Non-rifampin rifamycins in TB/HIV

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Consortium to Respond Effectively to the AIDS-TB Epidemic

Rifamycins for TB

- Inhibit bacterial DNA-dependent RNA polymerase
- Key “sterilizing” drug in TB treatment – basis of short-course therapy
- Three products available
  - Rifampin
  - Rifapentine
  - Rifabutin

Selected Pharmacokinetic Properties of Rifamycins

Property	Rifampin	Rifabutin	Rifapentine
Half life (T1/2), h	2-5	33-67	13-17
Cmax (mcg/L)	10.0	0.45	15.0
MIC (mcg/L)	0.15	0.06	0.05
Cytochrome P450 induction	++++	++	+++
Effect of cytochrome P450 inhibition	-	++++	-
Effect of food	↓ AUC	-	↑ AUC

Adapted from: Burman et al., Clin Pharmacokin, 2001;40:327-341

Important Drug Interactions with Rifampin*

- Protease inhibitors
  - RIF decreases levels >80%, except some RTV-boosted regimens
  - Increased hepatotoxicity with LPV/r and SQV/r
- NNRTIs
  - RIF decreases NVP 40-50%, EFV 20-35%, ETV "significantly"
- CCR5 Inhibitors
  - RIF reduces maraviroc by 63%
- Integrase inhibitors
  - RIF reduces raltegravir by 40-60%

*similar effects likely with rifapentine

Important Drug Interactions with Rifabutin

- Protease inhibitors
  - Rifabutin decreases levels >20-30%
  - RTV and azoles increase RBT levels significantly, causing uveitis and other toxicities – dose reduction necessary
- NNRTIs
  - Rifabutin has minor effect on NVP and EFV
  - EFV increases RBT clearance – dose escalation necessary
- CCR5 Inhibitors – no information
- Integrase inhibitors – no information

Potential Role of Rifabutin and Rifapentine in HIV-related Tuberculosis

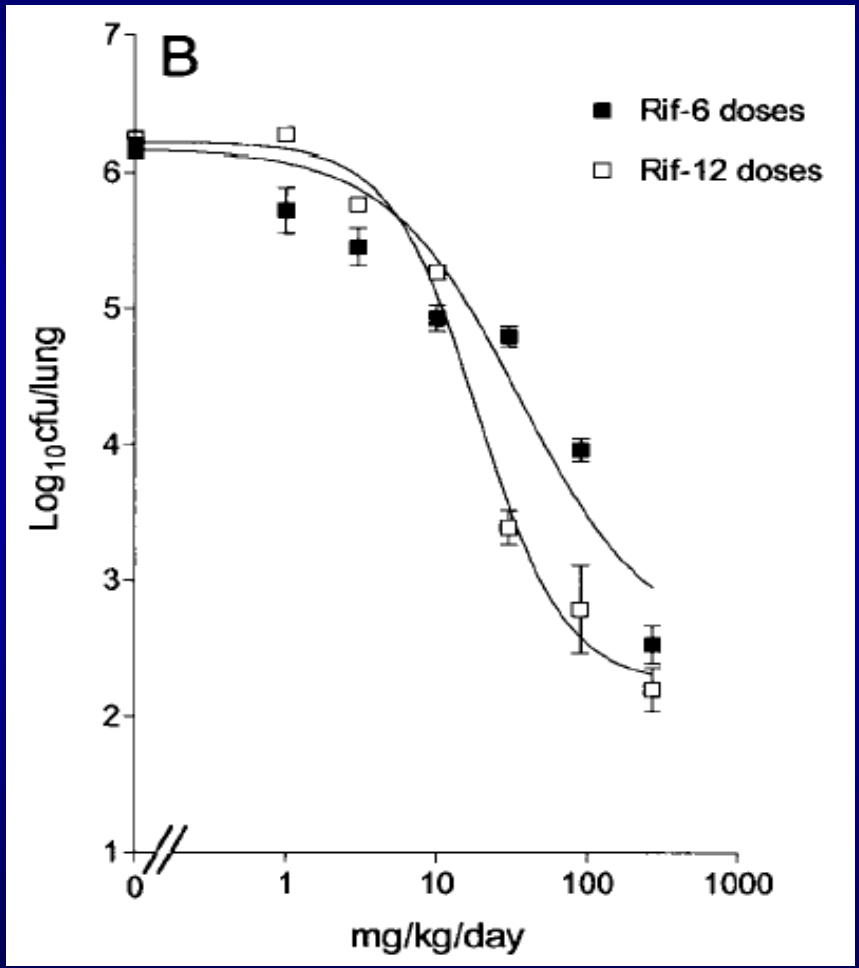
- Rifabutin
  - Permit treatment of TB in HIV-infected patients on boosted PI regimens
- Rifapentine
  - Shortening course of TB treatment in HIV+ and HIV- individuals
  - Short-course preventive therapy for HIV-infected people with latent TB

