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Safety and effectiveness of HAART in tuberculosis-HIV co-infected patients in Brazil

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SUMMARY

BACKGROUND—Antiretroviral therapy (ART) significantly reduces tuberculosis (TB) incidence among persons with human immunodeficiency virus (HIV), but the safety and effectiveness of concomitant treatment for both diseases remain unclear.

OBJECTIVE—To evaluate the impact of ART and anti-tuberculosis treatment on survival and risk of adverse events (AE) among co-infected individuals.

METHODS—In a retrospective cohort study, clinical data were collected from 618 TB-HIV patients treated with rifampin, isoniazid and pyrazinamide ± ethambutol between 1 January 1995 and 31 December 2003. Patients were categorized into two groups: highly active ART (HAART) or no ART. Different HAART regimens were evaluated. Bivariate analysis, multivariate logistic regression and survival analysis using Cox proportional hazards regression were used.

RESULTS—One-year mortality was lower for patients receiving HAART (adjusted hazard ratio [aHR] 0.17, 95%CI 0.09–0.31) compared to no ART. HAART increased the risk of AE (aHR 2.08, 95%CI 1.29–3.36). The odds of AE when receiving a ritonavir + saquinavir HAART regimen was eight-fold higher compared to no ART (OR 8.31, 95%CI 3.04–22.69), while efavirenz-based HAART was not associated with a significantly increased risk of AE (OR 1.42, 95%CI 0.76–2.65).

CONCLUSION—HIV patients with TB have significantly better survival if they receive HAART during anti-tuberculosis treatment. Efavirenz-based HAART is associated with fewer AEs than protease inhibitor-based HAART.

Keywords

tuberculosis; AIDS; HAART; adverse events; survival

TUBERCULOSIS (TB) is a common complication of human immunodefficiency virus (HIV) infection and a leading cause of death. One quarter of TB deaths globally occur

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among HIV-infected individuals. In 2009, there were an estimated 1.12 million HIV-infected TB patients globally, and 380 000 people died of HIV-associated TB.[1,2]

Since the advent of highly active antiretroviral therapy (HAART) for the treatment of HIV-infected persons, the incidence of HIV-related opportunistic infections, including TB, has markedly decreased;[3,4] however, TB still occurs frequently among HIV-infected people and remains a major cause of death in developing countries.[5]

Concomitant treatment for TB and HIV is clinically challenging and complex due to the high pill burden, variable drug absorption, immune reconstitution inflammatory syndrome (IRIS), overlapping toxicities, drug interactions and non-adherence to treatment.[6–12]

Drug interactions between rifampin (RMP) and protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) may potentially result in the loss of antiviral efficacy and the development of viral resistance.[13–15]

It is clear that HAART reduces mortality and the risk of other acquired immunedefficiency syndrome (AIDS) defining illnesses, and starting it during anti-tuberculosis treatment improves outcomes, as reported since 2001.[6,16–18] Two recent studies conducted in Africa concluded that the initiation of HAART regimen with efavirenz during anti-tuberculosis treatment significantly reduced mortality, that rates of adverse events (AE) were similar if anti-tuberculosis treatment and ART were concomitant or sequential,[19] and that early HAART initiation during anti-tuberculosis treatment reduced mortality in individuals with low CD4 counts.[20]

Our study was carried out to assess the impact of HAART on survival and the risk of AE during anti-tuberculosis treatment in Brazilian HIV-infected patients in a hospital setting where both TB and HIV constitute a high public health burden. Our results corroborate those from previous trials conducted in TB-HIV co-infected patients.

METHODS

Study design and selection of subjects

A retrospective cohort study was conducted in two reference hospitals for TB and HIV in Rio de Janeiro, Brazil: Clementino Fraga Filho University Hospital/Institute of Thoracic Diseases of the Federal University of Rio de Janeiro and Evandro Chagas Clinical Research Institute of Oswaldo Cruz Foundation, with the approval of their ethics committees. The inclusion criteria were all TB-HIV patients aged >15 years treated according to the standard Brazilian TB regimen between 1 January 1995 and 31 December 2003.

TB was defined per Brazilian standard definitions.[21] Patients with clinical (cough, weight loss, fever, night sweats, anorexia) and radiological (upper lobe opacities or cavitation) criteria were also included.[21] The standard regimen for TB in Brazil was 2 months of RMP, isoniazid (INH) and pyrazinamide, followed by 4 months of RMP and INH. Ethambutol was included for retreatment cases.[21] Patients who started anti-tuberculosis treatment based on clinical and radiological criteria who were furthered diagnosed with culture-proven non-tuberculous mycobacteria and those with multidrug-resistant TB were excluded. Patients who received a non-HAART regimen (defined as the single use or a combination of NRTIs), those whose diagnosis of TB was changed, those with data missing from their medical records and those transferred to other health units were also excluded.

