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Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme in South Africa

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Abstract

Objective—To describe the association between isoniazid preventive therapy (IPT) and mortality among individuals starting antiretroviral therapy (ART) in a workplace programme in South Africa where tuberculosis incidence is very high.

Methods—ART-naïve individuals starting ART from January 2004 to December 2007 were followed for up to 12 months. Deaths were ascertained from clinic and human resources data. The association between IPT and mortality was assessed using Cox regression.

Results—3,270 individuals were included (median age 45; 93% male; median baseline CD4 155 cells/mm^3 (IQR:87–221); 45% WHO stage 3/4). 922(28%) individuals started IPT either prior to, or within three months of, starting ART. Individuals who started IPT tended to have less advanced HIV disease at ART initiation. 259 (7.9%) deaths were observed, overall mortality rate 8.9/100 person years [pyrs] (95%CI:7.9–10.6). The unadjusted mortality rate was lower among those who received IPT vs. not (3.7/100 pyrs versus 11.1/100 pyrs respectively, hazard ratio (HR) 0.34 [95%CI:0.24–0.49]); this association remained after adjustment for age, baseline CD4, baseline WHO stage, year of ART start and individual company (HR 0.51, 95%CI 0.32–0.80). In sensitivity analyses restricted to those with no previous history of TB (n=3036) or with no TB symptoms at ART initiation (n=2251), IPT remained associated with reduced mortality (adjusted HRs 0.51 (95%CI: 0.32 – 0.81) and 0.48 (95%CI: 0.24–0.96) respectively).

Conclusions—Mortality was lower among individuals receiving IPT with or prior to ART start. These results support routine use of IPT in conjunction with ART.

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Keywords

isoniazid; mortality; antiretroviral therapy; South Africa; workplace

INTRODUCTION

Antiretroviral therapy (ART) is increasingly available in developing countries, delivered through a diverse range of programmes. Although reported outcomes of such programmes are encouraging, early mortality is high despite effective antiretroviral regimens[1] especially in the first 12 months of treatment [2]. Tuberculosis (TB) was the most important cause of morbidity and mortality among HIV-infected adults in developing countries in the pre-ART era[3, 4]. Although ART reduces the risk of TB substantially [5],[6],[7], tuberculosis remains the most common cause of morbidity and mortality in patients on ART[8],[9],[10, 11].

Isoniazid preventive therapy (IPT) reduces the risk of active tuberculosis by approximately 33% overall and by approximately 64% among those with a positive tuberculin skin test (TST)[12],[13]. IPT was also effective in preventing tuberculosis when implemented routinely in an HIV care programme for gold miners in South Africa prior to ART availability[14]. Despite World Health Organization guidelines recommending IPT as part of routine HIV care[15], there has been little IPT implementation at country level[16]. South African HIV treatment guidelines have previously not recommended IPT for individuals taking ART.

In a large workplace HIV programme in South Africa, where both the prevalence of latent tuberculosis and the incidence of active tuberculosis are very high (exceeding 4000 per 100,000 in 2002)[17, 18], IPT has been part of HIV care since its inception in 1999 and is recommended whether or not individuals are also taking ART. In this setting, we evaluated the effect of IPT, given either prior to or concurrent with the start of ART, on early mortality following ART initiation.

METHODS

Study design and population

We carried out an observational cohort analysis using prospectively collected data among individuals enrolled in a workplace ART programme in a group of industrial companies with operations primarily in South Africa. The design of the ART programme has been described elsewhere [19]. HIV disease management is based on guidelines developed in accordance with local and international best practice. During the time period of this analysis, employees were eligible for ART if they had a CD4 count below 250 cells/μl; were in World Health Organization (WHO) clinical stage 4 regardless of CD4 count; or were in WHO stage 3 with a CD4 count below 350 cells/μl. The preferred first line regimen was zidovudine and lamivudine (combined as Combivir) and efavirenz (with stavudine substituted for zidovudine for individuals with anaemia) until December 2007, replaced by tenofovir and emtricitabine (combined as Truvada) and efavirenz from January 2008.

