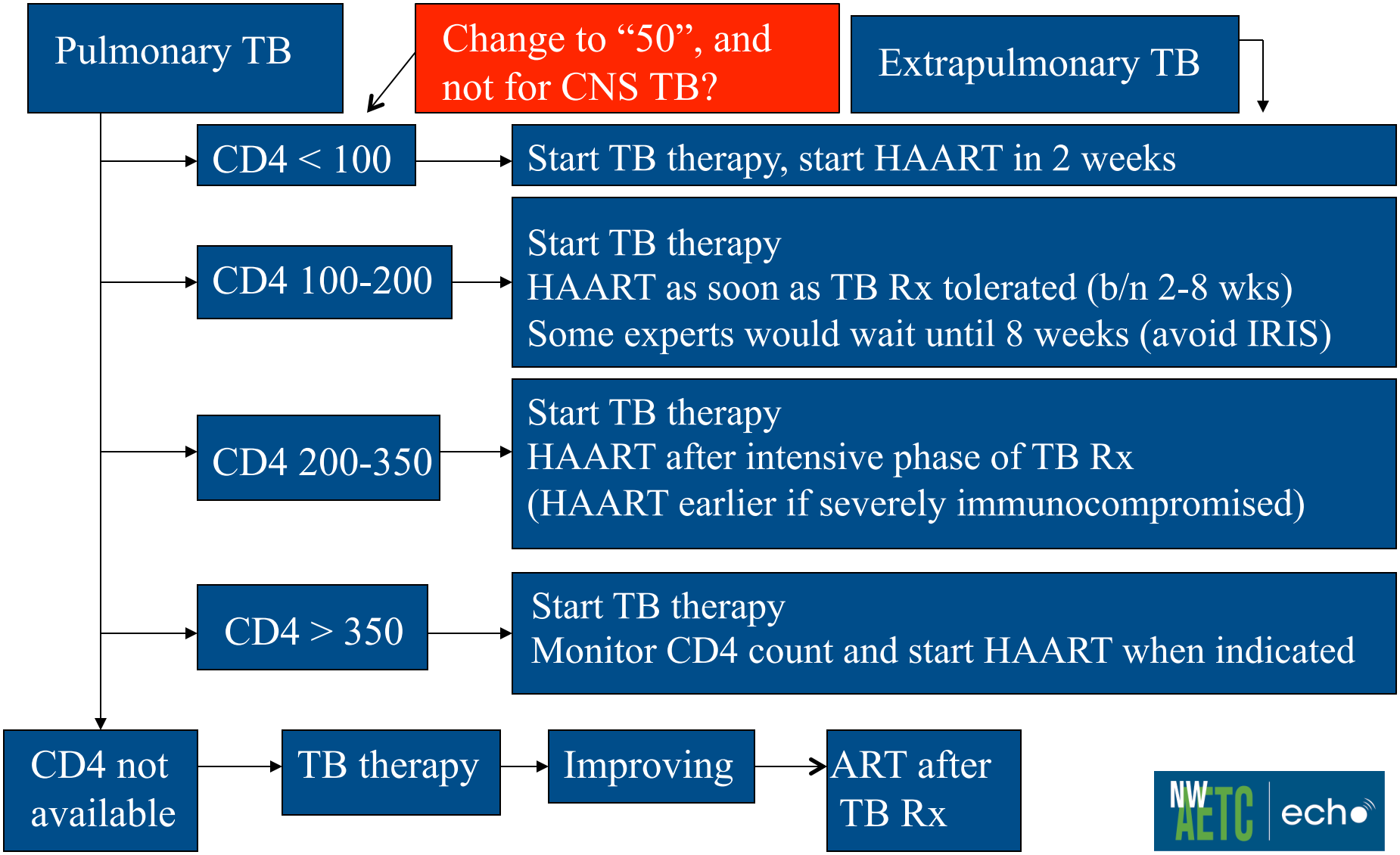
- No difference in mortality or new AIDS dx between groups
- More grade 4 AE in the immediate group
- No difference in neurological events between groups

Survival



(Torok, CID, 2011)

WHO/DHHS: Treatment



ART and Anti-TB Therapy: The Details

Case Presentation

…back to our patient. You decide to initiate ART now.

- What ART regimen is best
  - A. Atripla (EFV/FTC/TDF)
  - B. Atripla + 200 mg EFV
  - C. Nevirapine (200 mg per day for 2 weeks, then 200 mg BID) + FTC/TDF
  - D. Nevirapine 200 mg BID + FTC/TDF
  - E. Ritonavir-boosted Atazanavir + FTC/TDF and change rifampin to rifabutin at 150 mg QOD
  - F. Raltegravir 400 mg BID + FTC/TDF
  - G. Atripla and swap out the rifampin for a quinolone

TB/HIV Co-infection: Principles of Treatment

- Treatment generally the same as in HIV- patients (4 drugs for 2 months and 2 drugs for 4 months)
- Sub-optimal response (culture + after 2 months) – give 9 months, skeletal TB – 6 to 9 months, CNS TB – 9 to 12 months
- If using regimens without INH or a rifamycin - duration should be 12 to 15 months

Principles of Treatment: Its All About Rifampin

- Treatment with NON rifamycin-containing regimens is associated with:
  - Higher relapse rates
  - Higher mortality

Wallis, et al. (1996) Tuber Lung Dis 77:516-23
Hawken, et al. (1993) Lancet 342:332-38
Perriens, et al. (1991) AM Rev Resp Dis 144:750-55
Korwnromp, et al. (2003) CID 37:101-12

