Module 5

CHILD TB/HIV

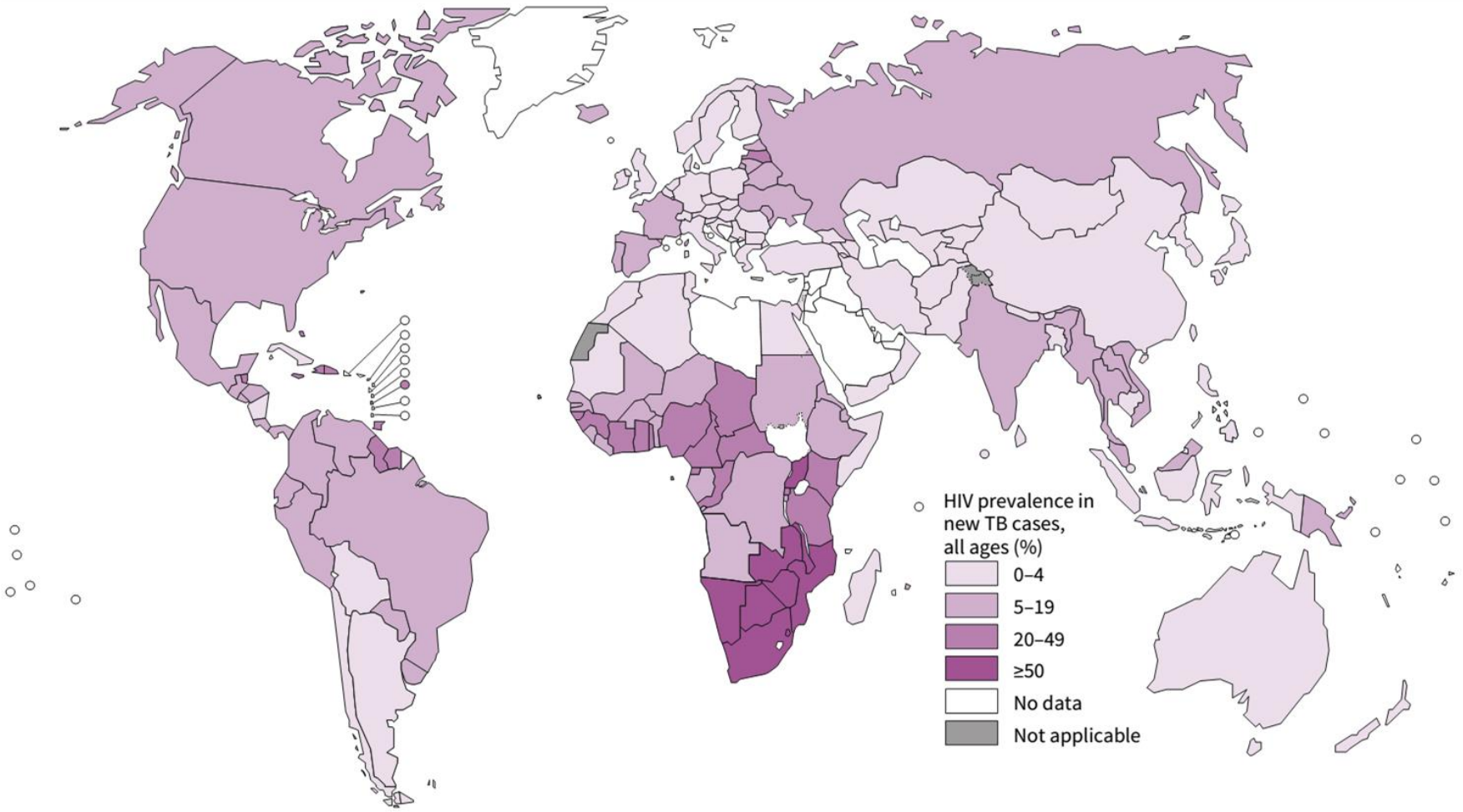
International Union Against Tuberculosis and Lung Disease

World Health Organization

The challenge of HIV and TB/HIV

- Increased caseload of child TB
- Greater difficulty with diagnosis
- Poorer response to TB treatment
- Drug interactions
- Implementation of the “three I’s” and the fourth “I”

Estimated HIV prevalence among new TB cases, 2013



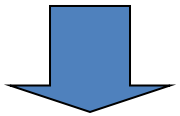
National TB/HIV data

- *This slide could include recent national or district data of TB/HIV indicators*

Child TB/HIV epidemiology

HIV epidemic

Large increase in TB cases in young adults



Increased number of child TB cases

HIV-infected children at risk of PTB because:

1. immune suppressed
2. more likely to be a contact of an adult with TB

Risk factors for TB infection and disease in children

For TB infection

- Contact with source case
  - Closeness of contact
  - Duration of contact
- Source case
  - Smear positivity
  - Cavities on CXR
- Increased exposure
  - Living in high TB endemic communities
  - Children of families living with HIV

For TB disease

- Young age
  - Especially 0-2 years
- HIV infection
  - Risk of infection and disease
- Other immunosuppression
  - Malnutrition
  - Post-measles
- Not BCG vaccinated
  - Risk of disseminated disease

The TB notification rate and notification rate of smear-positive disease rose in Malawi in the wake of the worsening HIV epidemic