Rifabutin for treating HIV-related TB TBTC Study 23

- Twice weekly RBT/INH for HIV/TB
- High efficacy for TB
- 5/156 HIV+ patients had relapse/failure with acquired rifampin resistance
- All CD4 <60
- CDC recommendation – do not use highly intermittent treatment for HIV+ patients with CD4 <100

MMWR 2002;51:214-5

Increasing regimen potency by increasing rifamycin exposure in a mouse model

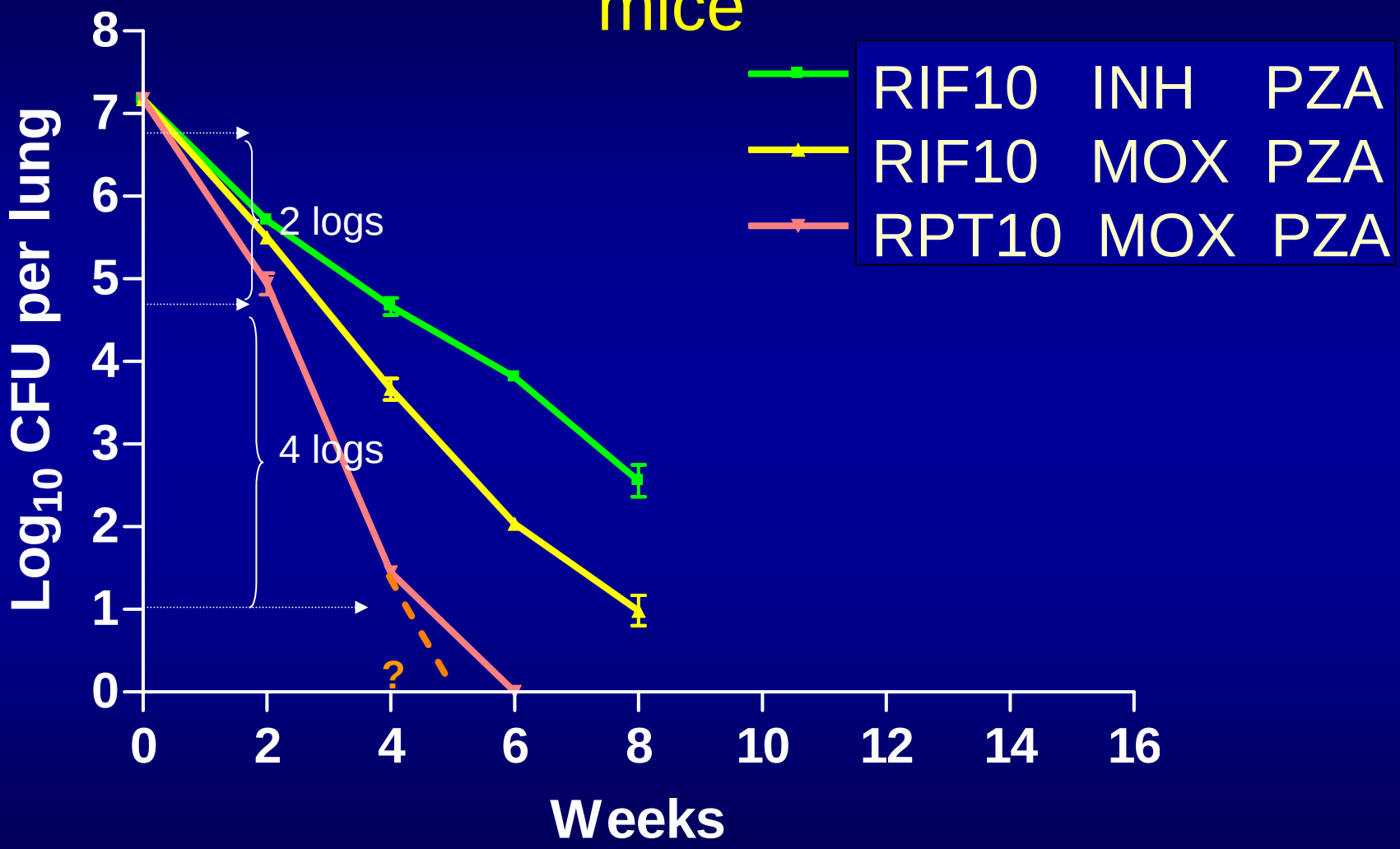


Jayaram et al Antimicrob Agents Chemother 2003;47:2118

Optimizing rifamycin exposure by using rifapentine

- Half-life 14-17 hours (rifampin 2-5 hours)
- MIC 0.05 mcg/ml (rifampin 0.15 mcg/ml)
- Less potent inducer of cytochrome P450 than rifampin
- FDA-approved for TB treatment at dose of 600 mg (10 mg/kg) given twice weekly

Bactericidal activity of daily regimens in mice



Rosenthal et al., PLoS Medicine 2007

Rifapentine Rx studies in humans

2008	2009	2010	2011	12	13	14
Complete development for registration of a short regimen						
P+M PK (JHU/NIH)						
P1: dose ranging – PK D14– safety; 300-900mg/d (JHU)						
