



# **A Randomized Clinical Trial Comparing 6 EH vs 36H for TB Prevention in HIV-infected Adults in south India: Impact on Mortality**

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**Partially funded by USAID through WHO**  
NIH Clinical Trials Registry No: NCT00351702

February 18 2010

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Chennai



# Cochrane Review: Treatment of LTBI

Akolo et al, Cochrane Database of Systematic Reviews  
2010 issue 1

- Reduction in mortality with INH monotherapy versus placebo in persons with + TST (RR 0.74, 95% CI 0.55 -1.0)
- INH+Rif reduced mortality vs placebo regardless of TST status (RR 0.69, 95% CI 0.5 – 0.95)
- Overall, no evidence that TB preventive therapy versus placebo reduced all-cause mortality RR 0.94, 95% CI 0.85-1.05



# Background

- Historical data from observational cohort at our centre<sup>1</sup>:
  - TB incidence 6.9/100 py (95% CI 4.1-9.6)
  - Similar in TST+ (7.1) and TST- (6.7)
  - Mortality in those who developed TB 10.5/100py (4.8-15.2)
  - Mortality among patients without TB 6.1/100py (3.2-8.8)

Other studies from India estimate TB incidence between 5 and 8/100py<sup>2</sup>

<sup>1</sup>Swaminathan et al *IJTLD* 2000;4:839 Gupta A et al *CID* 2007; 45:241



# Study Aims

- **Primary:** To reduce TB incidence by  $> 50\%$  from baseline and compare the efficacy of a six-month regimen (6EH) with a continuous regimen (36H) among HIV-infected adults
- **Secondary**
  - To compare the two regimens in reduction of overall mortality
  - To compare the efficacy among TST+ and TST- persons
  - To study the efficacy among persons with  $CD4 < 200$  compared to those with  $CD4 > 200$  cells/mm<sup>3</sup>



# Procedures

- At baseline: clinical examination, chest x-Ray, 3 sputum specimens for AFB smear and mycobacterial culture (L-J medium), hematology, liver and renal function tests, TST (1 TU PPD RT23), CD4, CD8 count, viral load
- Drug collection every 15 days – met nurse
- Clinical review every 3 months
- 2 sputum specimens (smear and culture), x-Ray, liver function tests, CD4, CD8 repeated every 6 months
- Relevant investigations performed if clinical deterioration/ symptoms of TB
- Clinical panel reviewed all cases before TB treatment initiation

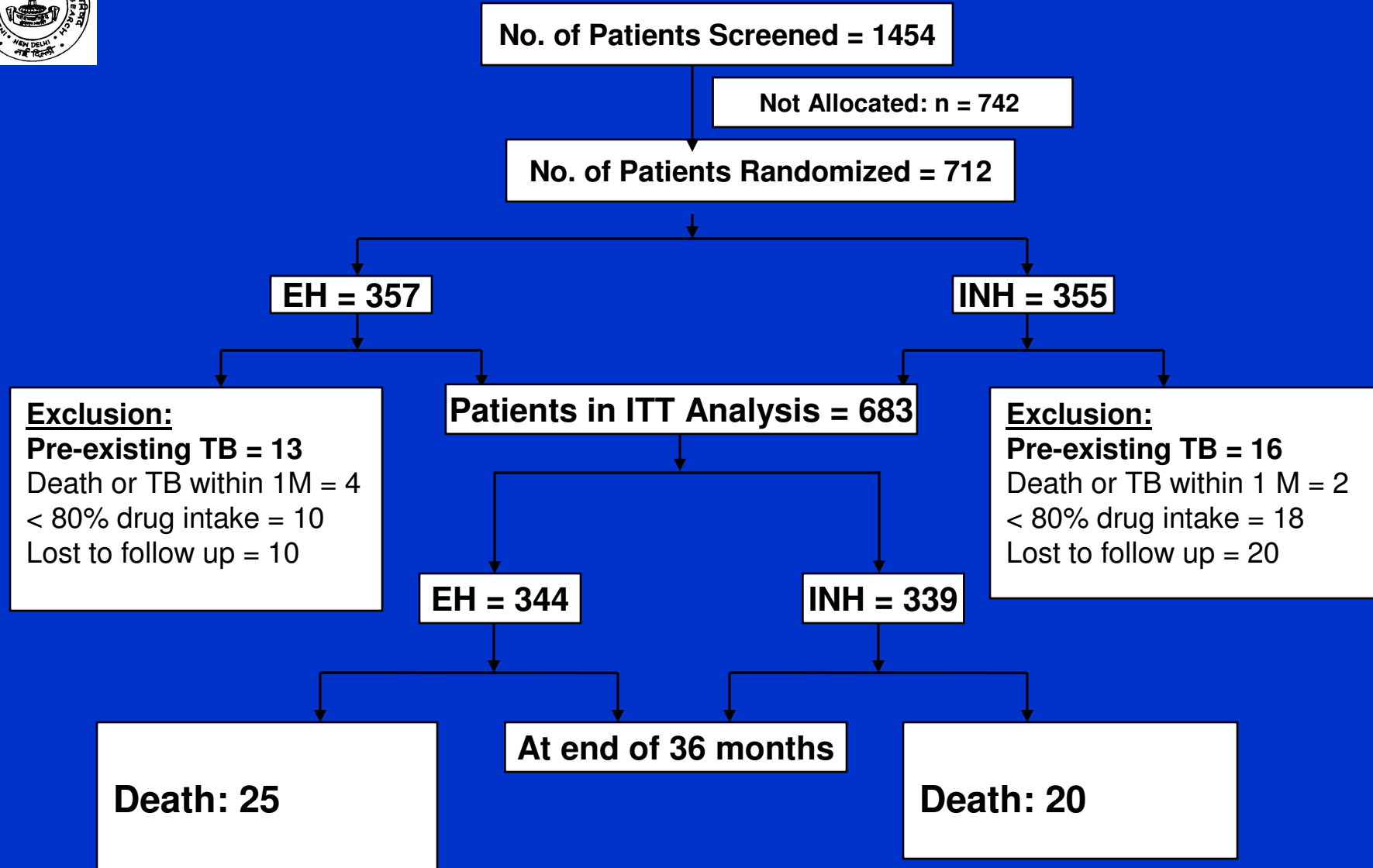


# Outcome Measures

- Development of tuberculosis (pulmonary or extra-pulmonary)
  - TB confirmed by culture or combination of clinical/radiographic/biopsy results
- Death due to any cause
  - Verbal autopsy if death at home, hospital records if in hospital to determine cause. If any evidence of TB at time of death, classified as TB death