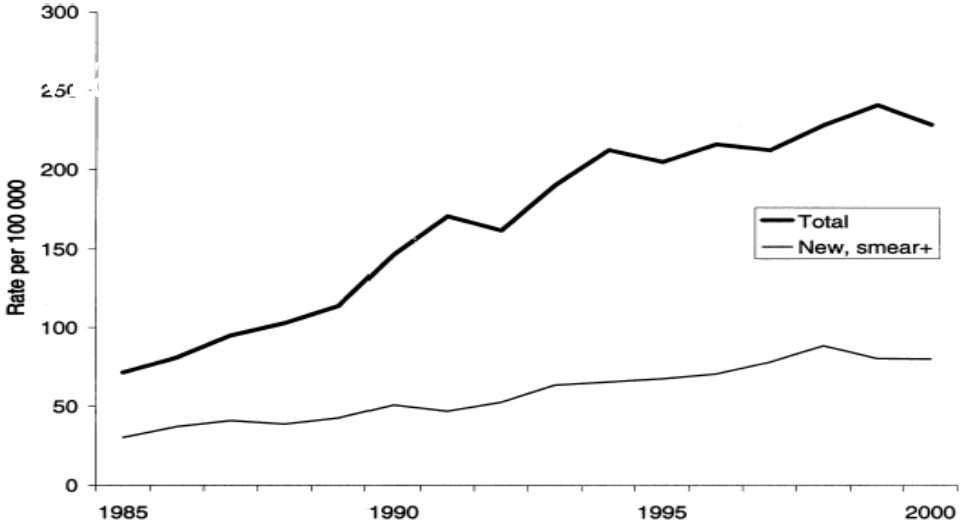
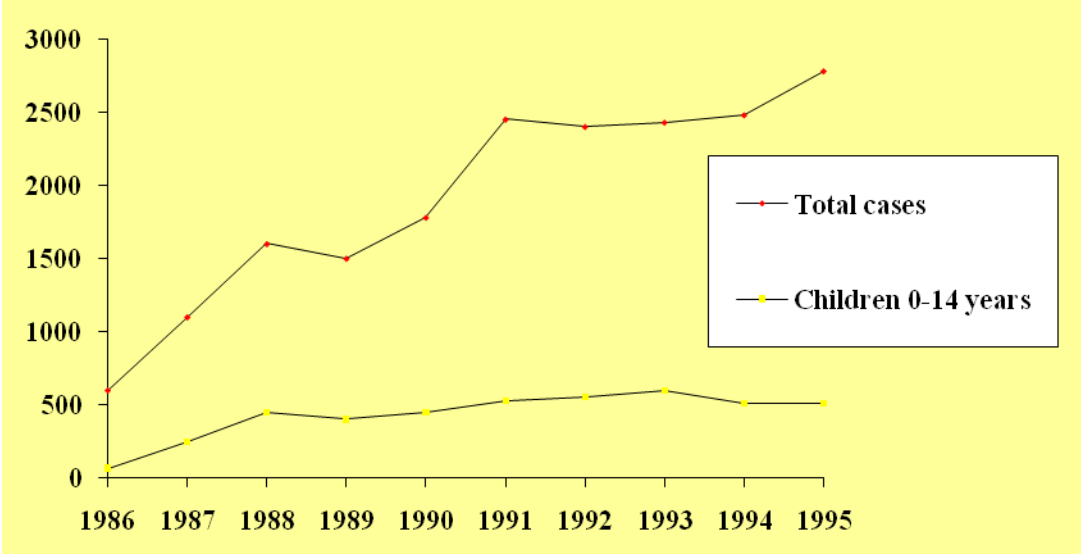


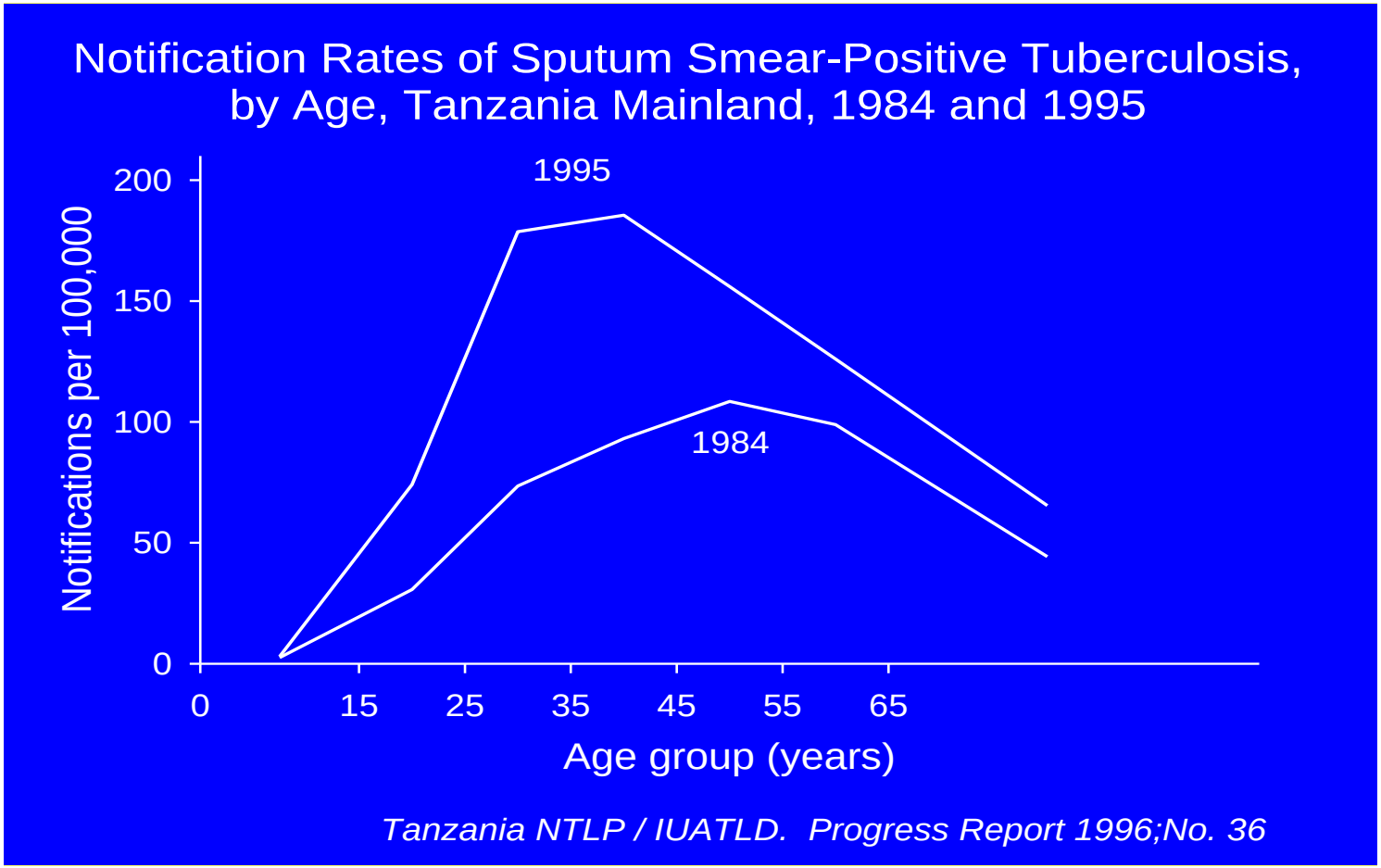
Figure 1 Tuberculosis notification rates in Malawi, 1985–2000. smear+ = smear positive.

