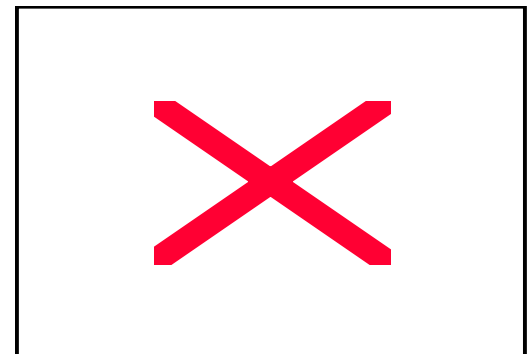
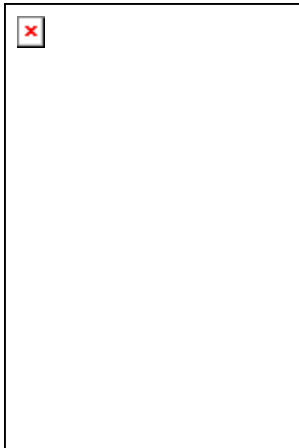


# Challenges in the Treatment of TB/HIV Co-Infected Patients

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# FOUR CHALLENGES

- When to start Antiretroviral Therapy (ART)
- What ART to start
- TB, Immune Reconstitution and ART Failure
- Second Line ART during TB treatment

# 1. When to Start Antiretroviral Therapy with a New TB and HIV Diagnosis

## BACKGROUND:

- TB is a common entry point for HIV diagnosis<sup>1</sup>
- TB occurs over broad range of CD4 cell counts<sup>2,3,4</sup>
- High rates of mortality associated with TB and low CD4 cell count<sup>2,3</sup>

## TWO ISSUES:

- Is antiretroviral therapy indicated?
- When should antiretroviral therapy be started?

<sup>1</sup>Chi, JAIDS, 2005;<sup>2</sup>Ya Diul, AIDS, 2001,  
<sup>3</sup>Ackah, Lancet, 1995, Scano, IAS, 2005

# IS ANTIRETROVIRAL THERAPY INDICATED?

## YES

CD4 < 200-350

AIDS/WHO STAGE 4

DISSEMINATED TB

## UNCERTAIN

CD4 > 350

**CAVEATS: CD4 may be transiently depressed, CD4 may not be available, Diagnosis of TB difficult**

# When to Start ART: Immediately?

TB, HIV+  
CD4<350



TB TREATMENT



ANTIRETROVIRAL THERAPY

# When to Start ART: Month 2?

TB, HIV+  
CD4<350



TB TREATMENT



ANTIRETROVIRAL THERAPY

# When to Start ART: After TB Treatment ?

TB, HIV+  
CD4<350



TB TREATMENT



ANTIRETROVIRAL  
THERAPY

# Potential Benefits and Risks of Starting ART Immediately With TB Treatment

## BENEFITS

- Reduced morbidity<sup>1,2</sup>
- Reduced mortality<sup>1,2</sup>
- Improved TB outcome

## RISKS

- Increased toxicity to TB and ART therapy<sup>3</sup>
- Drug interactions between HIV and TB medications<sup>3</sup>
- Pill burden
- Immune Reconstitution Syndromes (IRS)<sup>4</sup>

<sup>1</sup> Dean, AIDS, 2002; <sup>2</sup>Pedral-Sampaio, 2004, Brazil JID; <sup>3</sup>Harries, Lancet, 2006; <sup>4</sup>Lawn, Lancet ID, 2005

## Randomized “When to Start ART Treatment in TB” Studies

TRIAL/ SPONSOR	CD4/ N	ART	ART Randomization
CAMELIA ANRS 1295/NIH	<200 N=660	EFV/D4T/3TC	ART 2 vs 8 weeks
AA5221 NIH	<200 N=800	EFV/TDF/FTC	ART 2 vs 8-12 weeks
START NIH	>50 N=592	DDI/3TC/EFV	During vs after TB treatment

Blanc, 2006

**Table 13 - Initiating first line ART in relationship to starting anti-TB therapy**

CD4 Cell Count		ART recommendations	Timing of ART in relation the start of TB treatment
	CD4 < 200 cells/mm <sup>3</sup>	Recommend ART <sup>a</sup>	Between 2-8 weeks <sup>b</sup>
	CD4 between 200-350 cells/mm <sup>3</sup>	Recommend ART	After 8 weeks
	CD4 > 350 cells/ mm <sup>3</sup>	Do not initiate ART <sup>c</sup>	Re-evaluate patient at 8 weeks and at the end of TB treatment
	CD4 not available	Recommend ART <sup>d</sup>	Between 2-8 weeks

**a** an EFV containing regimen is the preferred first line regimen. Alternative first line treatment regimens to the EFV include NVP and triple NRTI (TDF- or ABC-based) regimens. For NVP containing regimens ALT should be checked at 4, 8 and 12 weeks and symptom directed thereafter.