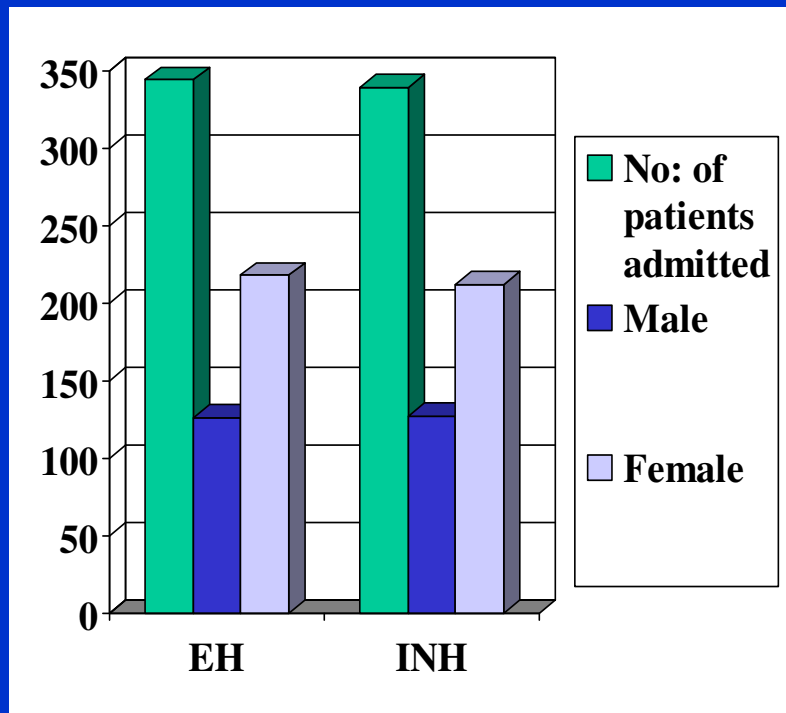


# Trial Profile





# Patients in ITT Analysis by Regimen



- HIV-infected patients > 18 years, not moribund, fulfilling clinical, social and lab eligibility criteria
- 683 patients enrolled at TRC units at Chennai and Madurai: 253 males and 430 females.
- Mean age  $30 \pm 7$  years
- Mean weight  $50 \pm 10$  kg
- Median CD4 count 325 cells/mm<sup>3</sup>
- Mean TST  $8 \pm 7$  mm





# Demographics (ITT) by Regimen

	6EH (n = 344)	36H (n = 339)
<b><u>Age</u> &lt; 25 years</b>	<b>30%</b>	<b>29%</b>
<b>25-40 years</b>	<b>61%</b>	<b>64%</b>
<b>40 years</b>	<b>9%</b>	<b>7%</b>
<b><u>TST</u></b>		
<b>&lt; 5mm</b>	<b>59%</b>	<b>61%</b>
<b>&gt;5mm</b>	<b>41%</b>	<b>39%</b>
<b><u>CD4 count</u></b>		
<b>&lt; 200</b>	<b>25%</b>	<b>27%</b>
<b>200-350</b>	<b>28%</b>	<b>28%</b>
<b>&gt;350</b>	<b>47%</b>	<b>45%</b>
<b><u>Viral load</u></b>		
<b>&lt; 10,000</b>	<b>26%</b>	<b>38%</b>
<b>10,000-30,000</b>	<b>17%</b>	<b>15%</b>
<b>&gt;30,000</b>	<b>51%</b>	<b>45%</b>
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# Survival free of TB, ART and Adherence

	INH (n = 299)	EH (n = 320)
TB-free survival at 36 months	273	261
Adherence (>80%)	93%	94%
Adherence (>90%)	90%	80%
On ART	93	76



# Death Rate

	6EH	36H
ITT, /100py	2.8	2.2
95% CI	(1.7 – 3.9)	(1.2 – 3.2)
Per Protocol	2.9	2.4
	(1.8 – 4.1)	(1.4 - 3.5)
Rate Ratio	1.3 (95% CI 0.7 - 2.3)	