Childhood tuberculosis notifications in Blantyre district, Malawi, increased 8-fold from 1986 to 1995 as the TB epidemic worsened

Harries AD, et al. Int J Tuberc Lung Dis 1997



Increased risk of TB exposure among young children in HIV-endemic countries



Pathogens found in lungs from autopsy studies of African children

Causes of pneumonia	HIV-infected N=473	HIV-uninfected N=338	Total N=811
Bacterial	238 (50%)	132 (39%)	370 (46%)
PcP	145 (31%)	11 (3%)	156 (19%)
CMV	121 (26%)	7 (2%)	128 (16%)
M.tuberculosis	50 (11%)	27 (8%)	77 (9%)
Co-infection	98 (21%)	5 (1.5%)	103 (13%)

Combined data from 7 autopsy studies from five TB endemic countries shows that tuberculosis is a common diagnosis in HIV-infected and uninfected children dying with lung disease

Child TB and TB/HIV

In HIV-endemic Africa, 40-60% of child TB cases are HIV-infected

Jeena PM et al, Int J Tuberc Lung Dis 2002; Schaaf HS et al, BMC Infect 2008

20 times higher risk of culture-confirmed TB in HIV-infected than in HIV-uninfected children

Madhi SA et al, Clin Infect Dis 2000; Hesseling AC et al, Clin Infect Dis 2008

TB risk 4-fold higher in HIV-infected children with low CD4% < 15% compared to HIV-infected children with higher CD4%

Elenga N et al, Pediatr Infect Dis J 2005

TB-related mortality significantly higher in HIV-infected children

Madhi SA et al, Clin Infect Dis 2000

Diagnosis of TB in HIV-infected child

HIV test should be routine in the assessment of a child with suspected TB

Diagnosis of TB in HIV-infected child

- HIV test should be routine in the assessment of a child with suspected TB
- Note that excluding HIV infection decreases the number of alternative diagnoses because chronic or persistent lung disease is common in HIV-infected children
- The approach to diagnosis of TB (PTB and EPTB) is similar in the HIV-infected child as for the HIV-uninfected child
- Diagnostic challenges are greater because co-infection with HIV reduces the specificity of the typical and clinical and radiological features of TB
- Samples should be taken for microscopy and culture (and sensitivity) whenever possible
- Symptomatic screening for TB should be routine for all HIV-infected children including upon HIV diagnosis and commencement of ART

Impact of HIV on clinical diagnosis of PTB

Features for TB diagnosis	Impact of HIV for TB diagnosis
• chronic symptoms	• less specific
• positive TB contact (if parent)	• less specific
• malnutrition	• less specific
• tuberculin test	• less sensitive
• CXR findings	• less specific
• satisfactory response to TB treatment	• less sensitive

Impact of HIV on TST positivity in children with confirmed TB

	HIV infected (% TST positive)	HIV uninfected (% TST positive)
South Africa Schaaf et al, BMC Infect Dos 2007	50/83 (60%)	190/232 (82%)
Ethiopia Palme et al, PIDJ 2002	12/58 (21%)	354/438 (80%)
South Africa Jeena et al, Int J Tuberc Lung Dis 2002	10/57 (18%)	21/44 (48%)
Cote d'Ivoire Mukadi et al, AIDS 1995	9/24 (38%)	74/106 (88%)

TST and HIV

Tuberculin skin test (TST) :

is often unavailable

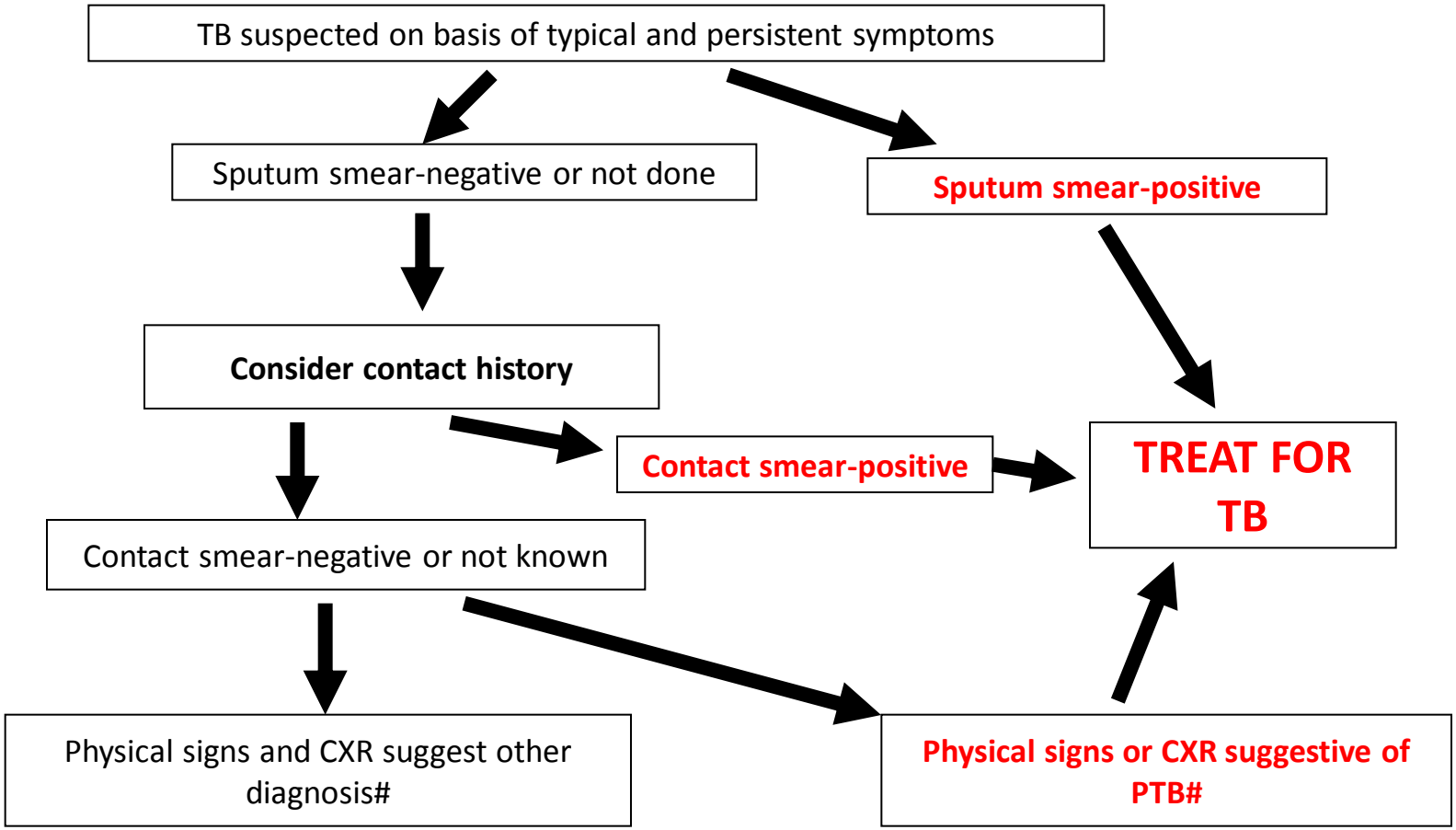
requires cold storage and repeated visits to the health facility

has low sensitivity in HIV-infected children, especially if not receiving ART

A positive history of TB contact is very important and provides similar epidemiological information to that provided by TST i.e. likely infection with *Mycobacterium tuberculosis*

Next slide provides a diagnostic approach at the primary and secondary level of care that does not rely upon availability or use of TST

Clinical approach to TB diagnosis in HIV-infected child



It can be difficult to clearly define what is “suggestive of PTB” on clinical or radiological findings in HIV-infected children because of clinical overlap between PTB and other forms of HIV-related lung disease: note further slides with Table and CXRs.