According to programme guidelines, IPT (isoniazid 300mg daily for 6 months) is recommended for individuals with no evidence of active tuberculosis, and no prior history of tuberculosis. Screening for active tuberculosis is done using symptom screening and chest radiography: sputum is sent for microscopy and culture from tuberculosis suspects. TST is not part of the eligibility criteria for IPT in this programme. Cotrimoxazole (960mg daily) is recommended for individuals with a CD4 count below 250 cells/μl. All employees

(regardless of HIV status) receive annual evaluation for TB disease through a workplace TB control programme based on radiological screening. All employees diagnosed with TB receive short-course directly observed treatment using a rifampicin-based four drug regimen.

In this analysis, we included all ART-naïve adults starting ART in this HIV care programme from January 2004 to December 2007. Subjects were followed until the earliest of: death, leaving employment or the end of the period of this analysis (12 months after ART start). We excluded individuals who were presumed to be on TB treatment at the start of ART (started TB treatment <6 months prior to ART start). In settings of high tuberculosis prevalence, the effect of IPT is thought to wane after 12 months [20], thus we excluded from the analysis individuals who started IPT greater than 12 months before starting ART. Since the risk of death changes rapidly after ART start, in order to have a more homogeneous IPT group, we excluded from the analysis individuals who started IPT more than three months after starting ART.

Data collection

Information on ART and all preventive therapies given was recorded routinely as part of the HIV disease management programme. Details of past medical history were collected at the first clinic visit. HIV clinical disease stage was derived from history and physical examination done by the physician at the first visit to the clinic. The baseline CD4 count and viral load values were those closest to the ART treatment start date, within a window of 6 months before or within 5 days after ART initiation. Virological response on treatment was determined using a viral load done closest to the 6 week time point (between 30 –120 days) after starting ART. For the purpose of this analysis, a satisfactory response was defined as a one log drop in viral load at 6 weeks. TB symptoms are collected routinely at every clinic visit on standardised clinic forms that required yes/no answers for the following symptoms: cough, night sweats, sputum production, fever and weight loss.

Ascertainment of outcome

All deaths among individuals enrolled in the ART programme are reported using standardised forms to the monitoring team by the clinic physicians. Human resources data were used as an additional source of information concerning deaths in employment, and reasons for leaving employment. To allow for the possibility of deaths among individuals who left employment due to ill-health, a secondary analysis was conducted using a combined mortality outcome defined as “death or termination from work on medical grounds”.

Laboratory methods

CD4 lymphocyte counts were measured by flow cytometry (FACSCount, BD Diagnostics, Franklin Lakes, New Jersey, US). HIV RNA quantification was carried out using the branched-DNA HIV-1 RNA 3.0 assay (Bayer Versant, New York, USA) according to the manufacturers’ instructions. For a small portion of patients (25) HIV RNA Quantitation was run on Roche COBAS Ampliprep/COBAS Taqman HIV-1 test version 2.0, Roche, NJ, USA.

Statistical methods

Baseline characteristics of individuals who started and did not start IPT were compared using the chi-square test or Wilcoxon rank sum test, as appropriate. Individuals were followed from date of ART initiation until the earliest of death, leaving employment, or the end of the analysis period (12 months from ART initiation). Kaplan Meier methods were used to illustrate the association between IPT and time to death. Cox proportional hazards

regression was used to investigate the effect of IPT on the risk of death following initiation of ART. Factors that showed a strong confounding effect (based on an important change in the hazard ratio for association of IPT with mortality) were considered for the full adjusted analysis. In the multivariable analysis we started by adjusting for the strongest confounder based on the previous analysis, and included other variables one at a time. These were retained in the model if the hazard ratio for IPT changed. We used a rule-of thumb of including a variable if the hazard ratio changed by more than 10%. Age was included in the model *a priori*. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) are reported and the likelihood ratio test used to assess whether use of IPT was associated with mortality. In addition, as an indicator of early response to ART, change in HIV viral load at 6 weeks was included in the model.

