REVIEW

Isoniazid preventive therapy for tuberculosis in South Africa: An assessment of the local evidence base

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Worldwide, South Africa (SA) has the worst tuberculosis (TB) epidemic. In SA, there are >6.1 million people living with HIV (PLWH) and the country now has the largest antiretroviral treatment programme with >2 million people receiving combination therapy. While there has been a marked recent decline in HIV-associated deaths, >50% of TB cases still continue to be diagnosed in PWLH. The current TB control strategy based on passive case finding, chemotherapy of childhood TB contacts and directly observed therapy has clearly failed to control endemic TB in SA. Two recent meta-analyses have shown a >60% reduction in TB in HIV-infected adults after isoniazid preventive therapy (IPT). SA has implemented the World Health Organization policy and IPT is now recommended for HIV-positive people for up to 36 months. Originally, there was only one SA study included in the evidence base supporting this policy, but subsequently four randomised controlled trials have been conducted in SA populations. These studies, together with local observational studies, are the subject of this local, evidence-based review.

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South Africa (SA) has the worst tuberculosis (TB) epidemic of any major country in the world, with >300 000 cases notified each year.[1] There are >6.1 million people living with HIV (PLWH) in SA, and the country now has the largest antiretroviral treatment (ART) programme with >2 million people receiving combination therapy.[2] While there has been a marked recent decline in HIV-associated deaths,[2] >50% of TB cases still continue to be diagnosed in PWLH.[1] However, even HIV-uninfected individuals continue to develop active TB at rates as high as those recorded before the availability of chemotherapy.[3] The current TB control strategy based on passive case finding, chemotherapy of childhood TB contacts and directly observed therapy has clearly failed to control endemic TB in SA.[4] This critical situation has produced a body of policy makers who have proposed that TB control may be restored in part by expanding previously targeted preventive strategies to all PLWH,[1,5,6] or to whole communities.[7] Isoniazid (INH) prophylaxis of TB infection was first demonstrated in animal models in the 1950s,[8] studied in childhood contacts of TB cases in the 1960s[9] and became recommended for children <5 years of age with an adult household contact.[10] A combined analysis of randomised controlled trials (RCTs) of isoniazid preventive therapy (IPT) in (HIV-uninfected) adults performed between 1962 and 1994 demonstrated a reduction of active TB by 60% in a variety of recently TB-exposed or -infected populations.[11] A subsequent Cochrane meta-analysis of 12 RCTs of IPT in HIV-infected adults, largely without ART, showed a 62% reduction in TB, restricted to individuals with positive tuberculin skin tests (TSTs).[12]

However, the World Health Organization (WHO) considered performing TSTs a stumbling block to the implementation of IPT and in 2011 revised the IPT guidelines, making a strong explicit recommendation that 'TST was not a requirement for initiating IPT in PLWH'.[1] SA has implemented WHO policy and IPT is now recommended for all 6.1 million PLWH[2] for up to 36 months.[5,6] Originally, there was only one SA study included in the evidence base supporting this policy,[13] but subsequently four RCTs have been conducted in SA populations.[14-18] These, together with local observational studies, are the subject of this local data review.

Mechanisms of IPT action

IPT is based on the widely accepted theory that primary infection with *Mycobacterium tuberculosis* is followed by a latent phase during which dormant tubercle bacilli may reactivate to cause TB disease.[19] INH sterilises these latent organisms. However, bacteriological latency may not correlate perfectly with clinical latency and a more dynamic balance between organism and host immunity may determine progression to active disease.[20] INH may act by altering this balance in favour of the host and against the organism.

Tuberculin skin testing

The TST has remained the primary method for targeting IPT to those with known TB infection, but the TST is subject to both physiological and post-treatment reversions.[21] A positive TST in childhood generally reflects recent infection with a high risk of progression to active disease. In contrast, the majority of SA adults are latently infected and a positive TST reflects earlier TB infection, which is associated with a lowered risk of endogenous reactivation[22] and protection (79% confidence interval (CI) 70 - 86%) against TB re-infection progressing to active disease.[23] HIV-infection increases TB incidence,[24] but TST-positivity decreases as $CD4^+$ cell counts decline.[25] While ART improves $CD4^+$ cell counts[26] and TB immunity,[27] the changes in the TST during ART have not been well characterised.

