The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting

L J Frigati,[1] K Kranzer,[2] M F Cotton,[3] H S Schaaf,[3] C J Lombard,[4] H J Zar[1]

[1]Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Cape Town, South Africa
[2]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
[3]Department of Paediatrics and Child Health, Stellenbosch University, South Africa
[4]Biostatistics Unit, Medical Research Council, Cape Town, South Africa

Correspondence to
Dr L J Frigati, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch 7700, South Africa; lisafrigati@yahoo.com

The data and safety monitoring board comprised J Kaplan (chair), W El Sadr, P Donald and N Beyers.

Received 27 November 2010
Accepted 17 February 2011
Published Online First
2 April 2011

ABSTRACT

Background Tuberculosis (TB) is a major cause of morbidity and mortality among children infected with HIV. Strategies to prevent TB in children include isoniazid preventive therapy (IPT) and antiretroviral therapy (ART). IPT and ART have been reported to reduce TB incidence in adults but there are few studies in children.

Objective To investigate the combined effect of IPT and ART on TB risk in children infected with HIV.

Methods A cohort analysis was done within a prospective, double-blinded, placebo-controlled trial of isoniazid (INH) compared with placebo in children infected with HIV in Cape Town, South Africa, a high TB incidence setting. In May 2004 the placebo arm was terminated and all children were switched to INH. ART was not widely available at the start of the study, but children were started on ART following the establishment of the national ART program in 2004. Data were analysed using Cox proportional hazard regression.

Results After adjusting for age, nutritional status and immunodeficiency at enrolment, INH alone, ART alone and INH combined with ART reduced the risk of TB disease by 0.22 (95% CI 0.09 to 0.53), 0.32 (95% CI 0.07 to 1.55) and 0.11 (95% CI 0.04 to 0.32) respectively. INH reduced the risk of TB disease in children on ART by 0.23 (95% CI 0.05 to 1.00).

Conclusions The finding that IPT may offer additional protection in children on ART has significant public health implications because this offers a possible strategy for reducing TB in children infected with HIV. Widespread use of this strategy will however require screening of children for active TB disease.

Trial registration Trial registration—Clinical Trials NCT00330304.

Key messages

What is the key question?
- Does isoniazid preventive therapy (IPT) reduce tuberculosis (TB) in HIV-infected children on antiretroviral therapy (ART)?

What is the bottom line?
- IPT provides additional protection against TB disease in children taking ART.

Why read on?
- To examine how to safely reduce TB using IPT and ART in combination.

INTRODUCTION

Tuberculosis (TB) is an important cause of morbidity and mortality in children living in high TB incidence settings.[1 2] The incidence and severity of childhood TB is increased by HIV infection. A recent study reported a RR for developing culture-proven TB in infants infected with HIV of 24.2 (95% CI 17 to 34) compared with infants without HIV infection.[3] Furthermore, children infected with HIV and TB are at risk of more rapid progression to disease, more severe disease and increased mortality.[4–6]

BCG vaccination, isoniazid preventive therapy (IPT) and antiretroviral therapy (ART) are possible strategies to prevent TB in children infected with HIV. WHO guidelines have recently been revised to recommend against BCG vaccination in infants infected with HIV because of the high risk of disseminated BCG and associated mortality.[7]

Limited data suggest that IPT[8] or ART[9 10] can independently reduce TB incidence and mortality in children infected with HIV. The authors have previously reported that IPT (irrespective of TB exposure) reduced the risk of TB in children infected with HIV not on ART by approximately 50%.[8 11] Another South African study found that IPT did not decrease risk of TB in children under 12 months infected with HIV.[12] These studies have informed the recent revised WHO guidelines recommending IPT for 6 months for all children over 12 months of age infected with HIV.[13]

A retrospective study found that ART substantially reduced TB incidence in children infected with HIV, with 53 TB cases per 100 patient years prior to use of ART compared with 6.4 on ART.[9] However, children infected with HIV on ART still have a higher risk of TB than children without HIV infection.[9]

Observational studies suggest that isoniazid (INH) preventive therapy is protective in adults receiving ART.[14 15] Several randomised trials investigating the combined effect of IPT and ART are underway in adults but data in children are scarce. The objective of this study was to investigate the combined effect of IPT and ART on TB risk in children infected with HIV living in a high TB incidence setting.