P1: P + Raltegravir PK (CDC)						
P2: P10HZE (5/7) efficacy @ 8 weeks (CDC TBTC Study 29)						
P2: P10HZE – P7.5HZE (7/7) efficacy at 8 weeks (JHU/FDA)						
P2:P7.5HZM (7/7) efficacy @ 8 weeks (JHU/NIH)						

Adapted from D. Leboulleux, Sanofi-aventis

Novel TB Preventive Regimens in HIV-Infected Adults in Soweto: Preliminary Results

Neil Martinson, Grace Barnes, Reginah Msandiwa, Lawrence Moulton, Glenda Gray, James McIntyre, Harry Hausler, Malathi Ram,
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Methods

- Open label, randomized trial Soweto, South Africa
- Eligibility:
  - HIV+
  - TST+ (>=5mm)
  - adults (>=18 yrs)
  - not eligible for HAART
  - No evidence of liver disease
  - No active TB
- Active TB: CXR, symptom screen and AFB smear and TB culture.
- Endpoint – TB-free survival

Novel Regimens for TB Preventive Therapy

Short-course

- Rifapentine 900mg + INH 900mg weekly – **12 doses**
  - effective in animal model, convenient for patients
- Rifampin 600 mg + INH 600mg twice weekly – **24 doses**
  - effective in one trial, widely available