As this was not a comparison of randomised groups, a number of sensitivity analyses were conducted to explore issues which might cause bias and to take into account informative censoring which may have arisen due individuals leaving the workforce due to medical reasons. These sensitivity analyses were conducted as follows: a) restricted to individuals with no previous history of tuberculosis, as IPT was only indicated for these individuals in the programme guidelines, b) restricted to individuals without any symptoms suggesting tuberculosis (cough, night sweats, weight loss, fever, sputum production, regardless of duration, thus a more sensitive definition than is generally used to define a TB suspect) within the period 30 days before to 15 days after ART initiation, to allow for the possibility that individuals that were symptomatic were less likely to start IPT and may have had a higher mortality rate c) classifying individuals who left employment on medical grounds as deaths and d) combination of two above, restricted to individuals with no previous history of TB and no TB symptoms at initiation. To assess whether the effect of IPT on mortality was modified by baseline CD4 count, we modelled an interaction between IPT and baseline CD4 strata. We also assessed for interaction between IPT and time period following ART (<3 months, >3 months).

Ethical considerations

The analysis was approved by the Research Ethics Committees of University of KwaZulu Natal, South Africa, and the London School of Hygiene and Tropical Medicine.

RESULTS

In total, 3752 ART-naïve individuals started ART between 1 January 2004 and 31 December 2007. 213 individuals were excluded due to starting IPT later than 3 months after ART start, and 14 who started IPT greater than 12 months prior to ART. 255 individuals were on TB treatment at the start of ART and were excluded. Of the 3270 included individuals, 93% were male, mean age was 44.9 years, median baseline CD4 155 cells/μl (interquartile range [IQR] 87 – 221), and median viral load 48 817 copies/ml (IQR 17 860 – 128 629). Total follow-up time was 2910 person-years (339 (9.03%) censored before 12 months). WHO stage at ART initiation (available for 3 270 individuals), was WHO stage 2 (1803, 55.1%), stage 3 (1123, 34.3%) or stage 4 (344, 10.5%).

922 (28%) individuals started IPT either before or during the first three months of starting ART; the vast majority (n=882, 96%) within 0–7 days of starting ART. 234 individuals (7.2%) had previously been treated for tuberculosis prior to starting ART. 1338 (40.9%) individuals started cotrimoxazole either before starting ART (94% within a month of starting ART) or during the follow up time on ART. Baseline and 6 week viral load results were available for 1986 individuals (60.6%), of whom 1648 (83%) achieved a greater than 1 $\log_{10}$ reduction in HIV RNA by 6 weeks.

Baseline characteristics among those who started versus did not start IPT are compared in Table 1. Individuals who were started on IPT tended to have less advanced HIV disease as they had higher CD4 counts (CD4 <100cells/μl, 26.2% vs. 32.9%), lower viral load (viral load >100 000copies/ml, 24.3% vs. 33.1%), and higher haemoglobin levels (haemoglobin >10g/dl, 94.1% vs. 87%) at ART initiation and fewer were in WHO stage 3 or 4 (29.8% vs. 50.3%). The groups also differed with regards to whether they had had an episode of TB (8.9% in those never started on IPT and 2.5% in those who had started on IPT) and markedly by whether they were also on cotrimoxazole (84.8% in those who had started on IPT and 29.9% in those never started on IPT).

In the first 12 months following initiation of ART, 259 (7.9%) individuals died giving an overall mortality rate of 8.90/100 person years (py) (95% confidence interval (CI) 7.88 – 10.05). The mortality rate of those never started on IPT was 11.08/100py (227/2047, 95% CI 9.74 – 12.63) and those who were started IPT was 3.71/100py (32/863, 95% CI 2.62 – 5.24). The unadjusted hazard ratio (HR) for mortality from the Cox model for those started on IPT compared to those not started on IPT was 0.34 (95% CI 0.24 – 0.49).

