High-dose rifampicin tuberculosis treatment regimen to reduce 12-month mortality of TB/HIV co-infected patients:

The RAFA trial results

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Trial Rationale

- TB is the leading cause of death among HIV + people in the LMIC
- Current strategy to reduce TB/HIV mortality: optimal management of HIV disease
- Mortality due to TB is high in TB/HIV population
- TB treatment in HIV patients might be sub-optimal
- More intensive TB treatment might help to reduce mortality

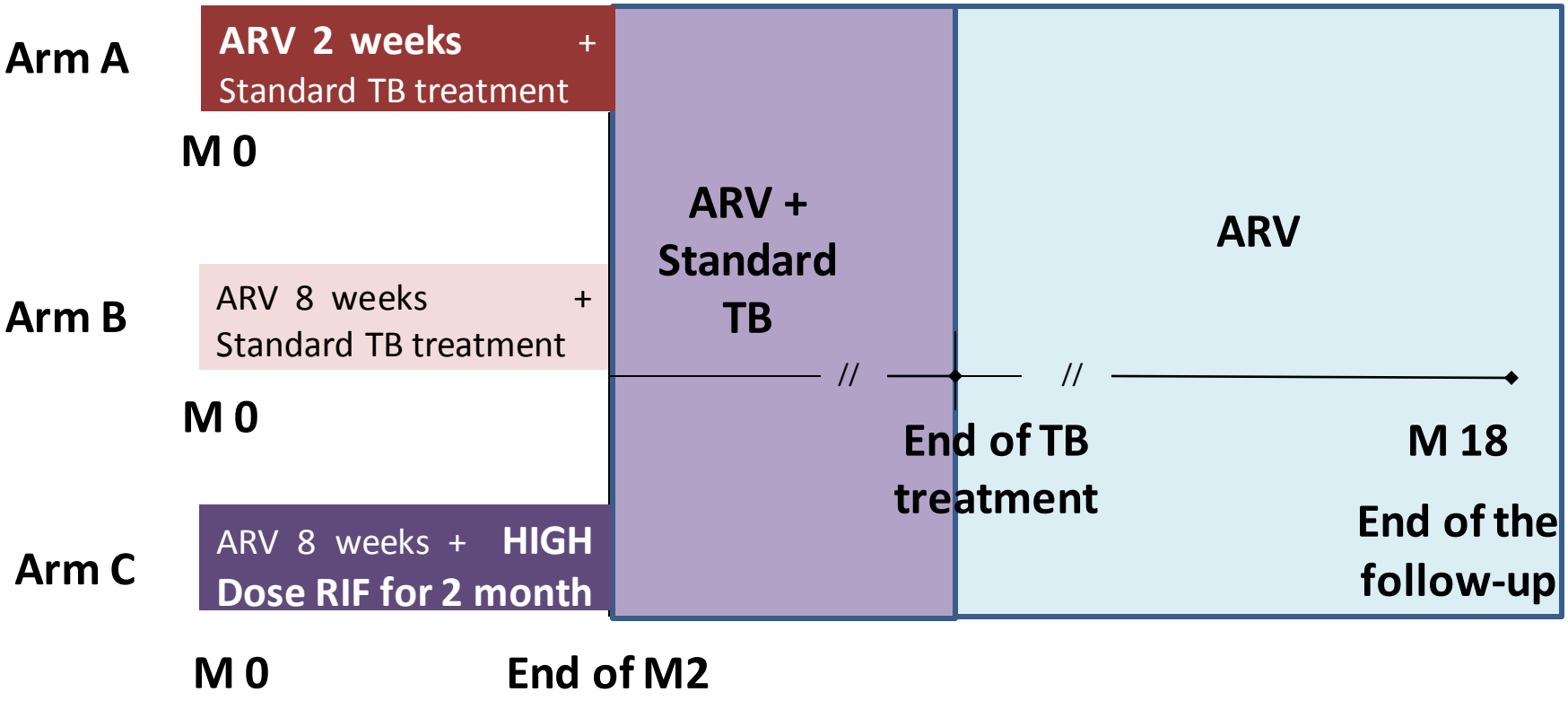
Methods(1): Primary objective

To assess in ARV-naïve TB/HIV patients with CD4 counts >50 cells/mm3 the efficacy in terms of morbidity and mortality at 2 and 12 months post randomisation of 3 treatment strategies:

- Early ARV initiation (week 2) with a standard TB treatment,
- Delayed ARV treatment (week 8) with a standard TB treatment,
- **Delayed ARV treatment (week 8) with high dose rifampicin during the intensive phase of TB treatment (15mg/Kg) and standard TB treatment in the continuation phase.**

Methods(2): Study design

- 3 parallel arms, multicentre, open-label RCT
- nested pharmacokinetic (PK) study in a sub-sample of patients



Methods(3): Study population

- **Sample size: 260** patients per treatment arm to be recruited

- **Main inclusion criteria**
  - Adults > 18 yrs
  - ARV Naïve HIV infected patients
  - CD4 cells ≥50 cell/mm3
  - All type of TB disease with bacteriological or molecular confirmation
  - written informed consent

- Patients were recruited in **Benin** (Cotonou and Porto-Novo), **Guinea** (Conakry) and **Senegal** (Dakar)

Methods (4)

Primary outcome

- Mortality at 12 months after starting TB treatment

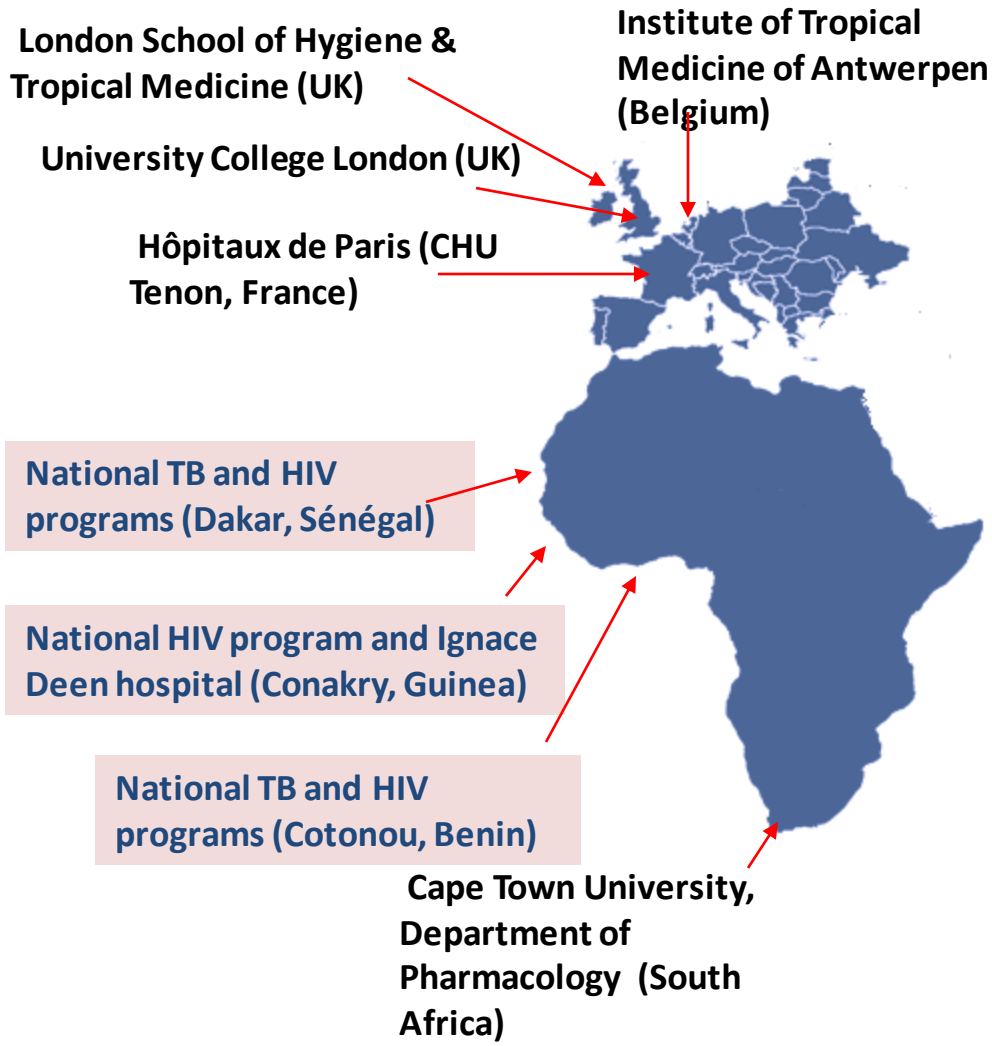
Visits schedule

- Clinical visit and 2 sputum taken: every 2 weeks during 2 months, every months until the end of the TB treatment and every 3 months until the end of the follow-up
- Total follow-up per patient : 18 months post randomisation

Quality Assurance & control

- Monitoring & supervision visits every 2 to 3 months
- Clinical Audit after 1 year of recruitment in all recruitment sites
- Internal and external laboratory and data QC in place

RAFA project partners



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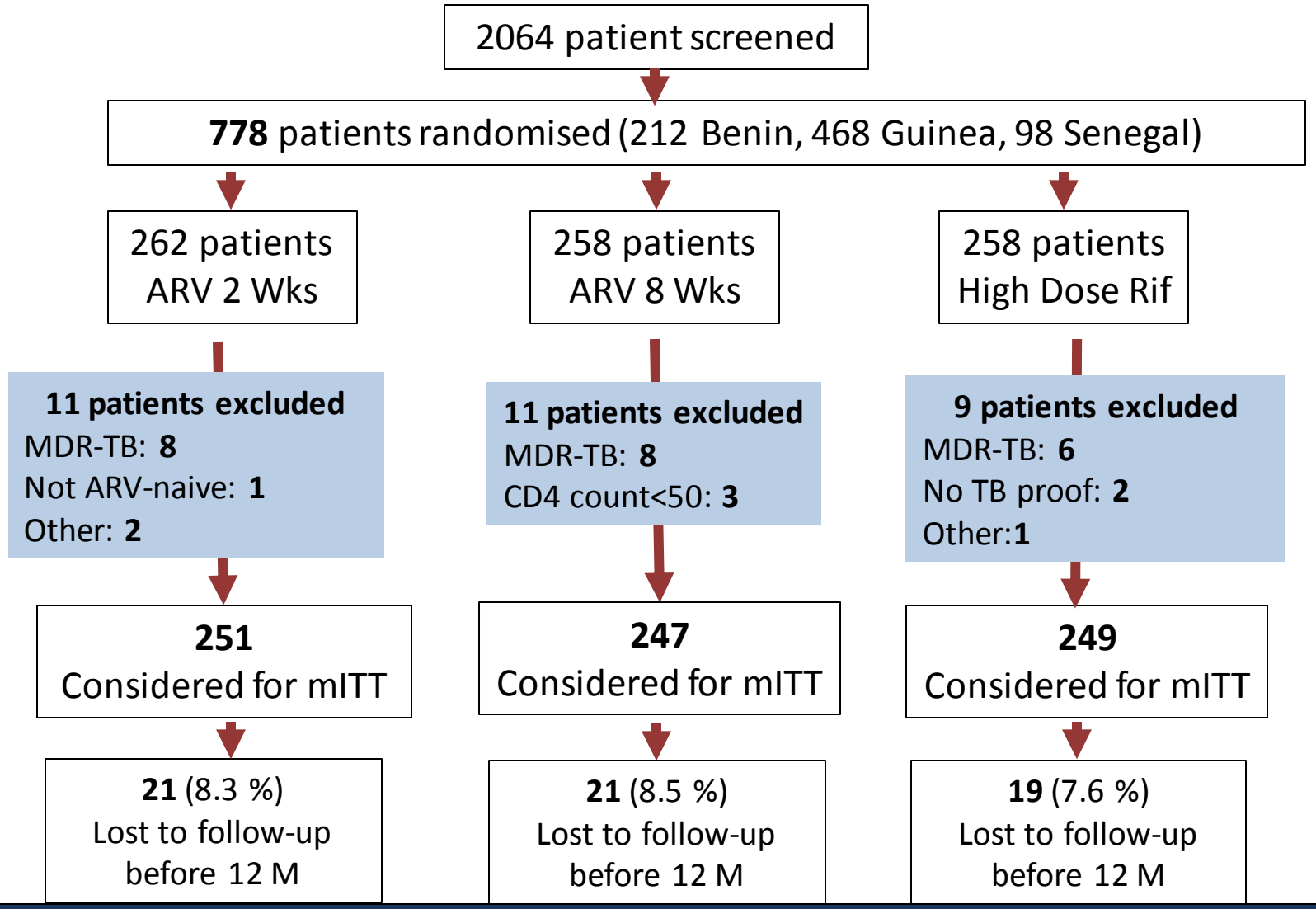
Results: CONSORT diagram



