Latest TB Science
CROI 2021

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Disclosures

Type of affiliation / financial interest	
• Receipt of grants/research supports:	• To my unit from Janssen, Merck, Viiv and Gilead
• Receipt of honoraria or consultation fees:	• To me from Janssen, Merck, Viiv and Gilead, Thera
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• Stock shareholder:	• None
• Spouse/partner:	• None

Content

Short Course TB therapy

High dose rifampicin in TBM

Effect of High dose rifampicin on ARVs

ARVs and Rifapentine in LTBI

Contact Tracing

Targeted TB Testing

Can TB Treatment be Made Easier?

TB treatment is Complex

–at least 6 months and multiple pills

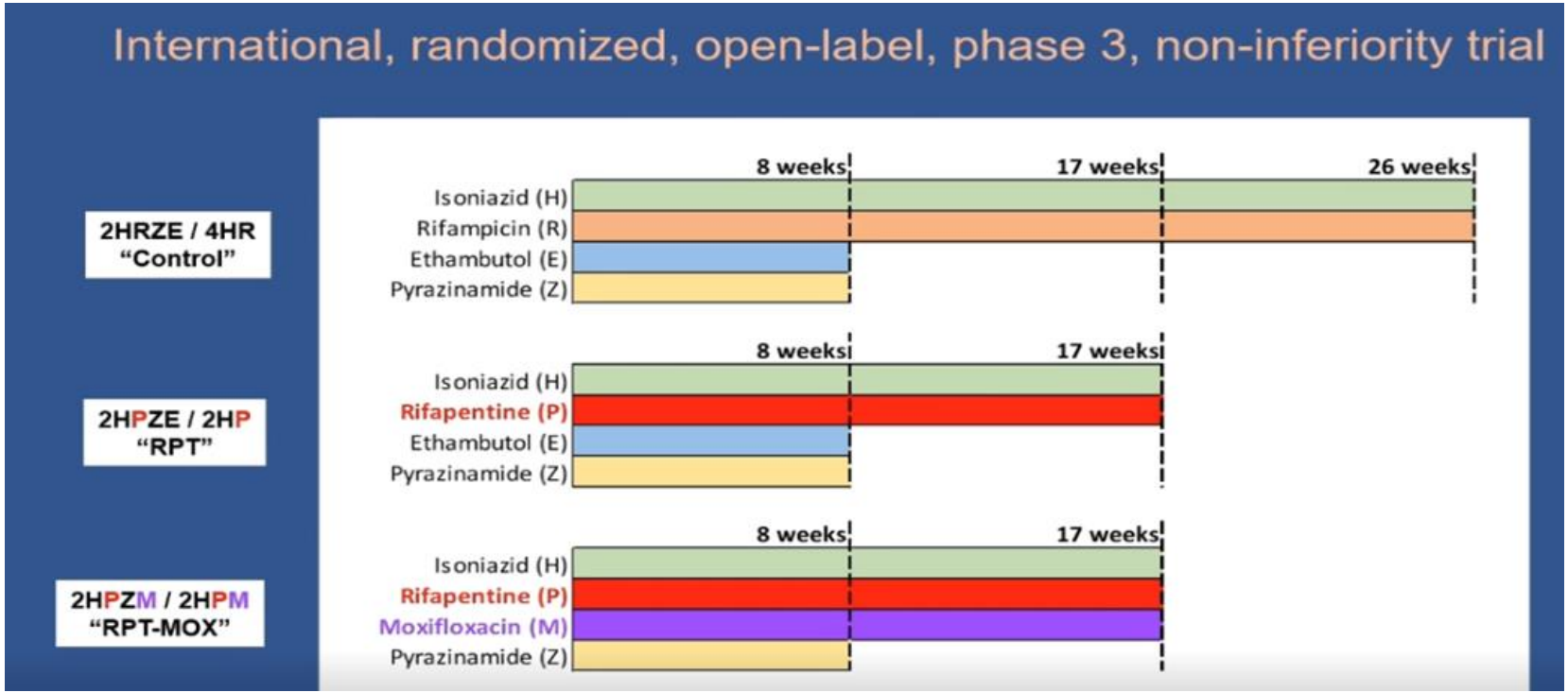
Shorten TB treatment to 4 months

- OFLOTUB study (gatifloxacin) **FAILED**
- RIFAQUIN study (moxifloxacin/rifapentine) **FAILED**
- ReMoxTB study (moxi instead of E or H) **FAILED**