Table 2 shows associations of various risk factors with mortality. The final adjusted model included age group, baseline CD4 group, WHO stage at ART initiation, year of starting ART, individual company and receipt of IPT Table 2). In the adjusted model, IPT use remained strongly associated with decreased mortality (adjusted HR: 0.50, 95% CI 0.32 – 0.80). Adding cotrimoxazole use, baseline haemoglobin and baseline viral load to the model did not change the hazard ratio substantially. As an indicator of early response to ART, change in viral load at 6 weeks was included in a model restricted to individuals with available data, who therefore survived at least this long (Table 2); however there was no evidence that this caused confounding in the association between IPT and mortality. All factors met the proportional hazards assumption (P<0.01). Other risk factors for mortality that remained in the adjusted model were older age group (P_{trend}<0.001), lower baseline CD4 count (P_{trend}<0.001), earlier year of ART start (P_{trend}=0.001) and company (P=0.30). We graphically illustrate the association between IPT and mortality using a Kaplan-Meier survival curve (Figure).

To assess whether the association between IPT and mortality differed by time period after starting ART we assessed for an interaction between IPT use and time period. The data were consistent with no interaction (unadjusted analysis p=0.89, adjusted analysis p=0.94). In the first three months following ART initiation, overall mortality rate was 16.28/100py, higher in those not on IPT (20.15/100py : 113/561py) compared to those started on IPT (6.65/100pyrs :15/226py), HR 0.33 (95% CI 0.19 – 0.57). In the period after three months on ART, overall mortality rate was 6.17/100py, higher in those not on IPT (7.67/100py : 114/1487py) compared to those started on IPT (2.67/100pyrs :17/638py), HR 0.35 (95% CI 0.21 – 0.58). In the multivariable model, the adjusted hazard ratio IPT in the time period less than 3 months was 0.50 (95% CI 0.27 – 0.93) and in the time period greater than 3 months was 0.51 (95% CI 0.29 – 0.91) (Table 4). Similarly we tested for effect modification with cotrimoxazole. When stratifying by whether patients were also on cotrimoxazole, those on IPT continued to have lower mortality rates than those not on IPT, both among individuals taking cotrimoxazole (HR 0.27 (0.11 – 0.56)) and not taking cotrimoxazole (HR 0.33 (0.21 – 0.51); P-value for interaction P=0.68)

Table 3 shows the association between IPT and mortality in sensitivity analyses. When analysis was restricted to only those who had not had previous tuberculosis (n= 3036) the adjusted HR was 0.52 (95%CI 0.32 – 0.82). When restricted to those who had data available regarding symptoms at baseline, and had no symptoms suggesting tuberculosis (n=1923), the adjusted HR for the association of IPT and mortality was 0.48 (95%CI 0.24 – 0.96).

Using a combined mortality end-point which classified individuals who left employment on medical grounds (n=99) as deaths, the adjusted HR for the association of IPT and mortality was 0.72 (95%CI 0.47 – 1.10). We also looked at the association of IPT with mortality, restricted to those who had no previous TB and also no symptoms suggesting tuberculosis with the period of ART initiation (N=1795); the adjusted HR for the association of IPT and mortality was 0.44 (95% CI 0.22 – 0.89).

To assess whether the association between IPT and mortality differed by CD4 count strata we assessed for an interaction between IPT use and CD4 count. The data were consistent with no interaction (unadjusted analysis p=0.84, adjusted analysis p=0.81). The effect of IPT use on mortality, stratified by CD4 group at ART initiation was as follows: CD4 <50 cells/mm^3, HR 0.80 (95% CI 0.36–1.78); CD4 50–100 cells/mm^3, HR 0.48 (95% CI 0.19 – 1.19); CD4 101 – 200cells/mm^3, HR 0.48, (95% CI: 0.22 – 1.07), and >200 cells/mm^3, HR 0.45, (95% CI: 0.15–1.33) (Table 4).

Discussion

In this observational cohort study, we found approximately a halving of the risk of mortality among people starting ART who were also given IPT. This association persisted after controlling for confounders and in sensitivity analyses exploring possible sources of bias. This is a major reduction in mortality among individuals whose risk of death is very high, with potential for a substantial public health impact. Clinical trials of IPT from the pre-ART era found a smaller reduction in mortality among people with HIV given IPT (RR 0.74, 0.55 –1.00)[13]. However, an effect of this magnitude is plausible among individuals starting ART in a setting of high tuberculosis incidence, given that tuberculosis is the most important cause of death among these individuals, and the incidence of tuberculosis during the first few months of ART is very high [21] [22].

