Eight weeks safety results of high-dose Rifampicin in HIV-Tuberculosis co-infected patients in Uganda: RIFAVIRENZ-ANRS 12292 Trial.

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BACKGROUND

- A 6-month WHO recommended TB treatment regimen consist of 4 drugs: Rifampicin (10mg/Kg) + Isoniazid(H) + pyrazinamide(Z) + ethambutol(E).
- Rifampicin(R) is a highly bactericidal and cornerstone drug.
- Optimization of R doses may shorten Tuberculosis (TB) treatment to lower than the current 6 months
  - Linear increase of the bactericidal effect with dose
  - Non-linear increase of the pharmacokinetic parameters with dose
  - Safety of R doses of up to 35mg/kg among HIV negative TB patients
- No data exists in HIV-TB co-infected patients on anti-retroviral therapy (ART).

OBJECTIVES

The RIFAVIRENZ trial compared the pharmacokinetic parameters of efavirenz (EFV) in same HIV-TB co-infected patients with and without anti-TB treatment using rifampicin (R) at 10 or 20mg/Kg/day and EFV at 600 or 800mg/day during the first 8 weeks of treatment in HIV-TB co-infected patients.

We present here the safety of high dose R in co-administration with EFV-based ART in HIV-TB co-infected patients by week-8 of TB treatment.

METHODS

- Phase-2, randomized, open-label therapeutic trial (NCT01986543)
- Sample size of 28 patients per arm calculated for the primary pharmacokinetic endpoint

Eligibility criteria

Inclusion
- ≥ 18years
- New TB case XpertMTB+
- HIV+ ART naïve
- Negative pregnancy test and physical contraception
- >35Kg
- Written informed consent

Exclusion
- R resistance
- Treatment of opportunistic infection
- Karnofsky score < 80%
- Transaminase > 5xULN
- Grade 4 laboratory/clinical sign
- Treatment interfering with R or EFV
- Contraindication to R or EFV
- Patient unable to give consent

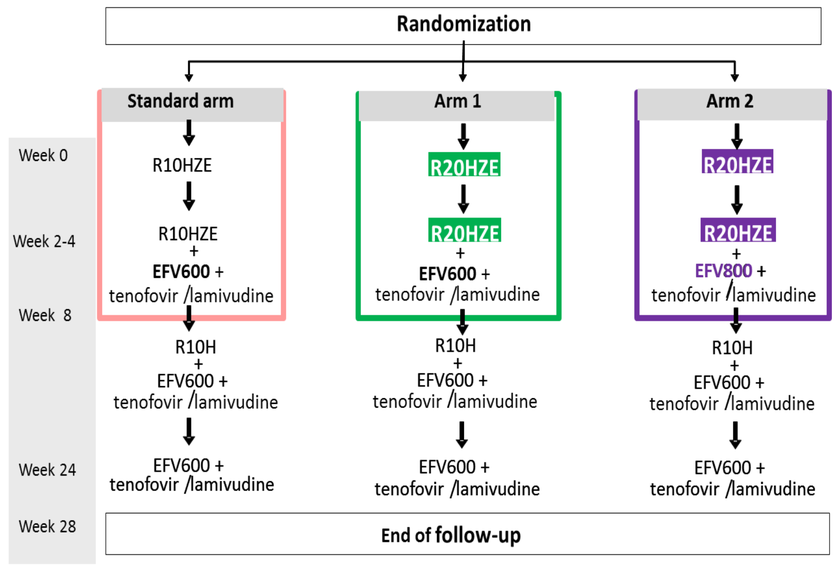

Figure 1. Trial Design

- ART was initiated at weeks 2 and 4 for patients with CD4<50 or ≥50 cells/ml respectively.
- At week 8: All patients were switched to R-10mg/kg and EFV 600mg.

Safety Monitoring

- Hepatitis B (HBV) surface Ag and hepatitis C antibodies (HCV) at baseline
- Weekly clinical assessments
- Full blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin monitoring after 2, 4 and 8 weeks
- Adverse event (AE) assessed using the DAIDS severity grading scale
- Adverse event of specific interest
  - Grade 3 (≥ 5xULN) and 4 (≥ 10xULN) increase of ALT or AST
  - Grade 2 or more neuropsychiatric AE : greater than minimal interference with usual social & functional activities

