

ART AS AN EMERGENCY: TB/HIV CO TREATMENT IN CHILDREN

Mike Reid, MD

November 1-4, 2010

3rd Annual PMTCT.PEDIATRICS Meeting



OBJECTIVES

- Review and understand the rationale behind new WHO TB-HIV co-treatment guidelines
- Recall the basics of prescribing antiretroviral therapy in children with TB:
 - Eligibility
 - ARV choice and timing
 - IRIS

TB/HIV Co-infection – BAD NEWS!

HIV infection:

↑ susceptibility to TB

↑ TB development of infection in kids with LTBI¹

Children with HIV, 20 x more likely to develop active TB¹

↑ risk of rapid progression in TB disease

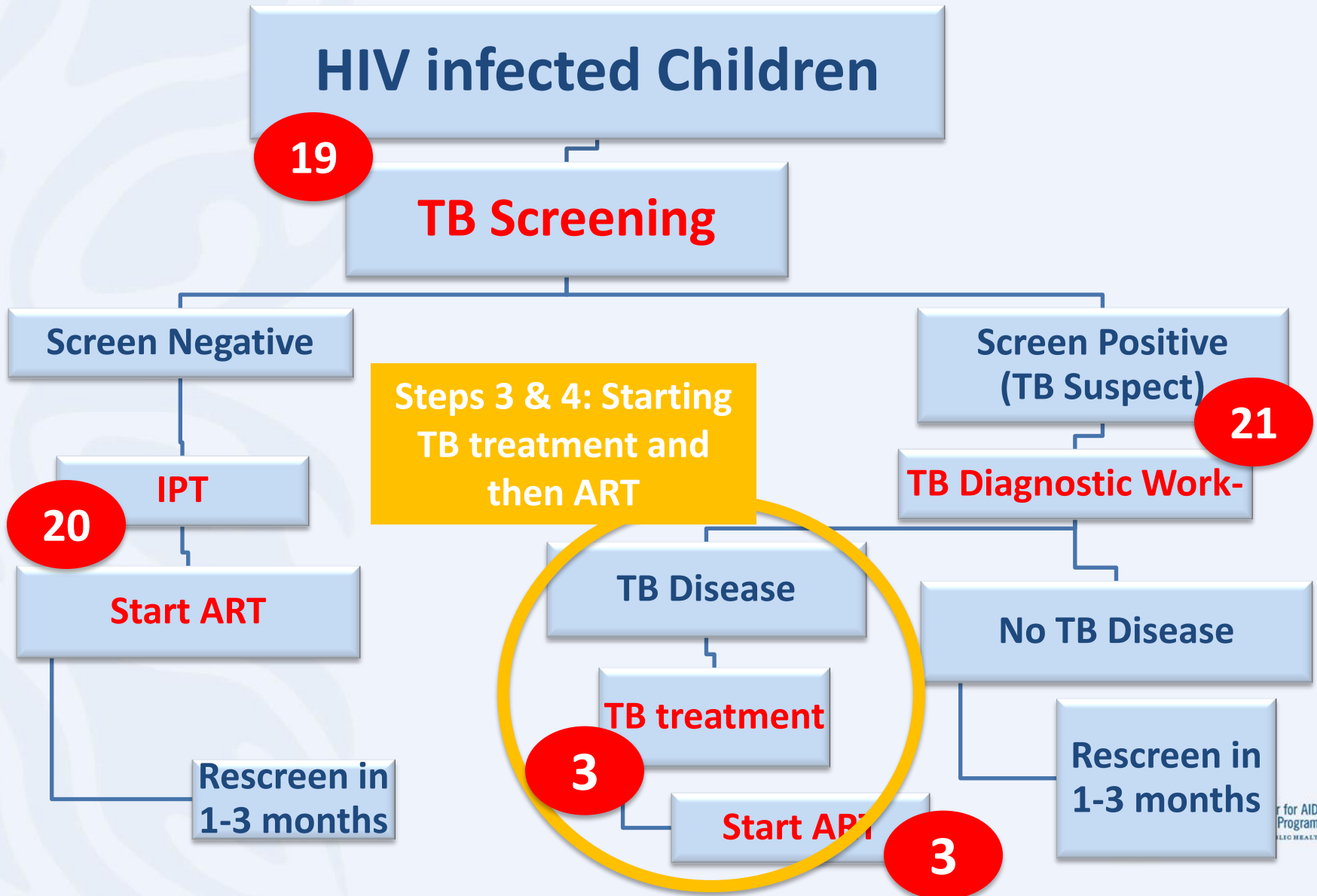
TB disease:

