Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting

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ABSTRACT

Objective

Despite World Health Organization recommendations, concerns about promoting resistance have impeded implementation of isoniazid preventive therapy (IPT) for tuberculosis. We describe characteristics of tuberculosis in individuals previously exposed to IPT as part of "Thibela TB", a cluster-randomised trial of community-wide IPT in gold miners in South Africa.

Design

Case series including participants who were dispensed IPT, attended at least one follow-up visit and were subsequently treated for tuberculosis.

Methods

Tuberculosis episodes were detected through surveillance and through follow-up if IPT was stopped early. Drug susceptibility data were compared with a) tuberculosis episodes detected through surveillance in control clusters (where IPT use was minimal) and b) a laboratory substudy of mycobacterial sputum culture from tuberculosis suspects in control clusters.

Results

Among 126 eligible individuals (125 male, median age 43 years), median time from starting IPT to tuberculosis treatment was 316 days (IQR 174-491). 94/126 (75%) were first episodes. 89/103 (86%) tested HIV-infected, median CD4 count 196 cells/mm^3 (n=51). 64/108 (59%) with known treatment outcomes were cured or completed treatment. Among 71 isolates with drug susceptibility results available, 12.1% (95% CI 5.0-23.3%) and 7.7% (95% CI 0.2-36.0%) from first and retreatment episodes respectively had isoniazid resistance, compared with 6.0% (95% CI 3.1-10.2%) and 18.7% (95% CI 10.6-29.3%) in control clusters and 11.8% (95% CI 8.2 – 16.3%) among first TB episodes in the laboratory substudy.

Conclusions

Tuberculosis after recent IPT has prevalence of drug resistance similar to background and treatment outcomes typical of this setting. These data support wider implementation of IPT.

Keywords: tuberculosis, isoniazid preventive therapy, drug resistance, HIV

INTRODUCTION

Despite World Health Organization recommendations [1] and strong evidence of effectiveness [1-3], implementation of isoniazid preventive therapy (IPT) to reduce HIV-associated tuberculosis has been limited. Reasons include concerns about promoting drug resistance, although there is little evidence that this occurs [5].

Tuberculosis incidence in South Africa was estimated at 948/100,000 in 2007 [6] and is higher still among miners, partly due to high prevalence of HIV (estimated at 29%) [7] and silicosis [8]. The prevalence of latent tuberculosis infection among gold miners was recently estimated at 89% [9]. We are conducting a cluster-randomised trial ("Thibela TB") of community-wide IPT among gold miners in South Africa. The aim of this analysis was to describe characteristics of tuberculosis disease in individuals previously exposed to IPT in this trial.

METHODS

Setting

Mining companies provide employees with free, on-site comprehensive health care, including tuberculosis and HIV services. In the Thibela TB study, clusters (all employees at a single or group of mine shafts) were randomised to control (routine tuberculosis control, including annual case finding by chest radiograph and targeted IPT offered to individuals with HIV or silicosis) or intervention (routine tuberculosis control as above plus the study intervention, i.e. tuberculosis screening and IPT offered to all employees without a specific contraindication, regardless of perceived tuberculosis risk or HIV status) arms. In intervention clusters, screening for active tuberculosis and other contraindications is by symptom questionnaire and chest radiograph [7, 10, 11]. Eligible participants are dispensed isoniazid 300mg and pyridoxine 25mg daily, self-

administered, for 30 days initially and nine months in total, with monthly review by nurses at workplace-based study clinics for tuberculosis symptoms and adverse events.

Study population and case ascertainment

Individuals were included in this case series ("TB after IPT" group) if they were dispensed IPT at one of eight intervention clusters (starting July 2006), attended at least one follow up visit and subsequently started tuberculosis treatment (up to 16th February 2009). Cases were identified through surveillance of incident tuberculosis as part of Thibela TB, through a concurrent mycobacterial culture substudy and through review of clinical records for individuals stopping IPT early. We included all those treated for tuberculosis, who attended at least one follow up visit (to be reasonably sure that some isoniazid had been taken), unless an outcome of “not TB” was recorded or only non-tuberculous mycobacteria were isolated from sputum.

Definitions

Sites of disease, episode type, treatment regimens and outcomes (standard WHO definitions [12]) were abstracted from tuberculosis treatment records. We estimated the maximum duration of IPT using the number of monthly dispensing visits. Participants stopping IPT before nine months were assumed to have taken medication for 15/30 days preceding their final visit.

