

TB-HIV: What is the research agenda in children?

Mark Cotton

Children's Infectious Disease

Clinical Research Unit

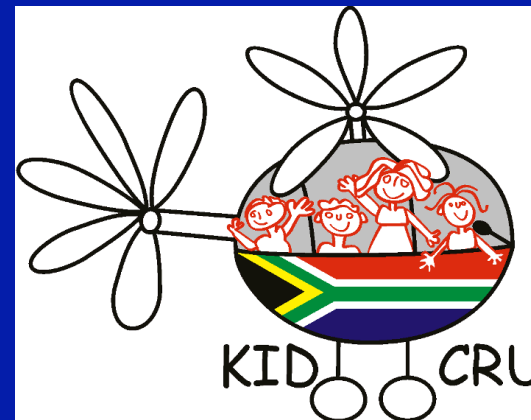
(KID-CRU)

Faculty of Health Sciences

Stellenbosch University

Tygerberg Children's

Hospital



Areas in common - TB & HIV

1. Co-exist
2. Can be silent until extensive disease
3. Can present acutely
4. Depress immune system (CD4 depletion)
5. Chronic
6. Lung disease common
7. Family disease
8. Programmatic approach in high prevalence settings
9. Treatment
 - a) \geq Triple therapy
 - b) Poor adherence leads to resistance
 - c) Do not add single drug to failing regimen
10. Post exposure prophylaxis

Clinical trials in childhood TB - is this all? PubMed 15/7/2007

Randomized

1. Te Water Naude JM, Donald PR, Hussey GD, et al. Twice weekly vs. daily chemotherapy for childhood tuberculosis. *Pediatr Infect Dis J* 2000;19(5):405-10.
2. Goel J, Singh H, Dhatt PS, Gupta HL. Comparative trial of ethambutol and thiacetazone in childhood tuberculosis. *Indian Pediatr* 1979;16(6):527-31.

Observational

3. Biddulph J, Kokoha V, Sharma S. Short course chemotherapy in childhood tuberculosis. *J Trop Pediatr* 1988;34(1):20-3.

