Isoniazid Preventive Therapy and Mortality in a Workplace Antiretroviral Therapy Programme

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Background

- TB is a leading cause of death in people with HIV in developing countries, including those starting antiretroviral therapy (ART)[1]
- Meta analysis of pre-ART era trials shows among HIV+, isoniazid preventative therapy (IPT) may reduce mortality in TST+ by 26%[2]
- No data on impact of IPT with ART on mortality
- We investigated the association of IPT with early mortality in a workplace ART program in South Africa

[1]Lawn SD et al, *AIDS* 2008;22(15):1897-908.
[2]Akolo C et al, *Cochrane Database of Systematic Reviews* 2010, Issue 1

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Setting

- A workplace HIV care program in South Africa, established 2002, prospective data collection
- ART starting criteria:
  - CD4<250
  - WHO stage 4
  - WHO stage 3 and CD4<350
- IPT promoted as part of HIV care since programme inception:
  - Indicated if no past history of TB and current TB excluded

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Methods

- Retrospective cohort study
- Including workers starting ART from Jan 04 – Dec 07
- Cohort entry: ART start date
- Cohort exit: earliest of death, leaving employment or 12 months after ART start
- Deaths ascertained from clinic & workplace records
- Excluded:
  - those on TB treatment at ART start (TB treatment start <6m before ART start)
  - those started IPT>12 m before ART start or >3m after ART start

Methods - statistical analysis

- Cox regression was used to determine association between IPT and mortality
- Multivariable analysis used to adjust for potential confounders
- Sensitivity analyses were conducted to explore issues which might cause confounding or bias.
- Assessed for interaction between
  - association of IPT and mortality with
  - time after ART start (<3 vs. >3 months)

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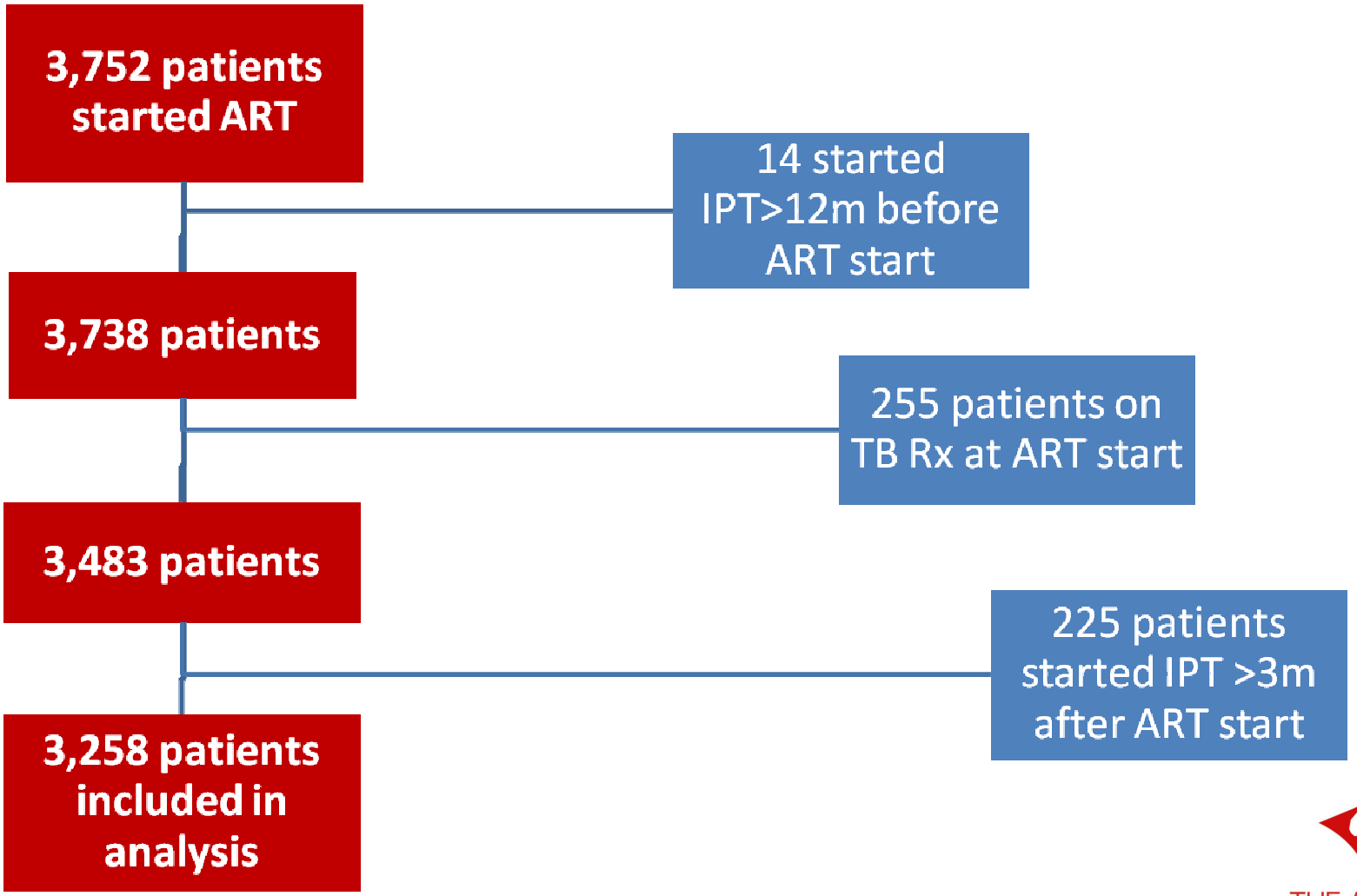
Results - Patient flow