Suggests underlying HIV infection:

HIV prevalence in TB (Pediatric studies): **32-71%**²

³ 1. Chintu, Mwaba 2005. 2. Mahdi et al, 2000. 3. Kiwanuku et al, 2001

ICAP APPROACH TO TB/HIV



TB TREATMENT: DRUG DOSING

- **Rifampicin:**¹

Prospective Study involving 21 HIV+ children & 33 HIV- children. Very low rifampicin levels in all children dosed according to adult based doses (8-12mg/kg)

- **Isoniazid:**²

Study: n =56, 22 HIV+ Children. 70% of children given INH at 4-6 mg/kg have peak INH concentration below the recommended reference range

- 1. Schaaf et al, BMC, 2009. 2. McIlleron et al, CID, 2009

TB TREATMENT: DRUG DOSING

WHO
2010

Drug	2006 Daily dosage in mg/kg Range (max)	2010 Daily dosage in mg/kg Range (max)
Isoniazid	4 - 6 (300 mg)	10 - 15 (300 mg)
Rifampicin	8 -12 (600 mg)	10 - 20 (600 mg)
Pyrazinamide	20 - 30	30 - 40 (2000 mg)
Ethambutol	Children: 15 - 25	15 - 25 (1200 mg)

All HIV infected children receiving TB treatment should also receive CPT.

TB TREATMENT: DURATION OF TREATMENT

- 6-month regimen for all children with HIV, then evaluate whether complete resolution has occurred



2006	2010
6 month regimen recommended Some national guidelines: 9 months for PTB	6 month regimen, then evaluate whether complete resolution has occurred. If inadequate then continue therapy

HIV TREATMENT

2 SCENARIOS

1. Children with HIV diagnosed with TB
2. Children diagnosed with TB on ART

1. Children with HIV diagnosed with TB

WHO
2010

Age	2008	2010
< 12 months	Start ART regardless of CD4/WHO	Start ART in all children with TB Regardless of CD4 or WHO Ideally start within 2-8 weeks after initiating TB treatment
12-35 months	Start ART if WHO IV or CD4 < 750 / 20%	
> 36 months	Start ART if WHO 4 or CD4 < 350 / 20%	

1. CHILDREN WITH HIV DIAGNOSED WITH TB

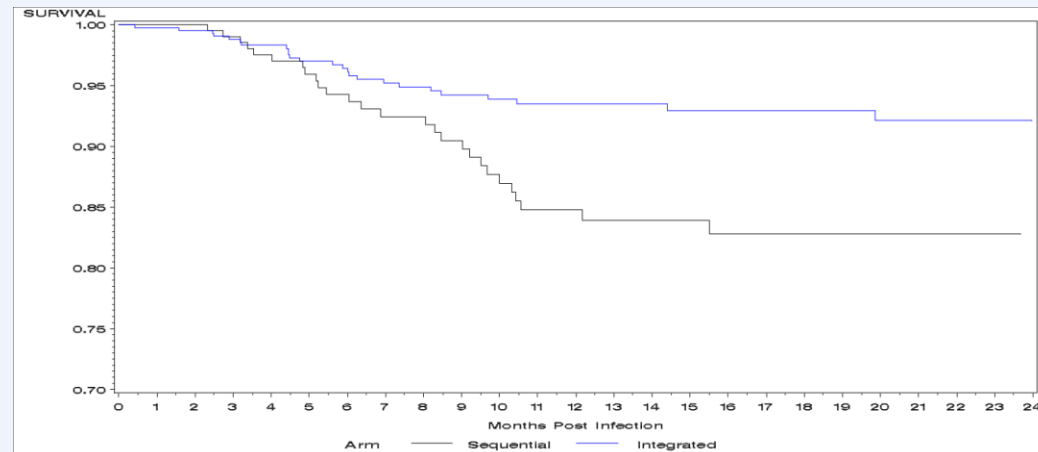
Start TB therapy and then ART within 8 weeks