RESULTS

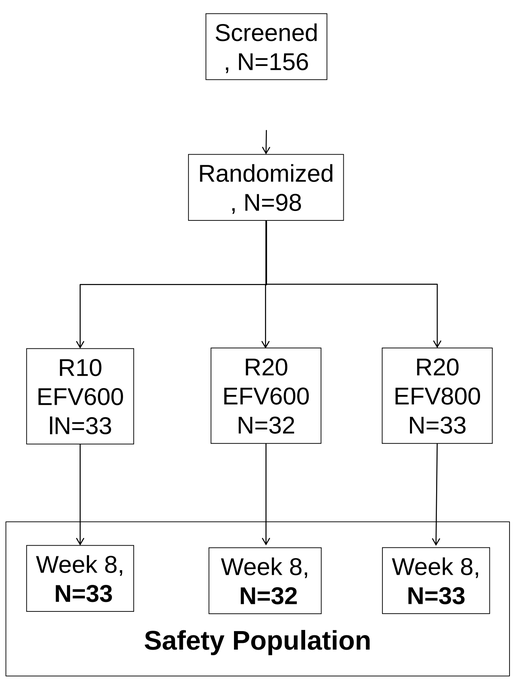

Figure 2: study profile

Table1. Baseline characteristics

	R10 EFV600 N=33	R20 EFV600 N=32	R20 EFV800 N=33
Males, n (%)	29 (87.9)	23 (71.9)	20 (60.6)
Age in years, median [IQR]	34.1 [29.6-38.1]	33.7 [28.3-38.1]	32.3 [27.8-43.1]
Weight in kg, median [IQR]	51.9 [49.2-56.0]	53.8 [48.4-59.1]	54.1 [50.9-58.1]
Chest cavities, n (%)	14 (42.4)	17 (53.1)	12 (36.4)
CD4 in cell/mm^3, median [IQR]	120 [66-252]	219 [70-357]	144 [86-367]
HIV-1 RNA in log copies/mL, median [IQR]	5.5 [4.6-5.8]	5.1 [4.5-5.7]	5.1 [4.8-5.9]
ALT*, median [IQR]	22 [15-29]	19 [13-37]	19 [11-35]
AST*, median [IQR]	37 [28-58]	27 [20-65]	37 [26-52]
HBV surface Antigen, n (%)	2 (6.1)	1 (3.1)	1 (3.0)
Anti-HCV antibody, n (%)	1 (3.0)	0	0

*ALT normal range: Male= 0-45; Female= 0-34
*AST normal range: Male= 0-35; Female= 0-31
IQR: interquartile range

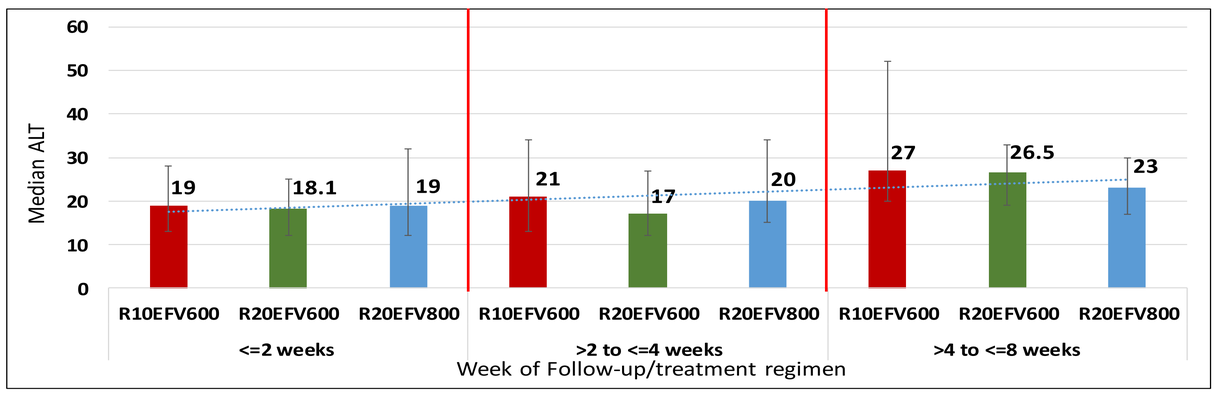

Figure 3. Evolution in median ALT per treatment regimen during first 8 weeks

SAFETY RESULTS

15 patients, 5 from each arm had grade 3 or 4 AE: 2 leading to death unrelated to treatment

Table 2. Hepatic and neuropsychiatric adverse events

	R10 EFV600 N=33	R20 EFV600 N=32	R20 EFV800 N=33
Grade 3 or 4 increase ALT or AST, n(%)	2 (6.1)	2 (6.2)	2 (6.1)
ALT grade ≥3, n	2	2	2
AST grade ≥3, n	2	2	2
Hyperbilirubinaemia grade ≥3, n(%)	2 (6.1)	3 (9.4)	0 (0)
Neuropsychiatric, grade 2, n(%)	1 (3.0)	1 (3.1)	2 (6.2)*

* p=0.780

- 2 patients from each arm had grade 3 or 4 increases in ALT or AST within the first 8 weeks:
  - 1 before ART initiation and 1 during co-administration for both high dose R arms
  - 2 before ART initiation for the control arm
- 2 patients had their treatment arm changed from 20mg/kg-10mg/kg of R dose
- No grade 3 or 4 neuropsychiatric AEs

Table 3. Non-hepatic grade 3 & 4 adverse events

	R10 EFV600 N=33	R20 EFV600 N=32	R20 EFV800 N=33
Hyponatraemia	1*	0	0
Leukopenia	0	1	0
Respiratory distress	0	1	0
Sepsis	0	0	1*
Thrombocytopenia	4	1	3
Total	5	3	4

* Leading to death

CONCLUSIONS

- First study with 20 mg/kg R and EFV in HIV-TB co-infected patients.
- Co-administration of a double-dose of rifampicin with efavirenz (600 or 800mg) among HIV/TB co-infected patients was well tolerated with very few severe transaminitis and no severe neuropsychiatric disorders.

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