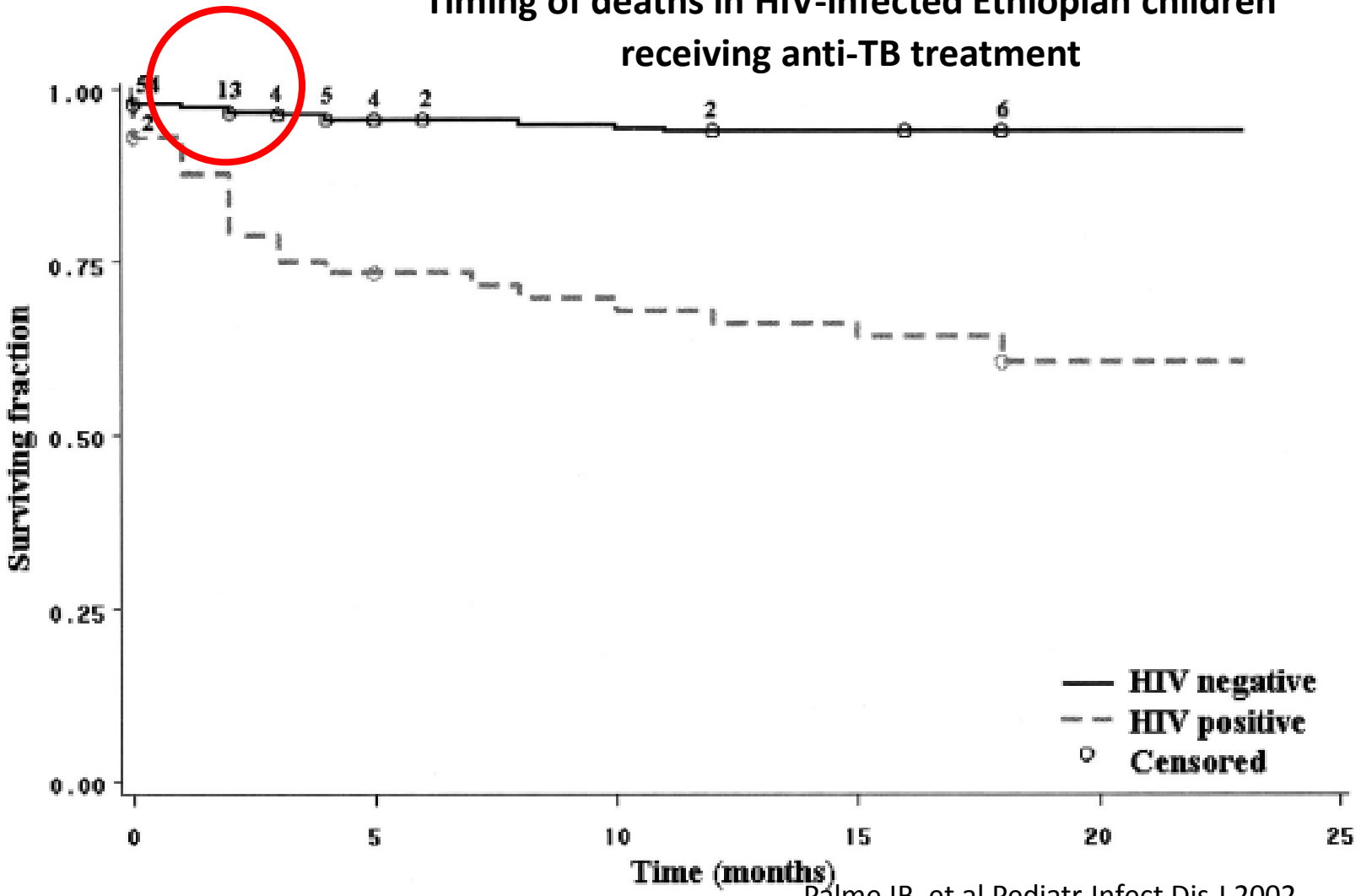
CXR abnormalities of PTB in HIV-infected children are mainly similar to those in HIV-uninfected children.

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

Mortality in HIV-positive and negative children with 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)

The diagnosis of PTB can be particularly challenging in HIV-infected child because clinical overlap with other HIV-related lung disease is common