METHODS

A cohort study was performed as part of a prospective, double-blinded, placebo-controlled trial of

INH, given with cotrimoxazole either daily or three times a week in children infected with HIV in two centers in Cape Town, South Africa. The study area has one of the highest incidence rates of childhood TB globally, 407/100 000 in children under 2 years of age.[16] The study started in January 2003; in May 2004 the placebo arm was terminated on the recommendation of the Data Safety and Monitoring Board (DSMB) because interim analyses demonstrated significant benefit of INH on mortality, the primary outcome. INH was found to reduce mortality by 54% (95% CI 0.22% to 0.95%).[8] Thereafter, all children were placed on INH daily or three times a week until December 2007 when INH was discontinued on the advice of the DSMB because almost all of the children had started on ART.

A cohort analysis was performed to investigate the combined effect of INH and ART on TB risk in children enrolled in the study from January 2003 to December 2007.

Study population

The study population comprised children older than 8 weeks infected with HIV attending Red Cross Children's Hospital, University of Cape Town or Tygerberg Children's Hospital, Stellenbosch University. Ninety eight per cent of children were black South African from low socio-economic background. Inclusion criteria were a weight greater than 2.5 kg, and ability to attend regular follow-up visits. Exclusion criteria were current use or need for IPT, prior hypersensitivity to sulphur drugs or INH, severe anaemia (haemoglobin <70 g/litre), neutropaenia (absolute neutrophil count <400 cells/μl) and non-reversible renal failure. TB disease at the time of enrolment was not an exclusion criterion but children completed TB therapy according to national guidelines and thereafter were randomised to INH or placebo. All children were classified according to WHO clinical staging (stage 1 to 4).

Follow-up

The study team evaluated the children every 4 weeks for the first 6 months, every 6 weeks for the second 6 months and thereafter every 2–3 months depending on medical and social circumstances. Clinical and historical data were collected at each visit. A tuberculin skin test (TST, 2 TU RT23, Staten Serum Institute, Copenhagen, Denmark), and chest radiograph were done at 6 monthly intervals. A child exposed to a TB source (case), hospitalised for respiratory illness, or developing symptoms of TB at any time during the study period was investigated for TB infection and disease. For pulmonary TB this included a TST, a chest radiograph and two induced sputum specimens for acid fast staining and *Mycobacterium tuberculosis* culture. Additional specimens were submitted as clinically indicated. Children exposed to a household TB case were given IPT according to standard guidelines and then returned to their initial randomisation without being unblinded.

Isoniazid preventive therapy

Enrolment began in January 2003. Children enrolled before May 2004 were randomly allocated to receive INH (10 mg/kg) or placebo. All children receiving placebo were switched to INH in May 2004. All children enrolled thereafter received INH. INH was stopped in all children in December 2007.

Antiretroviral therapy

ART was not widely available at the start of the study but was obtained for some children through participation in pharmaceutical trials or charitable donations. Children were started on a double nucleoside reverse transcriptase inhibitor (NRTI) backbone (zidovudine, lamivudine, stavudine) combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz or nevirapine) or a protease inhibitor (ritonavir/lopinovir or ritonavir only). Standard guidelines for ART in children