- ART in HIV-TB co-infected adults ↓ mortality risk by 64-95%¹

SAPIT RCT ADULTS

Early initiation of ART:

- ↓ all-causes mortality and improved TB outcomes².
- Mortality rate ↑4x in deferred *vs early ART*³



- Recent observational data in children support this guideline⁴ -
Delaying ART for 2 months = mortality HR 2.2 (95% CI 0.85-5.8)

1 Harries AD, et al. Lancet 2010;375:1906-1919 2 Karim et al, N Engl J Med 2010

3 Fitzgerald D. 5th IAS conference, Cape Town, July 2009; WESY201

4 Yotebieng M et al. AIDS 2010;24:1341-1349

ICAP PATIENT LEVEL DATA

HOW ARE WE DOING?

**Children with HIV diagnosed with TB:
Time from TB initiation to initiation of ART**

**What factors prevent more rapid ART initiation in children co-infected with TB?
What strategies could be implemented to get kids onto ART sooner once TB is confirmed?**

Children started TB treatment between July 2007 and June 2009 and who started ART by June 2010

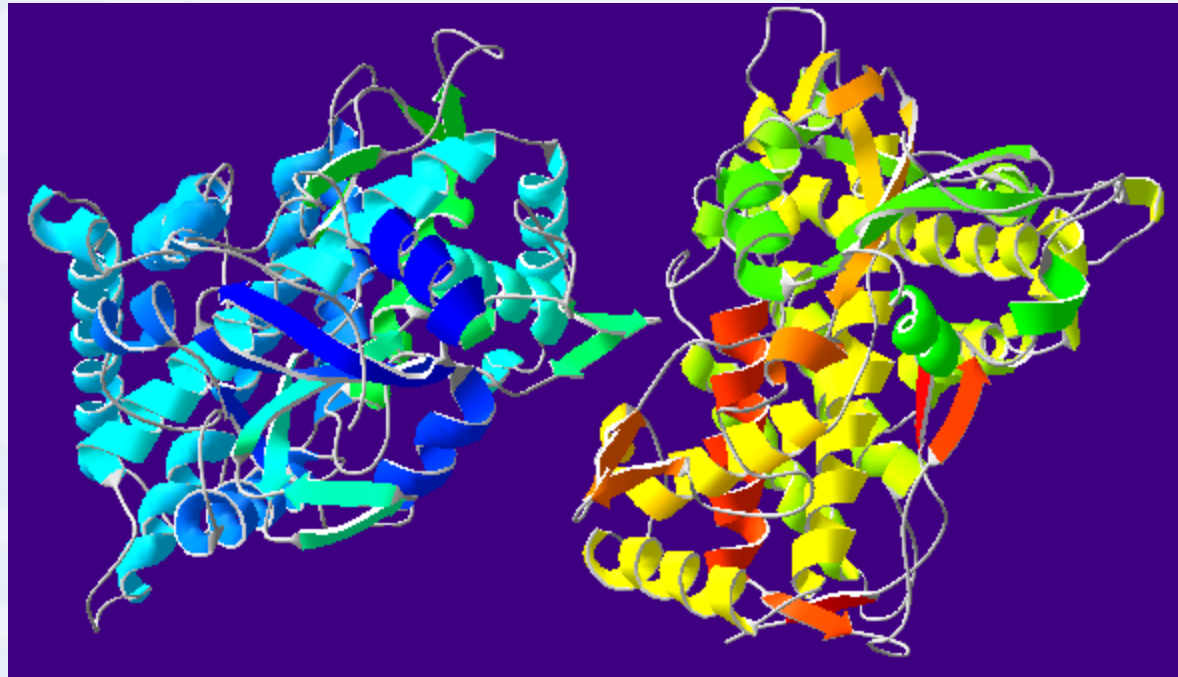
ART IS AN EMERGENCY!

HIV TREATMENT: WHICH ART REGIMEN SHOULD WE START?