**b** Start ART as soon as TB treatment is tolerated.

**c** If other non-TB Stage 3 or 4 events are present, start ART.

**d** For some TB diagnoses that respond well to anti-TB therapy (i.e. straightforward pulmonary TB, single lymph node TB, uncomplicated pleural effusion) consider delaying ART till after 8 weeks of therapy.

## 2. What ART to Start: Issues

- Drug Interactions
- Toxicity
- Teratogenicity

# Drug Interactions: HIV and TB Medications

- Rifampin is a potent inducer CYP3A of hepatic p450 system<sup>1</sup>
- NNRTI and PI levels are reduced in the presence of rifampin<sup>1</sup>
- Rifampin (vs non- rifampin) regimens have superior outcomes in TB treatment<sup>2,3</sup>

<sup>1</sup>Finck, Archives, 2002; <sup>2</sup>Jindani, Lancet, 2004;  
<sup>3</sup>Corbett, Lancet, 2006

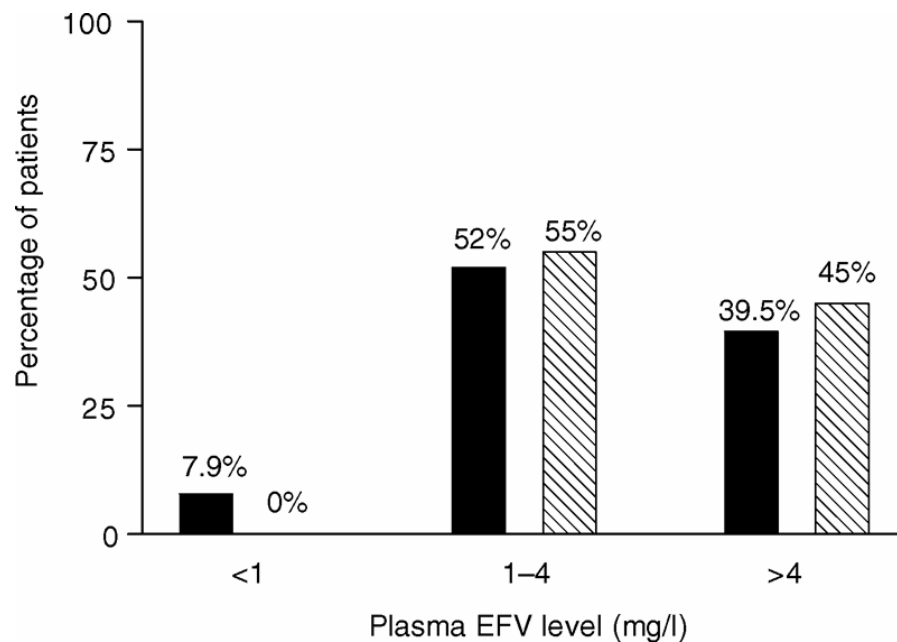
# Rifampin Interactions: First Line HIV Antiretroviral Therapy

- Efavirenz (EFV) and nevirapine (NVP) exposure reduced 20-40% with rifampin<sup>1,2,3,4</sup>
- Small PK studies support dose increase of EFV (800 mg) and NVP(300 mg bid)<sup>5,6</sup>
- There is large interpatient variability due to genetic determinants of metabolism<sup>7</sup>
- Clinical outcome studies to date do not support dose adjustment of EFV or NVP

<sup>1</sup>Ribera, JAIDS, 2001; <sup>2</sup>Lopez-Cortes, Clinical PK, 2002; <sup>3</sup>Manosuthi, AIDS, 2005 ; <sup>4</sup>Manosuthi, CID, 2006

<sup>5</sup> Lopez-Cortes, Clinical PK, 2002; <sup>6</sup>Ramachandran, JAIDS, 2006; <sup>7</sup>Haas, AIDS, 2004

# Clinical Outcomes Not Different with Efavirenz 600 mg vs 800 mg



**Fig. 2. Proportions of patients with plasma efavirenz (EFV) level < 1, 1-4 and > 4 mg/l in patients receiving 600 mg (n = 38; black columns) and 800 mg (n = 40; hatched columns) daily.**