- **S31/A5349 (Hi Dose RPT/INH/PZA/MOX) Success!**

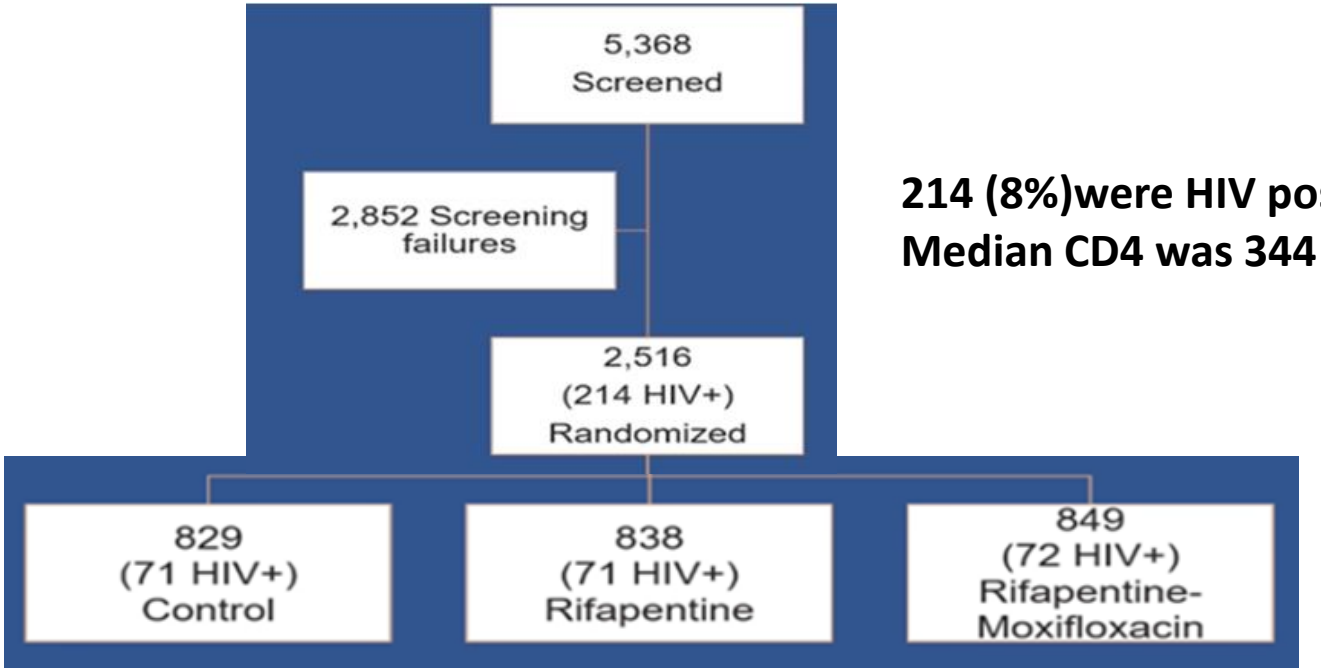
But does it work in HIV /TB?

Study 31/A5349
Shorten TB Treatment to 4 months



Pettit et al CROI 2021

Study Population



214 (8%)were HIV positive
Median CD4 was 344

Results-Baseline

Microbiologically Eligible Population Total n=2343	HIV-seropositive N=194	HIV-negative* N=2148
Median (IQR) age, years	36 (30 - 43)	30 (24 - 41)
Male sex	120 (62%)	**1549 (72%)**
Race		
Asian	0 (0%)	268 (12%)
Black or African American	**180 (93%)**	1495 (70%)
White	2 (1%)	34 (2%)
More than one race	12 (6%)	346 (16%)
Missing	0 (0%)	5 (0.2%)
Median (IQR) baseline BMI, kg/m^2	19 (17 - 22)	19 (17 - 21)
Cavitary Disease	139 (72%)	1563 (73%)
Current smoking	41 (21%)	500 (23%)
Diabetes Mellitus	1 (0.5%)	**76 (3%)**