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Results - Baseline characteristics

Baseline variable	No IPT (N=2,348)	IPT (N=910)	P-value
Male gender (%)	2,182 (93)	857 (94)	0.2
Median age (IQR)	45 (38-51)	46 (37-52)	0.31
Median CD4 (IQR)	152 (73-219)	158 (98-214)	0.59
Previous TB	211 (8.9)	23 (2.5)	<0.001
WHO stage 3/4 (%)	1,181 (50)	275 (30)	<0.001
Median Hb (IQR)	12.9 (11.2-14.1)	13.4 (12.2-14.6)	<0.001

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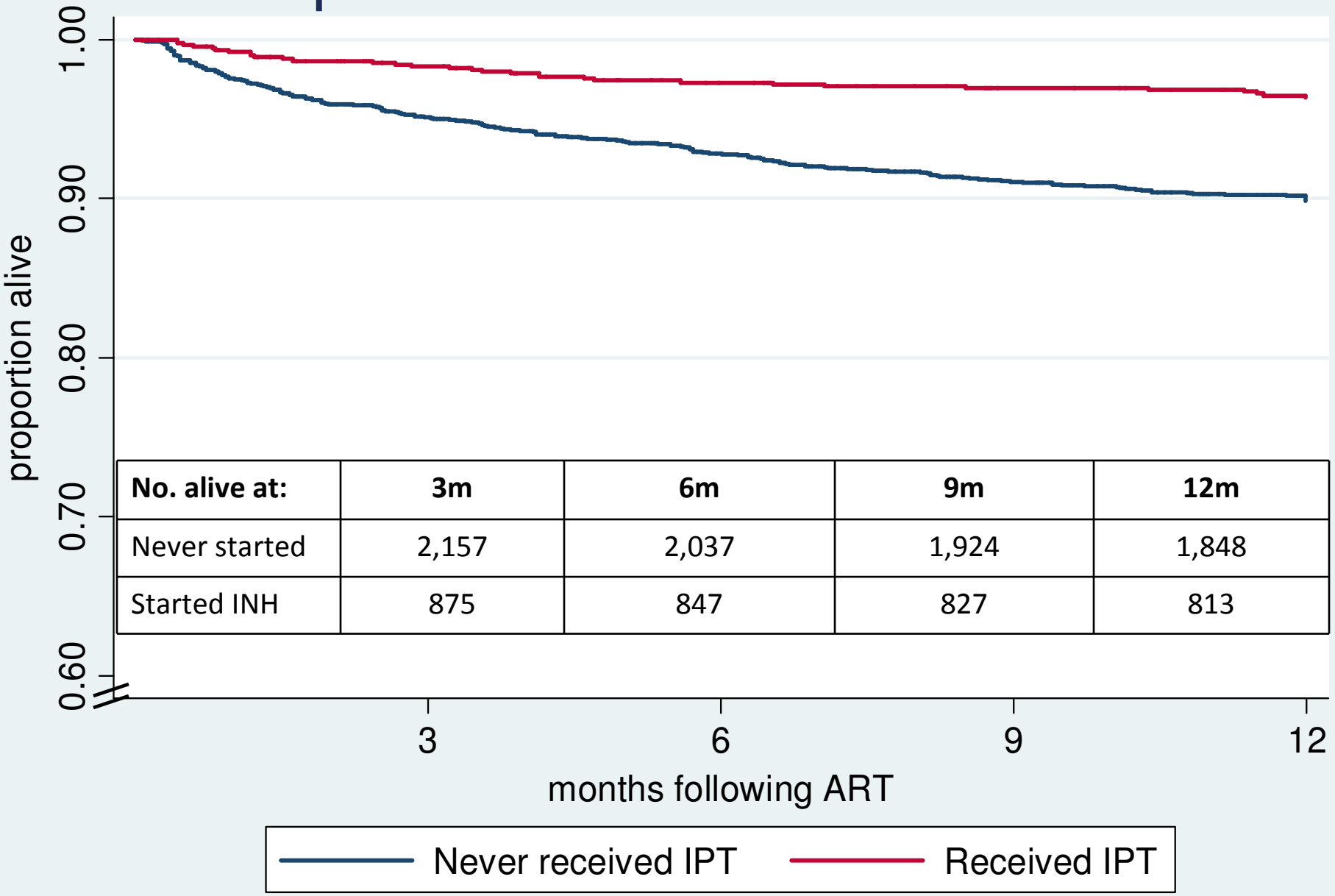
Kaplan-Meier survival estimates