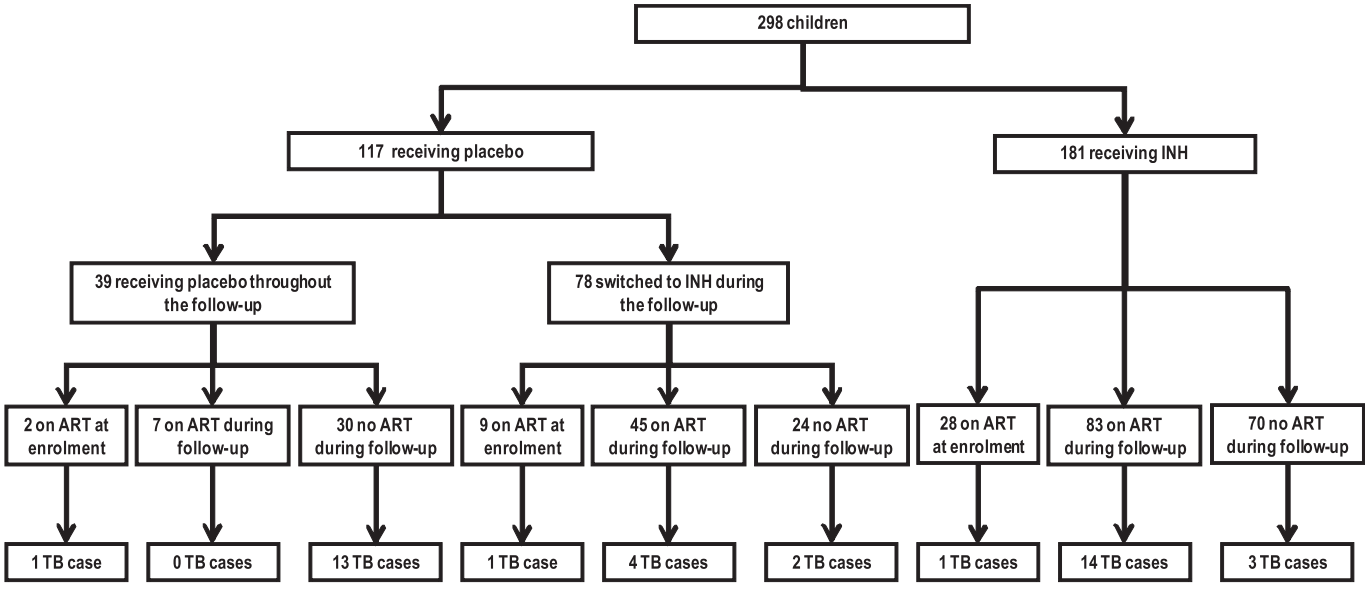

Figure 1 Children included in the study. ART, antiretroviral therapy; INH, isoniazid; TB, tuberculosis.

were developed after the establishment of the national ART program in 2004. Thereafter increasing numbers of children initiated therapy according to medical and social criteria described in the national guidelines.

Diagnosis of TB

Cases of TB were classified as definite or probable according to clinical, radiological and microbiological findings as follows: definite TB: culture positive for *M tuberculosis* on a sputum or other sample; probable TB: chest radiograph suggestive of TB (lymphadenopathy, miliary pattern, pleural effusion, bronchial compression or parenchymal infiltrate) plus at least one of the following: a positive TST, a history of a close contact with an adult with TB, loss of weight or failure to gain weight within the previous 3 months, or a positive smear microscopy for acid fast bacilli on sputum. Chest radiographs were reported by a single radiologist, blinded to the diagnosis of TB, according to a standardised format. Probable cases were reviewed by an independent experienced paediatrician blinded as to whether the child was on INH, placebo and/or ART.

Study design

A prospective cohort study was performed to investigate the effect of INH and ART on TB incidence. Children were censored at death, date of TB diagnosis, loss to follow-up or on the 31 December 2007. Children could contribute time to four groups: time on placebo only, time on INH only, time on ART only, time on ART and INH (figure 1).

Confounding variables

The degree of immunodeficiency at enrolment was grouped according to WHO CD4 classification.[17] Categories 1 and 2 (insignificant or mild) and categories 3 and 4 (moderate or severe) were grouped together. WHO clinical staging at enrolment was grouped as stage 1 and 2 or stage 3 and 4 combined. The z-scores for nutrition were grouped as less than −2 (normal or mild) or greater than −2 (moderate or severe).