Principles of Treatment: Its All About Rifampin

Intermittent Rifamycin Dosing: A Bad Idea

- Randomized study of weekly INH-rifapentine vs 2X/week INH-rifampin (cont phase)
  - Relapse in 5/30 (17%) vs 3/31 (10%)
  - 4/5 relapses in rifapentine arm were R to rifampin
  - These patients had lower CD4 count (16), more extra-pulmonary TB and more azole exposure
- Other studies of acquired rifampin resistance: all patients have CD4 < 100 and all patients on intermittent dosing in intensive phase of Rx

Vernon, et al. (1999) Lancet 353:1843-47.
Li, et al. (2005) CID 41:87-91

Principles of Treatment: Its All About Rifampin

Nevirapine Vs Efavirenz with Rifampin-based Anti-TB Therapy

- R, cohort study in South Africa 2001-06
- N=4117
  - 1975 started NVP, 249 had TB and 96 completed 18 months of follow up
  - 2142 started EFV, 1181 had TB and 238 completed 18 months of follow up
  - EFV dose 600 mg per day, NVP dose 200 mg /day lead-in then 200 mg BID
- Outcome: time to failure (VL > 400 or second VL > 5000)

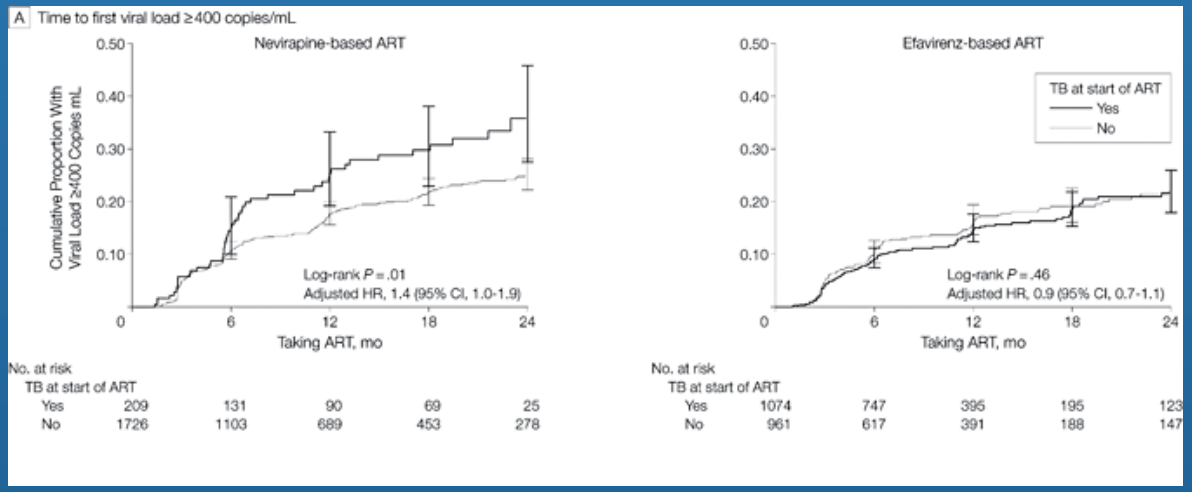
Boulle, JAMA, 2008

Principles of Treatment: Its All About Rifampin

Time to VL > 400 copies

Nevirapine

Efavirenz



These data from patients on TB Rx who are then started on HAART

Patients already on HAART who develop TB and are started on rifampin - no difference in failure rate between those on EFV and NVP

Boulle, A. et al. JAMA 2008;300:530-539

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Principles of Treatment: Its All About Rifampin

Rilpivirine with Rifampin

- 16 healthy HIV negative volunteers given rilpivirine and rifampin for 7 days – led to declines in rilpivirine: AUC24 80%, Cmax 69%, Cmin 80%. No effect of rilpivirine on rifampin

- 18 healthy HIV negative volunteers given rilpivirine and rifabutin for 11 days – lead to declines in rilpivirine: : AUC24 46%, Cmax 35%, Cmin 49%. No effect of rilpivirine on rifabutin

(Ford, HIV/AIDS, 2011)

Principles of Treatment: Its All About Rifampin

Protease Inhibitors and Rifampin

- Rifampin will induce the metabolism of Pis (including R-boosted PIs) DON'T DO IT!!!!
- Rifabutin may be substituted for rifampin but:
  - Need to dose reduce to avoid ribabutin toxicity (uveitis and cytopenias) but…..
  - Lower dose ribabutin (150 mg QOD) has been associated with relapsed TB and the development of rifampin resistance
  - If patients interrupts ARV treatment – they will be on insufficient doses of rifabutin

(Jenny-Avital, CID, 2009)

Principles of Treatment: Its All About Rifampin

Raltegravir and Rifampin

- Patients taking rifampin for TB and on Raltegravir-based ARV: RAL drug resistance developed in 4 patients on standard Raltegravir dosing of 400 mg BID and in 1 patient taking double dose 800 mg BID
- 19 Healthy HIV negative volunteers – given raltegravir and rifabutin: no effect of rifabutin on raltegravir pK

Maraviroc and Rifampin

- In healthy volunteers: rifampin led to a 70% reduction in Cmax and 67% reduction in AUC of MRV

(Brainard, J Clin Pharm, 2011)
(Grinsztein, IAS, 2012, ARNS 12-180 REFLATE)
(Yost, Am J Health Syst Pharm, 2009)

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Principles of Treatment: Its All About Rifampin

ARV agent	Rifampin	Rifabutin
Efavirenz	Yes: EVF at 600mg/d	Increase RFB to 450mg/d
Neviripine	Risky: No NVP lead-in	OK
Eravirine	No data, Not recommended	No data
Rilpivirine	NO	Increase rilpivirine?
Protease Inhibitors	NO	Decrease RFB to 150mg QD or QOD
Raltegravir	Increase Raltegravir to 800 mg BID	Probably OK?
Maraviroc	Increase Maraviroc	No data