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TB Outcomes with ATV/r and Two Rifamycin-containing TB Regimens In HIV/TB Co-Infected Patients in South India

Jeffrey D. Jenks[*1], N. Kumarasamy[2], C. Ezhilarasi[2], S. Poongulali[2], P. Ambrose[2], T. Yepthomi[2], C. Devaraj[2], Constance A. Benson[1]
[1]University of California, San Diego, La Jolla, CA, [2]YRG Centre for AIDS Research and Education, Chennai, India

Jeffrey D. Jenks, MD, MPH
University of California San Diego
200 Arbor Drive, MC 8208
San Diego, CA 92103, USA
E-mail: jjenks@ucsd.edu

Background

- Rifamycins are cornerstones of anti-tuberculous therapy (ATT)
- In HIV/TB co-infection, rifampicin lowers the serum levels of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Rifabutin (RBT) induction of CYP3A4 and other isoenzymes is less than with rifampin (RIF), and is the recommended rifamycin in ATT in HIV-infected persons on PI-based ART.
- In healthy persons, therapeutic levels of RBT when dosed with ART were achieved with intermittent dosing, but in studies in HIV-infected individuals levels have been more variable.

Objective

To compare TB treatment outcomes between those treated with an atazanavir/ritonavir (ATV/r) ART regimen plus 150mg of daily or thrice weekly rifabutin ATT regimen to those treated with an NNRTI-based ART regimen with daily rifampicin

Hypothesis

HIV/TB co-infected patients treated with a boosted ATV/r regimen coupled with thrice weekly rifabutin-containing ATT would have less favorable TB outcomes than those receiving ATV/r with ATT with daily RBT or NNRTI-based ART plus ATT with daily rifampicin

Methods

- HIV/TB co-infected adults enrolled in care between 1996 and 2014 at the YR Gaitonde Centre for AIDS Research (YRG CARE) Medical Center in Chennai, India
- On first-line NNRTI-based ART or started on NNRTI-based ART at time of enrollment and underwent symptom-based screening for TB, and if pulmonary TB suspected, had a CXR and AFB smear (if producing sputum)
- If ART failure was suspected patients were switched to second-line ART with ATV/r + NRTI backbone
- For patients on NNRTI-based ART, ATT included daily RHZE for 2 months, followed by INH plus daily RIF for 4-7 months. If on ATV/r-based ART, thrice-weekly RBT was substituted for daily RIF until June 2013, when intermittent RBT was changed to daily RBT according to new guidelines
- Most TB cases were diagnosed based on clinical and radiographic findings
- Patients were considered "cured" if completed ATT with resolution of clinical signs, symptoms and CXR findings; "failed" if either clinically improved and then worsened, or never improved on ATT; "relapsed/recurred" if they were deemed cured and subsequently had worsening clinical or CXR findings

Table 1: Baseline Demographics

Patient Characteristic	RBT+ (n =292)	RIF+ (n = 3740)	p Value
Sex, %			
Male	232 (79.5)	2759 (73.8)	0.03
Female	60 (20.5)	981 (26.2)	0.03
Hijra	0 (0)	3 (0.1)	0.63
Age at treatment, year median, [IQR]	42 [37-47]	42 [37-47]	NS
Hx of prior TB, %	125 (43%)	0 (0%)	<0.001
TB characteristics, %			
Pulmonary	273 (93.5)	3356 (89.7)	0.02
Extra-pulmonary	19 (6.5)	205 (5.4)	0.46
Both	0 (0%)	179 (4.7)	<0.001

Table 2: TB treatment outcomes by ATT regimen

Outcome	RBT Group+ Group (N, %)	RIF+ Group (N, %)	p Value	Relative Risk RBT+ vs. RIF+ (95% CI)
No. of subjects	292	3740		
Cured	179 (61.3)	2238 (59.8)	0.50	
Relapse/ Recurrence	19 (6.5)	768 (20.5)	<0.001	0.32 (CI 0.20 – 0.49)
All-cause death	7 (2.4)	197 (5.3)	0.04	0.45 (CI 0.22 – 0.96)
TB-related	1 (14.3)	42 (21.3)	0.67	
Other	6 (85.7)	155 (78.7)	0.59	
Unknown	17 (5.8)	3 (0.08)	<0.001	
Transferred out/lost to follow-up	70 (24.0)	534 (14.3)	<0.001	

Results

Of the 4032 patients with HIV/TB evaluated, 3740 (92.8%) were on NNRTI-based ART with RIF (RIF+) and 292 (8.2%) were on ATV/r plus RBT (RBT+). Of those in the RBT+ group, 118 (40.4%) were dosed with thrice-weekly and 174 (59.6%) with daily RBT

RBT+ vs. RIF+:
- No difference in clinical cure rates
- Lower recurrent/relapse rate in RBT+ group (RR 0.32, 95% CI 0.20-0.49)
- Lower rate of all-cause mortality in RBT+ group (RR 0.46, 95% CI 0.22-0.96)

Intermittent RBT+ vs. Daily RBT+:
- Decreased clinical cure rate in intermittent RBT+ group (RR 0.60, 95% CI 0.48-0.75)
- No difference in rates of clinical recurrence/relapse and all-

Limitations

- TB diagnosed primarily on clinical grounds
- CD4 counts, HIV VL, HIV genotypes not routinely obtained, limiting further analysis
- More patients lost to follow-up or with unknown outcomes in RBT+ group vs. RIF+ group and intermittent RBT+ group versus daily RBT+ group

Conclusions

- PI-based ART and ATT with RBT was associated with lower rates of clinically determined TB treatment failure, recurrence/relapse, all-cause mortality vs NNRTI-based ART and ATT with RIF. This was unexpected given that more patients in the RBT group were on second-line ART and had been treated for prior episodes of TB. However, limitations of our study may have biased our findings as a higher proportion of the RBT group were transferred out or lost to followup.
- ATT with daily RBT was associated with better TB treatment outcomes compared to intermittent RBT
- The limitations of our study warrant further studies to evaluate TB treatment outcomes in HIV/TB co-infection with RBT-based ATT.

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