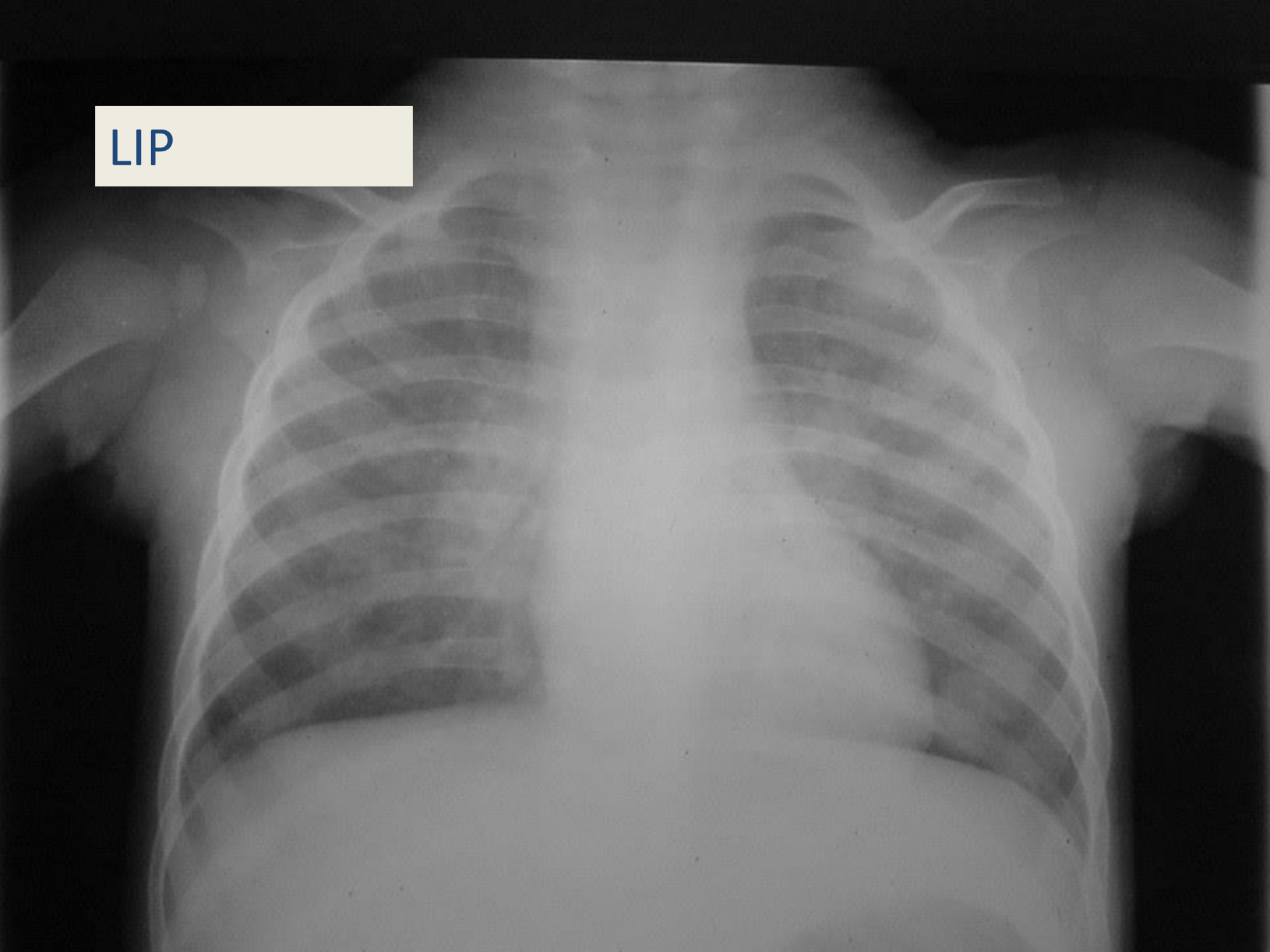
Cause	Clinical features
Recurrent pneumonia	Recurrent episodes of cough, fever and fast breathing that usually respond to antibiotics
LIP	Unusual before 1 year of age Associated with generalised symmetrical lymphadenopathy, clubbing, parotid enlargement. Nutritional status variable. CXR: diffuse reticulonodular pattern and bilateral perihilar adenopathy. No compression of airways
Tuberculosis	Persistent respiratory symptoms not responding to antibiotics. Often poor nutritional status; positive TB contact especially in younger children CXR: focal abnormalities and perihilar adenopathy
Bronchiectasis	Cough productive or purulent sputum; clubbing CXR: honeycombing usually of lower lobes Complicates recurrent bacterial pneumonia, LIP or TB
PcP	Common cause of severe, fatal pneumonia especially in infants. Persistent hypoxia is common Unusual after 1 year of age CXR: diffuse interstitial infiltration or hyperinflation
Mixed infection	Common problem: LIP, bacterial pneumonia, TB Consider when poor response to first-line empiric management
Kaposi sarcoma	Uncommon Characteristic lesions on skin or palate

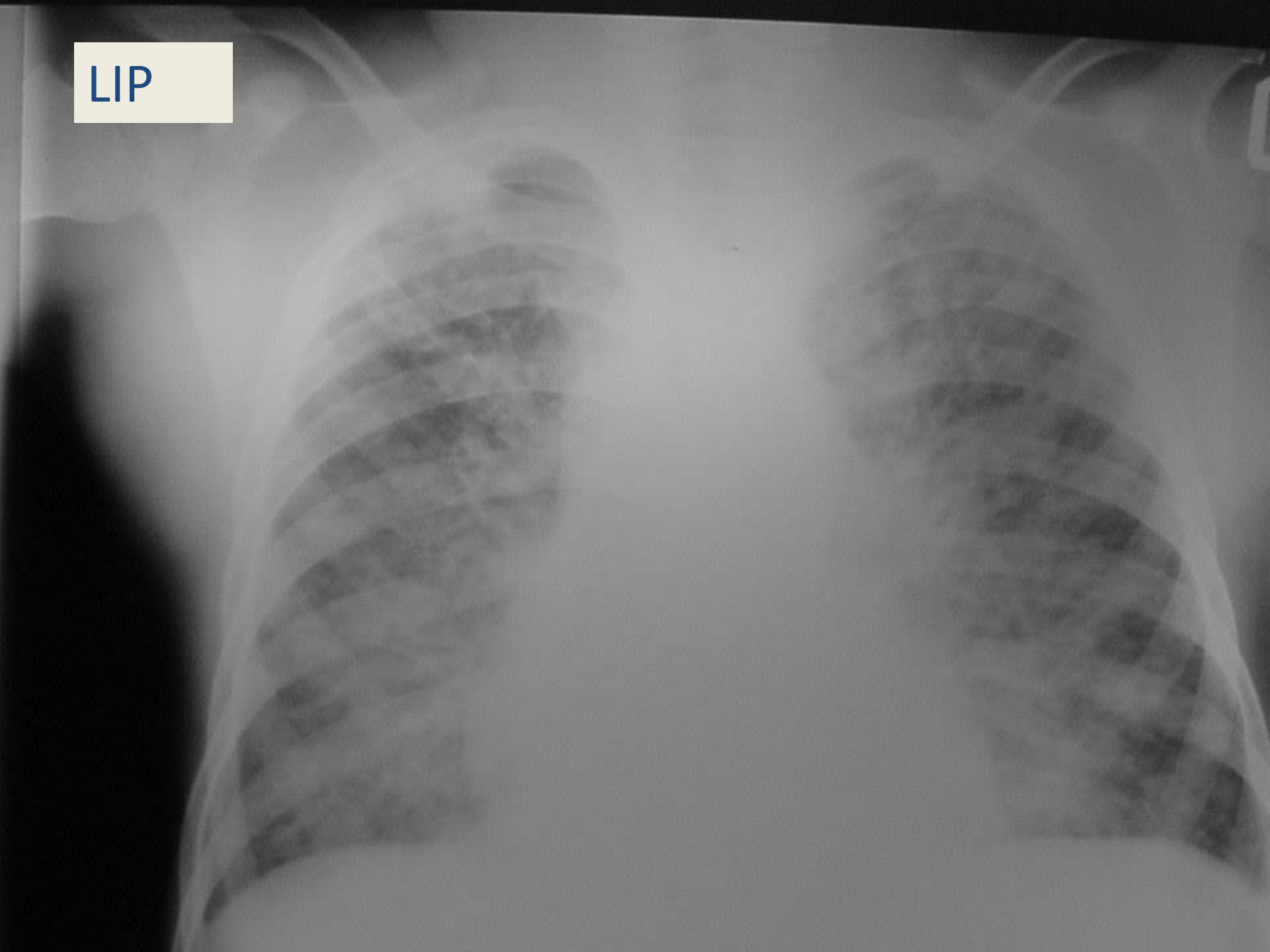
Clinical and radiological features that differentiate causes of chronic lung disease in HIV-infected children

