HIV-RELATED TB TREATMENT INTERMITTENCY IN THE CONTINUATION PHASE AND MORTALITY

Brenda Crabtree-Ramirez[1], Cathy Jenkins[2], Bryan E. Shepherd[2], Karu Jayathilake[2], Valdilea Veloso[3], Eduardo Gotuzzo[4], Claudia P. Cortes[5], Dennis Padgett[6], Catherine McGowan[2], Timothy R. Sterling[2] and the CCASAnet Region of IeDEA

1. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico 2. Vanderbilt University Medical Center, Nashville, TN 3. Instituto Nacional de Infectologia Evandro Chagas, Fundacao Oswaldo Cruz, Rio de Janeiro, Brasil 4. Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru 5. Fundación Arriarán, University of Chile, Santiago, Chile 6. Hospital Escuela and Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras

POSTER #719

Background

- The 2016 ATS/CDC/IDSA TB treatment guidelines recommend daily TB treatment in the intensive and continuation phases of treatment in HIV-infected persons to decrease the risk of relapse and acquired drug resistance.[1]
- TB treatment guidelines vary across regions and countries.
- The effect of TB treatment intermittency in the continuation phase on mortality in HIV-infected persons is unknown.

Methods

Study design: Observational cohort study

Study population: HIV-infected adults treated for TB with standard therapy (2-month initiation phase of daily Isoniazid, Rifampin/Rifabutin, Pyrazinamide ± Ethambutol) and continuation phase of Isoniazid and either Rifampin or Rifabutin, administered concomitantly with antiretroviral therapy (ART) at participating CCASAnet sites (Argentina, Brazil, Chile, Honduras, Mexico, Peru) between 2000-2015. Other inclusion criteria: known CD4 at TB diagnosis and timing of ART and TB treatment.

Statistical analysis: Kaplan-Meier and Cox proportional hazards methods compared time to death between groups.

Results

527 TB/HIV patients met inclusion criteria: 245 (46%) received TB treatment 7 days/week, 16 (3%) 5 days/week, 84 (16%) 3 days/week, and 182 (35%) 2 days/week in the continuation phase. Clinical characteristics at TB diagnosis are shown in Table 1. The crude risk of death was lower among those receiving treatment 5-7 vs. 2-3 days/week (Figure).

Figure. Survival curves according to frequency of TB treatment in the continuation phase: 5-7 days/week vs. 2-3 days/week.

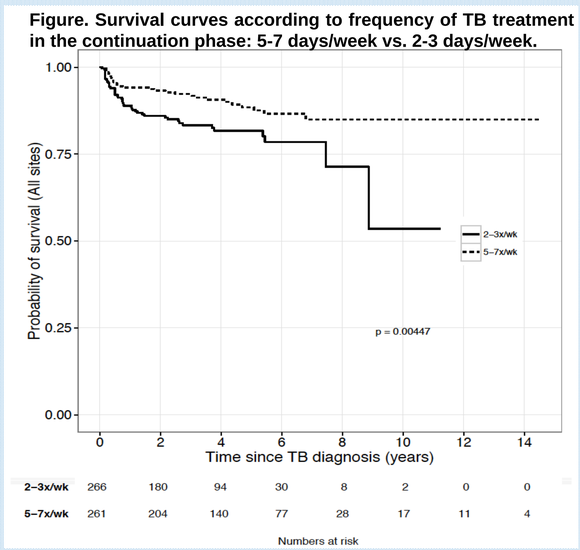


Table 1. Clinical and Demographic Characteristics of the Study Cohort. Data are presented as number (percentage) unless otherwise noted.