Results: mITT population Baseline (n=747)

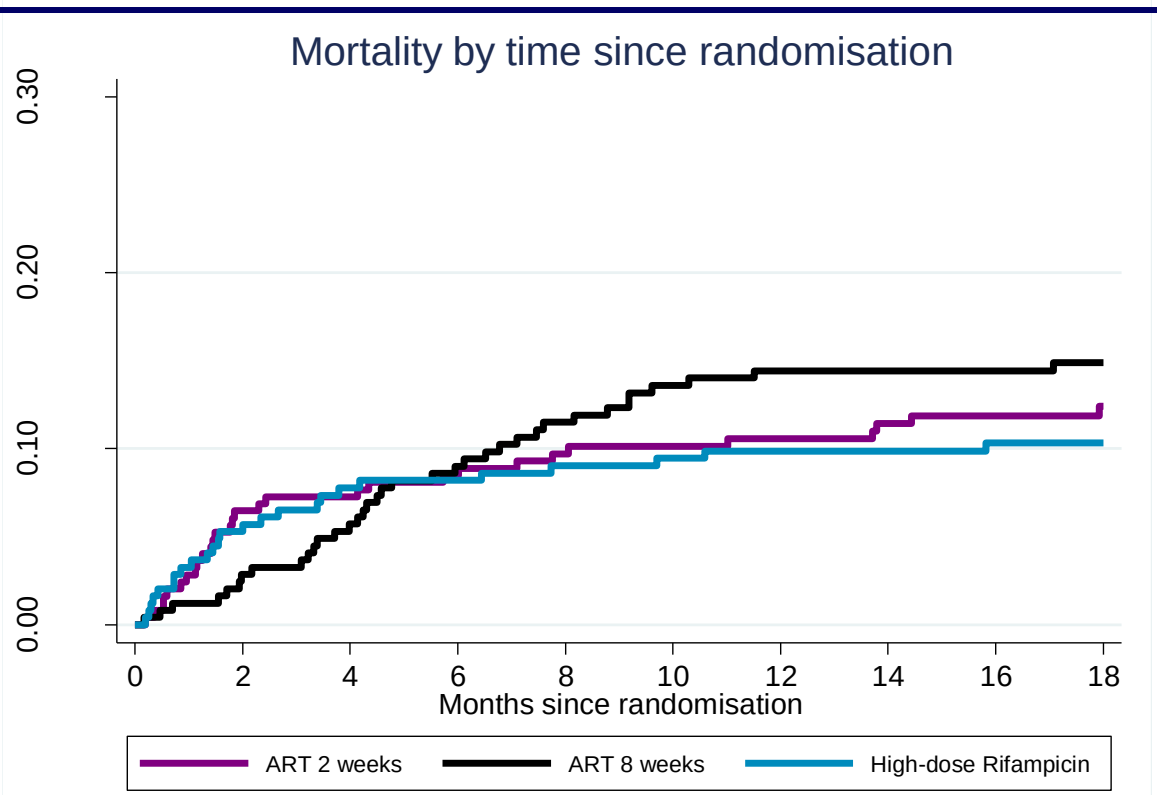
		ARV 2 WKs (n=251)	ARV 8 WKs (n=247)	High Dose Rif (n=249)
Country				
	Benin	71 (28%)	71 (29%)	70 (28%)
	Guinea	147 (59%)	147 (59 %)	145 (58%)
	Sénégal	33 (13%)	29 (12 %)	34 (14%)
Age (years)	mean (SD)	**36** (9.2)	**36** (10.1)	**35** (9.6)
Female	n (%)	**122** (49%)	**104** (42%)	**113** (45%)
BMI < 17	n (%)	**102** (41%)	**105** (43%)	**101** (41%)
Haemoglobin	Grade 3 & 4	**117** (47%)	**111** (45%)	**98** (40%)