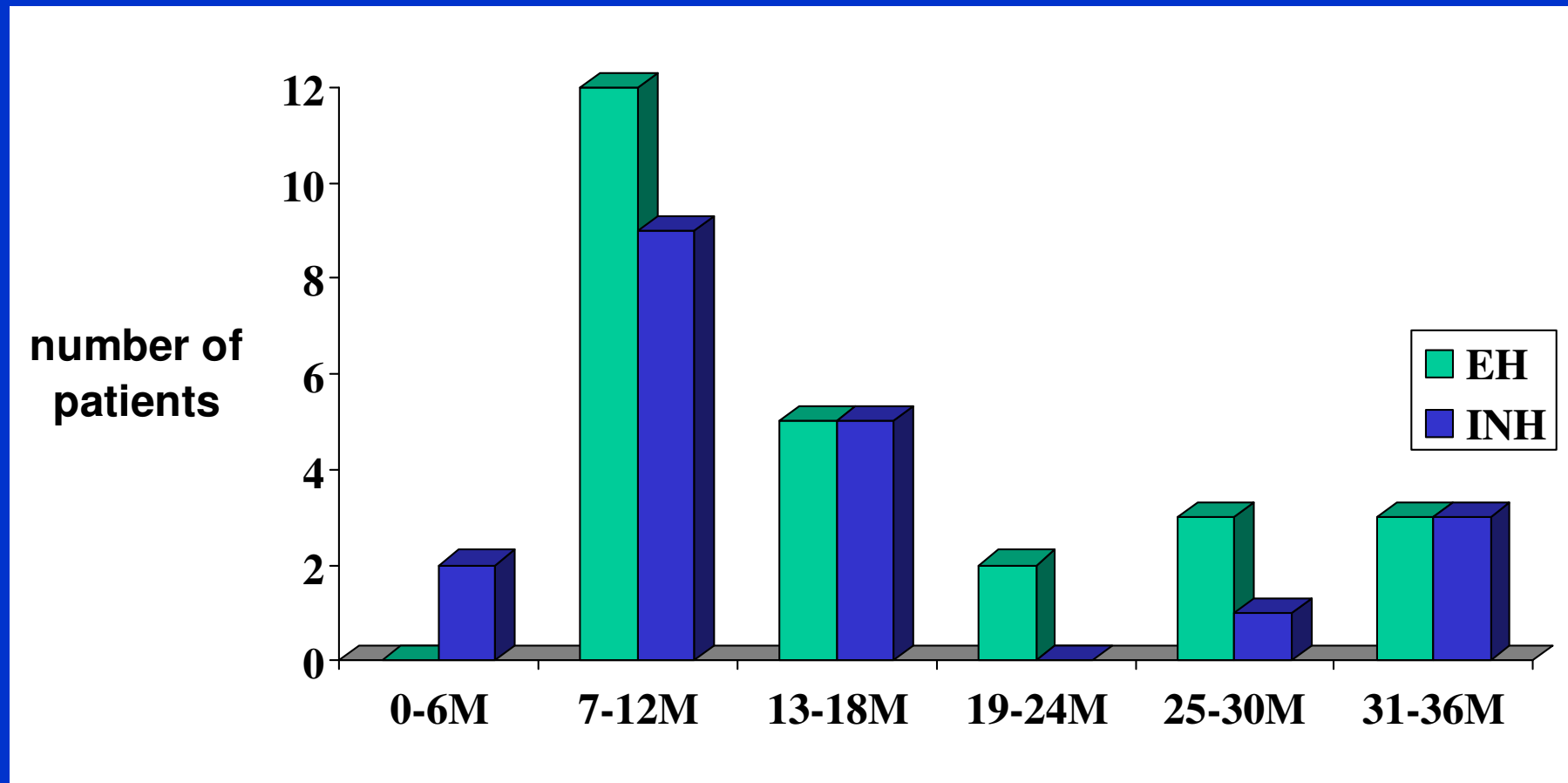


# TB Incidence and Death by TST status and CD4 count

	TB rate/100py	Death rate/100py
TST < 5mm (n=410)	1.6 (0.8 - 2.3)	2.5 (1.5 - 3.4)
TST > 5mm ( n= 273)	2.6 (1.4 - 3.8)	2.5 (1.3 - 3.6)
<b>Rate Ratio</b>	<b>0.6 (0.3 -1 .2)</b>	<b>1.0 (0.5 - 1.8)</b>
CD4 < 200 (n=175)	4.8 (2.7 – 6.8)	5.0 (2.9 – 7.1)
CD4 > 200 (n = 503)	1.1 (0.5 -1.6)	1.7 (1.0-2.4)
<b>Rate Ratio</b>	<b>4.4 (2.2 – 8.5)</b>	<b>3.0 (2.5 – 3.6)</b>



# Timing of Deaths



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# Causes, CD4 Count and Timing of Death

Cause	6EH7 (n=25)			36H7 (n=20)		
	n	Median CD4	Median Month	n	Median CD4	Median Month
CNS complication of HIV including CVA, HIV meningo-encephalopathy	6	94	12	5	66	23
AIDS progression	5	52	14	1	81	12
Serious OI (Crypto, MAC)	3	122	16	3	37	2
Diarrhoea	4	59	18	3	42	7
Others( malignancy, suicide, MI, pulmonary embolism)	5	91	12	7	181	19
TB	2	162	4	1	144	2



# Death details

	<b>6EH</b>	<b>36H</b>	
<b>Median CD4 at Death</b>	<b>66 (36 -132)</b>	<b>73 (40-308)</b>	
<b>Median M of death</b>	<b>10 (14 - 21)</b>	<b>15 (9 - 23)</b>	
<b>On ART</b>	<b>nil</b>	<b>nil</b>	



# Death details

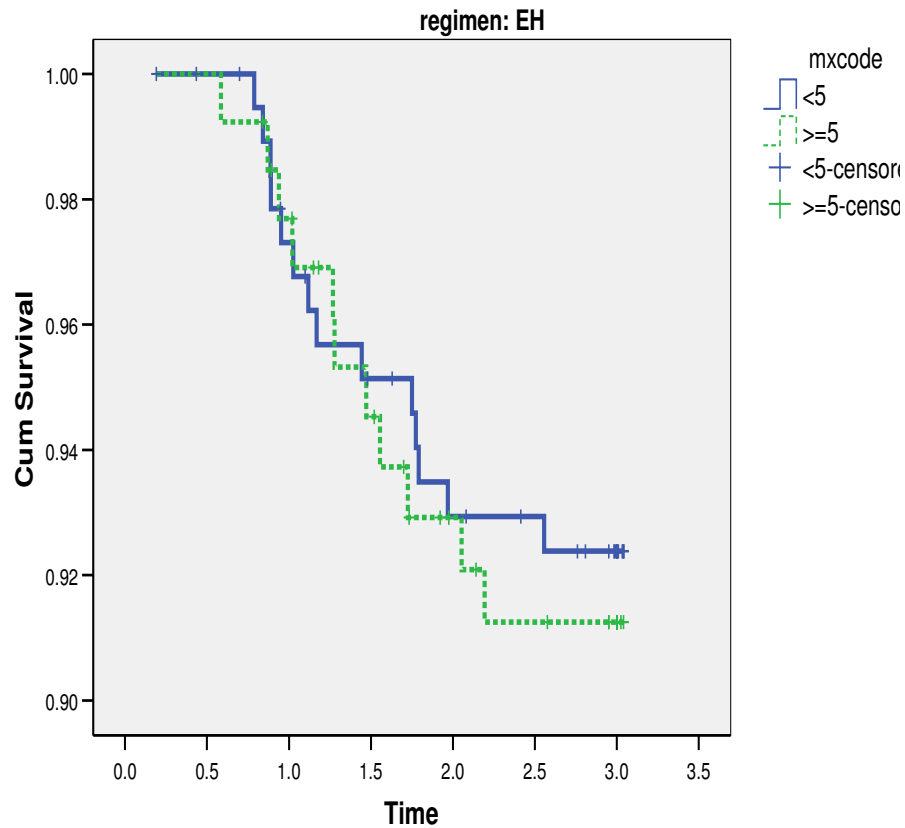
Regimen 6EH7	n	Regimen36H7	n
CNS complication of HIV	4	CNS complication of HIV	4
CVA( infarct)	2	CVA(infarct)	1
Diarrhoea with AIDS	4	Diarrhoea with AIDS	3
OI Pneumonia-1,Cryptococcal meningitis-1, MAC-1	3	OI Pneumonia-1,PCP-1, Extensive candidiasis-1	3
Progression of AIDS	5	Progression of AIDS	1
Others Unknown-3,CA- Lung-1,Suicide-1	5	Others Unknown-2,MI-3,RTA-1 Ca larynx-1,Suicide-1	8
TB	2		0
total	25		20