ICAP
International Center for AIDS
Care and Treatment Programs
MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

CYTOCHROME P450



**WHO
2010**

Preferred ART regimens for TB/HIV co-infected children <3 years of age /10kgs

2 NRTIs + NVP*
(except for infants and children <2 years if previously exposed to NVP)

3 NRTIs: (d4T or AZT) + 3TC + ABC

Preferred ART regimens for TB/HIV co-infected children \geq 3 years of age

2 NRTIs + EFV

3 NRTIs: (d4T or AZT) + 3TC + ABC

WHO
2010

Preferred ART regimens for TB/HIV co-infected children <3 years of age

2 NRTIs + NVP*

(except for infants and children <2 years if previously exposed to NVP)

Or

3 NRTIs: (d4T or AZT) + 3TC + ABC

* Since rifampicin is known to reduce levels of NVP, do not use lead-in dosing of NVP when initiating NVP-containing ART with TB treatment.

1ST LINE ART IN < 3YRS: 2 NRTIs + NVP / 3 NRTIs

Nevirapine & Rifampicin

- In adults NVP levels are ↓ 20-55%: Virologic outcomes *may* be impaired compared to those not taking Rifampicin
- Contradicting reports in children with regard to NVP concentrations when used with Rifampicin. Caution advised... (Thailand, Uganda, Zambia)^{1,2,3}
- WHO recommend dosing at higher dosing (200mg/m²) but given potential for hepatotoxicity, only when *regular* lab & clinical monitoring assured

1 Prasitsuebsai W, et al. 16th CROI, poster 908, Montreal, February 2009

2 Barlow-Mosha L, et al. 16th CROI, poster 909, Montreal, February 2009

3 Oudijk JM, et al. 5th IAS Conference, Cape Town, 2009,

1ST LINE ART IN <2 YRS + NVP EXPOSED: 3NRTIs

Triple Nuc Regimen

- No studies evaluating 3 NTRIs in TB-co-infected children
- SA: virological failure in 7/15 children after 24 wks of ART¹
- USA: 3NRTIs associated with delayed virologic control (< 1 log₁₀ VL drop after 12wks in 86%) and poor longer term virologic control (> 400 copies/ml in 44% after 24 wks and in 69% after 48 wks)
- Italian study: Children suppressed on PI-containing regimen and switched to 3 NRTIs: 19/20 maintained VL <50 c/ml for 96 wks³

1 Bobat R, et al. 4th IAS Conference, 2007, TUPEB053

2 Neely M, et al. 17th CROI, February 2010; Poster #879

3 Palma P, et al. AIDS 2007;21:2465-2472

Preferred ART regimens for TB/HIV co-infected children ≥ 3 years of age

2 NRTIs + EFV

Or

3 NRTIs: (d4T or AZT) + 3TC + ABC

1ST LINE ART IN > 3 YRS: 2 NRTIs + EFV

Efavirenz & Rifampicin

- Cannot use EFV in < 3ys because target trough levels difficult to achieve
- Rifampicin reduces levels of EFV by -20%, but good VL and CD4 response with standard dose in adults¹
- Studies in children in Thailand, good virologic response even at low EFV concentrations²
- Higher EFV doses assoc toxicity³

1 Patel, 2004

2 Puthanakit T, et al. Antivir Ther 2009;14:315-320

3 Hirt D, et al. Antimicrob Agents Chemother 2009;53:4407-4413

2. CHILDREN DIAGNOSED WITH TB ON ART

- **Find out the underlying cause of TB**
 - Is TB a primary infection?
 - Is TB part of IRIS? (first 6 months of ART)
 - Is TB a sign of treatment failure of 1st line regimen?
- **Continue ART and assess for need to change regimen.**
- **Check response to TB therapy:** to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicities and drug – druginteractions.

CHILD ON 2NRTIs + NNRTI FIRST-LINE REGIMEN

- **If TB is primary infection or part of IRIS:**
 - Continue on standard two NRTIs + NNRTI first-line:
 - if on NVP, substitute to EFV if the child is ≥ 3 years; if <3 years \uparrow NVP to maximum dose (up to a max of 200 mg/m²) , or
 - Substitute NNRTI to triple NRTI first-line regimen
- **If TB is a sign of treatment failure:**
 - Consider consultation with experts for construction of second-line regimen

CHILD ON STANDARD PI REGIMEN

- **If TB is primary infection:**
 - Continue same regimen, consider adding RTV to achieve full therapeutic dose (increase RTV until same dose as LPV in mg, ratio of 1:1)
- **If TB is a sign of treatment failure:**
 - Consultation with experts for construction of salvage regimen