Efficacy and Safety

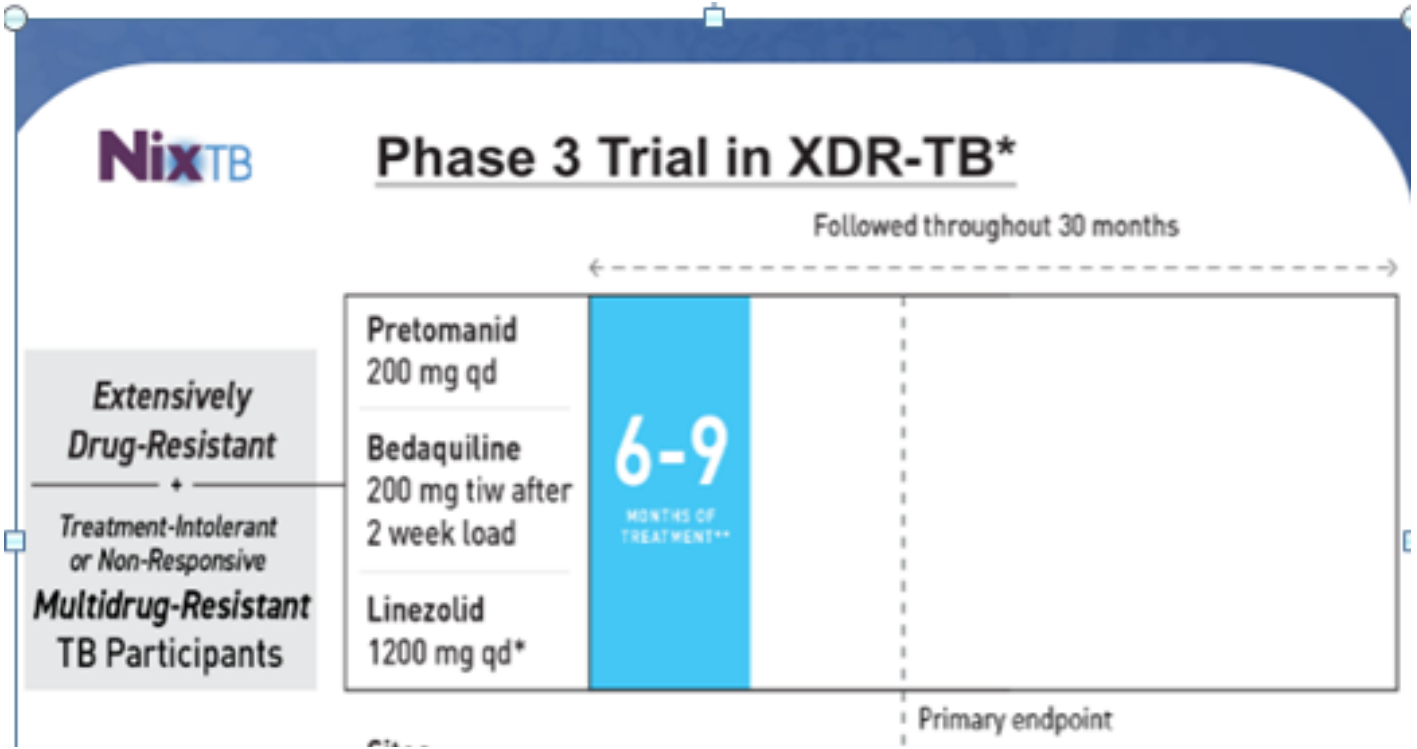
Efficacy outcomes (% favorable)	Control	Rifapentine Moxifloxacin	Rifapentine	Total
Microbiologically eligible	50/64 (78%)	**53/62 (85%)**	48/68 (71%)	151/194 (78%)
Assessable	50/59 (85%)	**53/58 (91%)**	48/65 (74%)	151/182 (83%)
Per-Protocol 95	**44/45 (98%)**	43/45 (96%)	41/52 (79%)	128/142 (90%)

Safety Outcomes	Control	Rifapentine Moxifloxacin	Rifapentine	Total
Total safety population	70	72	71	213
Primary Safety Outcome (Grade 3-5 AEs on treatment)	**15 (21%)**	10 (14%)	12 (17%)	37 (17%)
SAEs during treatment	**7 (10%)**	2 (3%)	6 (8%)	15 (7%)
Deaths	2 (3%)	0 (0%)	**3 (4%)**	5 (2%)

Study 31-Conclusions

- 4 month Rif-Moxi combination non-inferior to standard 6 month treatment
- Combination Rif –Moxi efficacious in HIV subgroup
- **Major milestone in TB Rx**

Short Course
MDR/XDR Treatment



Results

- 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT population (MITT population = 107)
- All surviving participants, except 1 withdrawal, completed the full course of therapy
- At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% mITT)
- After the primary endpoint one participant relapsed 15 months after treatment and one was lost to follow up
- Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% mITT) independent of sex or HIV status.