Although there is strong evidence from the pre-ART era that IPT reduces tuberculosis incidence in HIV-infected individuals,[12] [13, 23] there are far fewer data concerning the use of IPT in combination with ART. Observational cohort studies in Brazil and South Africa showed an effect of IPT in addition to ART in reducing TB incidence [24–26], although in the South African study most patients were given IPT a median of one year prior to ART[25]. Neither study assessed the effect of IPT on mortality.

In ART care programmes, IPT is delivered as part of a package of care, and screening to identify active tuberculosis both prior to and during IPT is an essential component. This screening may contribute to a reduction in tuberculosis case-fatality, an issue which is discussed in more detail in the accompanying Opinion piece.

Very few data are available concerning outcomes when IPT and ART are used concurrently, probably because the implementation of IPT has been so limited[27]. We restricted this analysis to individuals who started IPT relatively close to the ART start date in order that the exposure of interest (IPT at the time of ART start) was more homogeneous. Given that our HIV care programme guidelines promote early use of IPT as part of pre-ART care, it was a little surprising to us that the great majority of individuals started IPT within one week of starting ART (and thus this restriction resulted in few [227/3752] exclusions). There are concerns that IPT should not be given to individuals starting ART on the basis that it is difficult to reliably exclude active tuberculosis when the prevalence of undiagnosed tuberculosis is so high[7]. Our data suggest that such theoretical concerns should be weighed against a potentially large reduction in mortality if IPT is initiated with ART. Randomised trials currently in progress investigating the effect of adding IPT to ART may help resolve this issue.

Although INH was recommended by the programme for all patients with no previous TB, INH was not always prescribed in all eligible patients. We believe that the most important reason for inconsistent implementation is variability in clinician willingness to use IPT. Low uptake of IPT is acknowledged in many settings, mainly thought to be due to operational problems relating to feasibility of tuberculin testing, as well as concerns about the development of isoniazid drug resistance[28]. We recently conducted a study investigating barriers to IPT use, presented in this same supplement, showing that barriers to use of IPT were predominantly derived from clinic staff, in particular prescribing physicians who often lacked sufficient knowledge and familiarity with the use of INH[29]. It seems to be that certain physicians are more likely than others to prescribe INH mainly based on their own experience. We believe that this is the most likely explanation for why some patients received IPT and others did not.

Strengths of our analysis include the large number of individuals included, and the relatively complete ascertainment of deaths, via human resources records and follow-up of defaulters. Limitations include lack of data on the effect of IPT on tuberculosis incidence due to absence of electronic tuberculosis clinic records and no information on adherence to IPT, although we believe that the adherence in this programme may have been better than previously experienced due to the strong emphasis on adherence as this was offered as a “package” with ART.

An important limitation of this study is that it was not a randomised clinical trial and so we cannot exclude systematic differences between individuals who received IPT and those who did not. The analysis of baseline factors does indicate that the patients not given IPT may have been more unwell. Our analyses controlled for all well-recognised potential confounding factors, and the sensitivity analyses explored potential issues which could result in healthier individuals receiving IPT and hence experiencing lower mortality, yet in all analyses the association between IPT and lower mortality was of similar magnitude. However we cannot exclude that there may have been confounders that we did not control for. In addition, there were missing data for some variables such as viral load and haemoglobin at baseline, again making it harder to exclude residual confounding. Another limitation was that we were not able to report cause of death for these patients; however TB is an important cause of death in patients on ART, although it is often underreported[11], and is well documented to be an important cause of death in miners who have HIV infection[30]. In addition, we have documented high TB incidence among employees with HIV in the largest of the sites in this study[31].