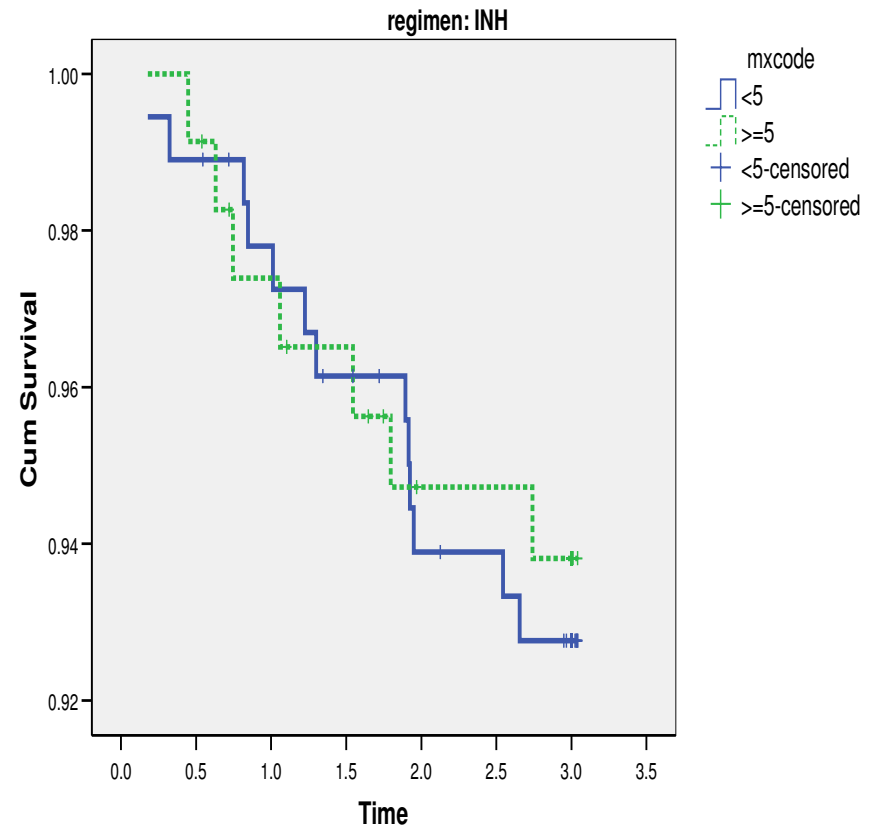


# Mortality by TST Status: similar both regimens

Survival Functions



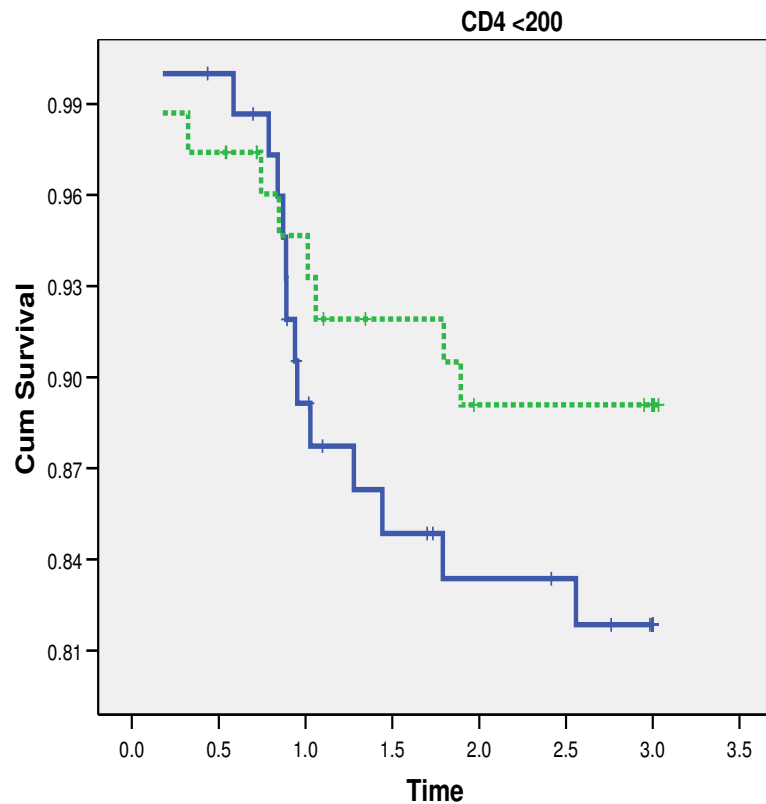
Survival Functions



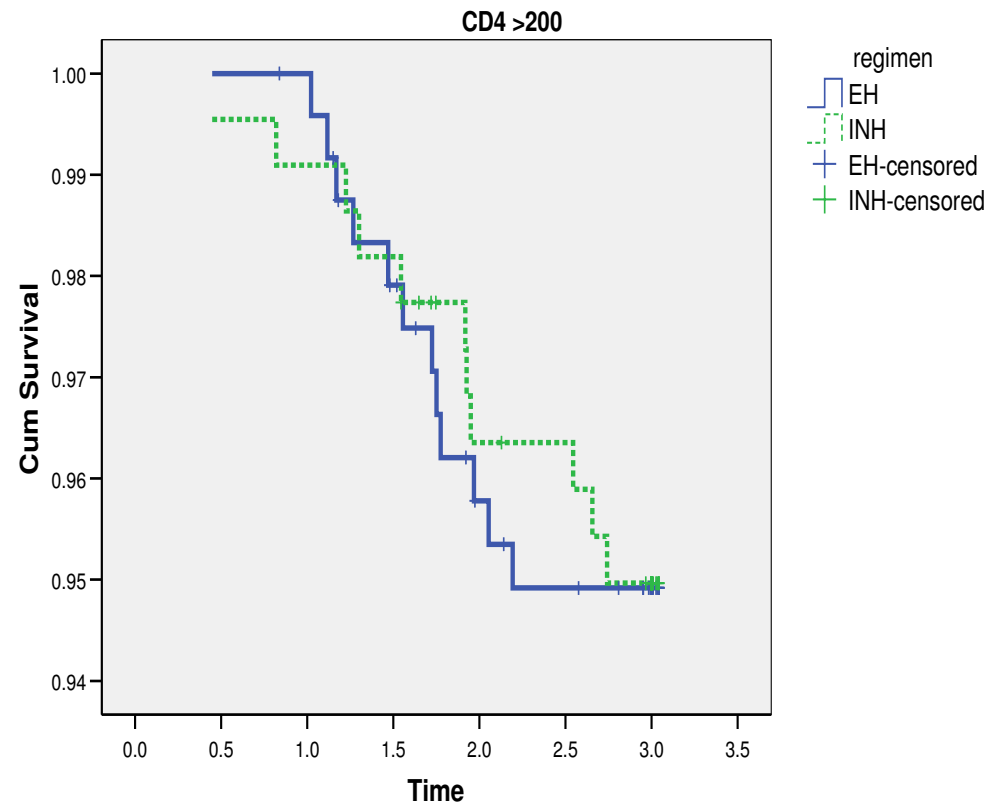


# Mortality by Immune Status: within each CD4 stratum, rate not