Statistical analysis

All analysis was conducted using Stata (version 10.1, College Station, Texas, USA). Descriptive statistics of the baseline data and follow-up data of the cohort were calculated as medians, 25th and 75th percentiles and frequencies.

Cox proportional hazards regression was performed using time since randomisation as the time scale. Records were split for time-dependent exposure and age at follow-up. The analysis was performed taking dependency of records into account. Univariable analyses were conducted using immunodeficiency, anthropometric z-scores and age at enrolment (grouped as 0–2 years, 2–5 years and more than 5 years), gender, prior TB, daily or three times per week regimens for INH/cotrimoxazole, placebo, INH, ART and INH and ART. Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals.

Age at follow-up and immunodeficiency at enrolment were included a priori in the multivariable model. Possible other confounders including WHO clinical staging and nutritional status at enrolment, prior TB, and gender were assessed for their impact on the effect estimates. Variables acting as confounders were included in the final model.

Ethical approval

The study was approved by the ethics committees of the Faculty of Health Sciences, University of Cape Town and of Stellenbosch University. Written informed consent was obtained from a parent or legal guardian.

Table 1 Baseline characteristics of children enrolled (N=298)

Variables	N (%) or median (IQR)
Age (years)	2.09 (1.03, 4.11)
Gender	
Female	135 (45.3%)
Male	163 (54.7%)
WHO clinical stage at enrolment	
Stage 1	12 (4.1%)
Stage 2	41 (14.1%)
Stage 3	177 (60.8%)
Stage 4	61 (21.0%)
WHO CD4 depletion at enrolment	
Category 1=not significant	30 (10.1%)
Category 2=mild	20 (6.7%)
Category 3=advanced	49 (16.4)
Category 4=severe	199 (66.8%)
Anthropometry at enrolment	
Height for age z-score	−1.91 (−2.87, −0.94)
Weight for age z-score	−1.34 (−2.41, −0.43)
Weight for height z-score	−0.17 (−1.07, 0.72)
History of TB disease	
None	236 (79.2%)
Prior to enrolment	21 (7.0%)
TB treatment at enrolment	41 (13.8%)
Cotrimoxazole/INH	
Daily	145 (48.7%)
3 times a week	153 (51.3%)
INH	
Placebo throughout the study	39 (13.1%)
Initial placebo, switched to INH	78 (26.2%)
INH throughout the study	181 (60.7%)
ART	
At enrolment	39 (13.1%)
Started during the study	135 (45.3%)
No ART	124 (41.6%)
Time on ART (months) N=174	17.92 (10.6; 26.2)
Time on INH (months) N=259	20.03 (14.5; 27.8)
Follow-up time (months) N=298	21.7 (9.5, 27.4)

ART, antiretroviral therapy; INH, isoniazid; TB, tuberculosis.

RESULTS

Baseline characteristics

Two hundred and ninety eight children (median age 2.09 years) were enrolled. At enrolment 117 children were randomly assigned to receive placebo and 181 to INH (figure 1). Of 117 children assigned to receive placebo, 78 were switched to INH after May 2004 while 39 were censored (lost to follow-up, died or diagnosed with TB) before May 2004. In summary there were three INH groups: children who received INH throughout follow-up (n=181); children who initially received placebo and were then switched to INH (n=78); and children who only received placebo during follow-up (n=39). Overall, 39 (13%) children were on ART at enrolment, while 135 (45%) started ART during the study. The total time of follow-up was 495.65 person years: 42.02 person years on placebo/no ART, 12.67 person years on placebo/ART, 207.73 person years on INH/no ART and 233.23 person years on INH/ART. A total of 37 children died: 15 on placebo, two on ART, 14 on INH and six on INH plus ART.