TREATING TB ON STANDARD PI REGIMEN

- Adults studies: Boosted LPV/r or double dose LPV/r may overcome the effects of rifampicin on LPV metabolism¹
- WHO recommend increasing RTV in children: dose RTV in the LPV/Rr regimen to a ratio of **1:1** to achieve adequate LPV exposure
 - ✓ Studies in children: additional RTV maintained LPV Cmin. But no data on boosted LPV/r in children aged < 6 mo^{2,3}
 - ✗ LPV/r needs a cold chain. ↑ RTV, ↑ side effects

1 La Porte CJL, et al. Antimicrob Agents Chemother 2004;48:1553-1560

2 Ren Y, et al. J Acquir Immune Defic Syndr 2008;47:566-569

3 McIlleron H, et al. 2010 (submitted); 4 Moodley M, et al. 17th CROI 2010, paper #160

2. CHILDREN DIAGNOSED WITH TB ON ART

Rifabutin: remains unclear and is not recommended in children

Concerns^{1,2}:

- limited efficacy data in HIV-infected adults,
- Expensive and not widely available in SSA
- Dosing modifications with RTV-co-treatment,
- Lack of paediatric formulations & dosing and efficacy studies

1 Cochrane Database Syst Rev 2007;4:CD005159

2 Maartens G, et al. Antivir Ther 2009;14:1039-1043

IRIS IN THE CONTEXT OF CO-THERAPY FOR TB/HIV

CLINICAL DEFINITION OF PARADOXICAL TB-ASSOCIATED IRIS

Onset within 3 mo of starting ART

Usually occurs in children with very low CD4 counts (<15%)

1 major and 2 minor criteria:

Major criteria:

- New/enlarging lymph nodes or other focal tissue enlargement
- New/worsening radiographic features
- New/worsening CNS tuberculosis
- New/worsening serositis

Minor criteria:

- New/worsening constitutional symptoms such as fever
- New/worsening respiratory symptoms such as cough
- New/worsening abdominal pain

CLINICAL DEFINITION OF PARADOXICAL TB-ASSOCIATED IRIS

Antecedent requirements:

- Diagnosis of TB made before starting ART
- A good initial response to TB therapy before the patient started ART

Exclusion of the following conditions:

- Poor adherence to TB therapy
- Failure of TB therapy due to TB drug resistance
- Another opportunistic infection or neoplasm
- Drug toxicity or drug reaction

MANAGEMENT: IRIS

Unmasking IRIS: continue ART. Start TB treatment. Strengthen TB screening strategies

Paradoxical IRIS: (Limited data in children)

- Mild-Mod IRIS is relatively common (about of 1/3 of cases)¹
- Usually resolves spontaneously and doesn't require treatment (Adult studies: SAPIt & CAMELIA)
- Prednisone (2 wks x 1.5mg/kgs, 2 wks 0.75mg/kgs – associated with less hospitalization and symptom improvement cf. placebo)²

TB/HIV CO TREATMENT FOLLOW UP

- Children who are given rifampicin and NVP concomitantly should be followed up more frequently and laboratory parameters – LFT - if available, should be checked
- Do not forget co-trimoxazole : better survival rates in patients co-infected with HIV and TB who received CTXpreventive therapy than in patients without preventive therapy ¹⁻³

1 Grimwade, Sturm et al. 2005

2 Grimwade and Swingler 2006;

3 Nunn, Mwaba et al. 2008.

CASES

CASE 1

S.M., male, 8 months old

- Is brought to the under-5 clinic with cough, weight loss, persistent fever, asthenia and fatigue.
- No previous health problems. Mother delivered at home.
- On examination:
- 7th centile for weight, malnourished, bulging tympanic membranes, crepitations in both lungs.

CASE 1

- Day 1: Diagnosis of severe malnutrition, pneumonia and bilateral otitis made
- Child is sent home with amoxicillin.
- Day 10: SM is brought back to the clinic later by the mother. No improvement. Fevers have persisted. Mother discloses that the father is on treatment for TB.
- Rapid HIV test: positive
- Tests send: CD4 sent
- TST: 0mm
- CXR is ordered.



