Module 3

TREATMENT OF CHILDHOOD TB

International Union Against Tuberculosis and Lung Disease

World Health Organization

Burden of TB in children

- Tuberculosis (TB) in children is common wherever TB is common in adults i.e. TB endemic settings
- TB is an important cause of illness and death in children in many TB endemic countries
- Over half a million (550 000) children become ill with tuberculosis (TB) each year.
- Up to 80 000 HIV-uninfected children die of TB every year*.
- 70–80% of children with TB, have the disease in their lungs (pulmonary TB). The rest are affected by TB disease in other parts of the body (extrapulmonary TB).
- There were over ten million orphans due to parental TB deaths in 2010.
- An understanding of the risks for infection and disease due to TB in children is critical for improved diagnosis and preventive management
- The HIV epidemic has increased the burden of childhood TB and the clinical challenges
- The main benefit of neonatal BCG is protection against severe disseminated TB in children

Treatment of TB in children

- Principles of treatment of TB in children are same as for adults – with similar regimens

- Most children have paucibacillary disease

Treatment response in children

- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome

- HIV-infected children with TB show poorer response to TB treatment – and require ART and CPT as well as TB treatment

Short-course chemotherapy in children

	n	Site	% EPTB	F/up period	Relapse	Mortality
Biddulph J. PIDJ 1990	639	PNG	35%	24 mths	7 of 373	2 %
Reis FJ et al. Am Rev Resp Dis 1990	117	Brazil	0%	21 mths	0	0 %
Te Water Naude et al. PIDJ 2000	206	South Africa	0%	18-36 mths	1	0 %
Al Dossary et al. PIDJ 2002	175	USA	9%	4 years	1	0 %