Results: mITT population Baseline (n=747)

			ARV 2 WKs (n=251)	ARV 8 WKs (n=247)	High Dose Rif (n=249)
CD4 cell/mm3					
	[50-100[		**60** (24%)	**47** (19%)	**52** (21%)
	[100 – 200[	n (%)	**79** (31%)	**84** (34%)	**82** (33%)
	[200 - 350[		**76** (31%)	**86** (35%)	**78** (32%)
	>350		**36** (14%)	**30** (12%)	**37** (15%)
Smear status	neg[1]	n (%)	8 (3%)	16 (6%)	18 (7%)
	1+ or scanty	n (%)	116 (46%)	94 (38%)	94 (38%)
	2+	n (%)	52 (21%)	59 (24%)	68 (28%)
	3+	n (%)	75 (30%)	78 (32%)	69 (28%)
Culture or Xpert positive		n (%)	**231**(88%)	**222** (90%)	**228** (92%)
Zone score		4-6	147 (59%)	134 (55%)	140 (58%)

(1) All patients with smear negative results at the time of the randomisation, had a positive Xpert result

Results: Overall Mortality (n=747)

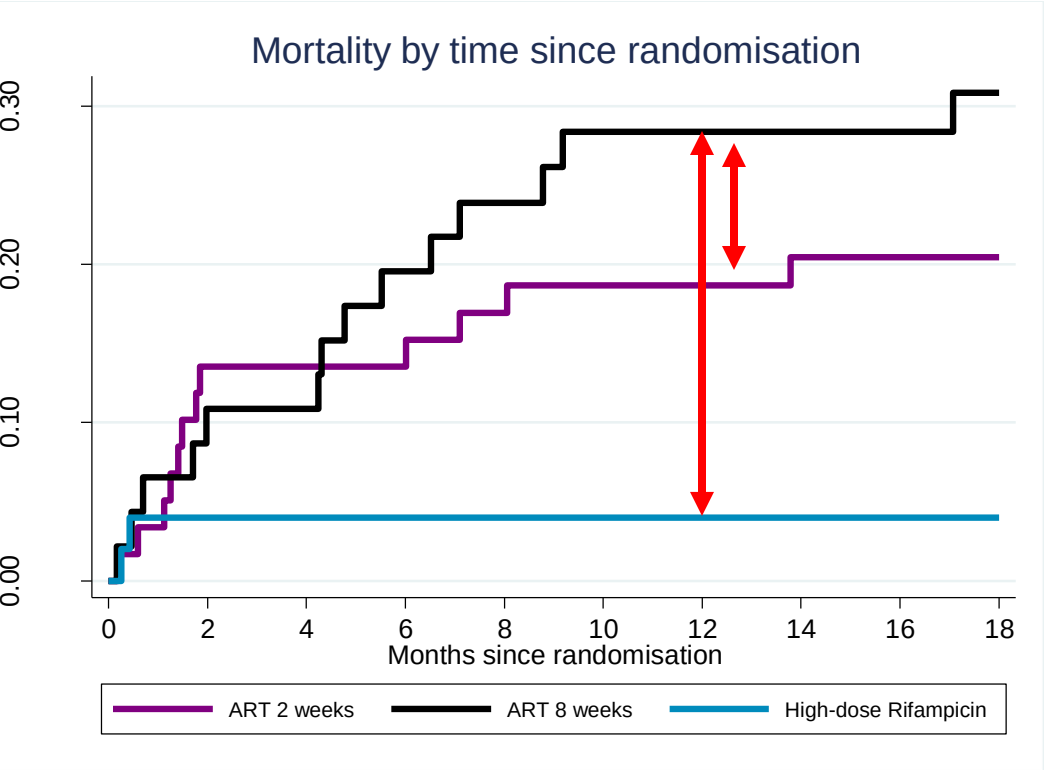


Interaction between treatment arm & CD4 level
p= 0.005

Treatment arm	n	Morality 2 M	Mortality 12 M	Mortality 18 M	HR*	CI 95%
Arm A – ARV 2 Wks	251	6.5 [4.0-10.3]	10.6 [7.3-15.1]	12.4 [8.8-17.3]	**0.75**	**0.45 – 1.24**
Arm B – ARV 8 Wks	247	2.9 [1.4-5.9]	14.4 [10.6-19.5]	14.9 [11.0-20.0]	/	
Arm C – HD RIF	249	5.3 [3.1-8.9]	9.9 [6.7-14.4]	10.3 [7.1-14.9]	**0.70**	**0.41 – 1.17**

* Cox regression adjusted on country – B is the reference arm

Mortality for patients with less than 100 CD4 (n= 159)



← ART 8 Weeks

← ART 2 Weeks

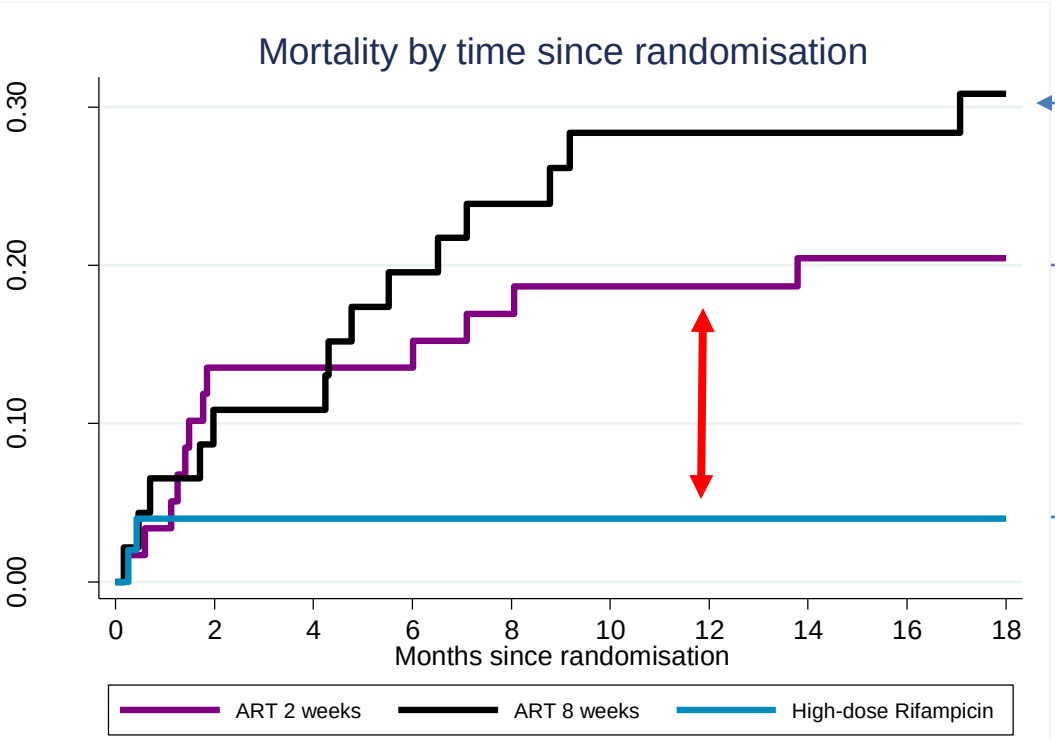
← High Dose Rifampicin

Cox regression adjusted on: country , CD4 interaction factor, sex, age, zone score & BMI and Haemoglobin level