different by regimen

Survival Functions



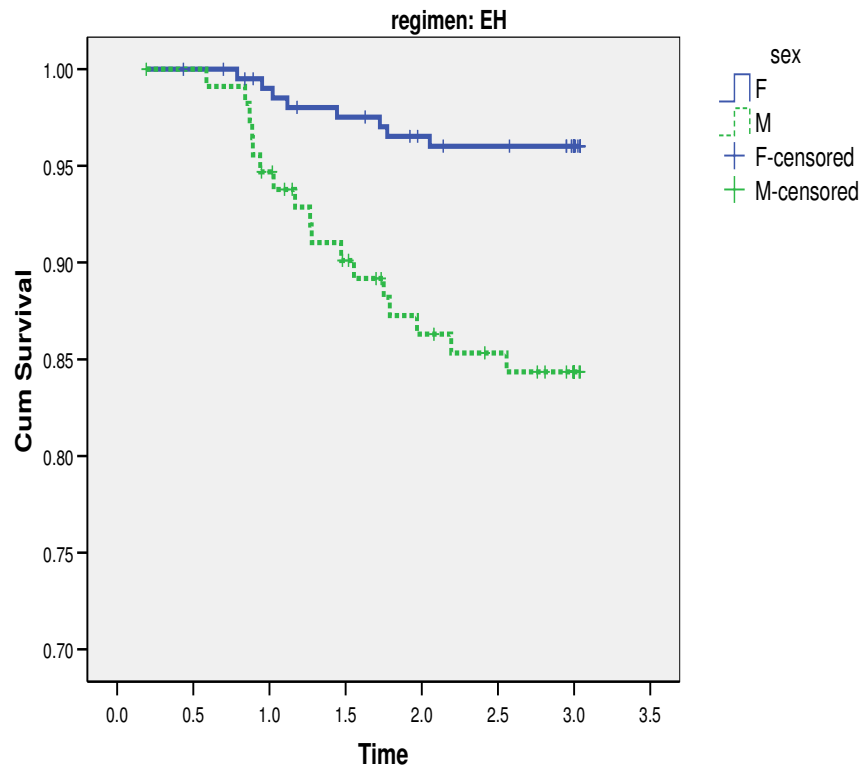
Survival Functions



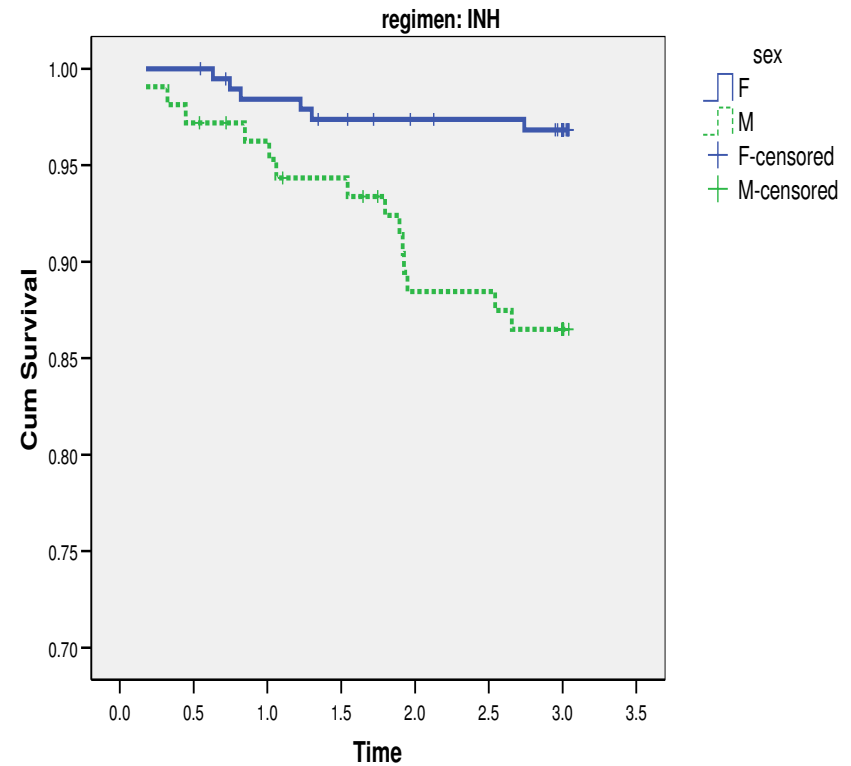


# Mortality Higher in Males in both Regimens

Survival Functions-Sex for EH(Mortality)



Survival Functions-Sex for INH(Mortality)