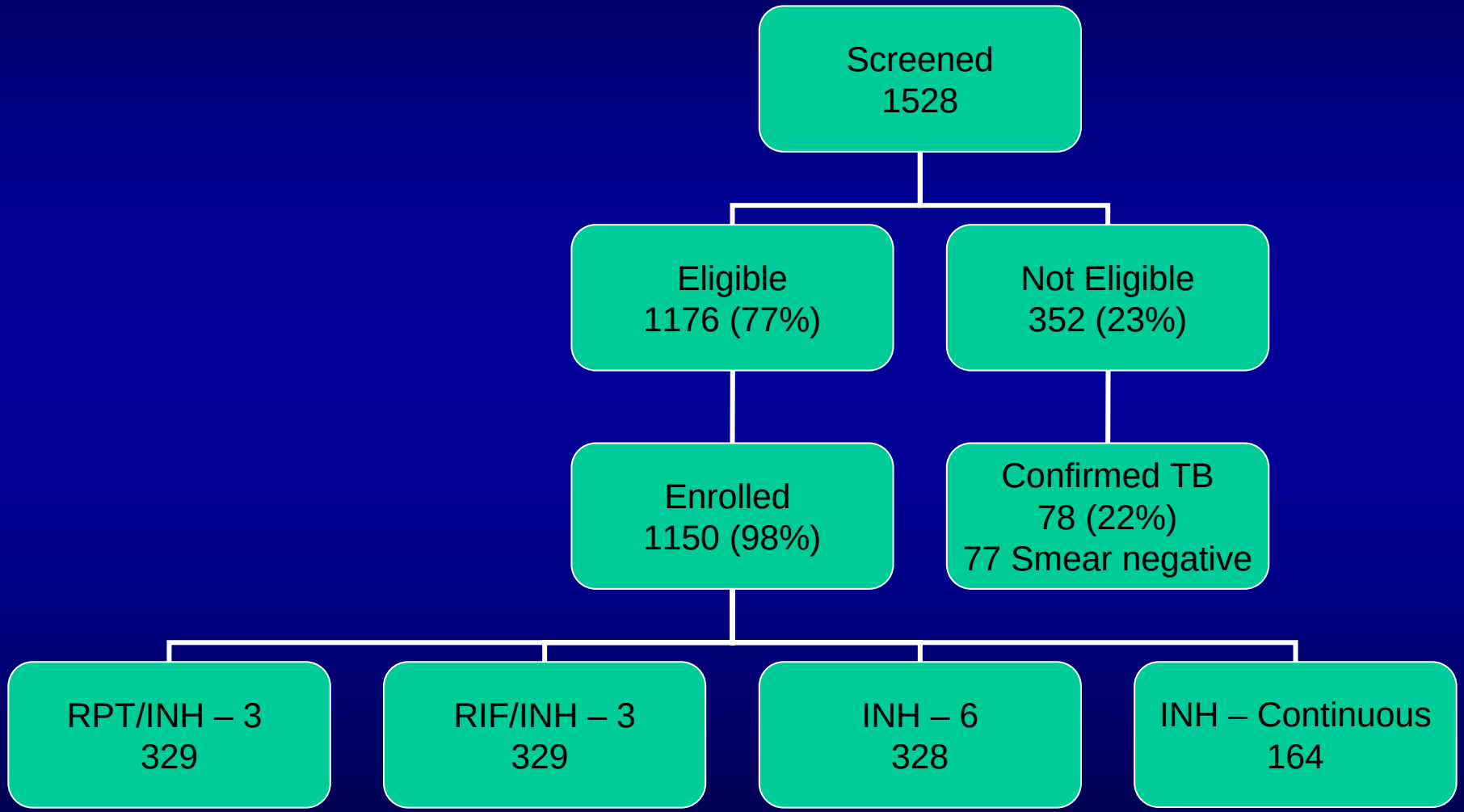
Long

- INH 300mg daily continuously – may be effective to prevent re-infection

Standard of care

- INH 300mg daily for 6 months

Study Flow and Recruitment



Baseline Characteristics

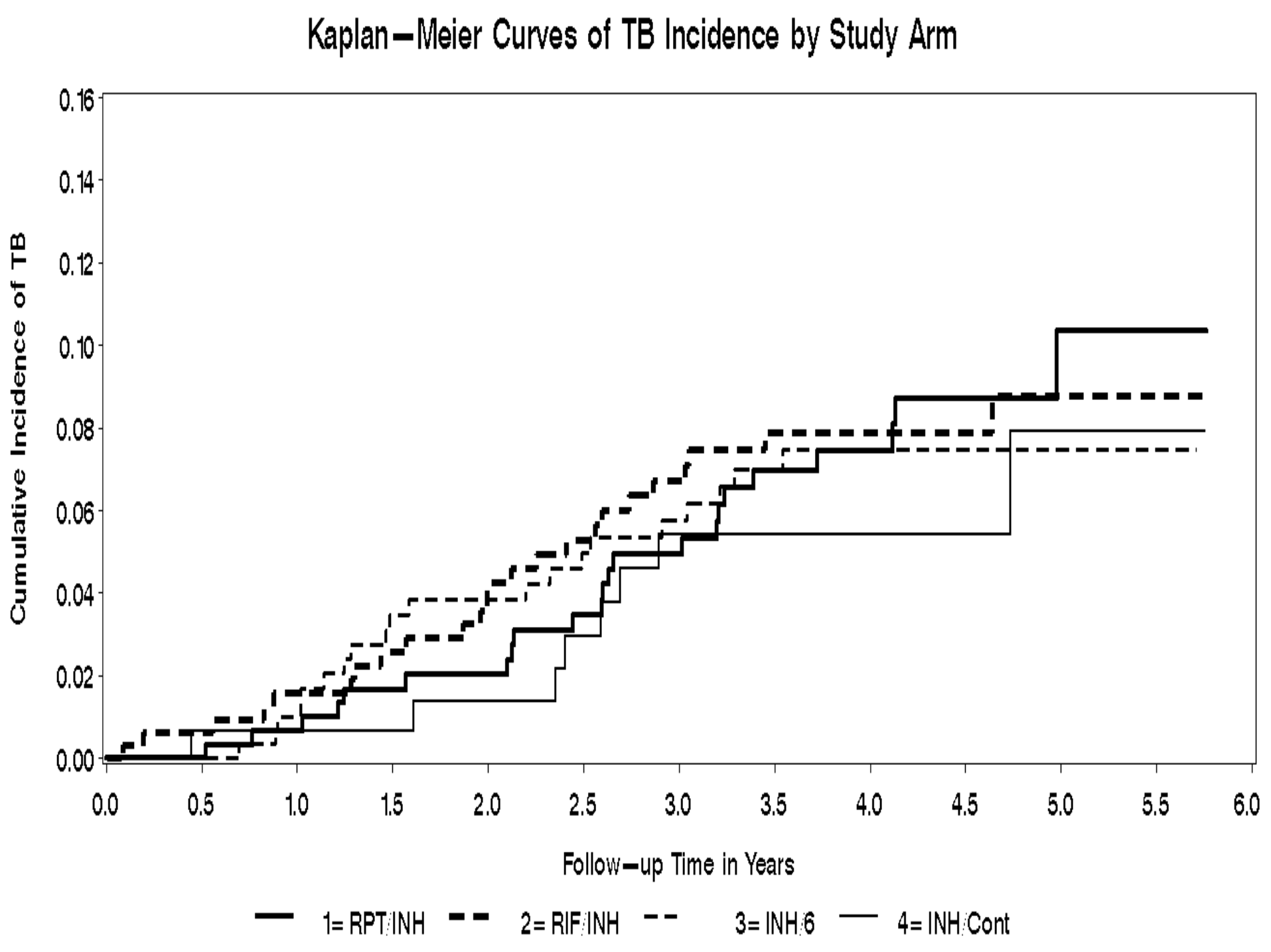
	RPT/INH (%)	RIF/INH (%)	INH -6 (%)	INH - Cont (%)	All (%)
Median Age	30	30	30	30	**30**
% Women	85.5	81.2	83.2	84.8	**83.2**
Education					
Grade 6-11	66.3	64.1	57.0	61.0	**62.3**
Grade 12	26.4	29.8	34.5	34.1	**30.8**
Diploma	1.8	1.2	1.5	3.1	**1.7**
Employment					
Employed	12.2	10.3	11.9	7.3	**10.9**
PPD (mm)					
Mean Range	15.5 6 – 45	15.8 6 – 34	15.6 6 – 50	16.1 5 – 33	15.7 5 – 50