Patients were categorized into groups according to ART use as HAART or no ART. HAART was defined as a combination of NRTIs plus a PI, or two NRTIs plus an NNRTI. Patients who were not receiving ART were classified as no ART. HAART was further

evaluated by type of regimen: efavirenz (EFV) based, saquinavir (SQV) + ritonavir (RTV) based or other associations of PI or NNTRIs (e.g., nevirapine, indinavir [IDV]+ SQV, lopinavir + SQV, RTV + IDV, amprenavir + RTV); and according to the time of initiation: early HAART (started during the first 2 months of anti-tuberculosis treatment), deferred HAART (started in months 3–6 of anti-tuberculosis treatment) or HAART initiated prior to anti-tuberculosis treatment (HAART started at least 3 months before TB treatment). Antiretroviral drug (ARV) doses were standardized by the Brazilian Ministry of Health (BMH) guidelines for the specific period of the study, and specifically for EFV the dose was 600 mg once daily.

AEs were assessed by review of medical records, interpreted by the assisting physician on their time of occurrence and defined as any unfavorable sign, including abnormal laboratory findings (e.g., liver enzymes of more than three times the normal value, platelet count <100 000/mm^3), or associated symptoms (e.g., paresthesia, jaundice, gastrointestinal intolerance, rash). AEs were classified as severe in cases that required a change in regimen. Radiological appearance was classified according to Greenberg et al.[22] as typical or atypical.

According to the BMH guidelines, patients were considered cured of TB if they completed TB treatment with clinical and radiological improvement, independently of acid-fast bacilli smear performed at the end of the treatment (non-proven cure), and dead if they died during anti-tuberculosis treatment. Other treatment outcomes were default and failure, defined according to BMH guidelines.[21]

An SPSS database (version 11.0 for Windows, Statistical Package for the Social Sciences Inc, Chicago, IL, USA) was constructed based on an electronic data collection tool (Teleform®, Hewlett Packard, Palo Alto, CA, USA). This was scanned to automatically generate a database, thus reducing the risk of errors during data entry. Sociodemographic characteristics, clinical data, treatment regimens, outcomes and mortality 1 year after anti-tuberculosis treatment were abstracted from medical records by trained health care workers (two physicians and two nurses). AEs and mortality were interpreted by the assisting physician on time of occurrence and were also assessed by review of medical records. For each case of TB-HIV co-infection, the same standardized questionnaire was filled out.

Statistical analysis

Patients were analyzed during anti-tuberculosis treatment, when AEs were identified, at the end of treatment to analyze TB outcomes, and 1 year after TB treatment, to evaluate the impact of HAART on TB-HIV co-infection. Descriptive statistical methods were used to provide a general profile of the study population. The χ^2 and Fisher's exact tests were used to compare distributions of categorical variables. Multivariable logistic regression models were used to adjust for potential confounders. The magnitude of association between the three ART regimens was estimated by odds ratios (ORs) with 95% confidence intervals (95%CI).

Time in days to the occurrence of AE and time to death were compared through survival analysis using the Kaplan-Meier method using the log-rank test. Cox proportional hazards regression models were used to estimate the magnitude of association by hazard ratios (HRs), with their respective 95%CIs. The use of ART was considered to vary in time; mortality was analyzed during and 1 year after anti-tuberculosis treatment. Patients contributed person-time up to the moment of the outcomes studied (AE or death) and were censored at the time of death (for AE outcome) or loss to follow-up, or were censored administratively at 1 year for those who survived, whichever came first. Statistical analyses were conducted using SPSS 11.0 for Windows and *R* (R Foundation for Statistical Computing, Vienna, Austria) for Windows 2.12.2 (Microsoft, Redwoods, WA, USA).

RESULTS

Study population data are shown in Figure 1 and Table 1.

Anti-tuberculosis treatment outcomes

Among the 347 cases, 196 (57%) were cured, 69 (20%) died, 71 (21%) defaulted and 7 (2%) failed treatment. Compared to the no ART patients, HAART patients were more likely to be cured of TB (OR 4.91, 95%CI 2.77–8.70). This association persisted in multivariate analysis adjusting for age, sex, marital status and total lymphocyte count (TLC), which was associated with cure when values were >1000 cells/μl (OR 2.64, 95%CI 1.49–4.68). The other factors were not statistically significant.

Adverse events

The risk of occurrence of AEs during anti-tuberculosis treatment was twice as high in the HAART group as in patients who were not on ART (adjusted HR [aHR] 2.08, 95%CI 1.29–3.36). These results were adjusted for age, sex, TLC and clinical presentation of TB (Table 2).

Of the 185 patients on HAART, 79 were using ARVs before TB treatment, 77 were in the early HAART group and 29 were in the deferred HAART group. Time of initiation of HAART was not associated with AE occurrence; however, those patients who were not on HAART had a protective effect against AEs (HR 0.68, 95%CI 0.48–0.97).

HAART regimens based on SQV + RTV were identified as the strongest risk factor for AE compared to no ART (OR 8.31, 95%CI 3.04–22.69), as were the other HAART regimens (OR 2.80, 95%CI 1.27–6.17). However, EFV-based HAART was not associated with AE occurrence (OR 1.42, 95%CI 0.76–2.65).

