Challenges of TB in the HIV-infected child

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- Epidemiology: Common, but incidence uncertain
- Clinical manifestations: Rarely cavitary, often disseminated
- Diagnosis: Difficult- need to overtreat
- Treatment: Need to start HAART, but difficult drug interactions
- Disease control:
  - HIV prevention
  - Aggressive TB and HIV case finding and treatment
  - Role for INH treatment of latent TB, but not all HIV-infected children

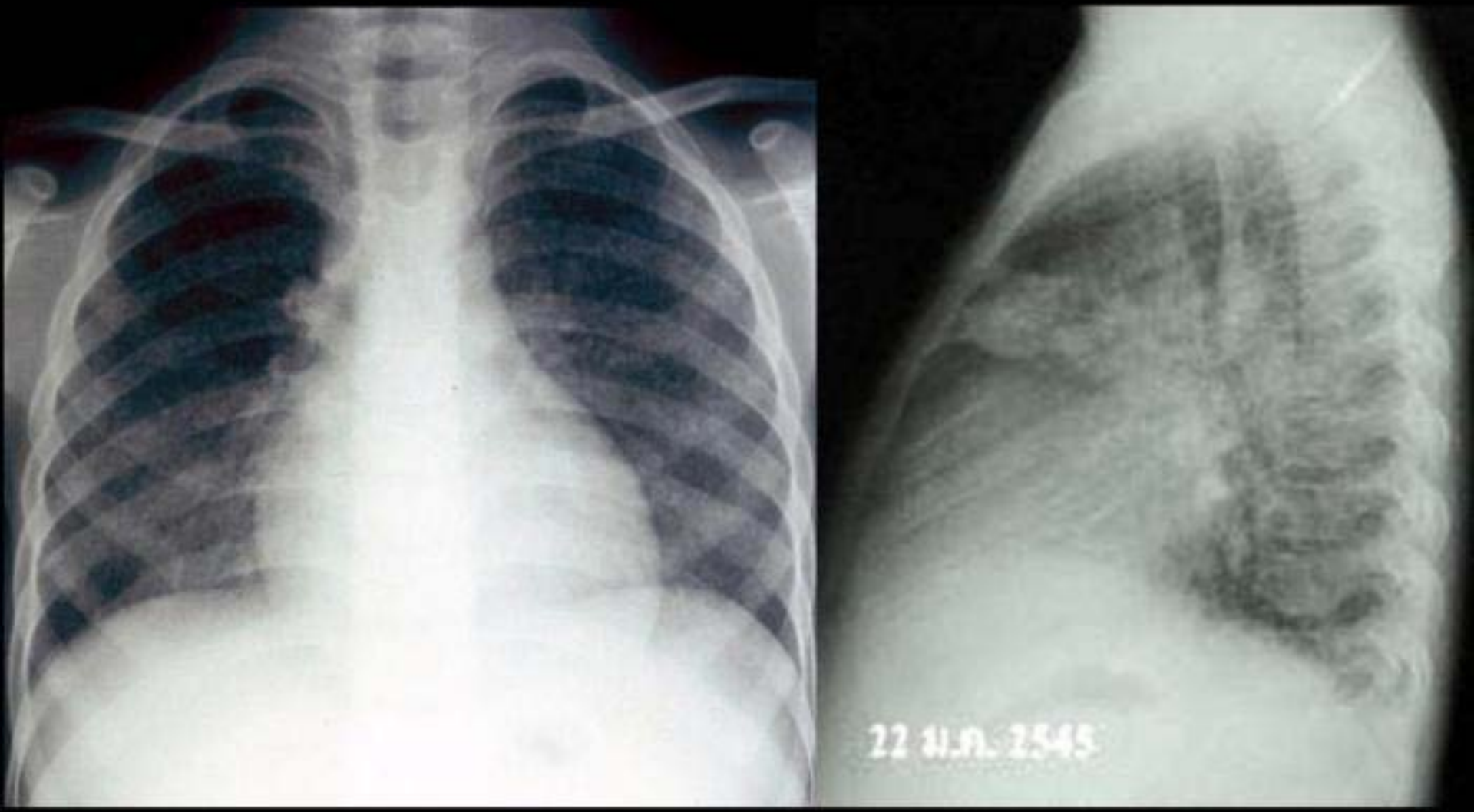
Epidemiology of tuberculosis in children with HIV

