

Mortality Associated with Tuberculosis in HIV Positive and HIV Negative Patients in the HAART Era, in Rio de Janeiro, Brazil

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Objectives

- To compare mortality associated with tuberculosis between HIV positive and HIV negative patients who started anti-TB therapy
- To analyze variables that influenced the risk of death associated with TB

Methods

- Prospective cohort study
- Site: the Tuberculosis Referral Center of Instituto de Pesquisa Clínica Evandro Chagas – Fiocruz, Rio de Janeiro, Brazil
- From January/2000 to August/2006. Follow-up censored one year after the end of TB therapy.

Methods

- Inclusion criteria –patients with a positive culture for *Mycobacterium tuberculosis* who started anti-TB therapy and who gave a written informed consent.
- Anti-TB therapy and HAART followed the Brazilian National Recommendations
- HAART was initiated at least 30 days after the start of TB therapy in naïve patients

Definitions

- Multiple drug resistance - resistance at least to rifampicin and isoniazid
- TB associated deaths – Deaths that occurred during TB treatment when no other cause was identified.

Statistical Analysis

- **Univariate analysis**
 - Chi-square and Fisher's exact test
- **Survival Analysis**
 - Kaplan-Meier survival curves compared by the log rank test
 - Survival since the date of TB diagnosis until death or censoring date (last contact).
 - Censoring: a maximum of 24 months of follow-up.

Survival Analysis

- Cox Proportional Hazards Regression.
 - HAART was modeled as a time-dependent covariate.
 - Variables with $p < 0.20$ in the univariate analysis were selected for forward stepwise multivariate regression analysis.
 - Variables associated with a $p < 0.10$ were retained in the final model.

Comparison of Demographic and Epidemiological Data

Variable	Category	HIV positive (n=106)	HIV negative (n=101)	p value χ^2
Race	White	56 (54%)	43 (44%)	0.16
Age	≤ 40	79 (75%)	55 (55%)	0.003
Sex	Male	72 (68%)	63 (62%)	0.39
Alcohol use		21 (20%)	20 (20%)	0.86
Drug use	I.V.	7 (7%)	6 (6%)	1.0
	Not I.V.	17 (16%)	14 (14%)	0.46
Monthly income	Less than U\$500	64 (62%)	55 (55%)	0.66

Comparison of Clinical Data

Variable	HIV positive (n=106)	HIV negative (n=101)	p value χ^2
TB Clinical presentation			<0.001
Pleural-pulmonary	52 (49%)	88 (87%)	
Extra-pulmonary	16 (15%)	11 (11%)	
Disseminated	38 (30%)	2 (2%)	
Treatment interruption due to Adverse events	10 (9%)	37 (37%)	<0.001
Rifampicin used up to the end of TB therapy	87 (82%)	98 (97%)	<0.001
Abandon of TB therapy	6 (6%)	17 (17%)	0.014

Baseline Laboratorial Data

Variable	Category	HIV positive (n=106)	HIV negative (n=101)	p value
Positive blood culture (n=144)		13 (15%)	2 (3%)	0.025
Susceptibility test	Sensitive	84 (89%)	81 (86%)	0.344
	Resistance to rifampicin	8 (8%)	1 (1%)	0.037
	MDR	7 (7%)	1 (1%)	<0.001
CD4 lymphocyte count - cells/mm ³ (n=49)		169 (72-252)*	–	
HIV viral load – 10 ³ copies/ml (n=41)		110 (19-255)*	–	

* Median (25th – 75th percentiles)

HAART regimens used during TB treatment

2 NRTI + EFV	57
2 NRTI + SQV/RTV	12
2 NRTI + other PI	4
2 NRTI + SQV/RTV replaced by EFV	8
2 NRTI + EFV replaced by other PI	2
Total	83