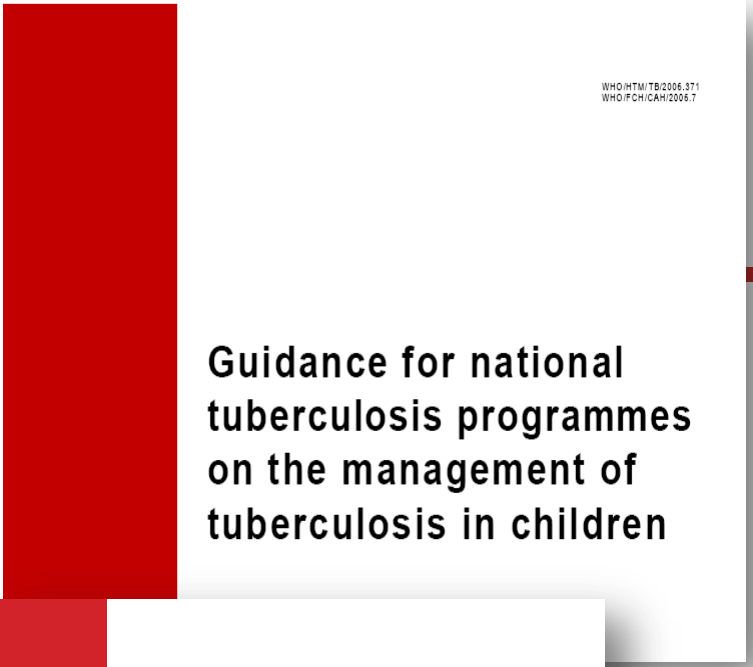
Impact of HIV on TB treatment outcome

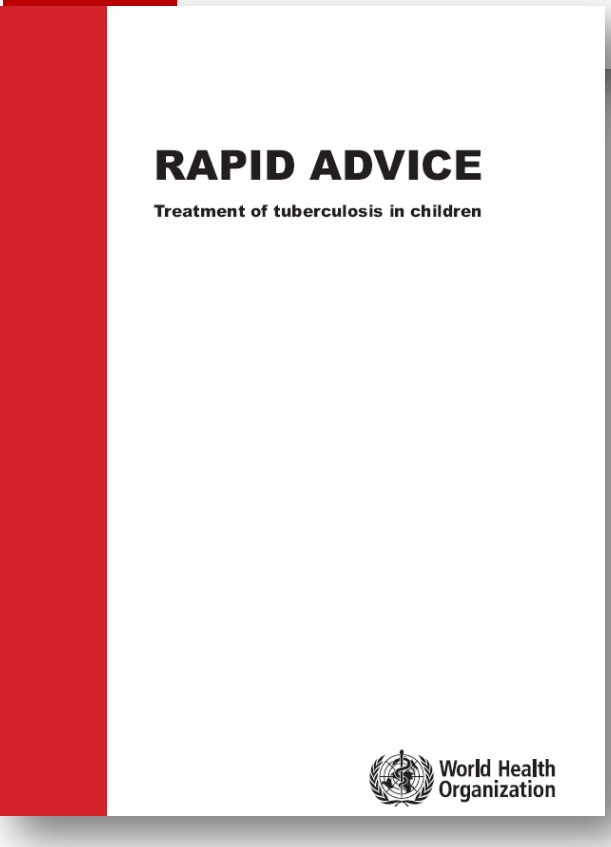
HIV infection was associated with a very poor outcome from TB in children in the pre-HAART era

	Complete recovery			Mortality		
	HIV+	HIV-	p value	HIV+	HIV-	p value
South Africa Jeena et al 1994	65%	95%	0.002	15%	0%	<0.05
Cote d'Ivoire Mukadi et al 1995				23%	3%	<0.01
Dominican Republic Espinal et al 1994	63%	97%	<0.001	16%	0%	<0.001
Ethiopia Palme et al 2002	55%	73%	0.01	38%	6%	<0.001

Treatment of TB in children - dosages

- Dosages are calculated according to weight (not age)
- Weight gain is an important indicator of improvement
- Record weight at each follow-up visit and dosages may need to be adjusted accordingly





Recommended dosages in WHO 2006 guidance have since been updated

TOWARDS ZERO DEATHS

The dosages were revised and changed in 2010 (Rapid Advice) but this has caused problems for implementation when using currently available FDCs – especially the ratio of R:H and the range for isoniazid

The revised WHO Guidance 2014 has revised dose range for isoniazid and provided weight band tables to facilitate implementation using FDCs

Important to be consistent with national guidelines and develop weight band tables depending on available drug preparations

Revised dosages

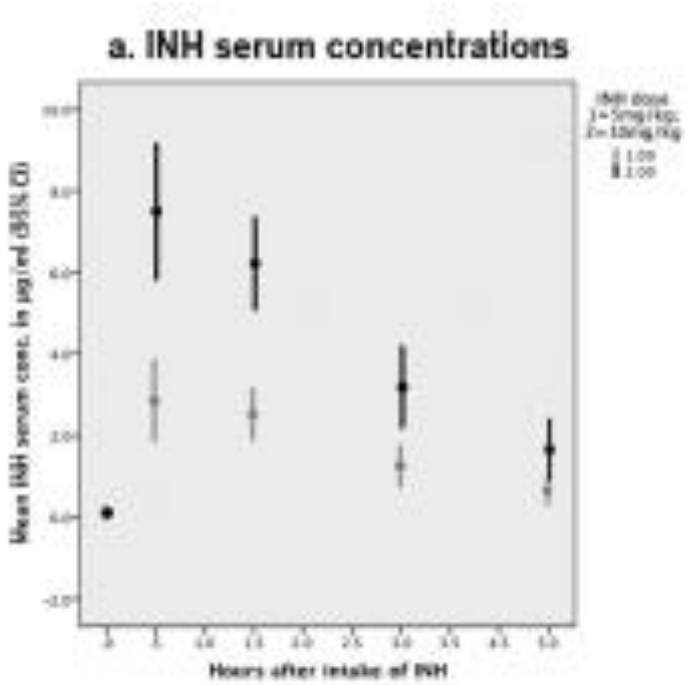
These are the revised dosages (WHO 2014) for children up to 25 kgs:

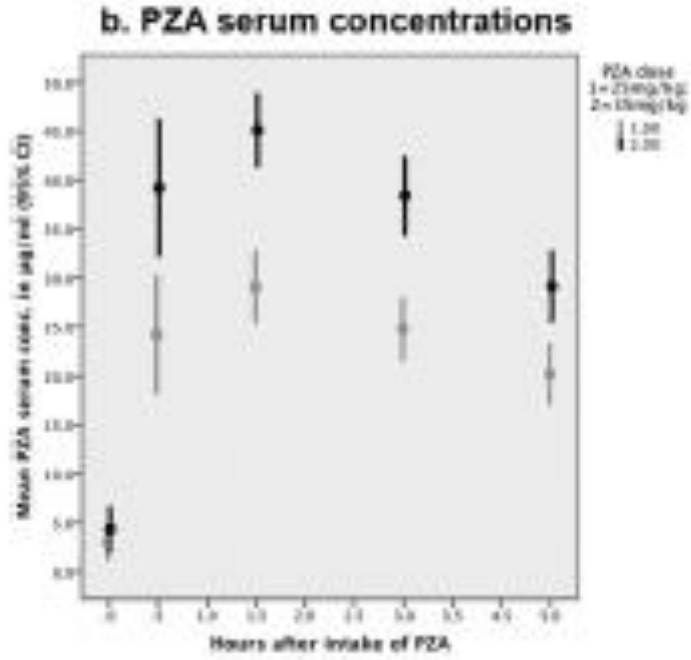
Rifampicin	**15 (10-20) mg/kg/day**
Isoniazid	**10 (7-15) mg/kg/day**
Pyrazinamide	**35 (30-40) mg/kg/day**
Ethambutol	**20 (15-25) mg/kg/day**

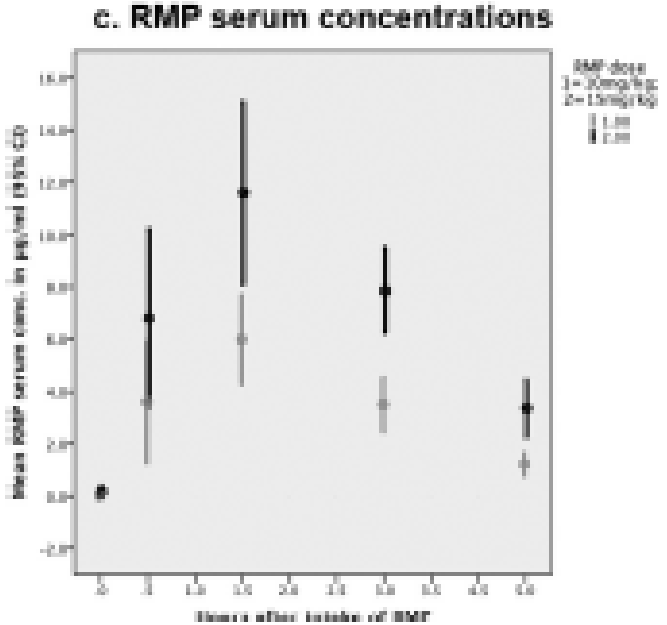
From 25 kgs, can change to adult dosages and preparations

Note also other revisions to recommendations:

1. Four drugs (RHZE) in intensive phase for all new cases in HIV endemic setting
2. No intermittent regimens in HIV-endemic setting
3. Streptomycin no longer recommended for first-line therapy
4. 12-month regimens for TBM and osteo-articular TB







Pharmacokinetics of Isoniazid, Rifampin, and Pyrazinamide in Children Younger than Two Years of Age with Tuberculosis: Evidence for Implementation of Revised World Health Organization Recommendations[v]

Thee S et al, AAC 2011

TB treatment and toxicity in children

- TB drugs are very well tolerated in almost all children
- Adverse events are unusual and the most important is hepatotoxicity
- Ethambutol can be safely used at recommended dosages in all ages

Adverse events are uncommon in children

	N	Regimen	Adverse events
Biddulph J. PIDJ 1990	639	2 RHZS 4 R_2H_2	2%
Tsakilidis D, et al Pediatr Infect Dis J 1992	36	2 RHZ 4 RH	Nil
Te Water Naude et al. Pediatr Infect Dis J 2000	117	6 RHZ	Nil
Te Water Naude et al. Pediatr Infect Dis J 2000	89	2 $R_2H_2Z_2$ 4 R_2H_2	Nil
Al Dossary et al. Pediatr Infect Dis J 2002	175	2 RHZ 4 R_2H_2	1.2%