At enrolment, most children were mildly undernourished with a median height for age z-score of −1.91 and weight for age z-score of −1.34 (table 1). The majority had severe clinical

Table 2 Effect of INH, ART and INH combined with ART on TB risk

	Univariable		Multivariable	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Gender				
Male	1			
Female	1.01 (0.54 to 1.90)	0.970		
Age at follow-up				
0–2	1			
2–5	0.78 (0.37 to 1.66)	0.511	0.74 (0.33 to 1.55)	0.445
>5	0.68 (0.29 to 1.60)	0.384	0.79 (0.33 to 1.91)	0.603
WHO clinical stage at enrolment				
1 or 2	1			
3 or 4	1.52 (0.60 to 3.86)	0.390		
Immunodeficiency at enrolment				
Mild	1			
Advanced/severe	2.44 (0.73 to 8.09)	0.144	2.74 (0.78 to 9.68)	0.117
z-Score (height for age) at enrolment				
Mild	1			
Moderate/severe	1.80 (0.96 to 3.39)	0.068	1.84 (0.99 to 3.42)	0.055
z-Score (weight for age) at enrolment				
Mild	1			
Moderate/severe	1.00 (0.51 to 1.96)	0.098		
z-Score (weight for height) at enrolment				
Mild	1			
Moderate/severe	1.20 (0.40 to 3.57)	0.760		
History of TB disease				
No	1			
Yes	0.83 (0.38 to 1.80)	0.625		
Cotrimoxazole/INH				
Daily	1			
3 times a week	0.89 (0.48 to 1.67)	0.714		
Placebo	1			
ART	0.35 (0.07 to 1.63)	0.179	0.32 (0.07 to 1.55)	0.157
INH	0.24 (0.11 to 0.55)	0.001	0.22 (0.09 to 0.53)	0.001
INH and ART	0.14 (0.05 to 0.35)	<0.001	0.11 (0.04 to 0.32)	<00.01

ART, antiretroviral therapy; INH, isoniazid; TB, tuberculosis.

disease, with 82% in WHO stage 3 or 4. Most (83%) had advanced or severe immunodeficiency (table 1). Forty-one (13%) children were diagnosed with TB at enrolment. The median follow-up time was 21.7 months with a median time on INH of 20.3 months and median time on ART of 17.9 months. During this period, 39 cases of TB were diagnosed (19 definite and 20 probable). INH was well tolerated with excellent adherence using pill count and adherence counselling.[18] There was no increased risk of elevated liver enzymes, jaundice or fulminant liver failure in children taking ART and IPT.[19]

Effect of INH, ART and INH plus ART

Univariable Cox regression analysis showed no association between gender, weight for age z-score, weight for height z-score and history of TB disease (table 2). More advanced clinical disease and immunodeficiency at enrolment increased the risk of TB disease, as did more severe stunting. ART alone and INH alone reduced the risk of TB disease by 0.35 and 0.24 respectively. INH and ART combined reduced TB risk by 0.14 (95% CI 0.05 to 0.35) compared with placebo.

Multivariable analysis showed that, after adjusting for age at follow-up, nutritional status and immunodeficiency at enrolment INH alone reduced the risk of TB by 0.22 (95% CI 0.09 to 0.53). ART alone reduced TB risk by 0.32 (95% CI 0.07 to 1.55) compared with placebo. The combination of INH and ART reduced the risk of TB by 0.11 (95% CI 0.04 to 0.32) (table 2).

Restricting the analysis to children receiving ART revealed a TB risk reduction of 0.23 (95% CI 0.05 to 1.00) comparing INH with no INH.

DISCUSSION

This is the first study to suggest that IPT reduces TB risk in children receiving ART. Overall, there was a 0.11 risk reduction of TB disease in children receiving both INH and ART compared with children receiving neither. While INH and ART independently reduced TB risk by 0.22 and 0.32 respectively, the combination of INH and ART reduced the risk by 0.11. In children on ART, INH reduced the risk of TB disease by 0.23.