Feature	PTB	Bronchiectasis	LIP	Miliary TB
Clinical				
Respiratory symptoms	Common	Common	Common	Uncommon
Persistent fever	Common	Common	Common	Common
Wasting	Common	Common	Variable	Common
Generalised lymphadenopathy	Uncommon	Uncommon	Common	Uncommon
Parotid enlargement	Rare	Rare	Common	Rare
Clubbing	Uncommon	Common	Common	Rare
Chest X-ray				
Focal parenchymal	Common	Common	Uncommon	Uncommon
Diffuse micronodular	Negative	Negative	Uncommon	Common
Diffuse reticular	Negative	Negative	Common	Negative
Lymphadenopathy	Common	Variable	Common	Uncommon

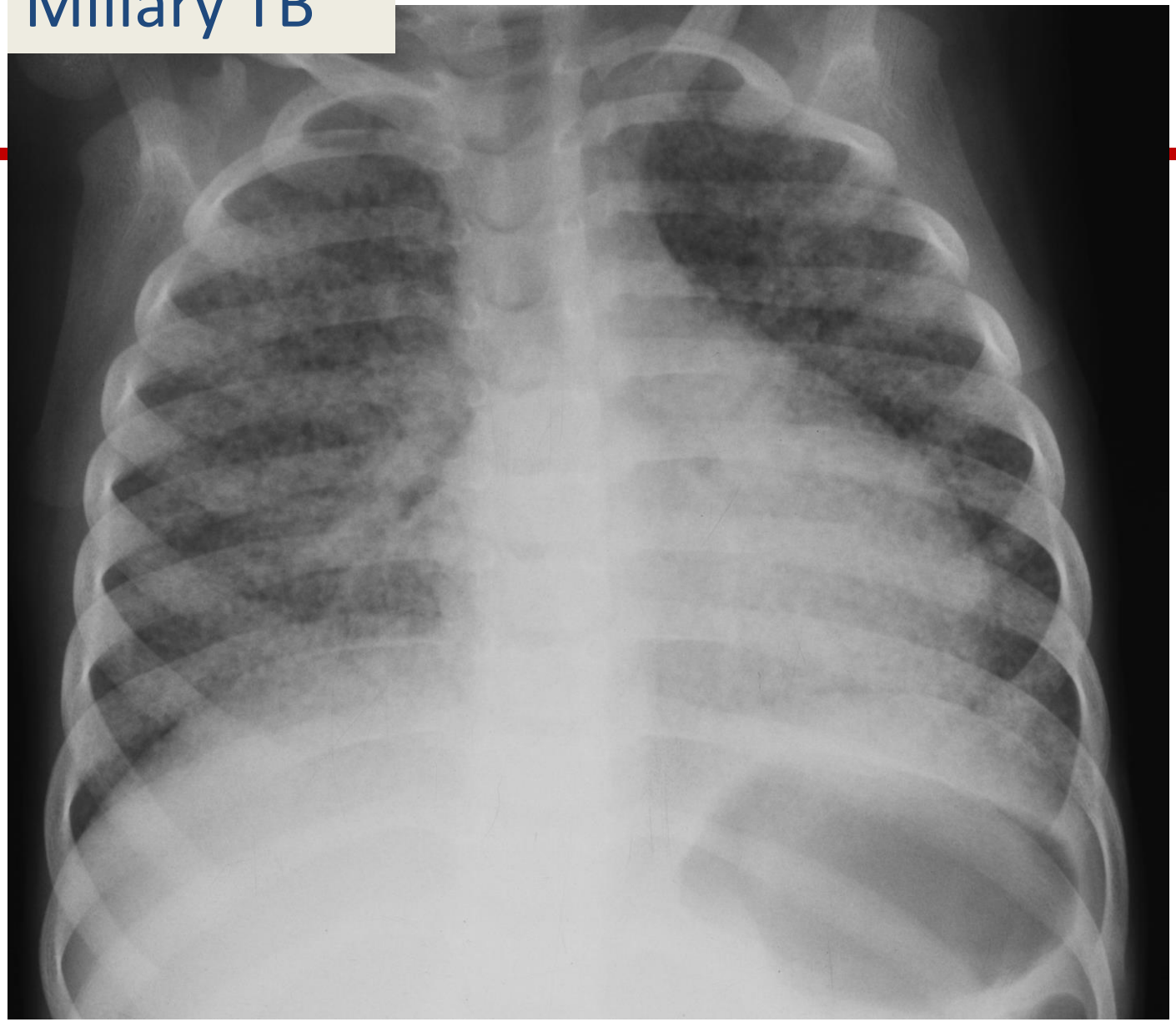
Note that co-morbidities are common in HIV-infected children