Use of ethambutol in children

- Ethambutol is recommended as fourth drug in intensive phase of first-line regimens
- Risk of toxicity is dose-related and related to duration of therapy
- The risk of toxicity is **negligible** for children of any age when ethambutol is used at recommended dosages – especially as duration is usually limited to 2 months
- **Ethambutol can be safely used at recommended dosages in all ages**

WHO/HTM/TB/2006.365
WHO/FCH/CAH/2006.3

Ethambutol efficacy and toxicity:

literature review and recommendations for daily and intermittent dosage in children

World Health Organization

Drug dosages in children are determined by weight

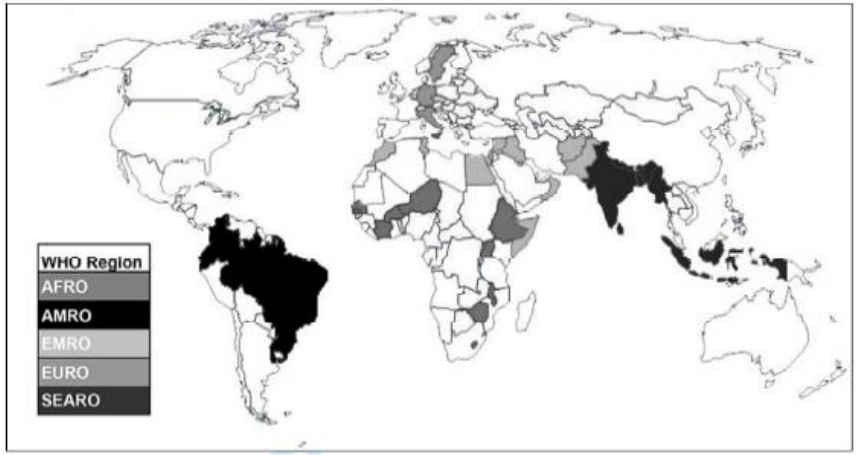
- Useful to have a table showing numbers or portion of tablets required for weight bands up to 25 kg
- This will depend upon what is available and used for each single drug or as fixed-dose combination
- Important to achieve consistency of usage nationally and to ensure availability
- Weight often changes (increases) with treatment so that dosages may need to be adjusted accordingly

Survey of NTPs and current recommendations

34 countries from 5 regions

Dec 2011-Feb 2012

10 TB high-burden countries



12 use 2006 dosage guidelines and

19 use 2010 dosage guidelines

Majority recommend RHZ (some add E in older children > 10 years)

Obstacles to implementation relate to awaiting update of guidelines, need for training, that available FDCs do not match dosage guidelines, the need for change not accepted by local experts, and quantity of pills required is increased

Preventive therapy not implemented and shortages and stock outs of H100

Detjen A, et al Pub Health Action 2012

Insert here the weight band charts for TB dosages in children consistent with NTP guidelines and available preparations

Recommended drug dosages should be consistent with national guidelines

Example of a weight band table when using the most widely available FDC

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	60/30/150	100	60/30
4-6kg	1	1	1
7-10kg	2	2	2
11-14kg	3	2	3
15-19 kg	4	3	4
20-24kg	5	4	5
25 kg+	Go to adult dosages and preparations		

Example of a weight band table when using the “new” FDC being developed

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	75/50/150	100	75/50
4-7kg	1	1	1
8-11kg	2	2	2
12-15kg	3	3	3
16-24 kg	4	4	4
25 kg+	Go to adult dosages and preparations		

Treatment of TB and NTP in children

- Register all children receiving anti-TB treatment in the NTP register

- Report treatment outcomes for children

Treatment failure in children

- Treatment response is commonly noted by the end of the intensive phase and is indicated by resolution of symptoms and weight gain
- Smear-positive cases should follow the standard NTP follow-up microscopy
- HIV status should be determined in all children treated for TB as important confounder for outcome and other HIV-related treatment required (see TB/HIV section)
- A poor response to TB treatment may indicate:
  - Poor adherence
  - Incorrect diagnosis
  - TB due to drug-resistant organism (see MDR-TB section)
  - Incorrect dosages
  - Co-morbidities not managed e.g. HIV