Comparison groups

To provide comparisons for the proportion with drug resistance in the TB after IPT group, we used two data sources:

a) "control clusters": Tuberculosis case ascertainment in the seven control clusters was identical to that in intervention clusters. All tuberculosis cases with available drug

susceptibility data from two large control clusters were included in this comparison group.

b) "laboratory substudy": Sputa from individuals presenting to clinics with symptoms but no prior history of tuberculosis underwent culture and drug susceptibility testing [13]. All tuberculosis cases in the laboratory substudy at any control cluster were included.

The TB after IPT group included those who had not yet completed treatment, in order to avoid excluding those with longer treatment duration; i.e. retreatment cases or drug-resistant tuberculosis. This was not possible in the control cluster comparison group as laboratory data are not abstracted until the end of treatment. In the laboratory substudy this was not an issue, as specimens were collected at the time of investigation for tuberculosis and thus drug susceptibility data were available in real time.

Statistical methods

Data analysis using STATA v.10 (Stata Corporation, College Station, Texas), included 95% confidence intervals (CI) (binomial exact method) for proportions of isolates with drug resistance.

Ethical considerations

"Thibela TB" was approved by Research Ethics Committees of the University of KwaZulu Natal and the London School of Hygiene and Tropical Medicine.

RESULTS

126 individuals fulfilled inclusion criteria for the TB after IPT group, from a total of 23,095 individuals starting IPT in Thibela TB up to 16th February 2009. Median age was 43 (interquartile range [IQR] 38, 47) years and 125 (99%) were male; consistent with

workforce demographics. In control clusters, 11/275 (4%) individuals had evidence from medical records of ever having had IPT.

Description of the TB after IPT group

77/126 sputum samples cultured *Mycobacterium tuberculosis*; 42 were culture-negative and seven had no culture results available. The median estimated duration of IPT was 105 days (IQR 45, 195), with 28/126 (22%) of this group completing all 270 days. The median time from starting IPT to starting tuberculosis treatment was 316 days (IQR 174, 491) and 53/126 (42%) started tuberculosis treatment within the planned 270 days IPT.

89/103 (86%) with known status were HIV positive. Median CD4 cell count was 196 cells/mm^3 (IQR 81, 296) (n=51). 21/89 (24%) HIV-positive individuals were known to be taking antiretroviral therapy at the start of tuberculosis treatment.
94/126 (74.6%) were first tuberculosis episodes and 87/126 (69.0%) pulmonary. 43 (34.1%) were smear and culture positive and 11 (8.7%) smear positive but culture negative.

Treatment outcomes

In 18/126, treatment was ongoing at the time of data collection and outcome not yet recorded. Among the remaining 108/126, 64/108 (59.3%) had documented cure or treatment completion, 33 (30.6%) were transferred out or had unknown outcome, 2/108 had treatment failure or interruption. There were nine deaths (8.3%), four within the first two months of tuberculosis treatment; all eight with known status were HIV-positive; median CD4 count 124 cells/mm^3 (n=6). Five of the deaths had culture-positive *M. tuberculosis* and all four cases with susceptibility results were susceptible to isoniazid and rifampicin.

Drug susceptibility: TB after IPT and comparison groups

Of 77 *M. tuberculosis* isolates in the TB after IPT group, 71 (92.2%) had susceptibility testing results for isoniazid and rifampicin. None of the five with concurrent non-tuberculous mycobacterial isolates had susceptibility data. In control clusters, of 319 *M. tuberculosis* isolates, 275 (86.2%) had susceptibility test results for isoniazid and rifampicin (table).

Among first tuberculosis episodes, 7/58 (12.1%; 95%CI 5.0-23.3%) were resistant to isoniazid in the TB after IPT group, compared with 12/200 (6.0%; 95%CI 3.1-10.2%) in the control clusters and 32/270 (11.8%; 95%CI 8.2 – 16.3%) in the laboratory substudy (figure). For retreatment episodes, isoniazid resistance occurred in 1/13 (7.7%; 95%CI 0.2-36.0) in the TB after IPT group and 14/75 (18.7; 95%CI 10.6 – 29.3) in control clusters.

Tuberculosis screening failures in the TB after IPT group

Four individuals most likely had tuberculosis that was missed at screening before IPT. Two were culture positive with fully susceptible *M. tuberculosis* from specimens taken due to abnormal chest radiographs, but IPT was dispensed in error: they were started on first-line treatment 9 and 184 days after starting IPT, and outcomes were transfer out and cure, respectively. The individual starting treatment after 184 days had taken an estimated 45 days of IPT and a later sputum specimen grew isoniazid-resistant *M. tuberculosis*. The other two had negative tuberculosis screens at the Thibela TB study site and were smear and culture negative on specimens taken later by mine health services, who initiated treatment based on results of occupational screening radiographs after 11 and 14 days of IPT. Both were documented to have completed treatment.