Data from large cohorts of patients in treatment programmes can be complementary to those from randomised trials; specifically, this analysis may give insights into the effect of the “package” of IPT along with more intensive tuberculosis case finding, which was not measured by clinical trials of IPT. In ART care programmes, IPT is delivered as part of a “package” of care, and screening to identify active tuberculosis both prior to and during IPT is an essential component. However, in randomised controlled trials of IPT, the intensive screening component was implemented in both arms[32–34], and thus only the IPT component was tested. We hypothesise that individually randomised controlled trials may have underestimated the impact of an IPT programme on TB case-fatality (see Opinion piece).

The risk of death after starting ART remains high until the CD4 cell count increases[22]. Additional interventions are therefore urgently needed to reduce the risk of death among ART initiators. These data from our treatment cohort suggest that individuals starting ART may have a substantial reduction in mortality if IPT is given concurrently, and add to accumulating evidence concerning the additional value of IPT along with ART[25] [26].

Although the results of randomised trials of IPT with ART are awaited[35, 36], our data support the routine use of IPT in HIV care programmes in line with WHO recommendations.

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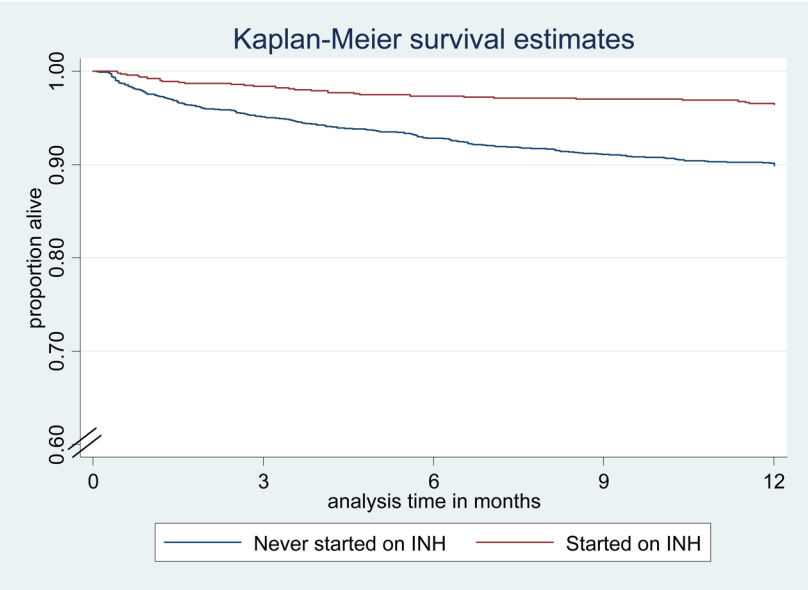

Number alive	3 months	6 months	9 months	12 months
No IPT	2157	2037	1924	1848
IPT	887	859	839	826

Figure 1.
Figure Kaplan Meier curve comparing survival among those who started or did not start isoniazid preventive therapy (IPT)

Table 1

Baseline characteristics of individuals starting antiretroviral therapy, comparing those who did vs. did not receive isoniazid preventive therapy (n=3270).

Baseline characteristic	No IPT N (%)	IPT N (%)	P value
All	2348	922	
Age (years)			
Median (IQR)	45 (38 – 51)	46 (37 – 52)	P[2]=0.25
18 – 29	220 (9.4)	93 (10.1)	P[1]=0.005
30 – 39	740 (31.5)	269 (29.2)	
40 – 49	965 (41.1)	346 (37.5)	
≥ 50	423 (18.0)	214 (23.2)	
Gender: number (%) male	2182 (92.9)	857 (94.0)	P[1]=0.26
Baseline CD4 count * (cells/μl)			
Median (IQR)	152 (81 – 224)	158 (98 – 215)	P[2]=0.56
<50	323 (14.6)	95 (10.7)	P[1]=0.002
50 – 100	383 (17.3)	138 (15.5)	
101 – 150	385 (17.5)	182 (20.5)	
151 – 200	395 (17.9)	194 (21.8)	
>200	718 (32.6)	281 (31.6)	
Baseline WHO stage			
1 or 2	1167 (49.7)	648 (70.3)	P[1]<0.001
3	873 (37.2)	233 (25.3)	
4	308 (13.1)	41 (4.5)	
Baseline viral load ** (copies/ml)			
Median (IQR)	52,071 (19,134–141,461)	42,418 (15,420–97,844)	P[2]<0.001
VL>100 000	654 (33.1)	202 (24.3)	P[1]<0.001
Baseline haemoglobin *** (g/dl)			
Median (IQR)	12.9 (11.2–14.1)	13.4 (12.2 – 14.6)	P[2]<0.001
Haemoglobin<10	250 (13.0)	50 (5.9)	P[1]<0.001
Previous tuberculosis	211 (8.9)	23 (2.5)	P[1]<0.001
Cotrimoxazole started	603 (25.7)	735 (79.7)	P[1]<0.001
Year started ART			
2004	633 (27.0)	91 (9.9)	P[1]<0.001
2005	587 (25.0)	181 (19.6)	
2006	692 (29.5)	284 (30.8)	
2007	436 (18.6)	366 (39.7)	