CASE 1

- Day 10: Child is started on cotrimoxazole and referred to the local TB clinic. TB treatment initiated the following day
- DOTs is performed at TB clinic.
- Day 46: Mother returns to ART clinic 6 weeks as requested
- However, labs from previous visit have been lost, & are resent. At that visit, 1st ART preparation counseling session 1 is performed

CASE 1

- Over the next week, the mother is sick and too weak to bring the child to clinic. She doesn't come for the next ART preparation session three weeks later
- Day 67: 3 weeks after last visit mother and child return.

CD4 count is 14. Session 2 counseling takes place.

- Day 77: 10 days after last visit mother comes for last ART preparation counseling. The child starts ART the following day.

CASE 1

Day 78: Child starts EFV+AZT+3TC

- Tolerates drug regimen well
- Completed TB treatment

CASE 1 - QUESTIONS

- What were the barriers to co-treatment in this patient?
 - At a facility level
 - At a national level

CASE 1 - QUESTIONS

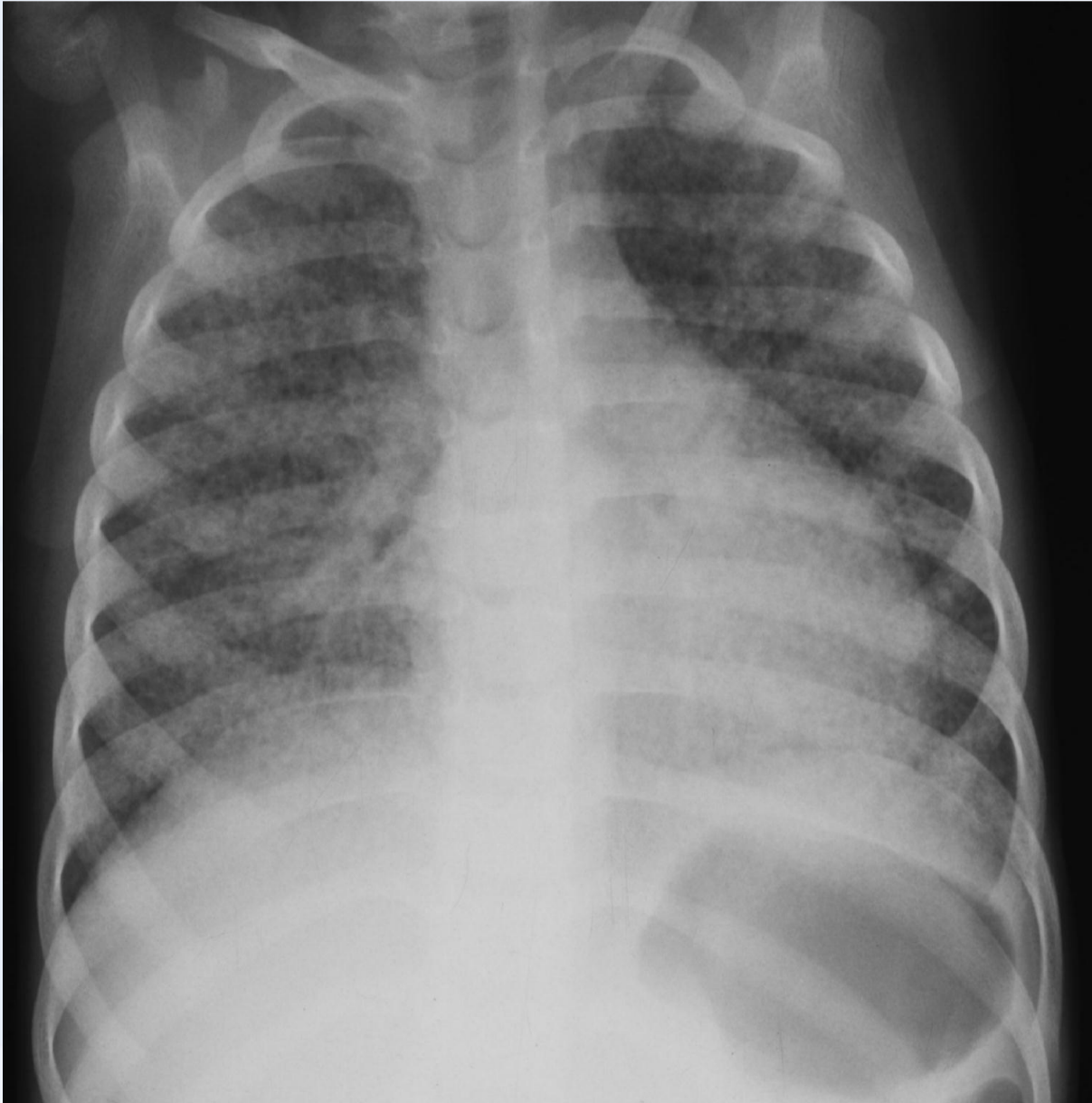
- What strategies could have been employed to ensure that the child was started on ART sooner?
 - In the TB clinic:
 - In the pediatric ART clinic
 - At a national level
- What quality improvement strategies could be used to enhance the care of this child? Give examples from your own country