- Common in TB-endemic areas, but incidence difficult to determine due to diagnostic difficulty
- Often recently infected from symptomatic adult in household
- Rare in U.S.
- 1.6%/year in HIV+ children in one study
- High incidence
- High mortality in children with HIV, especially infants or if no antiretroviral therapy (ART)
- Neonatal disease: 15% mother-to-child transmission rate (*give 3 months RH or 6 months H to exposed newborn)*

Manifestations of TB in children with HIV

- Pulmonary
  - Infiltrates- primary pneumonia, more likely lower or mid lung field
  - Hilar nodes
  - Milial
  - Cavitary disease uncommon in children with HIV- disease is paucibacillary
- Disseminated disease
  - Common in children with HIV, especially infants
  - Usually have CXR findings
  - In infants, may be BCG
- Cervical adenitis *including BCG*
- *Focal e*xtrapulmonary relatively more common in HIV *negative* children

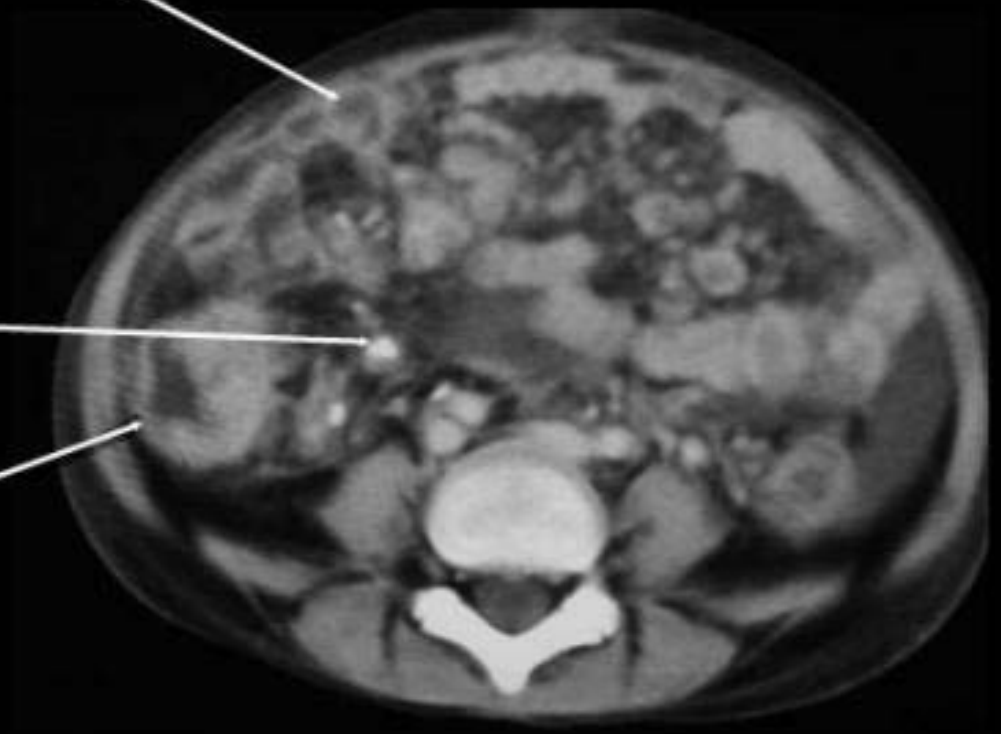
Case HIV-TB 12, slide # 2



Chest Xray showing perihilar, and diffuse reticulonodular infiltrates

Picture credit: V. Sirisanthana

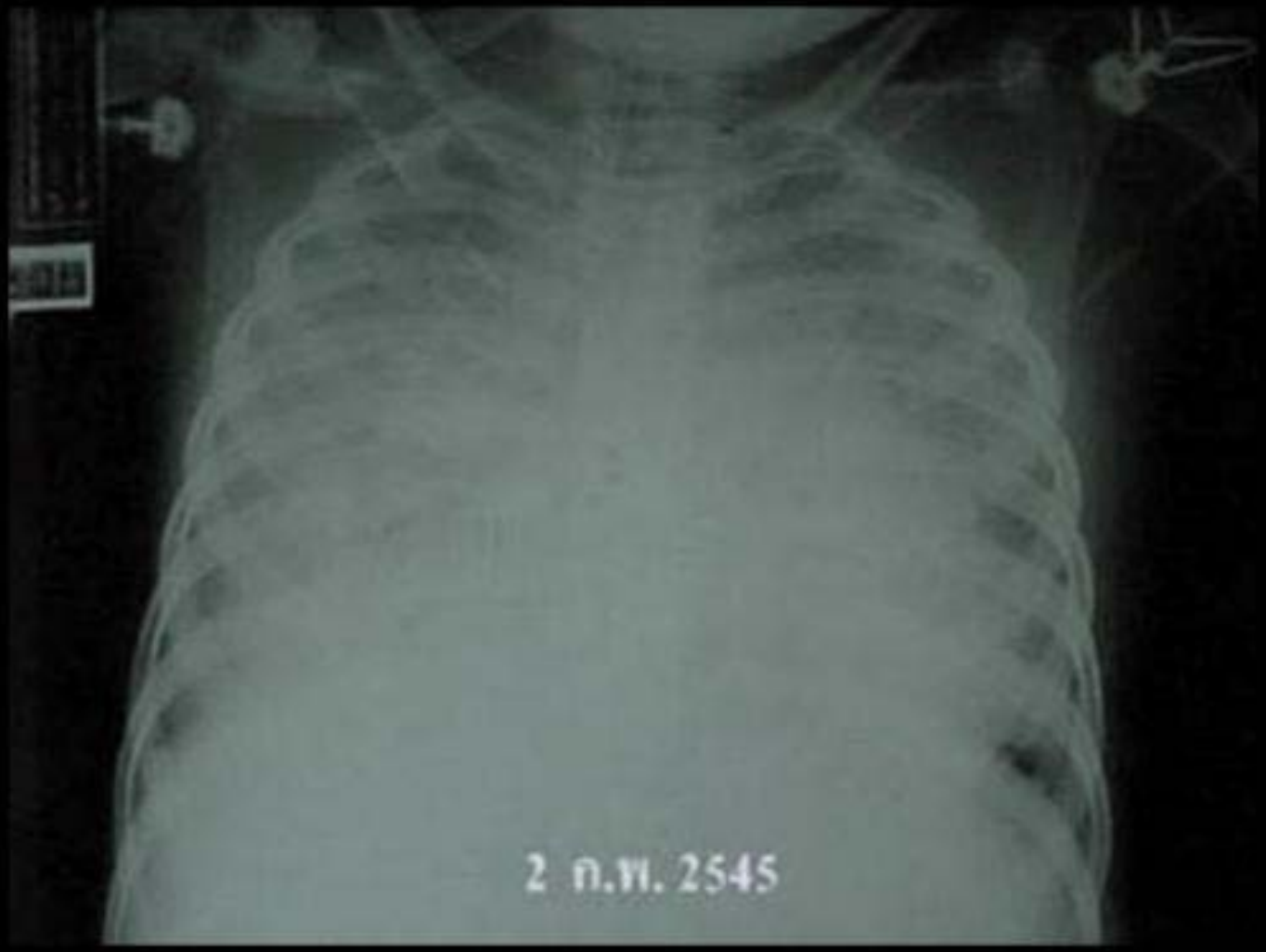
Case HIV-TB 12, slide # 3



Abdominal CT scan with findings typical of abdominal tuberculosis

Picture credit: V. Sirisanthana

Case HIV-TB 12, slide # 4



Respiratory failure due to ARDS followed, and the patient died

Picture credit: V. Sirisanthana

Differentiating pulmonary disease in paediatric HIV (1)