*From: Manosuthi: AIDS, Volume 19(14).September 23, 2005.1481-1486*

# Efavirenz and Nevirapine TB treatment Studies

SITE	REFERENCE	ART	OUTCOME: TB vs no TB
India (N=126)	Patel, JAIDS, 2004	EFV/D4T/3TC	CD4 rise similiar
Thailand (N=70)	Manosuthi, CID, 2006	EFV/TDF/FTC	CD4/RNA changes similar
South Africa (N=153)	VanCutsem, IAS, 2005	NVP/ 3TC/EFV	CD4/RNA changes similar

# Overlapping toxicities of ART with TB Medications

TOXICITY	ART	TB
Hepatitis	NVP, EFV	INH,Rif , PZA
Rash	NVP, EFV	INH,Rif , PZA
Hematologic	ZDV	Rif
Gastrointestinal	ZDV, d4T	Rif/PZA
Neuropathy	d4T, ZDV	INH, ETB

**Trimethoprim-sulfa also has overlapping toxicities**

## HIV/TB in Women of Child Bearing Potential



- EFV is contraindicated first trimester or in women where adequate contraception cannot be insured
- Nevirapine is an alternative, but careful monitoring is recommended, especially in women with >250 CD4 cell counts
  - Patient education, bi-weekly visits, ALT/AST at 0,2,4,8 and 12 weeks,
- Triple NRTI<sup>1</sup> is an alternative

<sup>1</sup>ZDV/3TC/ABC  
or ZDV/3TC/TDF

# 2006 WHO Guidelines: First Line ART Regimens and Active TB

<u>Regimen</u>	<u>Recommendation</u>	<u>Monitoring</u>
EFV/2NRTI	Preferred	Pregnancy
NVP/2NRTI	Alternate	ALT
Triple NRTI <sup>1</sup>	Alternate	HSR <sup>2</sup> with abacavir

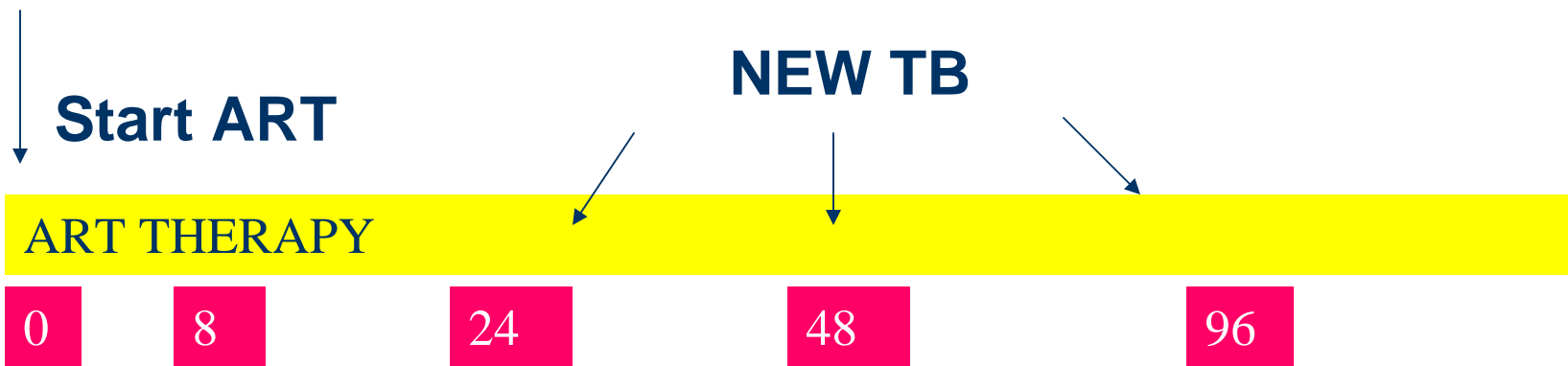
<sup>1</sup> ZDV/3TC/ABC or ZDV/3TC/TDF

<sup>2</sup> Hypersensitivity reaction

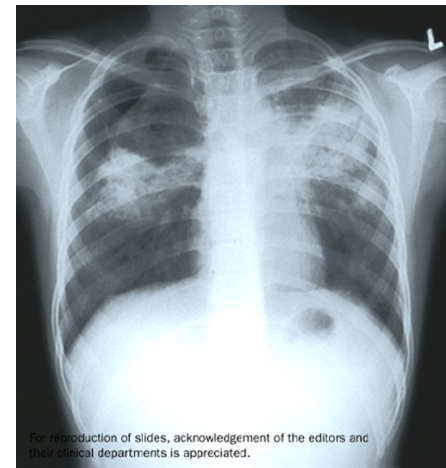
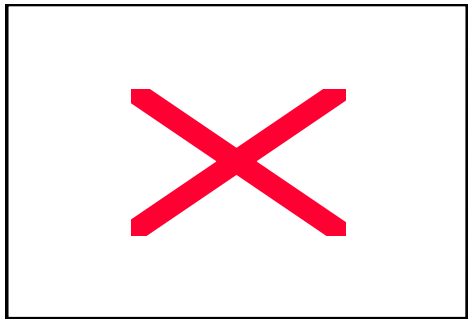
### **3. Determining if TB indicates ART Failure**

When TB develops after initiation of ART, does this indicate HIV treatment failure?