Treatment outcomes in children with TB

- Treatment outcomes should be routinely recorded and reported for child TB cases
- Outcome categories are the same as for adult cases (although few child TB cases would meet the criteria for “cured”)
- Treatment outcomes are important data for monitoring & evaluation
- There are few NTP data of treatment completion – but may be poor in children

Treatment adherence in children

Adherence for the full course of TB treatment is a challenge in children

		No.	Poor adherence or defaulted
Al Dossary et al. PIDJ 2002	USA	175	9% poor adherence
Biddulph J. PIDJ 1990	PNG	639	28% defaulted
Te Water Naude et al. PIDJ 2000	South Africa	206	22% poor adherence
Meissner PE et al. Int J TB Lung Dis 2002	Uganda	236	28% poor adherence
Harries AD et al. Int J TB Lung Dis 2002	Malawi	2,739	13% defaulted 21% unknown

Revised TB recording and reporting forms and registers – *version 2006*

WHO also now recommends that all cases of child TB should be registered and reported within age bands: 0-4 years and 5-14 years

Programme

Form 6

Quarterly Report on TB Case Registration in Basic Management Unit

: _____ Facility: _____

oordinator: _____ Signature: _____

Patients registered during[1]

_____quarter of year_____

Date of completion of this form: _____

Block 1: All TB cases registered [2]

Pulmonary sputum smear microscopy positive				New pulmonary sputum smear microscopy negative			Pulmonary sputum smear microscopy not done / not available			New extrapulmonary			Other previously treated [3]	TOTAL All cases
New cases	Previously treated			0-4 yrs	5-14 yrs	≥ 15 yrs	0-4 yrs	5-14 yrs	≥ 15 yrs	0-4 yrs	5-14 yrs	≥ 15 yrs		
	Relapses	After failure	After default											

Block 2. New pulmonary sputum smear microscopy positive cases – Age group

Sex	0-4	5-14	15–24	25–34	35–44	45–54	55–64	≥ 65	Total
M									
F									

Block 3: Laboratory activity - sputum smear microscopy [4]

No. of TB suspects examined for diagnosis by sputum smear microscopy	No. of TB suspects with positive sputum smear microscopy result

Block 4: TB/HIV activities [2]

	No. patients tested for HIV before or during TB treatment [5]	No. patients HIV positive [5]
New sputum smear microscopy positive TB		
All TB cases		

1 Registration period is based on date of registration of cases in the *TB Register*, following the start of treatment. Q1: 1 January–31 March; Q2:1 April–30 June; Q3: 1 July–30 September; Q4:1 October–31 December.

2 Transferred in' and chronic cases are excluded. In areas routinely using culture, a separate form for unit using culture should be used.

3 Other previously treated cases include pulmonary cases with unknown history of previous treatment, previously treated sputum smear microscopy negative pulmonary cases and previously treated extrapulmonary cases. "Transferred in' and chronic cases are excluded.

4 Data collected from the TB *Laboratory Register* based on "Date specimen received" in the laboratory during the quarter, without including patients with examination because of follow-up.

5 Documented evidence of HIV tests (and results) performed in any recognized facility before TB diagnosis or during TB treatment (till end of the quarter) should be reported here.

Importance of data of TB in children by NTP

- Value of audit to identify challenges/barriers
  - Situational analysis
  - Case management and outcome
  - Background data and potential focus for operational research