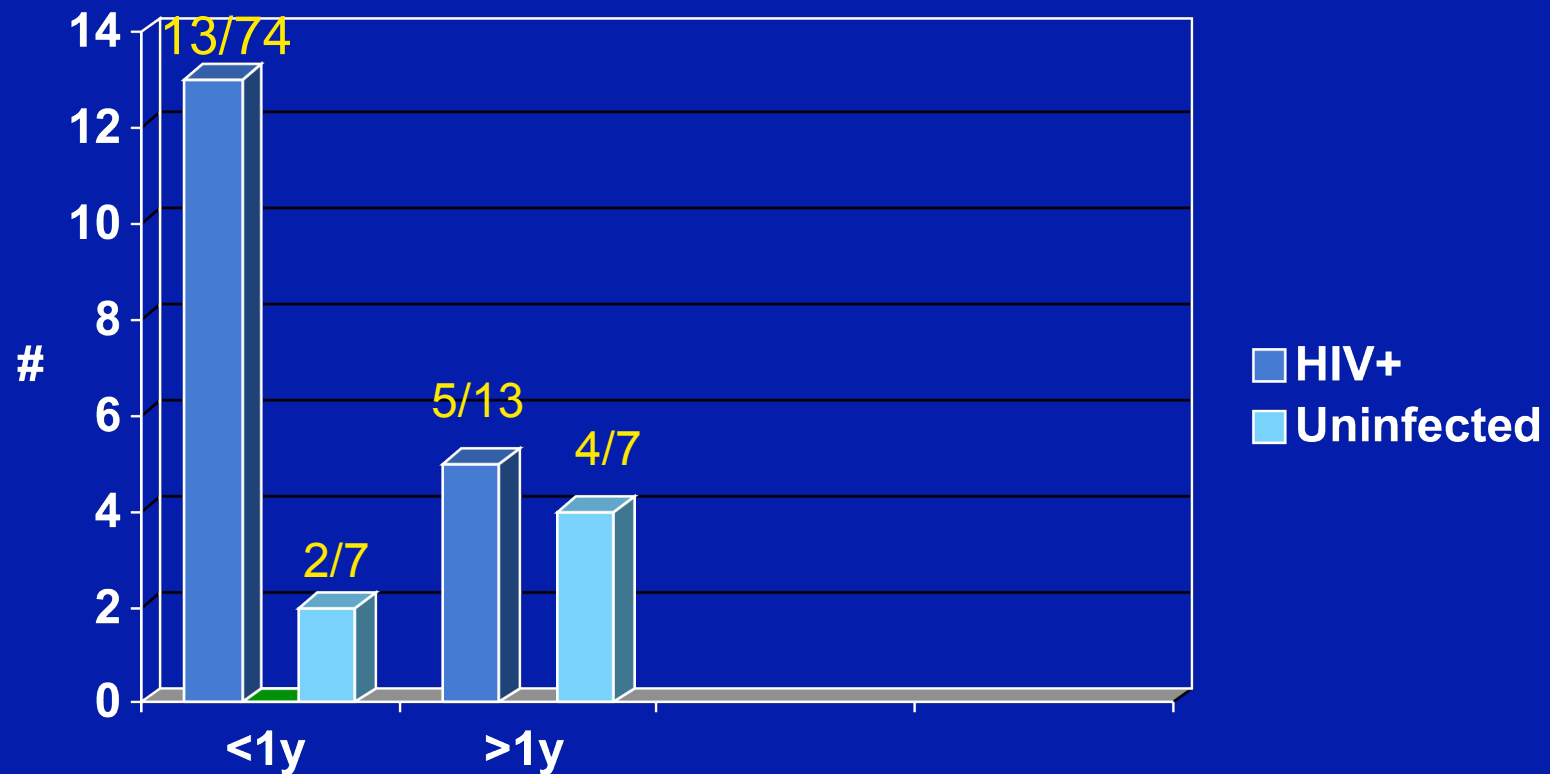
Childhood TB significant contribution to case load

- 13.7% total disease burden
- Incidence 400 per 100 000
- Marais B et al Int J Tuberc Lung Dis 2006; 10:259-63
Prospective study - Cape Town

TB common in HIV-infected children

- 23.4 of 100 HIV-infected children develop TB per year Zar et al BMJ 2006; 334: 136
- TB common in acute pneumonia

Extent of TB in 90 non-responders



Effect of age, polymicrobial disease, & maternal HIV status on Rx response & cause of severe pneumonia
McNally L et al Lancet 2007; 369: 1440-51

Childhood TB & HIV

- Presentation, diagnosis & outcome fairly well described in prospective & retrospective studies
- Virological & immunological outcome less well described
- Few data on long-term outcome on HAART

Culture confirmed TB in HIV-infected children n=87

- Poor response to std anti-TB Rx
- Not on HAART
- High mortality
 - Advanced HIV disease, severe malnutrition, and incomplete cure at the end of anti-TB are at greatest risk
 - Death is due to acute opportunistic infections
- High risk of recurrent tuberculosis

Hesseling, AC et al Arch Dis Child, 2005; 90: 1171

Diagnosis childhood TB becoming easier esp in HIV-ve

New Approaches & technologies

Marais B, Pai M Paediatr Resp Rev 2007; 8: 124-133

- Recognition of symptom complex of persistent non-remitting symptoms
 - Cough or wheeze
 - FTT in absence food insecurity
 - Fatigue or reduced playfulness
- Induced sputum = 3 Gastric washings
- New diagnostic tests - IGRA, skin tests

Time to laboratory diagnosis

- Acid-fast or auramine staining
 - 2 specimens on 2 consecutive days
 - 2 to 4 days
- Culture confirmation
 - Liquid media 7 - 14 days
 - 4 weeks for a definitive culture
 - Solid media
- Sensitivity tests
 - Direct from sample - 4 - 6w
 - Indirect 2 - 3 months

HIV/TB

DURATION OF TB THERAPY?