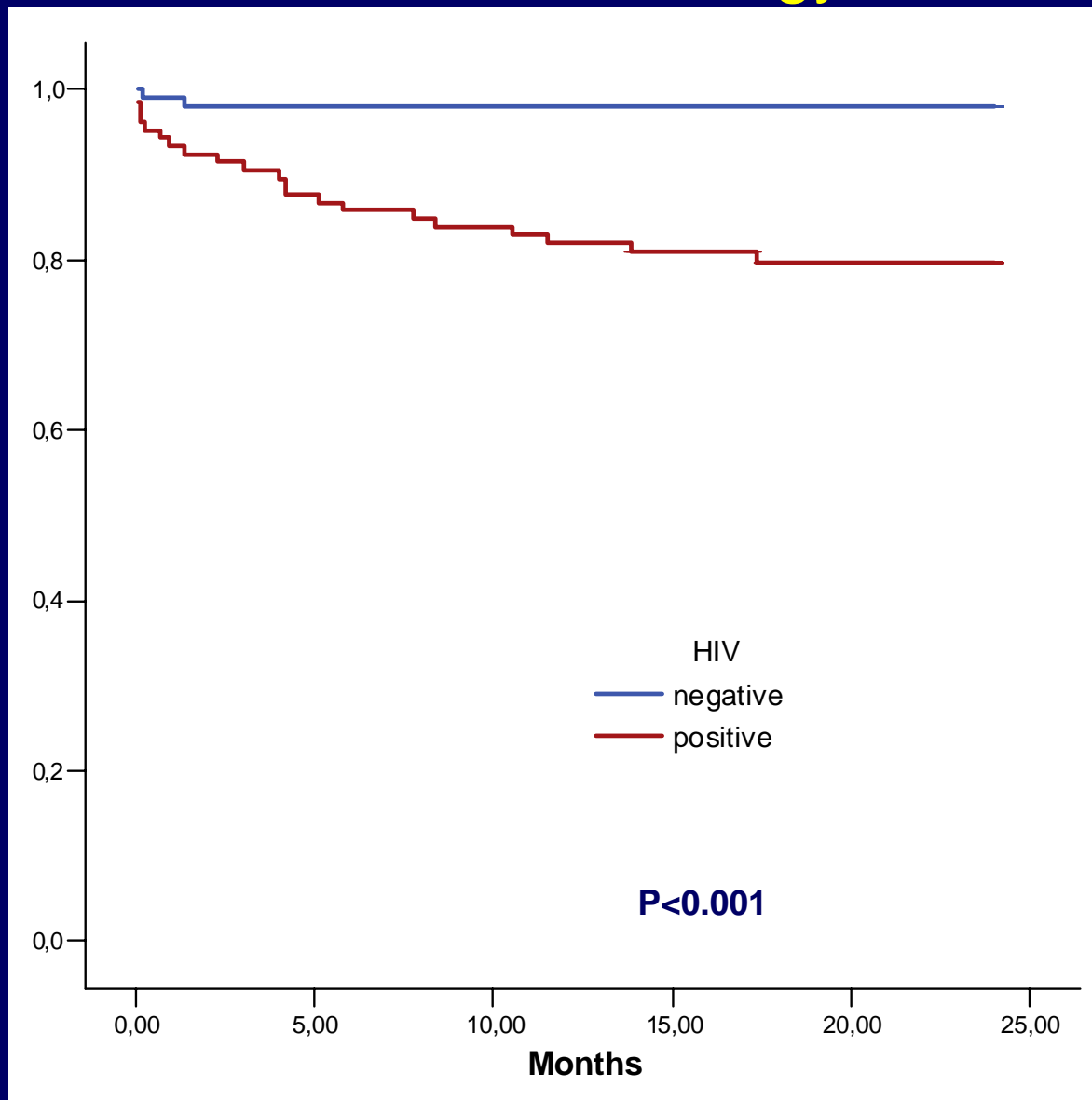
Efavirenz 600mg and ritonavir 400mg –saquinavir 400mg