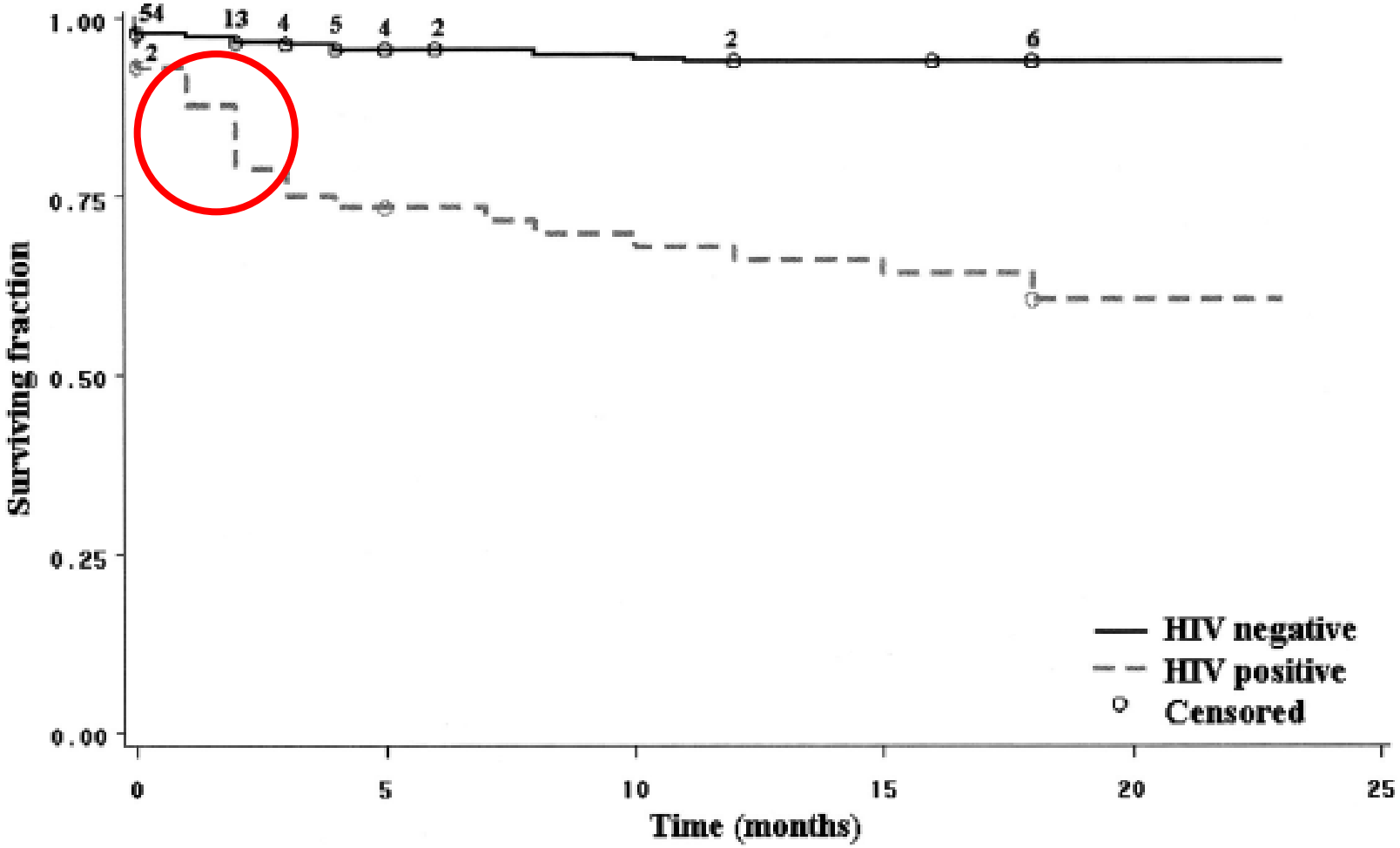
- Improved child-related NTP data and activities
  - Allocation of resources for child TB activities
  - Drug procurement
  - Focus for training
  - Advocacy

- Monitoring & evaluation

TB and HIV in children

- A comprehensive approach to management is critical
- HIV test is indicated in all children with suspected and confirmed TB
- Approach to diagnosis of TB is similar as for HIV-uninfected children
- Treatment for TB is same as for HIV-uninfected children
- All children with TB/HIV should receive CPT and ART – and nutritional support often needed
- All HIV-infected children need to be screened for TB disease.
- The management of children with TB/HIV should be integrated and all family members are counseled and tested for HIV and screened for TB