The protective effect of ART on TB risk has been previously reported in children.[9 10] ART reduces susceptibility to *M tuberculosis* by improving immunity, and enabling more effective containment of TB infection.[20 21] The benefit of IPT in preventing TB disease in TST-positive HIV-infected adults has clearly been shown.[22] Studies in HIV-infected adults found a TB risk reduction of 76% in those receiving IPT and ART compared with those receiving neither.[14 15] A possible explanation for this added benefit is the effect of INH in treating latent infection and preventing progression to disease. In young children, TB disease usually represents progression of primary infection rather than reactivation of latent infection, therefore the mechanism of the additional effect of IPT in children receiving ART as occurred in our study may be through containment of primary infection.

Diagnosis of TB infection or pulmonary disease is challenging in children infected with HIV because of anergy and difficulty in obtaining a microbiological diagnosis. A concern for implementing IPT is inadvertent use in pulmonary TB, thereby promoting drug resistance. In this study all children were carefully screened for TB at enrolment, including repeated induced sputum samples. As evidence of the effectiveness of screening, 41 (13.8%) children were diagnosed with TB at enrolment and started on TB therapy. This high proportion of newly diagnosed TB through active case finding highlights the importance of appropriate screening tools before the rolling out of IPT.

Intensive surveillance for TB infection and disease was done in the study through close clinical, radiological, immunological and microbiological follow-up. We did not identify TB in any of the children who died. Three children developed INH-resistant TB, although one had contact with a multidrug resistant case. A study including children from this cohort reported 3.4% of grade 3 and 4 elevation in alanine transaminase (ALT) in children on ART and INH. All children were asymptomatic and no children developed clinical jaundice or fulminant hepatic failure.[18]

Age, nutritional status and CD4 count at enrolment were confounders and as such included in the final multivariable model. The association between age and TB did not reach significance, which is not unexpected because unlike immune-competent children in whom the risk of developing severe TB disease is highest in infants, HIV-infected children are at risk of *M tuberculosis* disease at all ages. The level of immunodeficiency was not significantly associated with TB in this cohort. Most children had moderate or severe immunosuppression at enrolment but CD4 percentage is unlikely to correlate with CD4 percentage during follow-up because use of ART during the study would affect CD4 measures.

The strengths of this study include blinding to eliminate diagnostic bias and follow-up of long duration that ensured reliable outcome ascertainment. A limitation of this study was that ART was not randomly allocated. The early termination of the placebo arm reduced the follow-up time that this group could contribute, and may have reduced the power but continuation of the placebo arm was not ethically possible, given the effect of INH on mortality and the recommendation by the DSMB.[8]

Survival bias might have potentially influenced the results. When the data were analysed using a nested matched case control design, where one case was matched on age and follow-up time to one to four controls, the results were similar to the cohort study. Changes in TB incidence, for example, a decrease in TB incidence, could also have biased the estimates. National and local TB incidence was increasing during the study period.[23] Finally, the protective effect of ART is not immediate and may be seen many months after initiating treatment. The study was done over 5 years with a median follow-up time of 20 months, thus enabling sufficient time to investigate the effect of ART.

Initiation of ART may unmask TB, which could dilute the possible protective effect of ART on TB risk. Because of the young age group, latent TB infection is not common and thus immune reconstitution inflammatory syndrome (IRIS) because of unmasking would be unlikely. In addition, no cases of BCG IRIS were documented. Currently IPT is not recommended for children younger than 12 months infected with HIV (without history of TB exposure).[13] If IPT, ART and cotrimoxazole prophylaxis were to be initiated as a 'package of care' at 2–3 months of age, then the need to screen for active TB would be greatly reduced and IRIS would be less likely.

The finding that IPT is protective in children on ART has significant public health implications because this offers a possible strategy for reducing TB in children infected with HIV. The effect of IPT is obviously dependant on the level of TB exposure and the results of this study should be interpreted in a context of a high TB prevalence setting. They may not apply to a low TB prevalence setting. Widespread use of this strategy will however require screening of children for active TB disease. The optimal duration of IPT has not been established, but long-term use as in this study appears effective and safe.