Challenges for IPT implementation

In contrast to the implementation of the ART programme, non-targeted IPT implementation has been very poor.[28] Rationale for the reticence to implement IPT include: that short-term trial efficacy

Table 1. RCTs of IPT conducted in South Africa

	Study population							Deaths/100 PYs		TB incidence/100 PYs	
	N	Status	$CD4^+$ cell count, % or mean (IQR)	Age, mean	Regimen (weeks)	ART use at baseline, %	TB baseline prevalence, %	IPT	Placebo	IPT	Placebo
Zar *et al.*[14]	263	HIV-positive, hospital symptomatic	20% (14 - 28)	25 months	52*	9	N/A	15.7†	37.8	7.2‡	23.4
Madhi *et al.*[15]	548	HIV-positive, hospital outpatients	28% (6 - 58)	4 months	96	32	N/A	6.1	4.2	8.2	9.4
	804	HIV-negative, exposed outpatients	N/A	4 months	96	N/A	N/A	0.5	0.5	6.9	7.7
Mohammed *et al.*[13]	118	HIV-negative, symptomatic, TST-negative	99 (24 - 269)	38 years	52§	0	9.3	27.9	34.7	18	11.6
	20	HIV-positive, symptomatic, TST-positive	354 (191 - 466)	36 years	52	0	N/A	0	N/A	6.8	N/A
Rangaka *et al.*[16]	1 580	HIV-positive, ART clinic attenders	216 (152 - 360)	34 years	52	72	16.2	0.9	1.2	2.3¶	3.6
Churchyard *et al.*[17]	78 744	Mining workforce	N/A	41 years	39	2.7	6.9‖	N/A	N/A	3.02	2.95

RCTs = randomised controlled trials; IPT = isoniazid preventive therapy; IQR = interquartile range; ART = antiretroviral therapy; PYs = person years; TB = tuberculosis; TST = tuberculin skin test; INH = isoniazid; N/A = not applicable; HR = hazard ratio; CI = confidence interval.
*INH 5 mg/kg daily or thrice weekly until age of 12 months continued in immunological impaired ($CD4^+$ count <15%) and symptomatic HIV.
†HR: 0.46 (95% CI 0.22 - 0.95).
‡HR: 0.28 (95% CI 0.10 - 0.78).
§INH 15 mg/kg twice weekly.
¶HR: 0.63 (95% CI 0.41 - 0.94).
‖Intensified TB screening of 27 126 individuals randomised to the intervention cohort.

data preceded widespread introduction of ART and may lack current relevance; TST-positive ART-naive individuals who were the subgroup with demonstrable benefit, constitute only a minority of PLWH;[25] the TST-negative majority of PLWH may be subjected to therapy without personal benefit; any sustained benefit is considerably reduced in SA where the ongoing risk of TB re-infection is high; lack of long-term effectiveness limits potential epidemiological impact; where service delivery falls short of desired levels, the implementation of IPT may overburden the healthcare system and divert attention from more effective treatment priorities; INH is an important component of standard TB treatment, resistance is already high and clinical experience has shown that widespread use of antibiotics is inevitably followed by increasing drug resistance, a concern reinforced by a recent modelling study of the long-term impact of community-wide IPT.[29]

RCTs in SA

SA clinical scientists have performed several large and well-conducted RCTs of IPT, which have contributed significantly to the existing body of scientific evidence and are summarised in Table 1.

Two RCTs have been performed in SA paediatric populations. The first; randomised 263 HIV-positive children, recruited in two Cape Town teaching hospitals, to daily or thrice-weekly IPT or placebo.[14] The children had advanced symptomatic HIV manifested by low weight-for-age and height. The study was discontinued because of an early survival benefit largely in the first 6 months in the IPT arm compared with the control arm. TB incidence was also reduced in the intervention arm by 72%. Few of the children were receiving ART at baseline because the study was conducted prior to wide access to ART. Diagnosis of TB in sick HIV-infected infants is difficult and the early mortality benefit observed in this study may have resulted from INH treatment of unrecognised primary TB.[30]

A second paediatric RCT, a primary prevention with 96 weeks IPT v. placebo, was conducted in 548 HIV-infected and 804 HIV-exposed children <4 months of age, recruited from hospital clinics in Johannesburg, Cape Town and Durban.[15] The HIV-infected children in this study were less sick than in the prior study and ART use was higher, with 99% commencing ART during the study. There was no difference in TB infection, TB disease or death between the INH and control arms in either HIV-infected or HIV-exposed children. INH resistance was noted in 28% of TB cases.