Comparison of follow up and endpoints

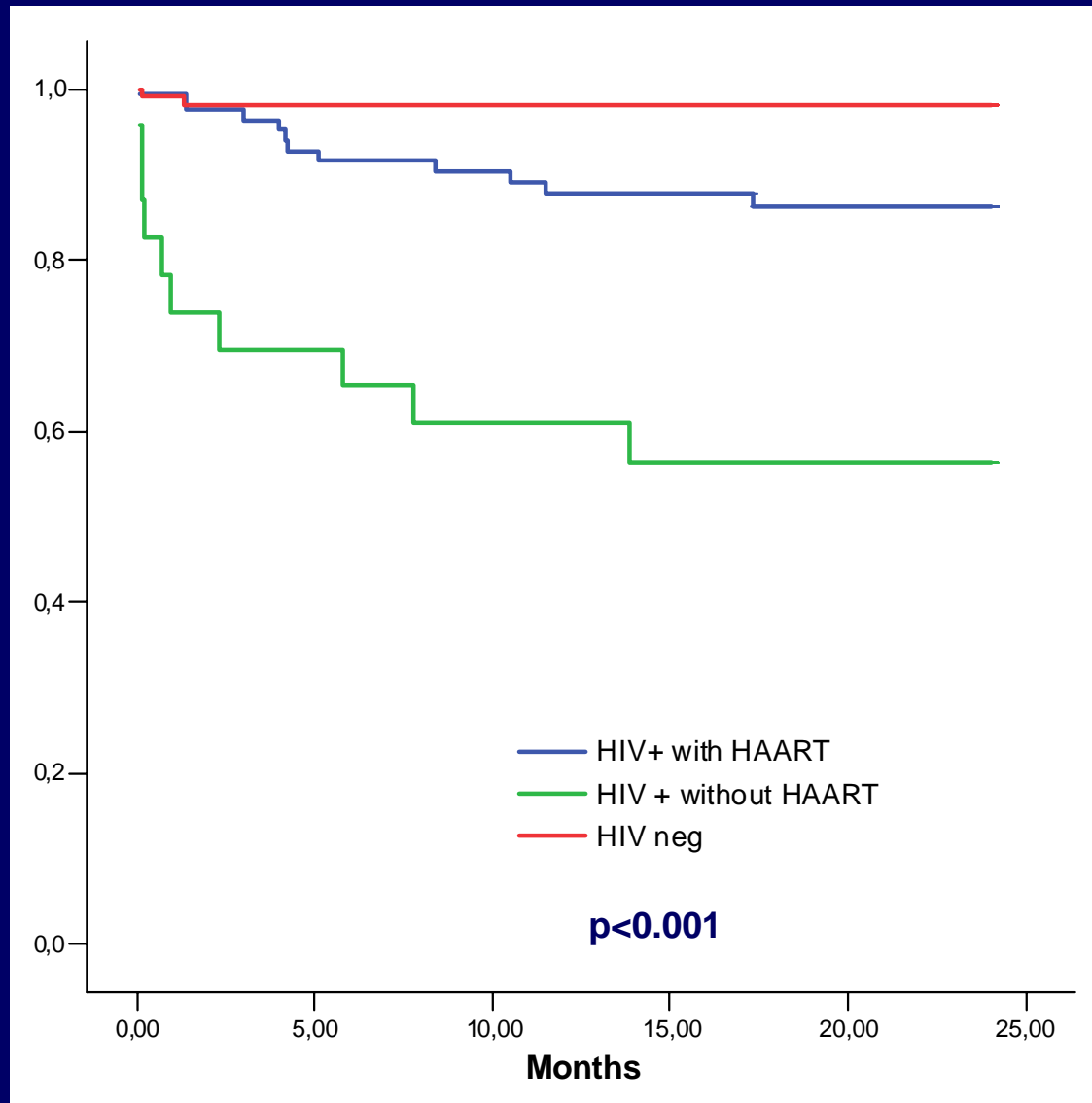
Variable	HIV positive (n=106)	HIV negative (n=101)	p value
Follow-up (months)*	19.8 (6.6 -24)	24 (13.9 – 24)	0.23
Crude mortality	23	5	<0.001
TB associated mortality	21	2	<0.001
Losses of follow-up	0	5	0.02

* Median (25th – 75th percentiles)

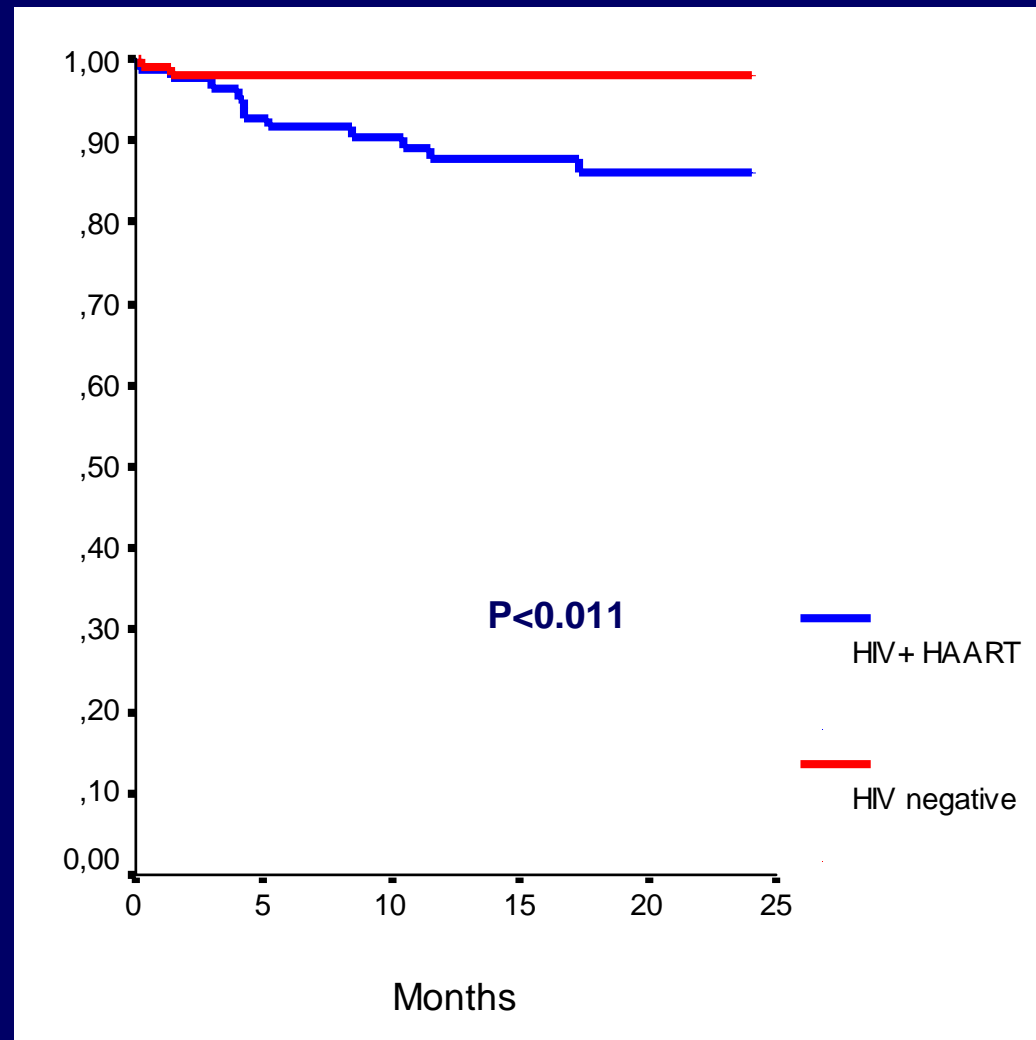
Cumulative Survival Probability according to HIV serology.