CASE 2

- 5 year old girl, P. M.
- Attends pre-ART clinic erratically
- Is started on ART when CD 4 count is 108 cells/mm³
- Starts: AZT + 3TC + NVP
- 8 weeks develops later fever and cough

CASE 2

- Mother takes the child to the emergency room and is with amoxillin.
- Child doesn't improve & mother returns three days to HIV clinic.
- The child is acutely unwell. Tachypneic and toxemic.
- Child is admitted to hospital



CASE 2 - QUESTIONS


- What is the most likely diagnosis? Why?
- How would you manage this child?
- What is the prognosis for this child? Why?
- What steps could have been taken to avoid this kind of clinical scenario
 - At a clinic level?
 - At a national level?

SUMMARY: TB/HIV COTREATMENT -1

- Any child with active TB disease should begin TB treatment immediately
- Any child with active TB should start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of the CD4 count and clinical stage.

Preferred ART regimens for TB/HIV co-infected children <3 years of age (WHO 2010)	Preferred ART regimens for TB/HIV co-infected children ≥3 years of age (WHO 2010)
<p>2 NRTIs + NVP*</p> <p>(except for infants and children <2 years if previously exposed to NVP)</p>	<p>2 NRTIs + EFV</p>
<p>or 3 NRTIs: (d4T or AZT) + 3TC + ABC</p>	<p>or 3 NRTIs: (d4T or AZT) + 3TC + ABC</p>

The preferred 1st line ARV regimen for children <2 yrs who have been exposed to NVP is a triple NRTI regimen.

Time of TB diagnosis in relation to ART	Underlying cause of TB	Considerations for ART	ARV regimen
Child on 2 NRTIs + NNRTI first-line regimen diagnosed with TB	1. Primary Infection	Continue ART but assess for need to change ART regimen	If > 3 yrs EFV based If < 3 years NVP based at max NVP dose or Switch to 3NRTIs
	2. IRIS		Consider consultation with experts for construction of second-line regimen
	3. Treatment failure		

Time of TB diagnosis in relation to ART	Underlying cause of TB	Considerations for ART	ARV regimen
Child on standard PI regimen (NRTI + boosted PI) diagnosed with TB	1. Primary Infection	Continue ART but assess for need to change ART regimen	Continue same regimen, consider adding RTV to achieve full therapeutic dose (increase RTV until same dose as LPV in mg, in a ratio of 1:1)
	2. Treatment failure		Consider consultation with experts for construction of salvage regimen

SUMMARY: TB/HIV COTREATMENT -2

- Continue ART in all HIV-infected children diagnosed with TB while on ART
- Make adjustments to ART regimens as needed :
 - If on a regimen of 2 NRTIs + NVP: substitute EFV for NVP if the child >3 yrs
 - If on a regimen of 2 NRTIs + NVP and substitution with EFV is not possible, ensure NVP is dosed at the maximum dose of 200 mg/m² per dose twice daily
 - If on a regimen of LPV/r, consider adding RTV in a 1:1 ratio of LPV: RTV to achieve a full therapeutic dose of LPV.

TB/HIV CO-INFECTION IS AN EMERGENCY!

Finally, need to emphasize that co-infection warrants an **urgent response**:

- Expand TB screening to all children presenting to health facility
- Think about TB and diagnose it early
- Prevent TB with INH in all eligible children
- Treat TB immediately
- Start ARVs as soon as tolerated

ACKNOWLEDGEMENTS

- MARIA GRAZIA
- SUZUE SAITO