Howell et al CROI 2021

High Dose Rifampicin in TBM

- Should we use higher doses of rifampicin than we do in standard treatment?
- Rifampicin concentration may be low in the CNS.
- Data suggests link between dose and survival
- In Pulmonary TB high dose rifampicin reduces time to culture conversion in sputum

Study Design

Inclusion Criteria

1. Suspected TB meningitis

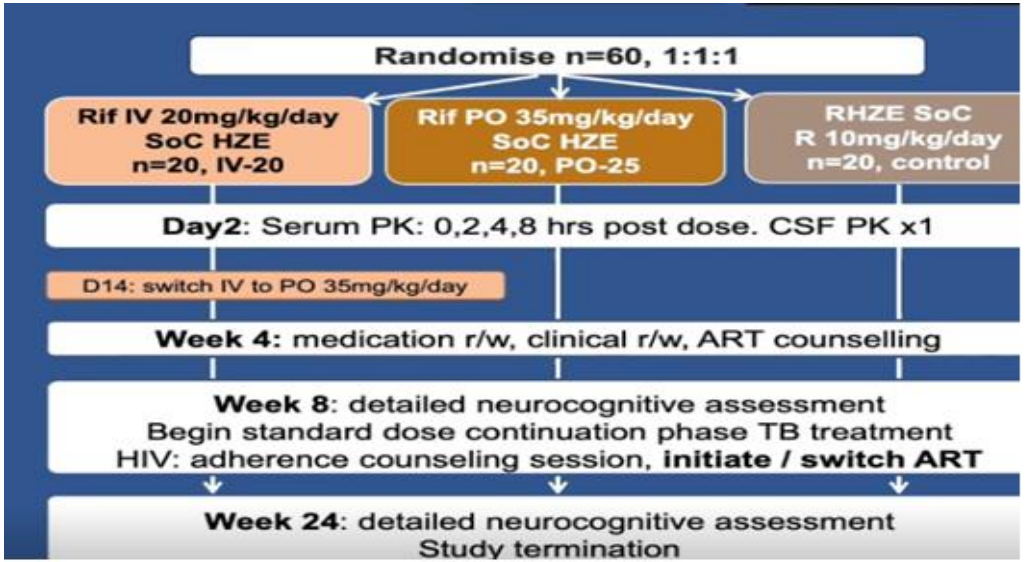
AND, EITHER

- CSF glucose to plasma ratio <50%, or absolute CSF glucose <65mg/dl or 3.6 mmol/L