LIP

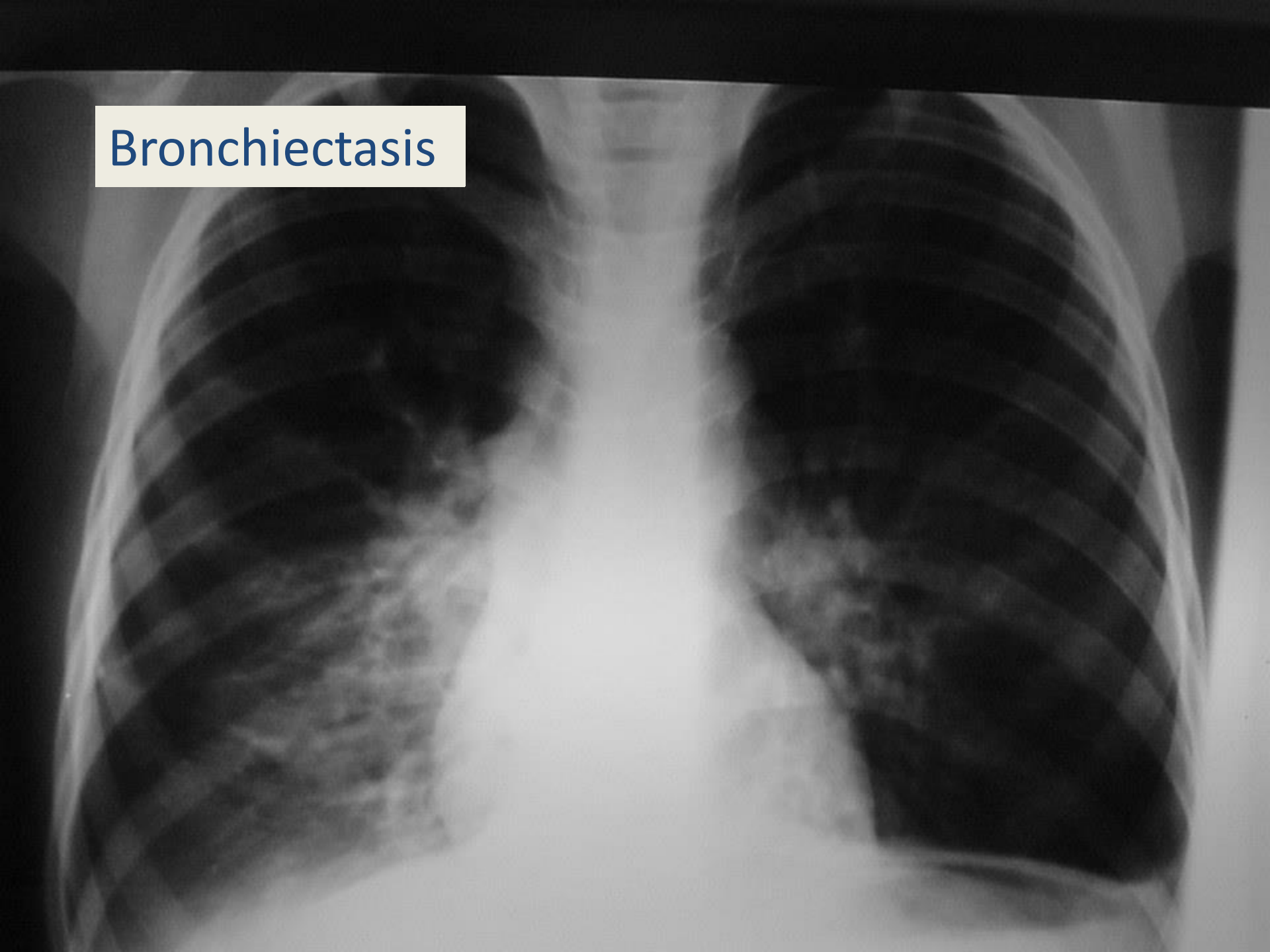


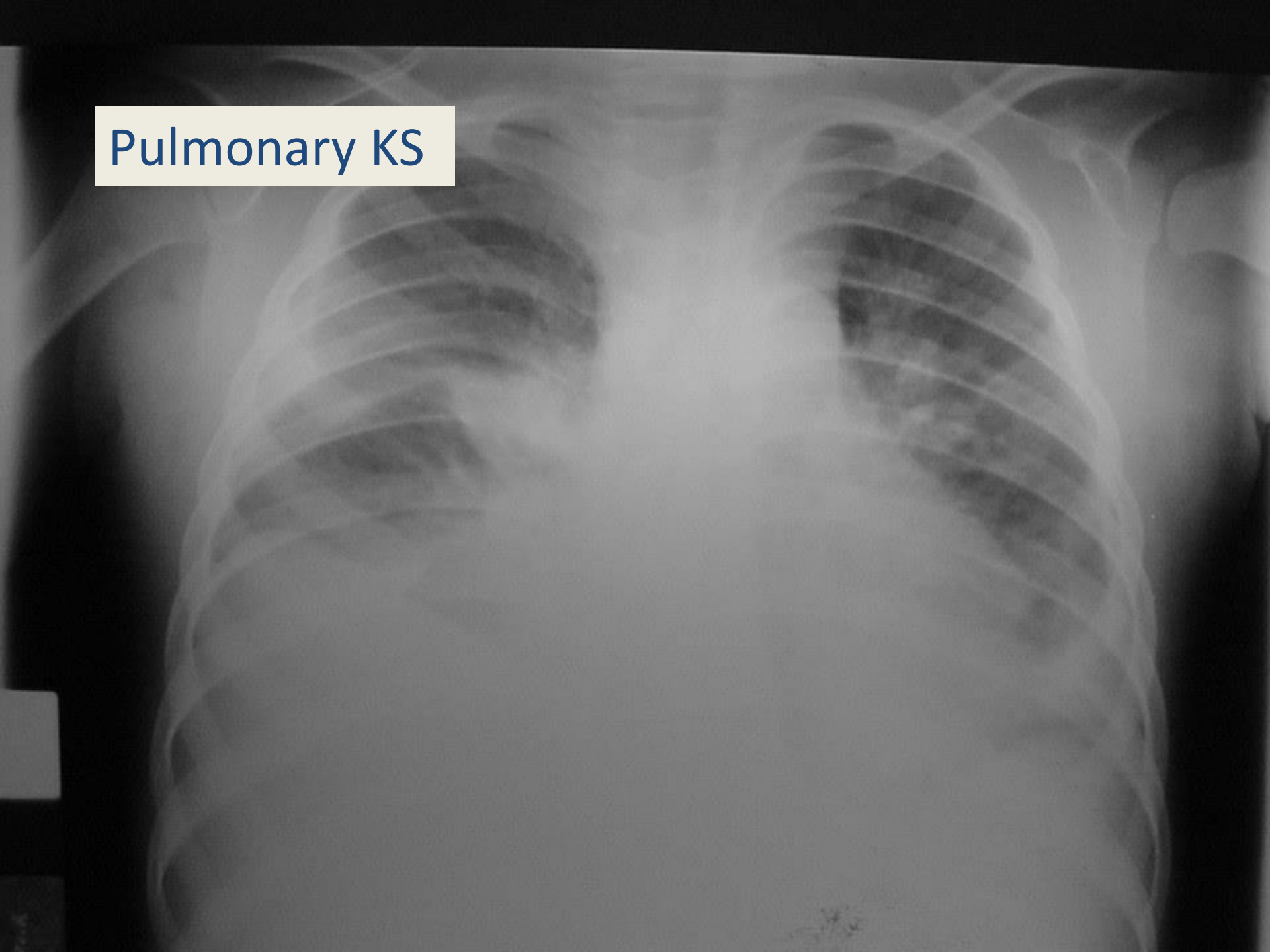

LIP

Miliary TB



Bronchiectasis




Pulmonary KS

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

Three “I”s for TB control

1) **I**ntensified Case Finding
2) **I**NH Prevention Treatment (IPT)
3) **I**nfection Control

….and a fourth?