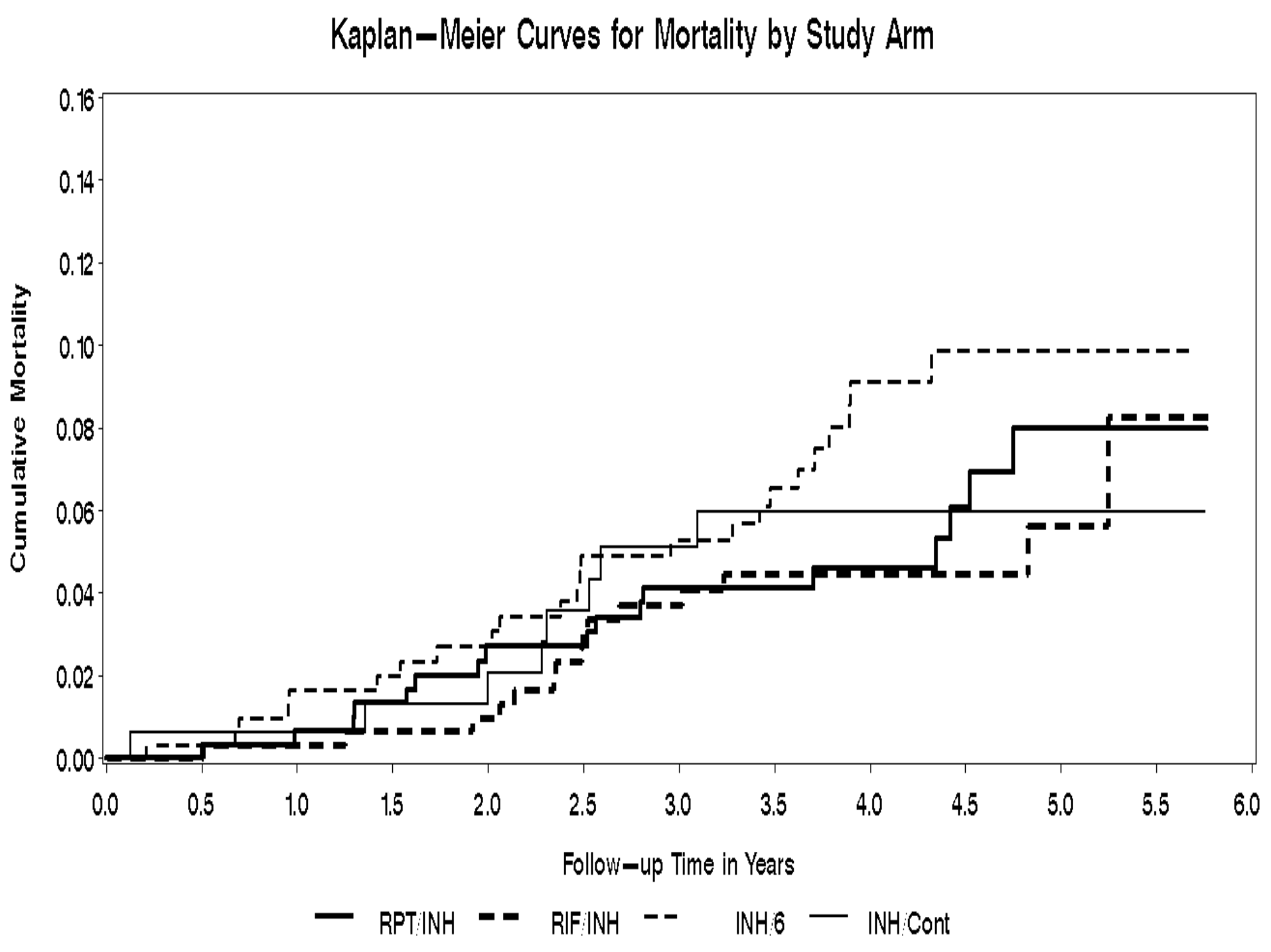
Baseline Characteristics - cont

Characteristic	RPT/INH	RIF/INH	INH-6	INH-Cont	Overall
Weight (kg)					
Mean Weight	66.9	67.1	67.3	68.4	**67.3**
CD4 count (cells/mm^3)					
Median Range	471 208 – 1521	498 202 – 1635	492 204 - 1720	476 202 - 1460	**485** **202 - 1720**
HIV Viral Load (copies/ml)					
Median	18,400	10,800	15,900	16,200	**15,200**

Primary Outcomes by Study Arm

Outcome	RPT/INH-3 (N=329)	RIF/INH-3 (N=329)	INH-cont (N=164)	INH-6 (N=328)
Median F/U (yrs)	3.98	3.99	3.81	3.78
TB Cases	23	24	8	20
TB incidence (per 100 PY)	1.94	1.97	1.43	1.77
TB incidence Rate ratio	1.10	1.11	0.81	1 (ref)
TB or death	3.03	2.87	2.67	3.53
TB or death Rate ratio	0.86	0.81	0.76	1 (ref)


Kaplan–Meier Curves of TB Incidence by Study Arm
Cumulative Incidence of TB
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Follow–up Time in Years
1= RPT/INH
2= RIF/INH
3= INH/6
4= INH/Cont


Kaplan–Meier Curves for Mortality by Study Arm
Cumulative Mortality
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Follow–up Time in Years
RPT/INH
RIF/INH
INH/6
INH/Cont

Resistance Testing of Isolates

Arm	Resistance Testing (N)	MDR (N)	Resistant to			
			INH (N)	R (N)	Strept. (N)	E (N)
RPT/INH-3	19	2	2	3	1	1
RIF/INH-3	16	0	0	0	0	0
INH-6	14	0	0	0	0	0
INH/Cont	7	1	1	1	1	0
Total	56	3	2	3	2	1

Serious Adverse Events by Study Arm