OR

- Positive CSF AFB smear or Xpert Ultra

Study Design

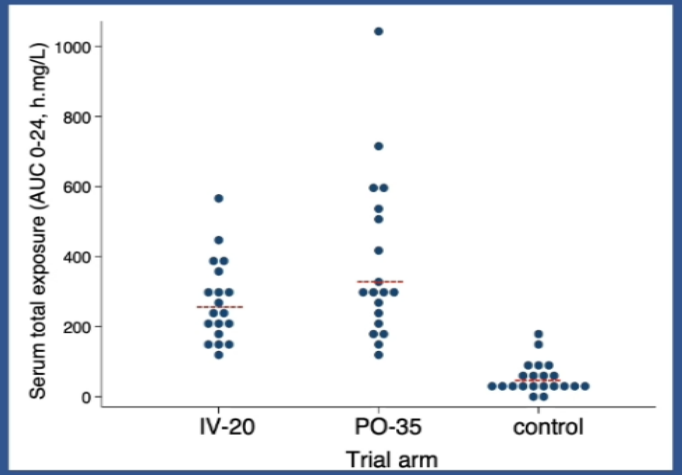


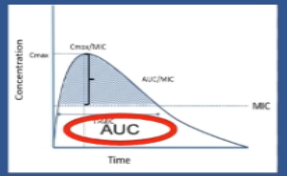
HIV Pos=55/60 patients
Median CD4 50

Cresswell et al CROI 2021

Drug Exposure-Serum

Rifampicin total serum exposure - AUC_{0-24}

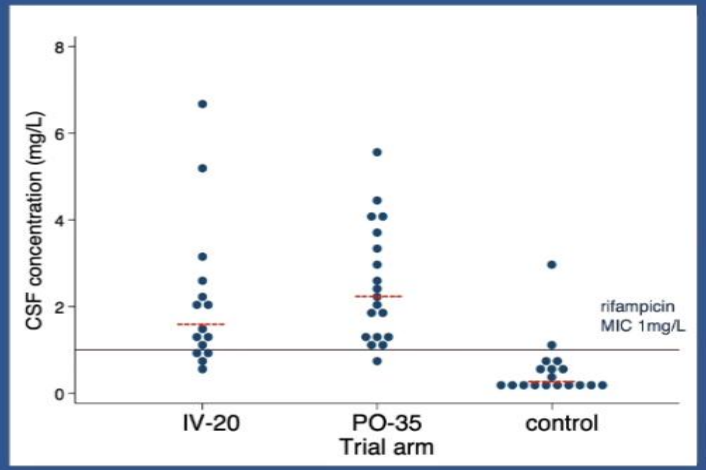




AUC_{0_24} (h·mg/L) [e]	IV-20	PO-35	control	P value
n observations	19	19	21	
Geometric mean (95% CI)	249 (202 - 306)	327 (248 - 430)	42.9 (29.2 – 63.0)	<0.001
Ratio to control	5.80	7.62	1 (ref)	
P value [d]	<0.001	<0.001	-	

Drug Exposure-CSF

Rifampicin CSF concentration - C_{CSF}

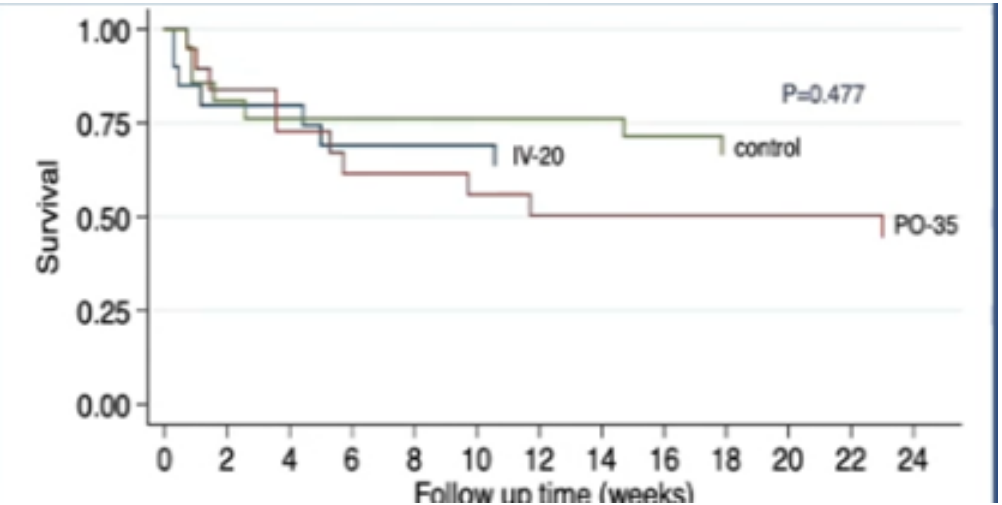


C_{CSF} (mg/l)	IV-20	PO-35	Control	P value
n observations	15	19	18	
Geometric mean (95% CI)	1.74 (1.20 - 2.53)	2.17 (1.64 - 2.86)	0.27 [h] (0.17 - 0.45)	0.058
Ratio to control	6.44	8.00	-	
P value	<0.001	<0.001		
n (%) with detectable CSF level	15 (100)	19 (100)	8 (44)	<0.001
n (%) with concentration above rifampicin MIC[1] (1 mg/L)	14 (93.3%)	18 (94.7%)	2 (11.1%)	<0.001

1. Kasule GW. *BMC Infectious Diseases* 2016; **16**: 173

Outcomes/Conclusions

K-M curve Time to death



- **In PO-35 and IV-20 groups >90%**
- **had CSF levels above MIC**

- **No Excess toxicity**

- **But NO difference in clinical outcome**
- **–but not powered to do this**

What is the Effect of High dose Rifampicin on ARVs?