Unsatisfactory response to standard 6-m regimens in HIV-infected adults and children

G Hussey & P Donald - 6 versus 9m in children IUATLD
2006

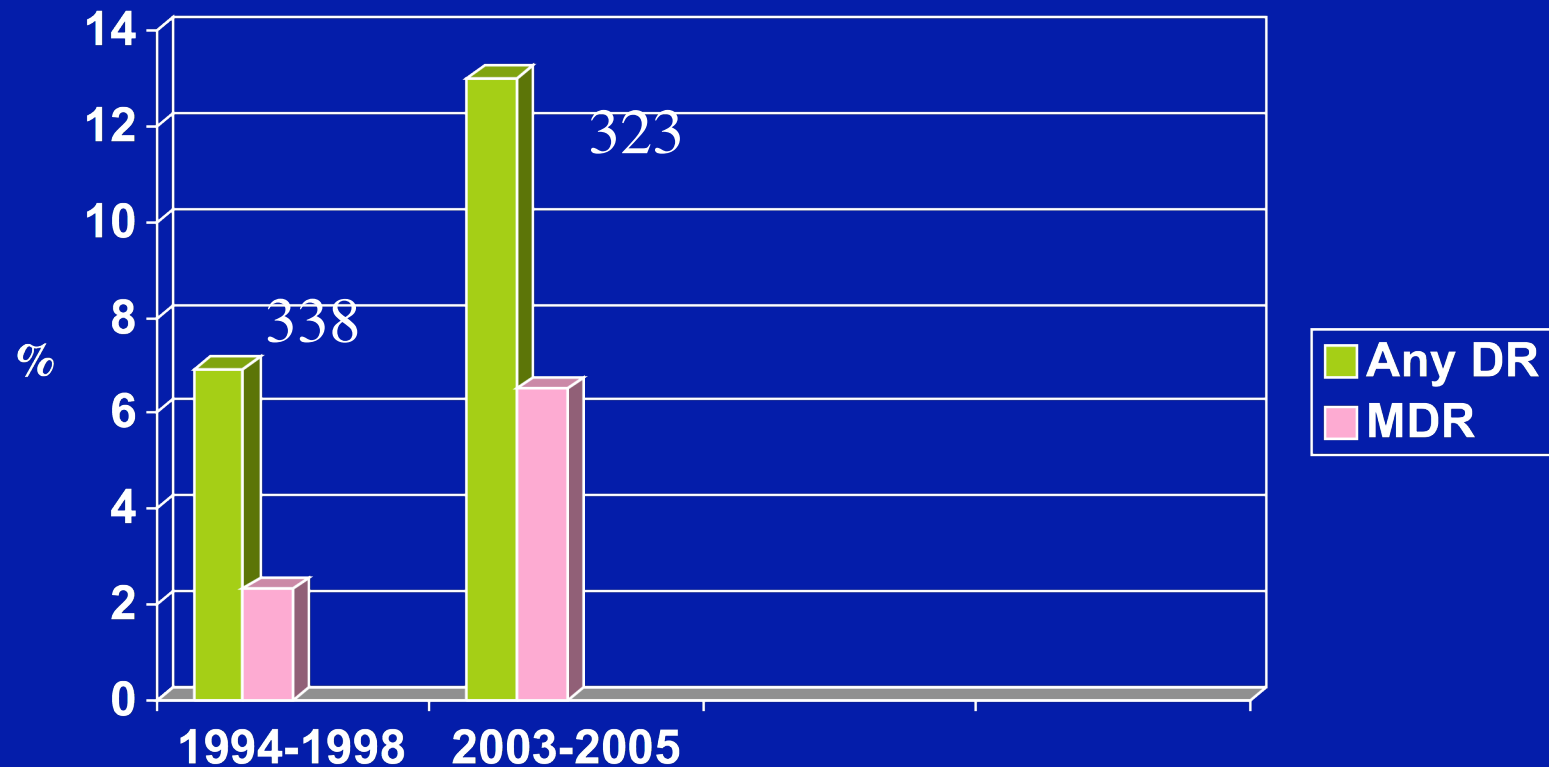
Espinal et al. J Acquir Immune Defic Syndr Hum Retroviral 1996;13:155-159.