- TB
  - HIV-infected children: non-cavitary pulmonary disease (primary pneumonia, nodes, milia) or disseminated disease (usually with some pulmonary signs)
  - ***Persistent, unremitting*** **cough for >2-4 weeks, weight loss, fever, decreased activity; contact history**
  - Smear or culture lower yield, not widely available
  - PPD useful if positive, but sensitivity low (about 20% in children)
- Lymphoid interstitial pneumonitis (LIP)
  - Chronic, slowly progressive- often older children
  - Cough, wheeze, hypoxia, clubbing

Differentiating pulmonary disease in paediatric HIV (2)

- *Pneumocystis* pneumonia (PCP)
  - Triad of cough, tachypnea, and hypoxemia
  - Acute or subacute, not chronic
  - CXR may not be impressive early in disease
  - Bilateral infiltrates in butterfly pattern
- Bacterial pneumonia
  - Very common
  - Acute presentation
  - Usually pneumococcal, but can be many others
- Bronchiectasis
  - Chronic with multiple episodes of acute worsening
  - CXR shows areas of atelectasis, especially right middle lobe
  - Result of multiple pneumonias or pulmonary TB

Diagnostic challenges in pediatric HIV

- Clinical manifestations non-specific: fever, weight loss, cough, fatigue
- History of household contact with symptomatic adult
- Cavitary disease unusual: fewer bacilli & harder to diagnose
- Induced sputum better than gastric aspirate
- Culture necessary but not widely available
- Drug resistance: probably common, but rarely tested

The value of combined variables, documented at presentation in relevant risk groups, to diagnose pulmonary TB in children