Efavirenz

Number and % compared to target minimum threshold (of 1 mg/L)			
	Arm 2A EFV + RIF 35 n=15	Arm 2B EFV + RIF 10 n=19	Fisher's Exact P-value
EFV mid-dose concentrations			
<1 mg/L, n(%)	1 (6.7)	1 (5.3)	P>0.999
≥1 mg/L, n(%)	14 (93.3)	18 (94.7)	

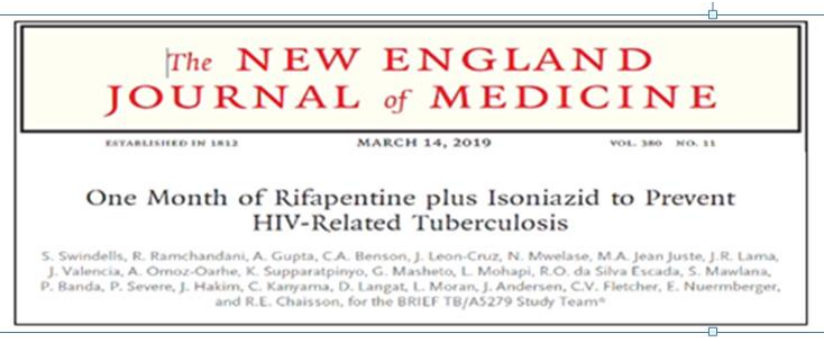
Dolutegravir 50mg BD

Number and % compared to target minimum threshold (of 0.064 mg/L)			
	Arm 1A DTG+RIF 35 n=25	Arm 1B DTG+ RIF 10 n=21	Fisher's Exact P-value
DTG C_0			
<0.064 mg/L, n(%)	4 (16.0)	1 (4.8)	P=0.35
≥0.0.64 mg/L, n(%)	21 (84.0)	20 (95.2)	

Still had similar viral suppression

Short Course LTBI

Now One month of therapy is Possible

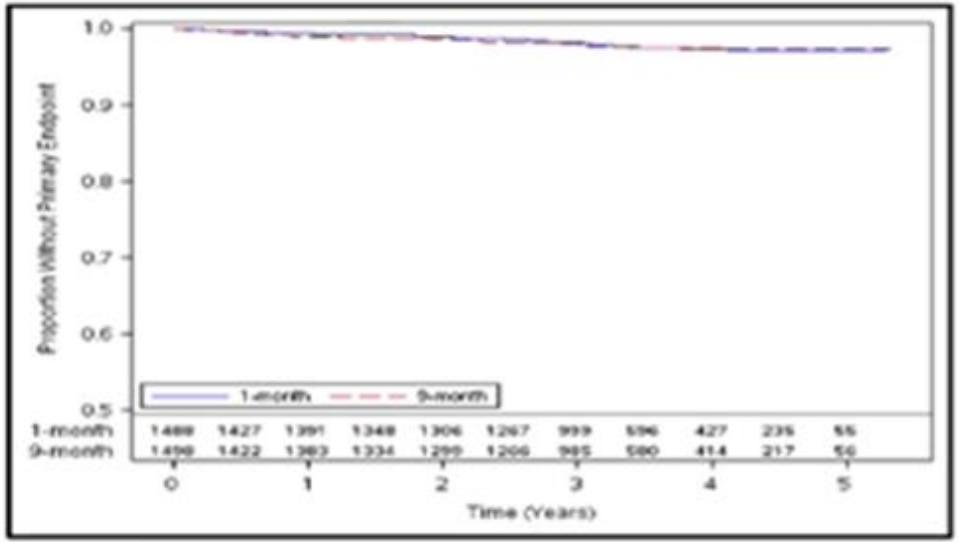


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2019 VOL. 380 NO. 11

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

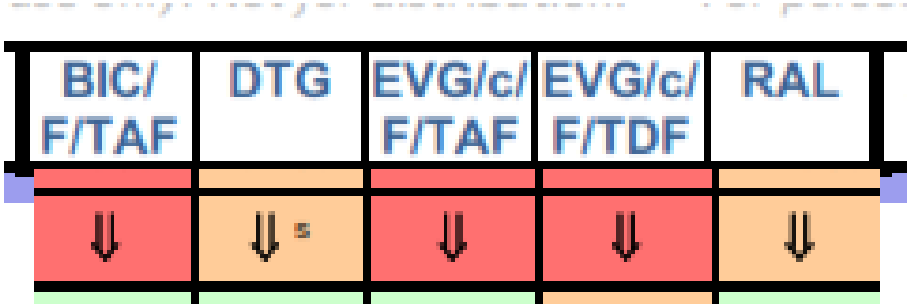
S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