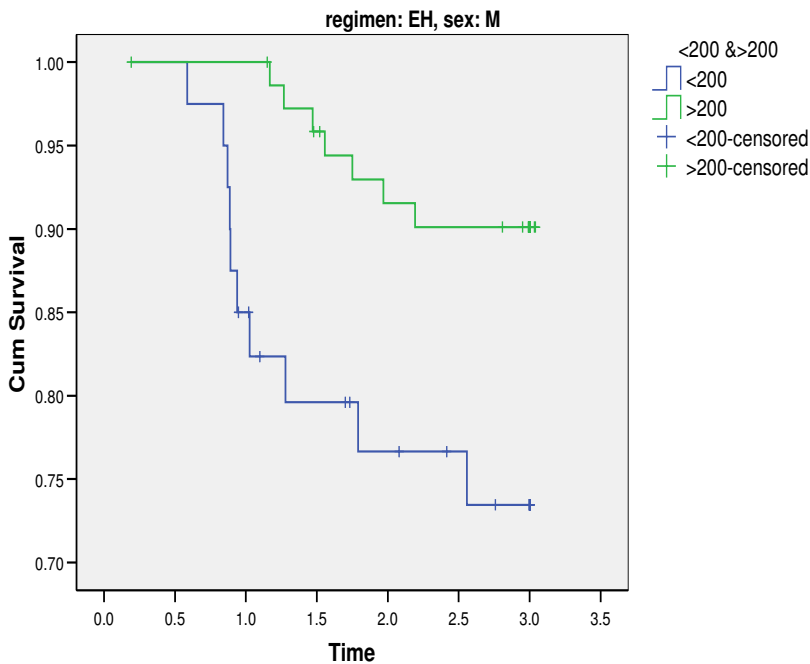


Log rank test  $p < 0.01$  for both

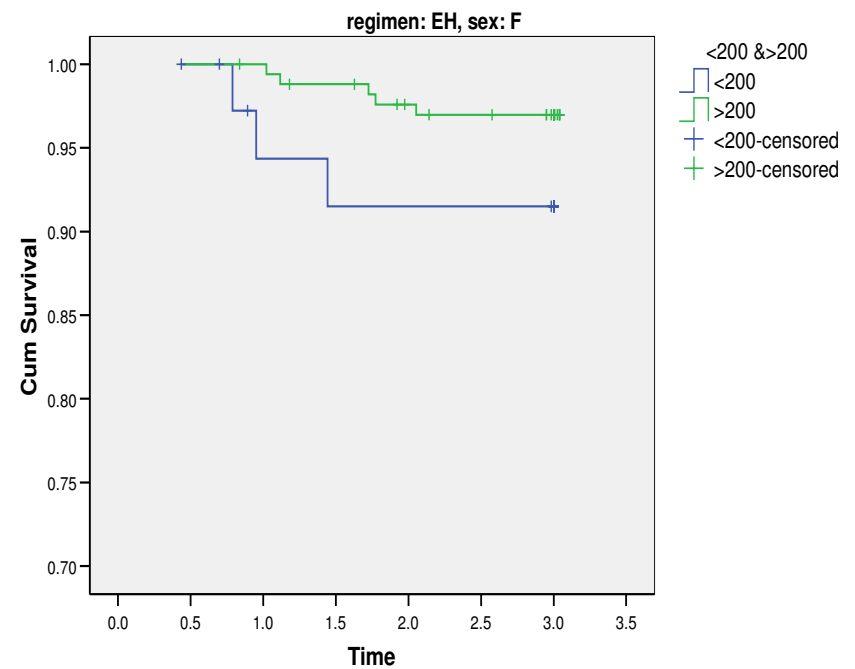


# Mortality in Men and Women stratified by CD4 count, 6EH Regimen

Survival Functions for Male based on CD4(Mortality)



Survival Functions for Female based on CD4(Mortality)





## Death Rates Among Men and Women by Regimen and CD4 Count

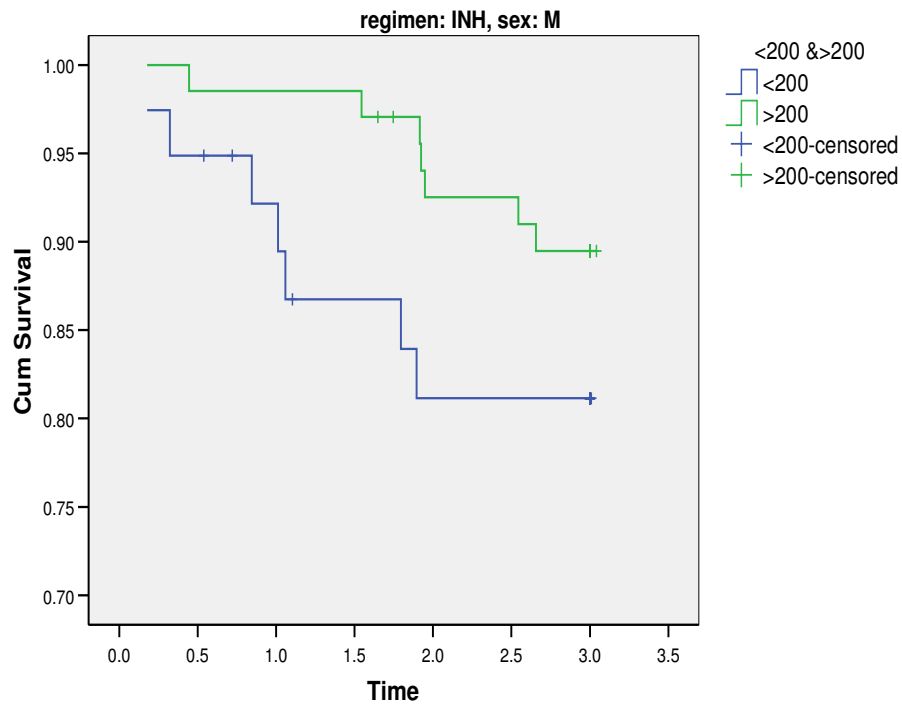
	6EH	36H
F < 200	2.9	1.0
M < 200	10.9	7.2
F > 200	1.0	1.1
M > 200	3.4	3.6