Characteristic	2-3x / week N = 266	5-7x / week N = 261	P-value
Age at TB diagnosis			
Median (inter-quartile range; IQR)	35 (29-43)	36 (30-43)	0.46
Male sex	223 (84%)	187 (72%)	<0.001
CD4 at TB diagnosis			
Median (IQR)	88 (41-194)	100 (42-237)	0.17
ART relative to TB diagnosis			<0.001
Not on ART at TB diagnosis	164 (62%)	208 (80%)	
On ART at TB diagnosis	102 (38%)	53 (20%)	
Site of TB disease			<0.001
Pulmonary only	144 (54%)	89 (34%)	
Any extrapulmonary	119 (45%)	171 (66%)	
Died	47 (18%)	28 (11%)	0.023

TB: tuberculosis; Dx: diagnosis; ART: antiretroviral therapy

Table 2. TB Treatment Intermittency by Study Site. Data are presented as number (percentage).

Treatment Intermittency in the Continuation Phase	Argentina N = 35	Brazil N = 182	Chile N = 31	Honduras N = 18	Mexico N = 26	Peru N = 235	Total
2-3x / week	0 (0%)	0 (0%)	30 (97%)	2 (11%)	25 (96%)	209 (89%)	266 (50%)
5-7 x / week	35 (100%)	182 (100%)	1 (3%)	16 (89%)	1 (4%)	26 (11%)	261 (50%)

Table 3. Multivariable Cox Proportional Hazards Models. Analyses were performed both without and with stratification by study site; the latter to account for other potential differences by study site.

Covariate	HR Not stratified by study site	95% CI	P-value	HR Stratified by study site	95% CI	P-value
Continuation phase frequency			0.07			0.31
2-3 x / wk	1.00	---		1.00	---	
5-7 x / wk	0.62	0.38, 1.04		1.60	0.64, 4.00	
Age at TB Dx	1.14	0.90, 1.44	0.27	1.15	0.90, 1.46	0.27
Male sex	0.75	0.44, 1.27	0.28	0.72	0.42, 1.23	0.23
CD4 at TB Dx*	0.79	0.71, 0.88	<0.001	0.80	0.71, 0.89	<0.001
Site of TB			0.29			0.35
Pulmonary only	1.00	---		1.00	---	
Any extrapulm	0.78	0.48, 1.24		0.78	0.47, 1.31	
ART relative to TB Dx			0.004			0.04
Not on ART at TB Dx	1.00	---		1.00	---	
On ART at TB Dx	2.06	1.26, 3.39		1.78	1.04, 3.07	

*square-root transformed; TB: tuberculosis; Dx: diagnosis; ART: antiretroviral therapy

Limitations

- Retrospective, observational cohort study.
- Study participants were not randomized.
- Treatment intermittency in the continuation phase was predominantly 2-3 days or 5-7 days per week, but not balanced by study site.

Conclusions

- TB treatment for 5-7 days per week in the continuation phase appeared to be associated with a decreased risk of death compared to 2-3 days/week in the continuation phase.
- The multivariable Cox proportional hazards model stratified by study site suggests that the results could have been driven by other differences between clinic sites.
- Prospective randomized trials are needed to assess the optimum TB treatment frequency in TB/HIV patients.

References

Nahid P et al. Clin Infect Dis 2016; 63:853-67.
Menzies D, et al. PLoS Med. 2009 Sep;6(9):e1000146
Kumar A, et al. Int J Tuberc Lung Dis. 2012 May;16(5):573-8.
Mwandumba HC, Squire SB (2008) Cochrane Database of Systematic Reviews.
Khan et al Clin Infect Dis. 2010 May 1;50(9):1288-99.
Narendran et al. AIDS Abstract WEAB0201; 2016.

We gratefully acknowledge all patients, caregivers, and data managers involved in the CCASAnet cohort.

CCASAnet
Caribbean, Central and South America Network for HIV Epidemiology Research

IeDEA
International epidemiologic Databases to Evaluate AIDS

Contact Information:
Brenda Crabtree- Ramírez
E-mail: brenda.crabtree@infecto.mx

http://www.iedea.org
http://www.ccasanet.org

Funding support: NIAID U01 AI069923