# TB and HIV Treatment Failure



WEEK ON ARV



## Clinical Scenario

23 year old female baseline CD4 35, start ART, develops pulmonary TB at 12 months. CD4 is 52. Patient states she is adherent to ART.

Does TB indicate ART failure????

# TB Early After ART Initiation

- Undiagnosed TB
- Activation of latent TB
- Transmitted TB
- Immune reconstitution<sup>1,2,3</sup>

<sup>1</sup>Seyler, AJRCC, 2005; <sup>2</sup>Breen, AIDS, 2005;  
<sup>3</sup>Lawn, AIDS, 2005

# TB Cases After ART Initiation

	<u>CAMB</u>	<u>THAI</u>	<u>KENYA</u>	<u>MALA</u>	<u>CAMER</u>
<b>PULM TB</b>	7.6*	10.4	17.6	14.3	4.8
<b>EXTRA PULM TB</b>	12.7	4.3	6.9	2.1	6

\*cases/100 PY

Bonnet, AIDS, 2006

## IDI/Makerere University, Kampala Uganda Study

- 538 HIV+/ART naïve/no evidence of TB
- TB developed in 25 subjects after ART
- TB incidence of 4.7 cases/100 PY
- TB diagnosed 17 weeks ( 3-50) after ART
- Median CD4 133
- HIV RNA undetectable in 14/25 cases

## Summary: TB as Indicator of ART Failure

- Early TB cases within first year of ART are common
- Most cases represent existing TB disease, and *not* ART failure
- Goal should be seamless transition to TB regimen with compatible ART regimen
- Improved TB diagnostics, access to HIV RNA would assist in management

## 4. Second Line ART and TB

- Drug interactions between rifampin and protease inhibitors
- Drug toxicity
- Drug Cost

# Protease Inhibitors and Rifampin

## Regimen

PI +2 NRTI

Boosted PI +2 NRTI

## Disadvantages

- PI levels decrease by >70%, cannot use with rifampin

- Drug interactions
- Cost
- Cold chain
- Toxicity

# Boosted PIs and Rifampin Interaction

## Lopinavir/rit

- Ritonavir 400 bid required
- GI toxicity and lipid perturbation
- High rates of elevated transaminase<sup>1</sup>

<sup>1</sup>La Parte, AAC, 2004

## Saquinavir/rit

- SQV 1000/rit100 BID
- 39% hepatitis
- Transaminase elevations 20x upper normal<sup>2</sup>

<sup>2</sup>Roche Dear Doctor, 2005

# What about Rifabutin?

## Benefits

**Can be administered  
With PIs**

## Limitations

**Expensive! Cost of 4 days of  
rifabutin = cost of an entire rifampin  
regimen**

**Toxicity: marrow suppression,  
arthralgias, uveitis**

**Dosing: Dose adjustments of ART  
regimens**

# The Future: New TB Drugs

	Development stage	Sponsor/coordinator
Gatifloxacin	Phase III	European Commission/OFLOTUB consortium, Institut de Recherche pour le Développement, WHO TDR, Lupin
Moxifloxacin	Phase II/III	Bayer, TB Alliance, Centers for Disease Control and Prevention, University College London, Johns Hopkins University
TMC 207 (previously R207910)	Early bactericidal activity	Johnson and Johnson (Tibotec)
OPC-67683	Early bactericidal activity	Otsuka Pharmaceutical
PA-824	Phase I	TB Alliance
LL-3858	Phase I	Lupin

<sup>1</sup>Spigelman, Lancet, 2006

# Conclusions

1. There are major challenges in treating HIV+/TB patients that define an urgent research agenda: First line ART, second line ART, treatment strategies
2. Research is key to move from “opinion” to evidence based approaches to treatment of TB and HIV
3. Treatment of HIV in TB patients must proceed with best available data while we are awaiting results of research
4. Integration of TB and HIV care is and will be critical for success of treatment of both diseases

# Challenges = Opportunities to improve outcomes for both TB and HIV

## HIV/TB Collaborators

### MU-CWRU Collaboration

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