Baseline characteristic	No IPT N (%)	IPT N (%)	P value
Company			
Company A	2165 (92.2)	484 (52.5)	$P^1<0.001$
Company B	78 (3.3)	347 (37.6)	
Company C	105 (5.5)	91 (10.0)	
Viral response at 6wks ****	1101 (82.7)	547 (83.6)	$P^1=0.58$

IPT: isoniazid preventive therapy; IQR: interquartile range; ART: antiretroviral therapy

* available in 3094 individuals

** available in 2806 individuals

*** available for 2771 individuals

**** >1 log reduction in viral load at 6 weeks after ART initiation, available for 1986 individuals

P^1= Pearson chi-squared test

P^2=Wilcoxon rank-sum (Mann-Whitney) test

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Table 2

Factors associated with mortality, unadjusted and adjusted analyses

		Unadjusted analysis (N=3270)		Adjusted analysis* (N=3094)	
	Rate/100py	**Hazard Ratio (HR)**	**95% CI (P value)**	**Hazard Ratio (HR)**	**95% CI (P value)**
IPT					
No	11.10	1	P<0.001	1	P=0.002
Yes	3.71	0.34	0.24 – 0.49	0.51	0.32 – 0.80
Gender					
Male	9.29	1	P=0.005		
Female	3.82	0.42	0.21 – 0.84		
Age (years)					
18–29	4.86	1	P^T <0.001	1.00	P^T <0.001
30 – 39	6.74	1.38	0.77 – 2.47	0.99	0.55 – 1.78
40–49	11.53	2.24	1.29 – 3.89	1.58	0.90 – 2.77
≥ 50	10.20	2.06	1.15 – 3.71	1.80	0.99 – 3.27
Baseline WHO stage					
1 or 2	6.36	1	P^T<0.001	1	P^T=0.005
3	9.66	1.49	1.13 – 1.98	1.06	0.86 – 1.57
4	21.68	3.27	2.38 – 4.50	1.75	1.21 – 2.54
Baseline CD4 (cells/μl)					
<50	19.34	4.11	2.79 – 6.06	3.58	2.39 – 5.36
50–100	12.91	2.78	1.87 – 4.14	2.57	1.72 – 3.83
101 – 150	9.08	1.97	1.30 – 2.99	1.93	1.27 – 2.94
151 – 200	3.81	0.84	0.50 – 1.42	0.86	0.51 – 1.46
>200	4.58	1	P^T <0.001	1	P^T<0.001
Baseline viral load (copies/ml)					
≤ 100,000	6.85	1	P<0.001		
>100,000	11.77	1.70	1.29 – 2.24		