CONCLUSION

This is the first study to suggest a protective effect of INH in children on ART. The expansion of IPT for children infected with HIV has a number of health system challenges, including the ability to detect and exclude active TB disease before commencing IPT. Nevertheless, IPT may safely reduce TB incidence in children infected with HIV on ART. Further studies are needed to determine the optimal duration that IPT can be safely continued in children infected with HIV who are continuously exposed to TB in high incidence settings.

Acknowledgements We thank the children and their caregivers for participating. We thank the study staff: P Apolles, H Bezuidenhout, P Brink, N Dlaku, E Dobbels, T Fakir, D Gray, L Holt, G Hussey, N Jele, T Jennings, J Karpakis, B Leibbrandt, A Loggie, G Lottering, M Louw, C Mulligan, I Mong, P Mtiya, D Nchuna, F Ngcokovana, V Nkondlala, K Orpen, H Rabie, SM le Roux, H Smit, E Swanepoel, E Walters, L Workman.

Funding Funding for the study was from Rockefeller Foundation, USA; Medical Research Council, South Africa and Department of Health, South Africa. All authors have completed the Unified Competing Interest form and declare financial support from Rockefeller Foundation, USA and Medical Research Council, South Africa and Department of Health, South Africa. All authors also declare no financial relationships with commercial entities that might have an interest in the submitted work; no spouses, partners or children with relationships with commercial entities that might have an interest in the submitted work; no non-financial interests that may be relevant to the submitted work.

Competing interests None.

Ethics approval This study was conducted with the approval of the ethics committees of the Faculty of Health Sciences, University of Cape Town and of Stellenbosch University.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Donald PR.** Childhood tuberculosis: out of control? *Curr Opin Pulm Med* 2002;**8**:178–82.
2. **Nelson LJ,** Wells CD. Global epidemiology of childhood tuberculosis. *Int J Tuberc Lung Dis* 2004;**8**:636–47.
3. **Hesseling AC,** Cotton MF, Jennings T, *et al*. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. *Clin Infect Dis* 2009;**48**:108–14.
4. **Madhi SA,** Petersen K, Madhi A, *et al*. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000;**31**:170–6.
5. **Jeena PM,** Pillay P, Pillay T, *et al*. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *Int J Tuberc Lung Dis* 2002;**6**:672–8.
6. **Zar HJ,** Hanslo D, Tannenbaum E, *et al*. Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa. *Acta Paediatr* 2001;**90**:119–25.
7. **Anon.** Revised BCG vaccination guidelines for infants at risk for HIV infection (in English and French). *Wkly Epidemiol Rec* Global Advisory Committee on Vaccine Safety 2007;**82**(21):193–6.
8. **Zar HJ,** Cotton MF, Strauss S, *et al*. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *BMJ* 2007;**334**:136–43.
9. **Walters E,** Cotton MF, Rabie H, *et al*. Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on anti-retroviral therapy. *BMC Pediatr* 2008;**8**:1–12.
10. **Edmonds A,** Lusiama J, Napravnik S, *et al*. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. *Int J Epidemiol* 2009;**38**:1612–21.