Timing of deaths in HIV-infected Ethiopian children receiving anti-TB treatment



Palme IB, et al Pediatr Infect Dis J 2002

Possible reasons why outcome is poorer on TB treatment in HIV-infected children

- Immunosuppression
  - emphasises the importance of early ART in reducing mortality
- High risk of co-morbidities
  - invasive bacterial disease: emphasises the importance of concurrent cotrimoxazole preventive therapy
  - severe malnutrition: emphasises the importance of nutritional support
- Poorer adherence due to pill burden and risk of illness/death of primary caregiver
- Risk of DR TB in HIV-infected populations
- Diagnosis is incorrect and child has other HIV-related lung disease, e.g. lymphocytic interstitial pneumonitis (LIP)

Child TB management and HIV

Principles of treatment of TB in HIV-infected children is similar to HIV-uninfected children

ART improves outcome for HIV-infected children treated for TB

It is recommended that HIV-infected children receive

1. **Four first-line drugs (RHZE) in intensive phase for suspected or confirmed drug-sensitive TB irrespective of severity of disease**
2. **Similar duration of regimens as for HIV-uninfected**
3. **ART as recommended within 2-8 weeks of starting TB treatment or continue ART**
4. **Cotrimoxazole preventive therapy**
5. **Pyridoxine supplement**
6. **Nutritional support**

HIV-infected children are at increased risk of relapse and drug resistant TB

Child TB management and ART

Age / weight	Antiretroviral therapy (ART)*
<3yrs or <10kg	*Retain or start on the following regimens* Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone – use 2 NRTI's Third drug If on nevirapine • switch to lopinavir/ritonavir (Kaletra®) with additional ritonavir to achieve mg for mg parity with lopinavir • continue for 1-2 weeks after TB treatment has been stopped • If not possible, – continue NVP dose at the upper end of the dosage scale If on lopinavir/ritonavir (Kaletra®) • use additional ritonavir as above • triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml
≥3yrs and ≥10kg	*Retain or start on the following regimens* 2 NRTI's as backbone Third drug If on nevirapine • switch to efavirenz • if not available continue on nevirapine dose at the upper end of the dosage scale If on lopinavir/ritonavir (Kaletra®) • consider switch to efavirenz, only if undetectable viral load* • alternatively use additional ritonavir as above • triple NRTI therapy is an option, if baseline viral load <100 000 copies/ml
TB treatment is not adjusted - should be initiated as soon as the diagnosis is made No ART adjustment is necessary with INH preventive therapy	
Monitoring If previously on ART - monitor clinically for signs of drug toxicity. If ART newly initiated - monitor ALT after 2 & 4 weeks, then clinically for signs of drug toxicity.	

All newly diagnosed TB cases with HIV infection should be started on TB treatment as soon as possible after completing the first 2 weeks of anti-TB treatment

from Marais BJ et al. Paediatr Resp Rev 2011

Child TB/HIV and IRIS

HIV-infected children should be regularly screened for symptoms of possible TB including on commencement of ART

TB Immune Reconstitution Inflammatory Syndrome (IRIS) can occur as:

"unmasking" IRIS – subclinical TB disease becomes evident with immune reconstitution → TB treatment should be commenced

"paradoxical" IRIS – symptomatic deterioration despite adequate TB treatment → continue TB treatment – consider steroids

TB IRIS usually occurs within 1-2 months after starting treatment and does NOT indicate failure of TB treatment

BCG (M.bovis) IRIS is common in young infants initiated on ART

TB IRIS or BCG IRIS can be associated with significant morbidity but not with a high mortality

Treatment of TB in children - summary

- Principles of treatment of TB in children are same as for adults
- Children with TB usually respond well with symptomatic improvement during intensive phase and good outcome
- Dosages are calculated according to weight (not age)
- Weight is important for monitoring treatment response
- TB drugs are very well tolerated in almost all children
- The most important adverse event is hepatotoxicity
- Register all children receiving anti-TB treatment
- Report treatment outcomes for children

Checklist: the child treated for TB

1. **Dosages and regimens** for anti-TB treatment in children should follow NTP guidelines.

2. **Weight** is important for calculating dosages and for monitoring treatment response.

3. All children treated for TB should be **registered with NTP** and reported by disease type within age bands (0-4 years and 5-14 years)

4. Follow-up is critical and **treatment outcomes** should be recorded as per NTP guidelines.

5. **Adherence** is a challenge especially during the continuation phase and counseling of child and family about importance of completion of full course of anti-TB treatment is important.