		Unadjusted analysis (N=3270)		Adjusted analysis* (N=3094)	
	Rate/100py	**Hazard Ratio (HR)**	**95% CI (P value)**	**Hazard Ratio (HR)**	**95% CI (P value)**
Year started ART					
2004	15.10	1	P^T<0.001	1	P^T=0.001
2005	9.98	0.67	0.49 – 0.92	0.78	0.55 – 1.11
2006	6.75	0.46	0.33 – 0.64	0.58	0.1 – 0.83
2007	5.62	0.38	0.26 – 0.55	0.60	0.41 – 0.89
Cotrimoxazole started**					
No	9.85	1	P=0.001		
Yes	7.57	0.78	0.60 – 1.00		
Previous TB					
No	8.88	1	P=0.97		
Yes	9.19	1.01	0.62 – 1.63		
Baseline Haemoglobin (g/dl)					
<10	26.28	1	P<0.001		
≥ 10	5.51	4.58	3.37 – 6.24		
Viral response at 6 wks (>1 log decrease)					
No	8.32	1	P<0.001		
Yes	3.01	0.36	0.22 – 0.59		
Company (clinic site)					
Company A	9.70	1	P=0.002	1	P=0.29
Company B	4.40	0.45	0.27 – 0.73	0.74	0.43 – 1.31
Company C	8.83	0.95	0.57 – 1.57	1.37	0.80 – 2.35

P^T = P value for linear trend

*Adjusted for age group, baseline WHO stage, baseline CD4 count, year started on ART, and company.

**Cotrimoxazole refers to those put on either cotrimoxazole or dapsone (used in cases of cotrimoxazole hypersensitivity)

IPT: isoniazid preventive therapy; ART: antiretroviral therapy

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Table 3

Sensitivity analyses for associations between isoniazid preventive therapy and mortality using various scenarios

		# death/pyrs	Rate per 100 pyrs	Unadjusted HR	Adjusted HR* (95% CI)
Restricted to those with no previous tuberculosis (N=3036)	No IPT	209/1872	11.16	1	1 (P=0.003)
	IPT	32/843	3.80	0.35	0.51(0.32 – 0.81)
Restricted to those with no tuberculosis symptoms at ART initiation (N=1923)	No IPT	66/1011	5.99	1	1 (P=0.08)
	IPT	15/683	2.19	0.37	0.48 (0.24 – 0.96)
Including all those medically boarded as deaths (N=3270)	No IPT	310/2047	15.14	1	1 (P=0.11)
	IPT	48/863	5.56	0.37	0.66 (0.45 – 0.97)
Restricted to no previous TB and no TB symptoms at initiation (n=1795)	No IPT	61/1007	6.06	1	1 (P=0.05)
	IPT	15/699	2.24	0.37	0.44 (0.22 – 0.89)

IPT: isoniazid preventive therapy; ART: antiretroviral therapy

*Adjusted for age group, baseline WHO stage baseline CD4 count, year started on ART and individual company

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Table 4

Interaction between CD4 count and isoniazid preventive therapy use on mortality (n=2540)

	IPT use	#deaths/pys	Rate per 100 pys	Unadjusted HR (95% CI)	Adjusted HR[2] (95% CI)
Baseline CD4					
< 50	No	58/259	22.41	1[1]	1[3]
	Yes	8/82	9.70	0.44 (0.21 – 0.93)	0.68 (0.30 – 1.51)
50–100	No	50/324	15.42	1	1
	Yes	8/125	6.40	0.42 (0.20 – 0.89)	0.58 (0.26 – 1.28)
101 – 200	No	56/699	8.01	1	1
	Yes	11/359	3.07	0.39 (0.20 – 0.74)	0.48 (0.24 – 0.96)
>200	No	38/650	5.85	1	1
	Yes	4/268	1.49	0.26 (0.09 – 0.73)	0.33 (0.12 – 0.95)
Time period following ART initiation					
<3 months	No	113/561	20.15	1	1
	Yes	15/226	6.65	0.33 (0.19 – 0.57)	0.50 (0.27 – 0.93)
>3 months	No	114/1487	7.67	1	1
	Yes	17/638	2.67	0.35 (0.21 – 0.58)	0.51 (0.29 – 0.91)

[1] P-value for interaction=0.84;

[2] Adjusted for age group, baseline WHO stage, year started on ART and individual company (and CD4 baseline for time period);

[3] P-value for interaction=0.79 pys=person-years