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Three Months of Weekly Rifapentine + INH for *M. tuberculosis* Infection in HIV-infected Persons

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ACTG, IMPAACT, and the TB Trials Consortium for the PREVENT TB Study (TBTC Study 26/ACTG 5259)

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Background

- 3 months of once-weekly rifapentine 900 mg + INH 900 mg under direct observation (3HP) is at least as effective as 9 months of daily self-administered INH (9H) in HIV-uninfected persons. [1]
- There are limited data on the effectiveness of 3HP in HIV-infected populations. [2]

Methods

Study design: prospective, randomized, open-label non-inferiority trial of 3HP (directly observed) vs. 9H (self-administered). Participants were followed 33 months from enrollment. To assess tolerability and effectiveness in HIV+ persons, enrollment into the PREVENT TB study was extended for HIV+ persons beyond Feb 2008, to Dec 2010.

Inclusion criteria: HIV + persons ≥2 years old who were tuberculin skin test positive or close contacts of TB cases. Could not receive antiretroviral therapy (ART) until > 90 days after enrollment.

Endpoint: culture-confirmed TB in adults and culture-confirmed or clinical TB in children. All cases confirmed by 3-member expert panel

Non-inferiority margin: 0.75%.

Study locations: United States, Brazil, Spain, Peru, Canada, Hong Kong

Enrollment dates: June 2001 - December 2010.

Follow-up: through September 30, 2013

Statistical analysis: categorical variables: Fisher's exact test
continuous variables: rank-sum test

Results

Table 1. Study populations.

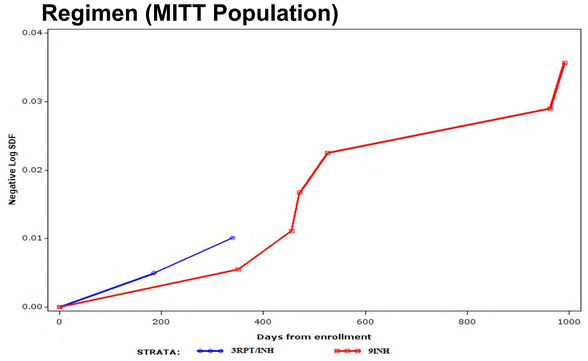
Study population	Assessment	3HP	9H
Enrolled		208[a]	195[b]
Enrolled + eligible (MITT)	Effectiveness	206	193
Per protocol (PP)	Efficacy	183	123
Received ≥ 1 dose	Safety	207	186

a. 4 persons < 18 years old; b. 1 person < 18 years old

Table 2. Characteristics of the MITT population.

Characteristic	3HP N=206	9H N=193	P-value
Median age-years (IQR)	36 (30-44)	36 (29-44)	0.85
Male sex	146 (71%)	131 (68%)	0.59
Race			
White	76 (37%)	73 (38%)	0.92
Black	75 (36%)	75 (39%)	0.68
Asian/Pacific Is.	6 (3%)	3 (2%)	0.50
North Am. Indian	5 (2%)	4 (2%)	1.00
Multiracial	44 (21%)	38 (20%)	0.71
Region of enrollment			
U.S. / Canada	91 (44%)	95 (49%)	0.32
Brazil/Peru/Spain/ Hong Kong	115 (56%)	98 (51%)	0.32
History EtOH use	113 (55%)	120 (62%)	0.16
History IDU	33 (17%)	27 (13%)	0.33
Current smoker (enrollment)	82 (40%)	90 (47%)	0.19
Hepatitis C virus	22 (11%)	26 (13%)	0.44
Median BMI—baseline	25 (22-28)	25 (22-28)	0.75
Median CD4—baseline	495 (383-681)	524 (407-722)	0.09

Figure. Cumulative TB Rates by Treatment Regimen (MITT Population)



Median baseline CD4 : TB cases (n= 7) vs. no TB (n= 359):
(P = 0.057) 344 (IQR 271-460) 510 (IQR 398-704)

Drug resistance in TB cases
3HP: 1 of 2 cases: resistant to RIF + PZA (*M. bovis*)
9H: 1 of 6 cases: resistant to INH + RIF + STM

TB rate with little/no treatment (< 2 doses HP or <31 days H)
1 TB case/ 14 persons (22.6 p-y f/u; cumulative rate: 12.5%)

Antiretroviral therapy use (> 90 days after enrollment)
3HP: 45/206 (22%) 9H: 38/193 (20%) P = 0.62

Table 3. TB Cases and Event Rates by Treatment Arm: MITT Population

Treatment Arm	N	#TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate	Upper bound of 95% CI (%)
9H	193	6	1.25	3.50	-2.49	0.60
3HP	206	2	0.39	1.01		

Table 4. TB Cases and Event Rates by Treatment Arm: PP Population

Treatment Arm	N	#TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate	Upper bound of 95% CI (%)
9H	123	2	0.63	1.81	-1.25	1.47
3HP	183	1	0.21	0.56		

Table 5. Safety and tolerability. Safety population except as noted.

Characteristic	3HP N=207	9H N=186	P-value
Treatment completion (MITT)	183/206 (89%)	123/193 (64%)	<0.001
Discontinue—adverse drug reaction	7 (3%)	8 (4%)	0.79
Grade 3 toxicity	14 (7%)	18 (10%)	0.36
Grade 4 toxicity	4 (2%)	10 (5%)	0.10
Grade 5 (death)	6 (3%)	5 (3%)	1.00
Hepatotoxicity → drug discontinuation	2 (1%)	8 (4%)	0.05
Possible hypersensitivity	2 (1%)	0 (0%)	0.50

Limitations

- Relatively small sample size; few children
- Open-label study design
- Patients unable to receive ART in first 90 days

Conclusions

- 3HP as effective as 9H (i.e., non-inferior)
- 3HP: higher treatment completion rates; well-tolerated
- 3HP should be considered for treatment of latent *M. tuberculosis* infection in HIV-infected persons.

References

1. Sterling TR, Villarino ME, Borisov AS et al. N Engl J Med 2011;365:2155-66.
2. Martinson NA, Barnes GL, Moulton LH et al. N Engl J Med 2011;365:11-20.

Study Sites (Number enrolled in parentheses)

TBTC: Barcelona TB Research Unit (UITB), Spain (70); Johns Hopkins University, Baltimore, MD (38); Univ. North Texas (29); Emory Univ (20); UC San Diego (15); HUCFF, Brazil (14); Boston Univ. (11); USC/L.A. County (10); Denver Public Health (8); Durham VA (7); Harlem Hosp (7); Vanderbilt Univ (6); UCSF (6); Washington VA (4); New Jersey SOM (4); Montreal Chest (3); Univ. Manitoba (2); Seattle-King County (2); Hong Kong (2); Houston VA (2); Columbia Univ (1); Univ British Columbia (1); Arkansas VA (1); Hines VA (1); Chicago-Lakeside VA (1); San Antonio VA (1)
ACTG: Impacta, Lima, Peru (65); Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, Brazil (42); Porto Alegre, Brazil (17); Denver Public Health (5); UTHSC Houston (2); The Miriam Hospital, RI (2); IMPAACT: Sao Paulo, Brazil (2); Hospital dos Servidores do Estado, Brazil (2);