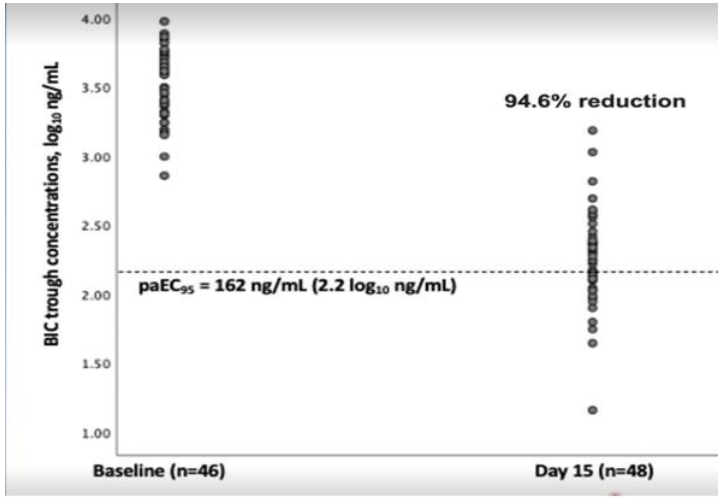


But what about drug Interactions with ARVs?

INSTIs and Rifapentine

What The Database predicts
To INSTI levels with Rifapentine

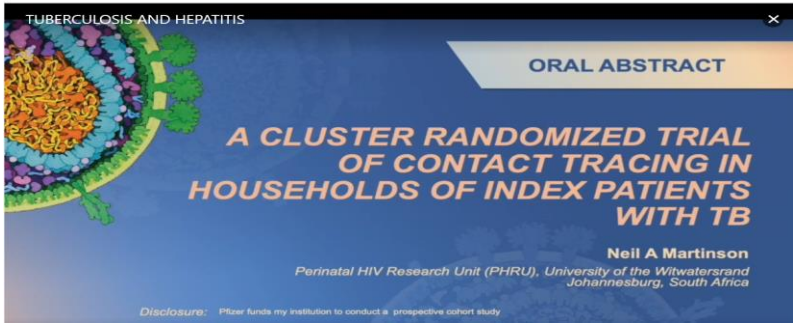




Bictegravir concentrations with Rifapentine
..And 2/16 patients had viral rebound from day 15 to day 30

H-Y Sun et al Croi 2021

What is the best way of Contact Tracing of TB?



Two different Strategies

Standard of Care

Referral Letters for all HH members

M1 telephone check-in visit

OR

Intensive Contact Tracing

Home-based Universal testing

- TB disease: sputum: Xpert and Culture
- TST
- HIV counselling and testing

Immediate referral:

- TB treatment
- ART

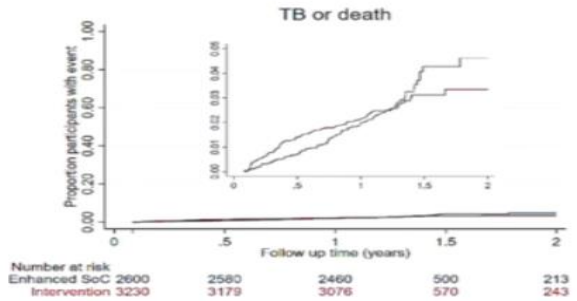
Home initiation IPT

M3 check-in visit

No Difference in Outcome

Trial outcomes at 15 Months

	Referral Letter	Int. Contact Tracing	Hazard ratio (95% CI)
Primary			
Contacts diagnosed with TB	31/2551 0.92/100py	51/3188 1.24/100py	1.33 (0.83, 2.16)
Contact deaths	49/3961 (1.2%)	42/4242 (1.0%)	0.72 (0.47, 1.10)
TB or death	**80/2600 (3.1%)**	**93/3230 (2.9%)**	**0.90 (0.66, 1.24)**