(from Marais BJ et al. *Pediatrics 2006;118;e1350-e1359)*

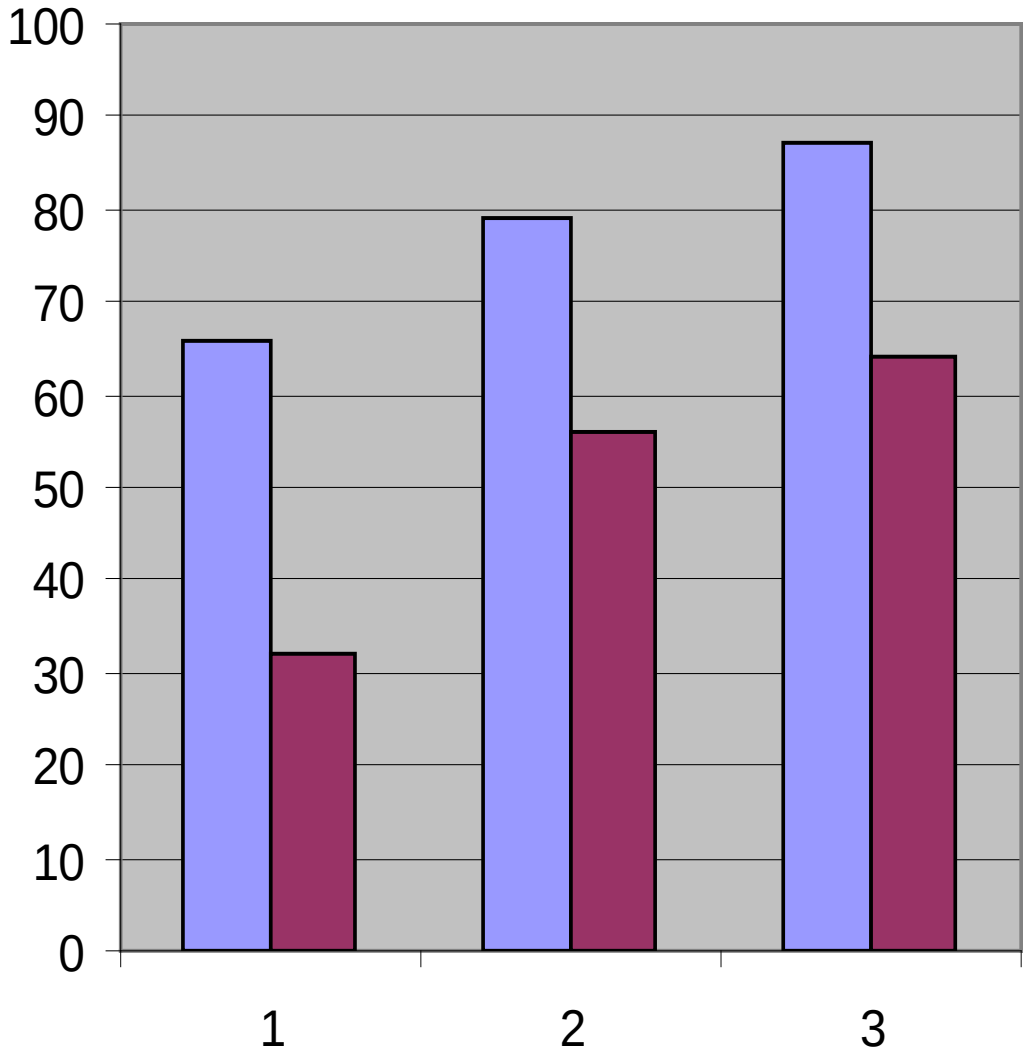
	Diagnostic value using ≥ 2 weeks of cough			Diagnostic value using continued cough after additional 2 wks follow-up		
	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)
≥ 3 years of age, HIV negative	82.3	90.2	82.3	--	98.9	85.1
< 3 years of age, HIV negative	51.8	92.5	90.1	--	82.6	88.6
HIV infected, all ages	**56.2**	**61.8**	**61.9**	**--**	**75**	**77.2**

Data represent diagnostic utility of history based on presence of all of:

1. Persistent, unremitting cough X ≥ 2 weeks *and*
2. Objective weight loss over 3 months *and*
3. Reported fatigue (decreased activity/playfulness since onset cough)

Definitive diagnosis based on variety of criteria, including CXR, stain, culture, PPD, and response to therapy

Stain and culture of induced sputum versus gastric lavage for diagnosis of TB in 250 children with suspected TB (38% HIV infected) ages 1month-5 years
(from Zar et al, Lancet 2005; 365:130)



- **Entry: Cough > 4 wk + 1 of:**
  - **Contact**
  - **Weight static or loss**
  - **+ PPD**
  - **+ CXR**
- **TB dx: sputum or GA+**
- **25% of screened children TB+**
- **Cumulative sensitivity of smear ~ 50%**
- **Smear increased yield by about 10%**

Dilemmas and controversies in HIV/TB co-treatment in children (1)

- Rifampicin/isoniazide/pryazinamide X 2 months + rifampicin/isoniazide X 4 months standard treatment (RHZ2/RH4)
- When should ART be started in children with TB co-infection?
  - Tolerability and complexity of co-treatment
  - Immune reconstitution inflammatory syndrome (IRIS)
  - *But HIV-infected children- especially young children and those with TB- do poorly without ART*
  - HIV prognosis more related to age than CD4 count

Dilemmas and controversies in HIV/TB co-treatment in children (2)

- Pharmacologic challenges- rifampicin induces metabolism of:
  - NNRTIs- Nevirapine (NVP) > *efavirenz (EFV) (preferred, including < 3 years of age but must use high dosage)*
  - Protease inhibitors
  - NRTIs- Zidovudine, abacavir
  - Current WHO guidelines advocate inadequate antiretroviral therapy for small children, especially those with TB