Cumulative Survival Probability according to HIV serology and HAART.



Cumulative Survival Probability. Comparison between HIV negative patients and HIV positive patients treated with HAART.



Risk of Death Associated with Tuberculosis according to the Studied Covariates. Univariate Cox Regression Analysis.

Variable	Hazard ratio	CI 95%	P value
HIV + HAART *			
HIV negative	1.0		
HIV + with HAART	4.3	0.84 - 22,26	0.08 **
HIV + without HAART	16.8	3.86 – 73.05	<0.001 **

* Time-dependent variable

** Wald's test of significance for each category level

Risk of Death Associated with Tuberculosis according to the Studied Covariates. Univariate Cox Regression Analysis.

Variable	Hazard ratio	CI 95%	P value
Age (years)			0.68
≤ 40	1.0		
> 40	0.84	0.35 – 1.97	
Disseminated TB			<0.001
No	1.0		
Yes	5.99	2.63 – 13.66	
Blood cultures			0.001
Negative	1.0		
Positive	6.29	2.47 – 16.0	
Not done	1.67	0.70 – 3.96	
Completed rifampicin use			0.007
No	1.0		
Yes	0.26	0.11 – 0.63	

Risk of Death Associated with Tuberculosis according to the Studied Covariates. Univariate Cox Regression Analysis.

Variable	Hazard ratio	CI 95%	P value
Abandon of TB therapy			0.27
No	1.0		
Yes	0.38	0.05 – 2.80	
Resistance do rifampicin			0.045
No	1.0		
Yes	3.49	1.03 – 11.85	
Multi-drug resistance			0.21
No	1.0		
Yes	2.54	0.59 – 10.89	
Severe adverse reaction			0.029
No	1.0		
Yes	2.50	1.10 – 5.71	

Risk of Death Associated with Tuberculosis according to the Studied Covariates. Univariate Cox Regression Analysis.

	HR	CI	P value
Initial CD4 cell count			
Not applicable (HIV negative)	1.0		
<200 cells/mm ³	6.0	1.25 – 28.90	0.025
≥200 cells/mm ³	3.28	0.46 – 23.30	0.23
TB as AIDS definition criterion			
Not applicable (HIV negative)	1.0		
No	15.90	3.21 – 78.84	<0.001
Yes	8.95	2.05 – 39.16	0.004

Risk of Death Associated with Tuberculosis according to the Studied Covariates. Multivariate Cox Regression Analysis.

Variable	Hazard ratio	CI 95%	p
HIV + HAART *			<0.001
HIV negative	1.0		
HIV + with HAART	2.46	0.26 – 23.28	0.43**
HIV + without HAART	18.27	2.32 – 143.8	0.006**
Disseminated TB			<0.001
No	1.0		
Yes	7.21	2.79 – 18.66	

* Time-dependent variable

** Wald's test of significance for each category level

Conclusions

- Despite free access to HAART in Brazil, TB-associated mortality among patients who started anti-TB therapy is still significantly higher among HIV/TB co-infected subjects than among HIV negative patients.
- Patients with disseminated TB at presentation, resistance to rifampicin, who did not use rifampicin up to the end of TB therapy and HIV+ who were not prescribed HAART had a significantly higher risk of death associated with TB.
- The comparison between the HIV+ patients who were prescribed HAART and HIV negative patients are still not conclusive.

Acknowledgements

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