Driver et al. Clin Infect Dis 2001;33:1762-1769.

Schaaf et al. Pediatr Infect Dis J 1998;17:599-604 .

Increasing Drug Resistance

Schaaf HS et al Acta Paediatrica 2006; 95: 523 - 528



OR: Drug resistant 0.49 (0.27-0.88)

MDR 0.40 (0.15-1.04)

Large prospective trials of TB possible in HIV-infected children

- Reasonable case definitions
 - Definite - Culture proven
 - Probable - combination of factors
 - Close contact with source case
 - Symptoms
 - Fever
 - Unremitting cough
 - Failure to thrive
 - Radiology
 - TST
 - Possible & unlikely but still treated
- Mechanism for impartial expert/s to review cases and X-rays
- Should be “blinded” to treatment arms in study

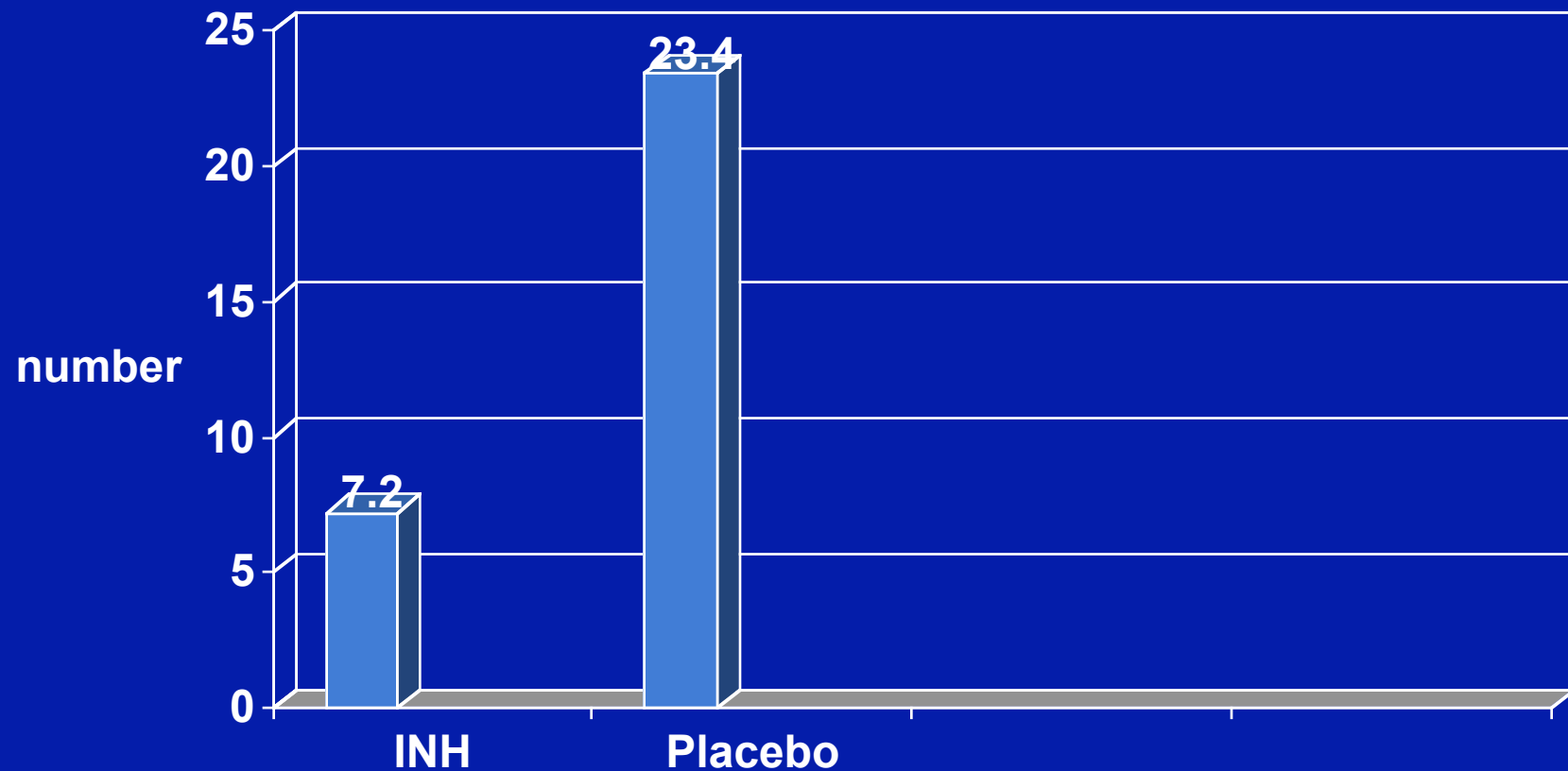
Large INH Prophylaxis studies for HIV+ (or HIV-exposed) children

- Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf HS, Rabie H, Lombard CJ. **Effect of INH prophylaxis on mortality and incidence of TB in children with HIV: randomized controlled trial** – *BMJ*, 2007; 334: 136
- Gastric washings, Mantoux, CXR, meticulous follow-up
- “Blinded” expert reviewed TB diagnoses

Results

- 11/132 (8.3%) died on INH group
- 21 /131 (16%) died in the placebo group
- Intent to treat analysis”
- None suspected of TB

TB disease per 100 HIV-infected children per year



H Zar, M Cotton, S Strauss et al BMJ 2007; 334: 176

IMPAACT 1041 - A randomized double blind, placebo controlled trial to determine the efficacy of INH in preventing TB disease & latent TB infection in African infants perinatally exposed to HIV

- Large sample size HIV-exposed and infected infants
- 3 centers in RSA
- 3 more SSA study sites to open 2007
- Rigorous diagnostic algorithms
- 5 year study
- Sponsored by DAIDS

IMPAACT (International Maternal Pediatric Adolescent AIDS **Clinical Trial Group** -

What about absorption of anti-TB drugs

- Low levels Ethambutol & PZA in Malawian children Graham et al Antimicrob Agents Chemother 2006; 50: 407 - 413
 - Worse:
 - <5y & HIV+

ART: should timing be studied?

- Usually delay until TB Rx established
- Urgency depends on clinical & immunological situation
- Younger infants have higher mortality
- TB IRIS
 - 14/32 Mycobacterial
 - 1 Mtb

Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Thai Children

Thanyawee Puthanakit, MD, Peninnah Oberdorfer, MD, PhD,* Noppadon Akarathum, MD,† Pornphun Wannarit, MD,‡ Thira Sirisanthana, MD,* and Virat Sirisanthana, MD**

PIDJ 2006; 25: 53

Rifampicin & ARVs

- EFV (Low levels with & without Rif - Ren Y, CROI 2007)
- RTV
- RTV + LPV (increase RTV to same mg/kg as LPV) (Ren Y, CROI 2007)
 - Double dose LPV/r study in process - UCT
 - Double dose NVP?
- **NRTI increased glucuronidation**
 - ZDV
 - ?ABC