Randomized trial of INH in HIV+ children

Heather J Zar et al. *BMJ 2007;334;136*

- INH vs placebo
- N = 263 HIV-infected children (median age 24.7 months)
- Mortality
  - INH group: 11/132 (8%)
  - Placebo group 21/131 (16%)
  - HR 0.46, (0.22- 0.95, P = 0.015) by ITT analysis
  - Benefit applied across CDC clinical categories and in all ages. The reduction in mortality was similar in children on 3/7 or daily INH.
- TB incidence
  - INH group (5 cases, 3.8%)
  - Placebo group (13 cases, 9.9%)
  - (HR 0.28, 0.10 - 0.78, P = 0.005)
  - All cases of TB confirmed by culture were in children in the placebo group.

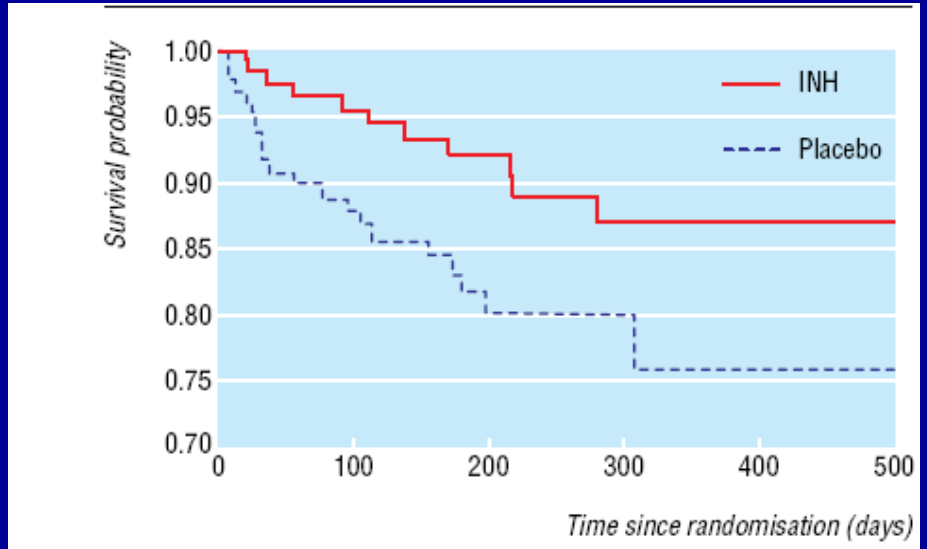


Fig 2 Survival in children on isoniazid (INH) or placebo

Effect of HAART

- **23 (9%) taking HAART at entry**
- **Mortality in subjects taking HAART: 0% [versus 9% (INH group) or 17% (placebo) for subjects not taking HAART]**
- **TB incidence on HAART: 1/23 (4%) [vs 4% (INH group) or 10% (placebo) for subjects not taking HAART]**

P1041: INH has no effect on TB-free survival in HIV-infected infants

P1041 Study Team IAS 2008

- 452 PCR+ infants 3-4 months old
- Randomized to INH or placebo
- 27% on ART at randomization; 71% on ART at conclusion (median 36 weeks)
- No difference in TB diagnoses
- No difference in TB or death
- No trend favoring INH: study stopped

When to use INH in HIV-exposed or infected children

- Always rule out active TB as best as possible
- Give INH
  - Household exposure
  - + PPD

Control of TB in HIV-exposed or infected children

- Prevent HIV in children
- Diagnosis and early treatment of HIV- *before* serious immunosuppression
- Screen (by symptoms CXR) all HIV+ children for TB
- Control of HIV and TB in adults
  - Treat HIV before CD4 < 350
  - Aggressive case finding: consider TB in ALL HIV+ adults and test for HIV in anyone with TB
  - DOT or other structured adherence program
  - Effective regimens: 2RHZE/2RH (not HE)
  - Monitor for MDR & XDR TB
- BCG and HIV in children: use in exposed infant, but not untreated infected infants
- Role of INH of in all HIV-exposed and infected children? Probably not.

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