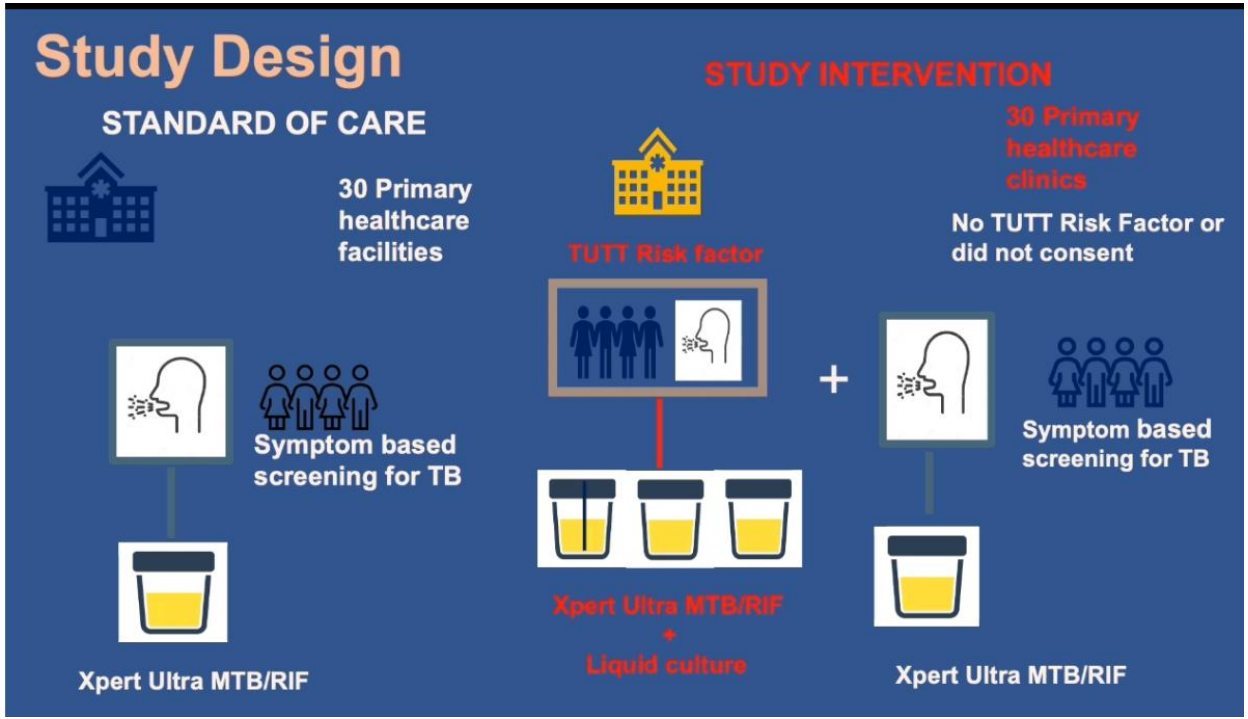
Standard of Care (Letters to Contacts) saves on valuable resources used in the Intensive Strategy In a SA setting

Targeted UniversaL Testing For TB in Clinics

- To ascertain if augmenting routine symptom-based sputum testing with Targeted Universal Testing for TB (TUTT) in clinics increased the number of patients diagnosed with TB per month by 25%
- Targeted clinic attendees:
  - **HIV+**
  - **Close contact <1 year**
  - **Prior TB <2 year**

Trial Outcome: TB patients diagnosed per month per clinic

TARGETED UNIVERSAL TESTING FOR TB IN CLINICS



Labinah et al CROI 2021

Results

The yield of universal risk-factor based testing for TB was high in the three targeted risk groups:

- HIV-infected: 5%
- TB contacts: 8%
- Prior TB: 12%

Clinics are diagnosing 8% fewer patients with TB year on-year under the standard of care

The TUTT intervention resulted in a 17% net increase in TB cases diagnosed per clinic per month as compared to the standard of care clinics.

Conclusions

- We now have 4 month Treatment for Drug sensitive TB and 6 months for MDR/XDR.
- High Dose Rifampicin improves CNS concentrations and trials are planned for clinical benefit.
- High dose rifampicin lowers DTG levels without effecting clinical outcomes.
- Rifapentine should not be used with Bictegravir.
- Simple Contact tracing of contacts is as efficient as intense methods and saves on resources.
- Targeted TB Testing Improves Yields.