11. **Gray DM,** Zar H, Cotton M. Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children. *Cochrane Database Syst Rev* 2009;(1):CD006418.
12. **Madhi SA,** Nachman S, Violari A, *et al*. *Lack of efficacy of primary isoniazid (INH) prophylaxis in increasing tuberculosis (TB) free survival in HIV-infected (HIV+) South African children*. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, 25–28 October 2008. Washington. Abstract G2–1346a.
13. **Anon.** *Guidance for National Tuberculosis and HIV Programmes on the Management of Tuberculosis in HIV-Infected Children: Recommendations for a Public Health Approach*. Geneva, Switerland: World Health Organization, 2010.
14. **Golub JE,** Saraceni V, Cavalcante SC, *et al*. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 2007;**21**:1441–8.
15. **Golub JE,** Pronyk P, Mohapi L, *et al*. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS* 2009;**23**:631–6.
16. **Marais BJ,** Hesseling AC, Gie RP. The burden of childhood tuberculosis and the accuracy of routine surveillance data in a high-burden setting. *Int J Tuberc Lung Dis* 2006;**10**:259–63.
17. **Anon.** *Antiretroviral Therapy of HIV Infections in Infants and Children: Towards Universal Access. Recommendations for a Public Health Approach*. Geneva, Switzerland: World Health Organization, 2006.
18. **Gray D,** Nuttall J, Lombard C, *et al*. Low rates of hepatotoxicity in HIV-infected children on anti-retroviral therapy with and without isoniazid prophylaxis. *J Trop Pediatr* 2010;**56**:159–65.
19. **le Roux SM,** Cotton MF, Golub JE, *et al*. Adherence to isoniazid prophylaxis among HIV-infected children: a randomized controlled trial comparing two dosing schedules. *BMC Med* 2009;**7**:67.
20. **Hung CC,** Chen MY, Hsiao CF, *et al*. Improved outcomes of HIV-1-infected adults with tuberculosis in the era of highly active antiretroviral therapy. *AIDS* 2003;**17**:2615–22.
21. **Kampmann B,** Tena-Coki GN, Nicol MP, *et al*. Reconstitution of antimycobacterial immune responses in HIV-infected children receiving HAART. *AIDS* 2006;**20**:1011–18.
22. **Akolo C,** Adetifa I, Shepperd S, *et al*. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010;(1):CD000171.
23. **Anon.** *Global Tuberculosis Control: Epidemiology, Strategy, Financing: WHO Report 2009*. Geneva: World Health Organization, 2009.

Journal club

Gefitinib as first-line treatment in advanced NSCLC with mutated EGFR

Non-small cell lung cancer (NSCLC) is a leading cause of cancer deaths. Standard cytotoxic chemotherapy has a response rate of only 20–35% and median survival among patients with advanced NSCLC is between 10 and 12 months. Gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is used in patients with NSCLC with sensitive mutations of EGFR, and this study sought to compare the efficacy and safety of gefitinib with standard chemotherapy.

Two hundred and thirty patients with metastatic NSCLC and positive EGFR mutations who had previously received no chemotherapy were randomly assigned to receive either gefitinib or carboplatin-paclitaxel. Interim analysis of the first 200 patients showed that median progression-free survival was significantly longer in the gefitinib group than in the standard chemotherapy group. Other efficacy outcome measures included a higher response rate and better median overall survival in the gefitinib group.

While the grouped analysis for significant toxic effects (as graded by the National Cancer Institute Common Terminology Criteria) demonstrated a superior toxicity profile for gefitinib compared with carboplatin-paclitaxel, striking differences were evident. Neutropenia, anaemia and thrombocytopenia were most commonly observed with traditional chemotherapy, as were arthralgia and sensory neuropathy. In contrast, rashes, raised aminotransferase levels and sensory neuropathy were statistically more likely to occur among those receiving gefitnib, as was pneumonitis, with one death being observed from interstitial lung disease in this trial arm.

This study demonstrates a relative superiority in terms of progression-free survival for gefitinib compared with standard chemotherapy for patients with advanced NSCLC, provided that they are selected on the basis of sensitive EGFR mutations.

► **Maemondo M,** Inoue A, Kobayashi K, *et al*. Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR. *N Engl J Med* 2010;**362**:2380–8.

Salma Naheed

Correspondence to Salma Naheed, Royal London Hospital, Whitechapel Road, Whitechapel, London, E1 8PR, UK; salma.naheed@gmail.com

Published Online First 22 October 2010

Thorax 2011;**66**:501. doi:10.1136/thx.2010.151308