DISCUSSION

Concern about generating isoniazid resistance is a major obstacle to wider implementation of IPT. These data do not support this concern. Treatment outcomes were typical of this setting, taking into account the high numbers of transfers to other treatment programmes and unrecorded outcomes. South Africa as a whole has not yet met the WHO targets for treatment outcomes [6]. Drug resistance was not more prevalent than in comparison groups. Among first episodes of tuberculosis, the prevalence of isoniazid resistance, at 12.1%, was higher in the TB after IPT than in control clusters (6.0%), but similar to that in the laboratory substudy (11.8%). In retreatment cases isoniazid resistance was less common in the TB after IPT group than control clusters (7.7 vs. 18.7%). The prevalence of isoniazid resistance among the TB after IPT group is also in keeping with a drug-resistance survey among gold miners in this area in the 1990s, in which 7.3% (95% CI 6.1 – 8.7) of first tuberculosis episodes and 14.3% (11.3 – 17.9) of retreatment episodes had isoniazid resistance [14]. In this analysis we present several comparators, acknowledging that each has limitations. Overall, although numbers of resistant cases were small and confidence intervals accordingly wide, the data do not suggest an increase in proportion of isoniazid-resistant cases among those exposed to tuberculosis screening and IPT.

Treatment of latent tuberculosis should not, theoretically, promote anti-tuberculous drug resistance, as in latent infection the probability of selecting for a spontaneously-occurring isoniazid-resistant organism is remote, as organism numbers are low and bacterial division slow [15]. In a population of individuals with latent tuberculosis exposed to IPT, a higher prevalence of isoniazid resistance among subsequent tuberculosis cases would be expected even if IPT use did not itself generate resistance, as IPT is assumed to be

more effective in treating isoniazid-susceptible than isoniazid-resistant latent tuberculosis.

We reported on tuberculosis episodes occurring during or relatively early after completing IPT. Given the high prevalence of HIV and tuberculosis in this population, the majority of tuberculosis cases are likely to have been due to recent infection [16]. However, this relatively short follow up inevitably biases towards cases identified during IPT, who are those most likely to have been screening failures, to have received inadvertent monotherapy for active disease, and hence to have acquired isoniazid resistance. With longer follow up, we would expect an increasing proportion of cases to be due to re-infection after IPT. The control cluster comparison group may be biased towards a lower proportion with resistance, as drug susceptibility data are collected at the end of the treatment episode, thus potentially excluding individuals with longer treatment durations, due to previous treatment exposure or known baseline resistance. Effective screening before administering IPT is essential to avoid inadvertent isoniazid monotherapy for active tuberculosis. Overall consensus on the optimal screening method in resource-limited settings is yet to be reached.

Three previous papers specifically describe active tuberculosis following IPT [17-19]. Methods differ and numbers are very small, so it is difficult to draw clear conclusions in terms of drug resistance from these studies. Data concerning tuberculosis after IPT from clinical trials have been reviewed previously in a meta-analysis [5]. The summary estimate for the risk of isoniazid resistance following IPT compared with those not exposed to IPT was 1.45 (95% CI 0.85-2.47), suggesting no evidence for an increase in resistance.

In conclusion, tuberculosis disease among mostly HIV-infected people previously exposed to IPT had treatment outcomes typical of this setting and a similar prevalence of isoniazid resistance to background. Concerns about generating drug-resistance should not impede implementation of IPT.

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Author contributions

Clare van Halsema: Study design, data collection, paper writing

Katherine Fielding: Study design, epidemiological and statistical advice, paper writing

Violet Chihota: Laboratory work, management of Thibela TB substudies, manuscript review