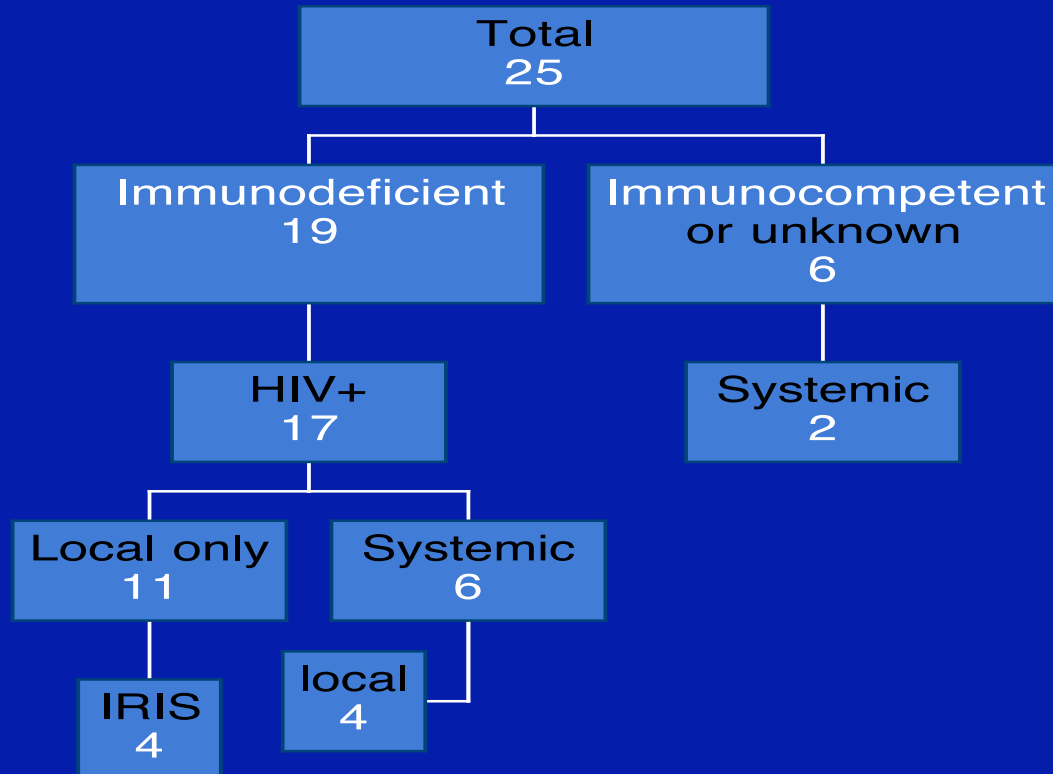
BCG: WHO advisory note for HIV-infected infants

- BCG given to all neonates in Africa
- Prevents disseminated TB in infants
- Risk of disseminated BCG 110-417/100 000 HIV-infected vaccinees per year versus 1 to 2 $\times 10^6$ in immunocompetent infants Hesseling A, Vaccine 2006



Retrospective study of BCG complications

- A Hesseling et al - CID 2006; 42: 548-558



Disseminated disease - 75% mortality

New drugs for TB

- Children must be included

New MDR studies - Bill Burman, UCHSC, CO

- Optimized background therapy
- **Plus** new drug or Placebo
- Children should not be left out as reflect ongoing transmission in communities
- Post-exposure prophylaxis

Research agenda for TB-HIV in children?

- Prospective natural history studies including virological, immunological & microbiological outcome
- Pharmacokinetics
 - TB drugs
 - ARVs
- BCG -
 - should administration be delayed?
 - How protective is it?
- New diagnostic tests in childhood TB
- Transmission in Health Care Facilities

Research Agenda

- TB therapy
 - Standard versus long course
 - INH prophylaxis
 - Routine or targeted
 - New TB drugs esp for MDR
 - Short course therapy
 - In standard therapy
 - Contact prophylaxis

Mail & Guardian Apr 26 - May 3, 2007

- Global plan to stop TB \$ 1,1 billion 2007
- Cost of ARVs for 6 million - \$1.5 billion
- Replacement of Trident missile system \$26 billion
- Smallpox research receives same funding as TB



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