Treatment arm	n	Morality 2 M	Mortality 12 M	Mortality 18 M	HR*	CI 95%
Arm A – ARV 2 Wks	251	13.6 [7.0-25.3]	18.7 [10.8-31.2]	20.4 [12.2-33.2]	**0.71**	**0.30 – 1.68**
Arm B – ARV 8 Wks	247	10.9 [4.7-24.2]	28.4 [17.6-43.8]	30.9 [19.6-46.5]	/	
Arm C – HD RIF	249	4.0 [1.0-15.1]	4.0 [1.0-15.1]	4.0 [1.0-15.1]	**0.13**	**0.03 – 0.59**

* B is the reference arm

Mortality for patients with less than 100 CD4 (n= 159)



ART 8 Weeks

ART 2 Weeks

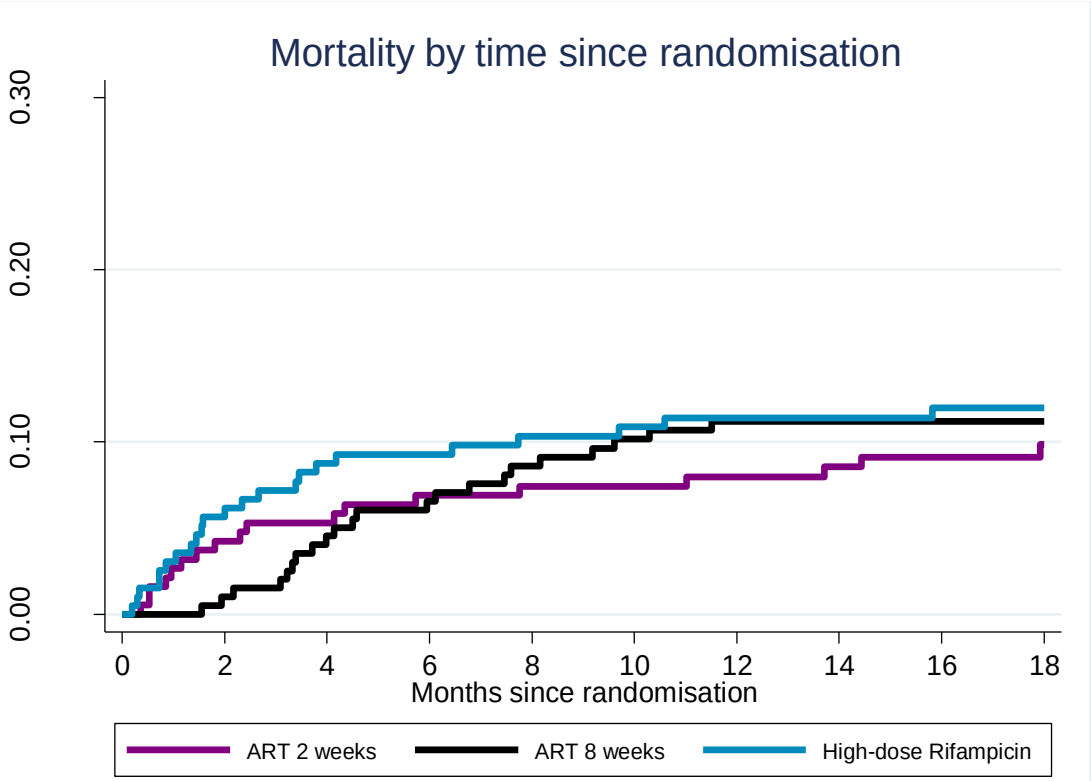
High Dose Rifampicin

Cox regression adjusted on country , interaction factor, sex, age, zone score & BMI