Elizabeth Russell: Data management and logistical input, manuscript review

James Lewis: Epidemiological input and statistical advice, manuscript review

Gavin Churchyard: Study design, supervision, manuscript review

Alison Grant: Study concept and design, epidemiological input, paper writing

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Conflict of Interest

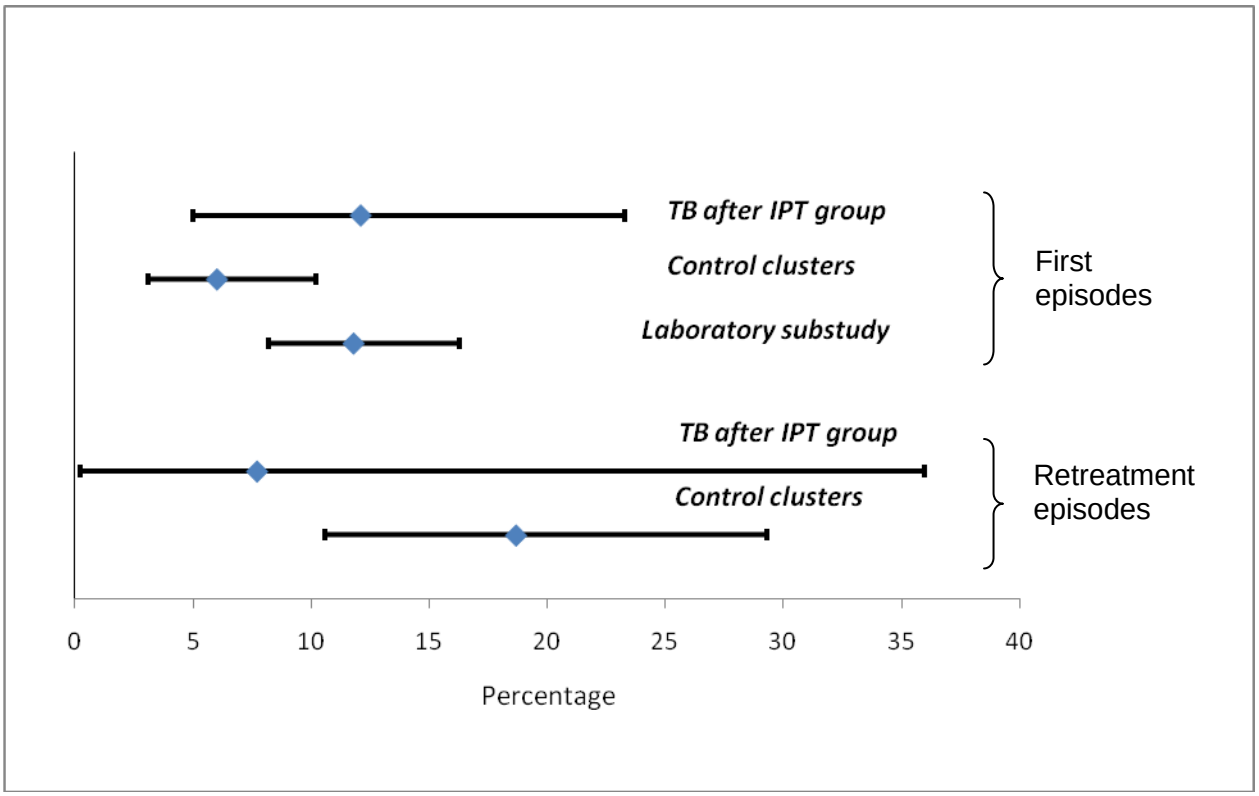
All authors: no conflict

Table 1: Proportions of TB after IPT group and comparison groups with drug-resistant tuberculosis

	TB after IPT group n=71		Thibela TB control clusters n=275		Laboratory substudy n=270
Drug susceptibility	First episodes n=58 %(95%CI)	Retreatment episodes, n=13 %(95%CI)	First episodes n=200 %(95%CI)	Retreatment episodes, n=75 %(95%CI)	First episodes n=270 %(95% CI)
Susceptible to both isoniazid & rifampicin	51 87.9% (76.7-95.0)	11 84.6% (54.6-98.1)	187 93.5% (89.1–96.5)	60 80.0% (69.2-88.4)	225/269[a] 87.7% (83.1-91.4%)
Any isoniazid resistance	7 12.1% (5.0-23.3)	1 7.7% (0.2-36.0)	12 6.0% (3.1-10.2)	14 18.7% (10.6-29.3)	32 11.8% (8.2 – 16.3)
Resistant to both isoniazid and rifampicin	1 1.7% (0.0-9.2)	1 7.7% (0.2-36.0)	6 3.0% (1.1-6.4)	10 13.3% (6.6-23.2)	21/269[a] (7.8%) (4.9 – 11.7)

[a] Drug susceptibility results for rifampicin were missing for one individual

Figure 1: Percentages of TB episodes with any isoniazid resistance (Bars show 95% confidence intervals)



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