Integration

of TB/HIV including maternal TB/HIV

of other health services such as maternal child health/IMCI

HIV and TB contact

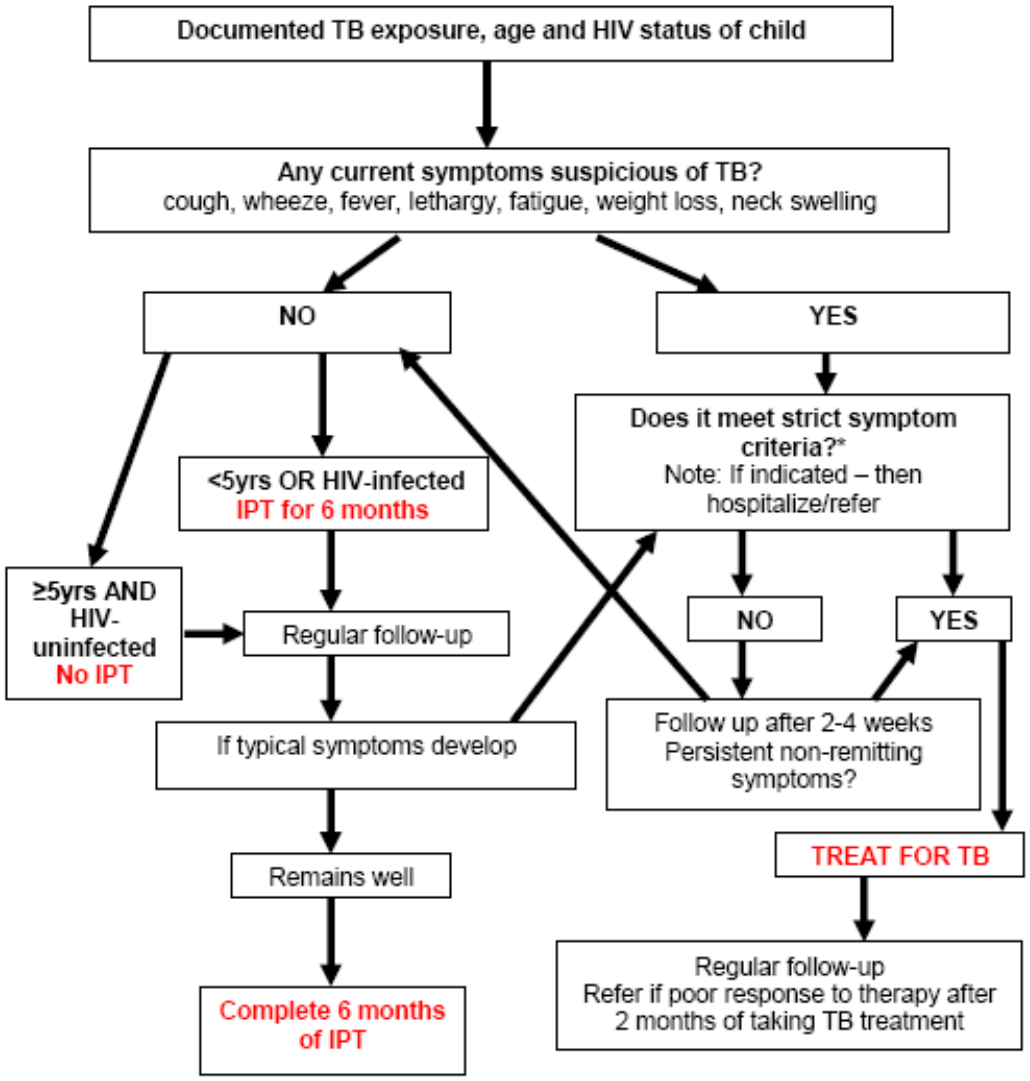
- HIV infected children at increased risk of exposure to TB and therefore infection
- HIV-infected children at high risk of TB disease if infected with *Mycobacterium tuberculosis*
- All HIV-infected children that are exposed to contact with a TB case should be screened using symptom-based screening approach
- All child contacts of case with TB/HIV should be tested for HIV

Management of HIV-infected contacts

- **HIV-infected contacts**
  - with symptoms suggestive of TB disease require assessment/referral for possible TB
  - with no symptoms suggesting TB require IPT for at least 6 months and careful follow-up

- **IPT reduces risk of TB disease in HIV-infected contacts**
- **ART reduces risk of TB disease in HIV-infected contacts**
- **ART + IPT provides better protection than ART alone**

Approach to management of child TB contact



IPT: isoniazid 5-15 mg/kg daily for at least 6 months

Weight band	INH 300 mg tab
4-9 kg	¼ tablet
10-19 kg	½ tablet
20-30 kg	1 tablet

Maternal/infant TB/HIV

TB in pregnancy or post-partum is common especially in HIV-infected women

Associated with maternal mortality, low birth weight and infant mortality

The risk of TB infection and disease to the infant of a mother with TB is extremely high

Maternal TB increases the risk of HIV transmission to the infant

HIV and infection control

- HIV infected children at increased risk of exposure to TB including drug resistant TB
- This risk includes health-care facilities especially also attended by adults such as HIV clinic, maternal clinic
- NTP has infection control guidelines emphasising importance of simple and feasible measures to optimize patient flow and air flow to reduce the risk of transmission

HIV and BCG

- HIV infected infants are at increased risk of disseminated BCG disease which is often fatal
- The benefits of BCG for HIV-infected infants are uncertain but may include protection against disseminated TB disease as for HIV-uninfected
- Early ART markedly reduces the risk of BCG disease
- BCG IRIS is common in infants (3-6 months) when early ART is commenced but is usually not fatal

HIV and TB in children

- HIV infected children at increased risk of exposure to TB and therefore TB infection
- HIV-infected children at high risk of TB disease in TB endemic setting
- Clinical approach to TB diagnosis in HIV-infected children is similar as for HIV-uninfected children
- Management of TB more complicated in HIV-infected children with significantly poorer outcomes
- Clinical diagnosis is more difficult especially for PTB as other HIV-related lung disease is common
- CPT and ART have a role in reducing TB-related death which is especially common within the first months following TB treatment