**Does continuous IPT reduce mortality among patients with advanced disease?**

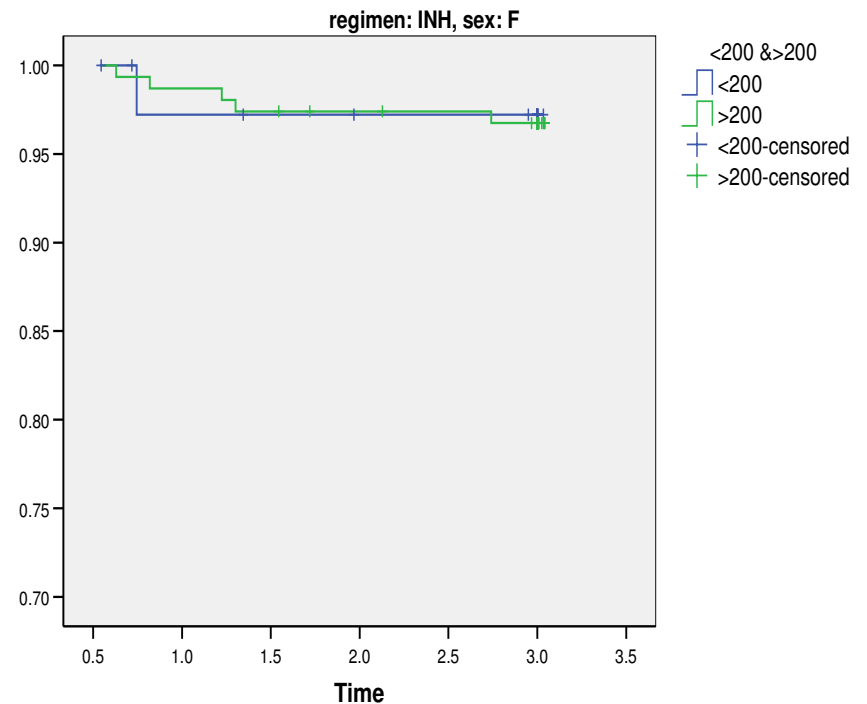


# Mortality in Men and Women stratified by CD4 count, 36H Regimen

Survival Functions for Male based on CD4(Mortality)



Survival Functions for Female based on CD4(Mortality)





## Death Rate Higher in Men (Both Regimens)

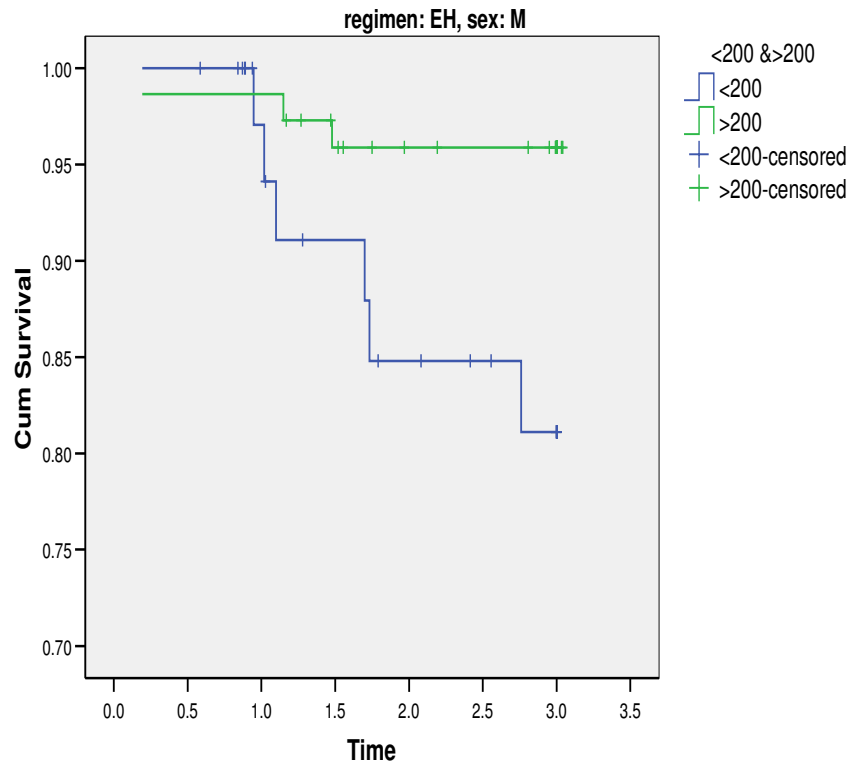
	6EH	36H
Male Rate/100py (95% CI)	5.7* (3.0 – 8.5)	4.8* (2.3 – 7.4)
Female Rate/100py (95% CI)	1.4 (0.4 – 2.3)	1.1 (0.2 – 2.9)

\* P < 0.01 by log rank test

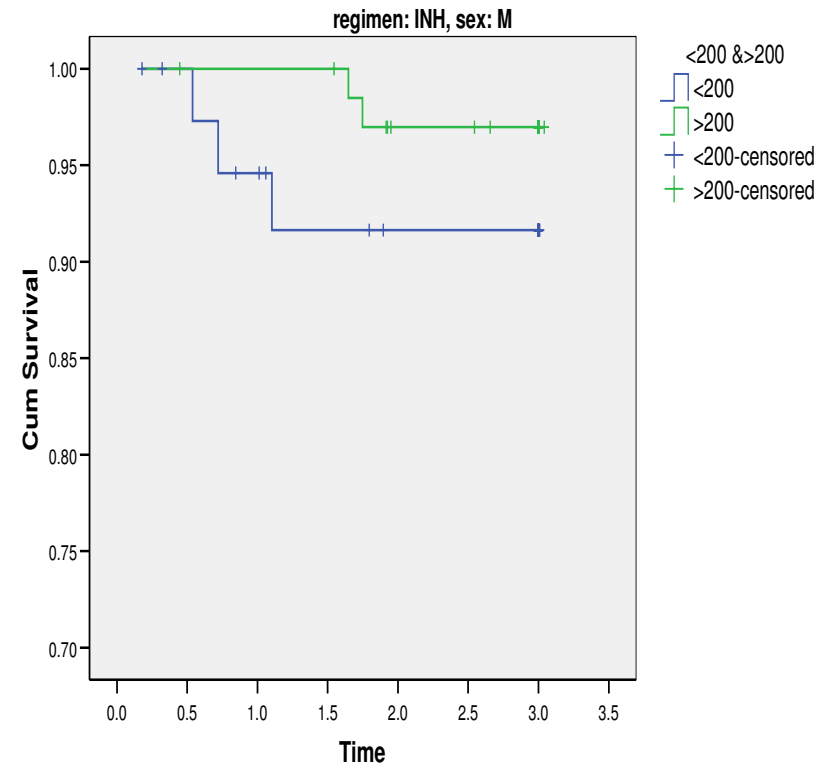


# TB rate Lower in Males at CD4 < 200 in 36H compared to 6EH

Survival Functions for Male based on CD4(TB incidence)



Survival Functions for Male based on CD4(TB incidence)



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# TB Incidence and Death by Sex and Regimen