The very different outcomes in these two paediatric studies underscore the importance of exercising great care when generalising beyond the population under study.[29] The study populations differed by age, severity of HIV disease, nutritional status and ART use, as illustrated by very different TB and mortality rates in the control arms of each study.

The single SA study included in the Cochrane review[12] was an RCT of IPT given twice weekly to TST-negative, HIV-infected adults, all of whom were anergic.[13] The study, which was conducted before ART availability in a population with advanced HIV disease, showed no effect on mortality or TB incidence.[13] The majority of screened subjects were TST-negative and the 17% of subjects with a positive TST who qualified for IPT under existing guidelines had much higher $CD4^+$ cell counts than those in the randomised study population. The statistical power of the study was reduced, as TB incidence rate in the study was considerably lower than reported previously, probably due to exclusion of TB cases treated within the previous 5 years and baseline TB screening including sputum culture.

Over 2 000 patients attending an ART clinic in Cape Town were assessed for entry into an RCT with 12 months IPT.[16] Of the 1 536 otherwise consenting and eligible patients, 250 were diagnosed with prevalent active TB disease by screening, including sputum culture, at baseline. Of the finally enrolled population, 43% reported a history of prior TB, only 30% were TST-positive and the majority was already established receiving ART before initiating IPT. During a follow-up of mean 2.4 years, 37 and 58 incident cases were identified in the IPT and control arms, respectively; (hazard ratio (HR) 0.62; 95% CI 0.41 - 0.94). Drug-resistance testing

identified INH resistance in 6/25 (24%) cases tested. All-cause mortality did not differ between intervention and control arms. In secondary analysis there was no evidence that the effect of IPT was restricted to those who were TST-positive. The authors concluded that the ' … modest effects described and the high rate of TB in the IPT arm, suggest ART plus IPT alone may not be adequate to control TB at the population level'.

These two studies again underscore the hazard of generalising beyond any study population, as it appears that the predictive value of TST testing for IPT may be more important before ART when immunity is deteriorating than after ART when immunity is improving. TB screening in both studies had a very high yield of TB cases.

A very large community-wide RCT in SA miners randomised the workforce of eight mineshafts to receive 9 months of IPT and of seven mineshafts to receive placebo. The primary endpoint was TB incidence during the following year and secondary endpoint TB prevalence at the study end.[7] The placebo clusters were screened within the normal mining healthcare service but those in the IPT arm underwent more intensive TB screening.[31] There were no differences in either primary or secondary endpoints between treatment and control arms.[17,18] A *post hoc* analysis of participants commencing IPT in the intervention cohort had a temporary non-sustained decrease in TB incidence compared with controls.[17,18] The positive results of the *post hoc* analysis were attributed to a temporary benefit of IPT. However, the differential screening procedures between the two study arms did not allow for attribution of benefit to either IPT or to intensified TB screening. A laboratory sub-study of INH resistance reported 12% resistance in first TB cases but no significant increase in the IPT arm compared with the control group.[32]

Observational studies in SA

A large observational study (*N*=2 778) in urban and rural SA compared TB-free survival during a mean of 1.5 years, split into time accrued receiving IPT, ART, and IPT with ART, and reported a significantly high effectiveness of IPT in combination with ART.[33] Exceptionally wide confidence limits and selection bias did not support the conclusion of significant IPT benefit.[34] A second large observational study of 3 270 workers in an occupational health setting reported a 49% reduction in mortality associated with receipt of IPT prior to or during ART.[35] The HR remained significant after adjustment for clinical parameters, $CD4^+$ cell count, calendar year and employing company. Although the authors' reporting of a halving of mortality by IPT was plausible among individuals initiating ART in a setting of high TB incidence,[35] no similar mortality benefit of additional IPT with ART has been reported in any randomised adult study.