No. alive at:	3m	6m	9m	12m
Never started	2,157	2,037	1,924	1,848
Started INH	875	847	827	813

Results – Unadjusted / Adjusted analysis

Unadjusted analysis				N=3,258	
Variable	**Parameter**	**Deaths/ pyrs**	**Rate/100 pyrs**	**Hazard ratio**	**P value 95% CI**
IPT	No	227/2045	**11.10**	1	P<0.001
	Yes	32/851	**3.75**	0.35	0.24 – 0.50

Adjusted analysis*		N=2,562	
Variable	**Parameter**	**Hazard ratio**	**P value 95% CI**
IPT	No	1	P<0.001
	Yes	0.47	0.30 – 0.72

*Adjusted for age, WHO stage, CD4, haemoglobin and year of ART start

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Sensitivity analysis (1)

- Excluded those with a prior history of TB:
  - should not have been offered IPT by programme guidelines
  - could be associated with higher mortality

	IPT	# death/ pyrs	Rate/100 pyrs	Unadjusted HR	Adjusted HR* (95% CI)
No prev. TB (N=3,024)	No	209/1870	11.17	1	1 (P<0.001)
	Yes	32/830	3.85	0.35	0.46 (0.29 – 0.71)

*Adjusted for age, WHO stage, CD4, haemoglobin and year of ART start

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Sensitivity analysis (2)

- Excluded those with symptoms possibly associated with active TB at ART start (i.e. cough, night sweats, weight loss, fever, sputum production)
  - those with TB symptoms should not have been started on IPT
  - could be associated with higher mortality

	IPT	# death/ pyrs	Rate/100 pyrs	Unadjusted HR	Adjusted HR (95% CI)
No TB symp. (N=2,241)	No	99/1309	7.56	1	1 (P=0.005)
	Yes	23/755	3.05	0.41	0.47 (0.28 – 0.79)

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Interaction with time after ART start

Stratified by <3m & > 3m	IPT use	#death/ pyrs	Rate / 100 pyrs	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
<3m	No	113/560	20.15	1	1
	Yes	15/223	6.74	0.34 (0.20 – 0.58)	0.39 (0.20-0.76)
>3m	No	114/1485	7.68	1	1
	Yes	17/628	2.71	0.35 (0.21 – 0.59)	0.54 (0.31-0.93)

No evidence of interaction between association of IPT with mortality and time after ART start (p=0.64)

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Limitations

- Observational cohort, not RCT
- Adjusted analysis may not completely control for residual confounding between those who received / did not receive IPT
- Guidelines stated that all those with no prior history of TB should have been offered IPT (though most were not)
- Cause of death was not captured in this study

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Conclusions

- This study suggests that IPT may reduce the risk of death among individuals starting ART
- These data add to the evidence supporting the routine use of IPT in addition to ART among people living with HIV

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Interaction with CD4 count

Stratified by baseline CD4	IPT use	#death/ pyrs	Rate / 100 pyrs	Unadjusted HR (95% CI)[1]	Adjusted HR[2] (95% CI)[3]
≤ 50	No	58/259	22.42	1	1
	Yes	8/80	9.95	0.45	0.65 (0.30 – 1.39)
50-100	No	50/324	15.43	1	1
	Yes	8/124	6.46	0.42	0.39 (0.17 – 0.93)
101 – 200	No	56/698	8.02	1	1
	Yes	11/355	3.09	0.39	0.42 (0.19 – 0.90)
>200	No	38/650	5.85	1	1
	Yes	4/261	1.53	0.26	0.40 (0.14 – 1.16)

[1] P-value for interaction=0.85; [2]Adjusted for age group, baseline WHO stage, year started on ART and haemoglobin level at baseline; [3] P-value for interaction=0.81

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