Treatment arm	n	Morality 2 M	Mortality 12 M	Mortality 18 M	HR*	CI 95%
Arm A – ARV 2 Wks	251	13.6 [7.0-25.3]	18.7 [10.8-31.2]	20.4 [12.2-33.2]	/	
Arm B – ARV 8 Wks	247	10.9 [4.7-24.2]	28.4 [17.6-43.8]	30.9 [19.6-46.5]		
Arm C – HD RIF	249	4.0 [1.0-15.1]	4.0 [1.0-15.1]	4.0 [1.0-15.1]	**0.20**	**0.05 – 0.91**

* A is the reference arm

Mortality for patients with more than 100 CD4 (n= 588)



Cox regression adjusted on country , interaction factor, sex, age, zone score & BMI

Treatment arm	n	Morality 2 M	Mortality 12 M	Mortality 18 M	HR*	CI 95%
Arm A – ARV 2 Wks	191	4.2 [2.1-8.3]	8.0 [4.9-12.9]	9.9 [6.3-15.3]	**0.71**	**0.42-1.19**
Arm B – ARV 8 Wks	200	1.0 [0.2-4.0]	11.2 [7.5-16.5]	11.2 [7.5-16.5		
Arm C – HD RIF	197	5.6 [3.2-9.9]	11.4 [7.7-16.8]	12.0 [8.1-17.5]	**0.71**	**0.42-1.20**

* B is the reference arm

TB and HIV treatment outcomes (2)

Treatment arm	ARV 2 Wks	ARV 8 Wks	HD RIF
CD4 count			
After 6 Month - Median (IQR)	340 (228-481)	331 (212-494)	307 (201-470)
After 18 month - Median (IQR)	423 (247-707)	432 (269-695)	390 (260-653)
HIV (Viral Load)			
Undetectable after 6 M (post ART*)	77%	66%	77%
Undetectable after 18 M (post Random)	75%	78%	78%
IRIS			
IRIS TB related	10 (4%)	5 (2%)	3 (1.2%)
Tuberculosis			
Culture positive at M2	34 (15.7)	28 (12.6)	34 (15.6)
Treatment failure	10 (4.0)	7 (2.8)	6 (2.4)
Recurrence	8 (3.7)	5 (2.4)	4 (1.8)
Unfavourable outcome (Failure, Recurrence, death during treatment)	40 (15.9)	38 (15.4)	30 (12.1)

Hepatotoxicity: ALAT grade, by trial arm

ALAT laboratory results pooled across visits 1-10

	Normal		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%	n	%
Overall	3635	**93.3**	241	**6.3**	8	**0.2**	3	**0.1**	1	**0.03**
ARV 2Wks	1263	**93.2**	88	**6.5**	3	**0.2**	**1[a]**	**0.08**	0	**0**
ARV 8Wks	1242	**92.2**	102	**7.6**	3	**0.2**	0	**0**	0	**0**
HD RIF	1263	**94.6**	67	**5.0**	2	**0.1**	**2[b]**	**0.2**	**1[c]**	**0.1**

a) **IRIS & Death**
b) **Grade 3 at visit 3 and normalisation**
c) **DRESS syndrome - B Hepatitis co-infection (grade 3, 4 and death)**

Conclusion

- More aggressive TB treatment using high dose of rifampicin, in addition to ARV treatment, could reduce TB/HIV mortality among co-infected TB/HIV patients with severe immunocompromised state.
- No evidence of an increased risk of hepatotoxicity with higher dosage of rifampicin (15mg/Kg) given daily for 2 months to TB/HIV patients
- More explorations are needed to better explain these results and PK/PD results will be important to consider
- The results of the RAFA trial provoke an interesting area of further research

Acknowledgements

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- **Data Monitoring Committee:** K Fielding (chair), C Perronne, C T Ndour
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