Implications of local studies

Variable study results can provoke one of two scientific responses: to look harder within our existing theory with even larger and longer studies with more meta-analyses; or alternatively, to question our basic biological and epidemiological assumptions. Much of the inter-study variability in IPT efficacy can be explained by differential baseline screening procedures, differential use of ART and different TB exposures. The two studies, which screened all participants with TB culture, reported much lower TB rates in the control arms than predicted.[13,16] The control arm of the mining study with no additional TB screening at baseline was followed by TB incidence similar to historic levels.[17] Intensified baseline TB screening in the IPT arm that identified and excluded an additional 1 705 (6.9%) prevalent TB cases was followed by a transient lowered TB incidence.[17] Additionally, the magnitude of the prevalent TB cases identified by intensified screening was two-fold higher than all the cases identified during each of these studies and far exceeded the numbers of cases prevented by IPT.

Studies with ART had much lower clinical event frequencies in both paediatric and adult studies than those without ART. Furthermore, INH performed different biological roles, each with differential efficacy, in the different populations including: prophylaxis both before and after a known TB exposure; treatment of childhood primary TB; sterilisation of recent or distantly acquired 'latent' infection; and treatment of either pauci- or multibacillary adult disease. Table 2 outlines a conceptual framework of the different population groups in each of the studies. While in the TB-susceptible paediatric populations, stratification can be by known TB exposure (household contact) and primary disease (symptomatic), adult studies are stratified by TST status which, in an already infected population, reflects distantly acquired primary infection, but also TB re-infection and in PLWH, immune decline and recovery before and after ART, respectively.

Treatment of active TB disease with INH monotherapy will occur more frequently in situations where TB diagnosis is difficult or when screening procedures are less stringent. Paediatric TB diagnosis is difficult; therefore undiagnosed primary TB would be highest in symptomatic HIV disease, lower in asymptomatic HIV disease and lowest in the asymptomatic HIV-uninfected children.

All TST-negative adult subjects prior to ART were anergic, a reflection of poor immunity rather than identification of a group without prior TB infection. It is unclear how TST-positivity after

Table 2. Study populations by HIV, TST and probable TB exposure

Paediatric subjects	**HIV status**	**Pre-primary exposure***	**Known primary exposure**	**Primary disease***
Zar *et al.*[14]	Positive	++	Excluded	++
Madhi *et al.*[15]	Positive	+++	Excluded	+
	Negative	+++	Excluded	+
Adult subjects	**HIV status**	**TST-negative***	**TST-positive: Recent***	**TST-positive: Distant***
Mohammed *et al.*[13]	Positive	+++		
	Positive			+++
Rangaka *et al.*[16]	Positive	++	+/-	++
Churchyard *et al.*[17]	Positive	++	+/-	++
	Negative	++	+/-	+++

TST = tuberculin skin test; TB = tuberculosis; ARI = annual risk of TB infection.
*Estimated frequencies: +/- determined by the ARI; + determined by ARI and rate of progression of primary infection to active TB; ++: 10 - 50%; +++: >50%.

initiating ART reflects immune recovery or new TB exposures. However, TSTs appeared to identify groups with different responses to IPT pre and post ART. Extrapolation of results from the pre-ART era may now lack relevance in an era of greater access to ART.

The observation that INH resistance was not increased in well-conducted IPT studies in which screening procedures ensured unrecognised active TB was minimal;[31] is not necessarily reassuring for future scenarios where IPT is given to 6.1 million PLWH without similar screening procedures.[5,6]

Conclusions

The total lack of IPT efficacy in the community-wide study, and only modest benefits in the ART clinic population, indicate that hopes that IPT would positively impact the TB epidemic in SA are optimistic. Intensified TB screening at study entry identified a large number of previously unrecognised TB cases, was associated with a decrease in subsequent TB incidence and identified many more cases than occurred during the course of the studies. Of concern, the prevalence of INH resistance was high in all those studies where it was measured. Therefore expansion of IPT to all PLWH in SA must be associated with efficient TB screening and monitoring of INH resistance. Importantly, implementation of this modestly beneficial intervention should not divert us from the priority to increase access to ART urgently and reduce the treatment gap. TB control will require a new focus on reducing ongoing transmission, which results in the majority of our population becoming TB infected before adulthood.[36]

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