	6EH	36H
TB Incidence rate/100py (95% CI)		
Male (n=114, 107)	3.0 (1.05 – 5.02)	1.7 (0.2-3.2)
Female (n=206, 192)	1.5 (0.5 – 2.5)	1.08 (0.2-1.9)
Mortality rate/100 py		
Male	5.7 (3.0-8.5)*	4.8 (2.3-7.4)*
Female	1.4 (0.4-2.3)	1.1 (0.2-1.9)

\* P < 0.01 for mortality M vs F



# Conclusions

- Mortality of patients in 6EH and 36H arms similar over 3 year period
- Of 45 deaths, only 3 due to TB
- Most deaths occurred within 12 months of enrolment in patients with advanced immunodeficiency (pre-ART era)
- Causes included neurological complications, diarrhoea and OIs

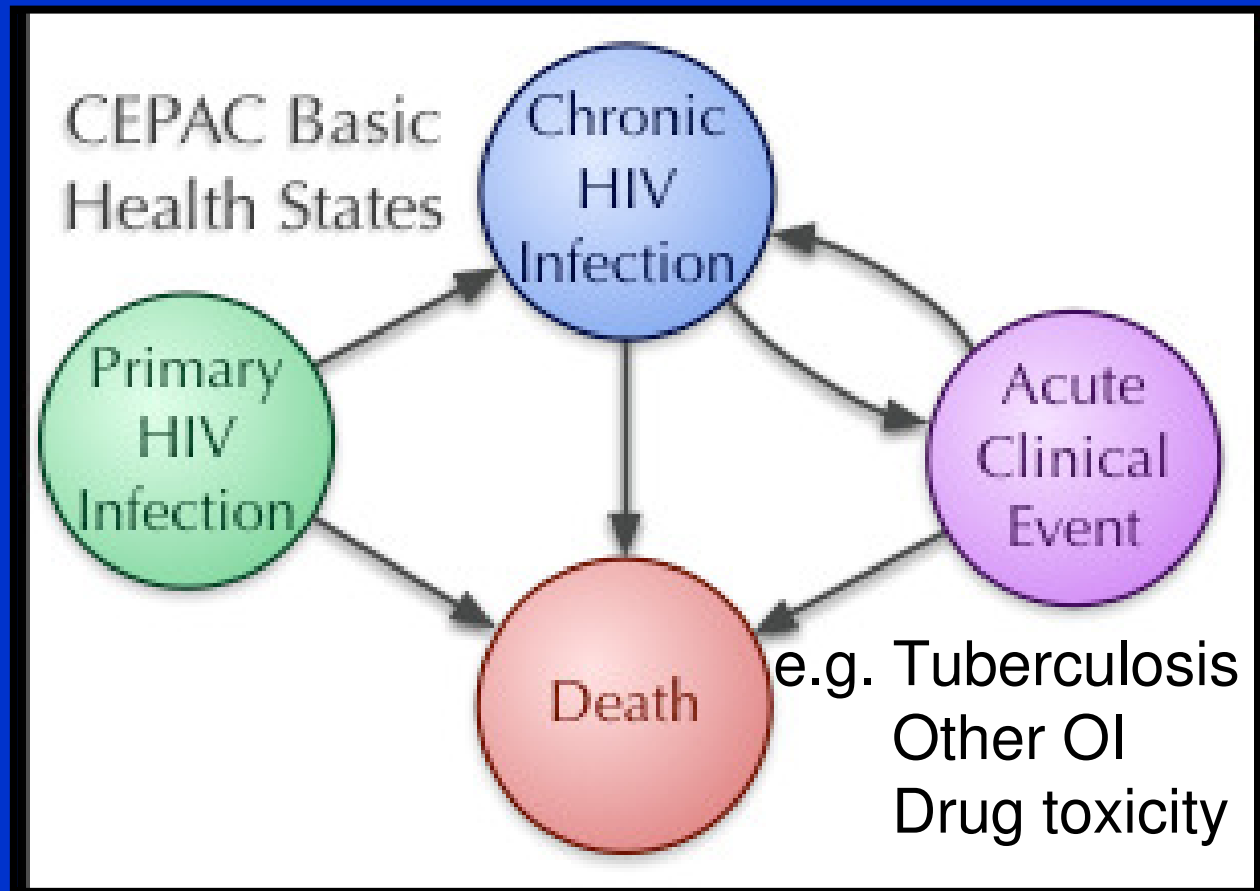


## Some Intriguing Observations ...for Future study?

- Mortality similar in TST+ and TST- patients, not different by regimen
- Mortality 3 times higher in patients with CD4 < 200 regardless of regimen
- Men had higher death rate than women even after stratifying for CD4 count (men with CD4 < 200, 3/40 died in EH regimen and 6/39 in 36H regimen)
- Does continuous IPT have mortality benefit for patients with advanced disease?



# The Cost-Effectiveness of Preventing AIDS Complications “CEPAC” Model



February 18 2009

Supported by NIAID AI42006 and AI05876

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# Cost-effectiveness is about Value for Money

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- Two different outcome measures
  - Cost in dollars (2008 USD)
  - Effectiveness: years of life saved (YLS)

- Cost-effectiveness ratio:

Additional Resource Use (\$)

Additional Health Benefits (YLS)

**What is the value?**



# “Rough guide”

## Cost-effectiveness Thresholds

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The Commission on Macroeconomics and Health and WHO have suggested that interventions are:

- **Cost-effective**: the CE ratio is  $< 3 \times$  GDP per capita for a country
- **Very cost-effective**: the CE ratio is  $< 1 \times$  GDP per capita for a country



# Cost-effectiveness Analysis

Strategy	Mean per person LE (months)	Mean per person cost (\$2008)	\$/YLS	TB cases per 100 pts	TB deaths per 100 pts
No TPT	96.4	2,460	--	66	10
6m TPT	97.4	2,490	\$620	42	7

Pho MT, Swaminathan S, et al. Clinical Impact and Cost-Effectiveness of Treatment for Latent Tuberculosis in HIV+ Patients in India [abstract]. Presented at: the 47<sup>th</sup> Annual Meeting of the Infectious Diseases Society of America; 2009 Oct 29-Nov 1; Philadelphia (PA), USA.



# Cost-effectiveness Analysis

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- Preliminary analysis suggests that providing six months of tuberculosis preventive therapy to HIV-infected, ART-naïve patients in southern India is very cost-effective
- Further sensitivity analyses of length of treatment, toxicity, length of treatment and cost are currently underway





**Thank you**

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