	Study Arm				Total N (Rate)
	RPT/INH	RIF/INH	INH-6	INH-Cont	
	N (Rate*)	N (Rate)	N (Rate)	N (Rate)	
Hospitalization	95 (29.0)	89 (27.1)	104 (31.8)	38 (23.2)	326 (28.4)
Pregnancy	81 (24.7)	74 (22.5)	49 (15.0)	31 (18.9)	235 (20.5)
Grade 3 Toxicity	17 (5.2)	15 (4.6)	17 (5.2)	35 (21.3)	105 (9.1)
Grade 4 Toxicity	4 (1.2)	9 (2.7)	14 (4.3)	18 (11.0)	45 (3.9)
All Adverse Events	250 (76.2)	244 (74.2)	241 (73.7)	150 (91.5)	885 (77.1)

Rate= per 100 enrolled persons

Conclusions

- RPT/INH-3, RIF/INH-3 and H-cont are not superior to INH-6, but may be as efficacious.
- INH-cont had the lowest TB rate but significantly higher adverse event rate
- All 3 experimental regimens had lower risks of TB/Mortality, but not significantly so

Conclusions

- The shorter two novel regimens may be useful to improve adherence to TB preventive therapy in HIV-infected adults in sub-Saharan Africa.

- We cannot make recommendations about the use of continuous isoniazid preventive treatment.

Rifamycins for TB
Summary

- Rifamycins essential for TB therapy
- Rifampin is safe and effective for HIV/TB patients on efavirenz
- Rifabutin allows use of boosted PI regimens to treat HIV in patients on TB therapy
- Rifapentine has the potential to shorten TB therapy significantly
- Rifapentine is a promising agent for short-course TB preventive therapy