Mortality

HAART use was associated with a marked reduction in the risk of death during anti-tuberculosis treatment when compared to no ART (aHR 0.10, 95%CI 0.03–0.29), even after adjustment for possible confounding factors such as sex, age and TLC, which was inversely associated with death (aHR 0.29, 95%CI 0.11–0.76; Table 3). The use of HAART was also associated with a reduction in the risk of death 1 year after anti-tuberculosis treatment (aHR 0.17, 95%CI 0.09–0.32; Table 3). The timing of HAART initiation did not show statistical significance against mortality 1 year after anti-tuberculosis treatment.

DISCUSSION

In this retrospective study of TB-HIV co-infected patients, the concomitant use of HAART and a rifamycin-based regimen for TB is associated with a reduction in deaths, regardless of HAART regimen, as published by previous studies.[6,17,19,20,23–26] HAART increased the risk of AE among co-infected patients, but regimens containing EFV were better tolerated. It is known that the frequency of AEs during anti-tuberculosis treatment is higher in patients with AIDS, varying between 18% and 37%.[27,28] We found that >50% of patients receiving HAART experienced AEs compared to 31% of patients who did not receive ART. The most common AEs were gastrointestinal intolerance (45–13.1%), hepatitis (43–12.5%), paresthesia (21–6.1%) and rash (19–5.5%). Of the 143 patients who presented AEs, 66 (46%) had to stop anti-tuberculosis treatment due to their severity. Our results are similar to those found by Dean et al.,[6] where 54% of patients receiving HAART developed similar presentations. Another study in 2006 showed that HIV-positive patients receiving HAART presented AEs more frequently than HIV-negative patients (40% vs. 26%), with paresthesia

and vomiting being the most common AEs.[25] All ARVs (including NTRIs such as didanosine and/or stavudine) are associated with the most common AEs, such as paresthesia, as are drugs used for anti-tuberculosis treatment.

Our mortality results are in agreement with several studies reporting better treatment outcomes and reductions in mortality or absence of effect in survival for co-infected patients receiving HAART,[6,17,23–25] as shown by studies conducted in England[6,17] and the United States.[25] In a Taiwan hospital cohort, authors found no mortality difference between HIV patients treated with HAART with and without TB (HR 0.89, 95%CI 0.6–1.7).[24] A meta-analysis recently concluded that TB increased the risk of death in HIV patients (HR 1.8, 95%CI 1.4–2.3) and that patients not exposed to HAART had an even higher risk of dying (HR 2.6, 95%CI 1.8–3.6).[26] The SAPiT (Starting An-tiretroviral therapy at three Points In Tuberculosis therapy) trial showed that the initiation of EFV-based HAART during TB treatment reduced mortality by 56%, with proven benefits even in patients with CD4 count < 200 cells/mm^3.[19]

Our results showed that HAART comprising SQV + RTV and other ARVs were associated with AEs, with the exception of regimens containing EFZ, which were better tolerated.[26,27] EFV-based HAART is the first choice for HIV-TB patients receiving RMP as per US, European and Brazil guidelines based on the results of previous studies.[12,29,30] However, PIs are still an alternative for cases previously treated with HAART who have failed on NNRTIs or when there are no other options available.[31] Our results corroborate these recommendations and suggest EFZ-based HAART when clinical and virologic characteristics allow its use.

Schiffer and Sterling[32] have suggested that although early and deferred HAART reduce mortality and have similar risks for severe drug toxicity, the early group may develop higher rates of IRIS. However, the SAPiT trial recently had to stop the sequential arm of the study, i.e., patients who started HAART after anti-tuberculosis treatment, because those who started HAART earlier showed significantly lower mortality rates in addition to fewer AEs, including IRIS.[19] Our study was not designed to capture this clinical syndrome; however, clinicians should be aware of this risk when determining the best time to initiate HAART in an individual patient. On the other hand, we did not find a statistically significant association between time of HAART initiation and AE occurrence, which, in association with other studies showing increased survival, corroborate the earlier use of HAART even during anti-tuberculosis treatment.

There were limitations to our study, most of which were attributable to the retrospective cohort design. We were dependent on documentation and interpretation of AEs in the medical records, which may have led to information bias. However, data were reported in medical records according to standard questionnaires by the attending physicians of two university and research institutions, where physicians, nurses and students are trained to document data that could be used for research. Data on AEs were not collected in the standardized way essential for prospective studies, but we adapted their definition in such a way that we could use this important information. The level of immunosuppression was based on the TLC, as the majority of patients did not have CD4 cell count or plasma viral load data during the period of analysis. Some studies suggest that TLC is a viable alternative for CD4 count in the follow-up of HIV-infected patients in resource-poor settings.[33–36] The analysis of AEs and mortality according to the association of ARVs and the time of initiation of HAART showed limited statistical power due to the small number of patients analyzed in each group, limiting the conclusions. Overall, although the total number of patients included in this cohort is relatively large, the overall results of this study should make these numbers reliable.

In conclusion, our retrospective cohort study demonstrated clear benefits in prescribing HAART for TB-HIV co-infected patients, with successful anti-tuberculosis treatment outcomes and survival 1 year after TB diagnosis; however, the occurrence of HAART-associated AEs is significant during anti-tuberculosis treatment. Based on our results and on recently published studies, we suggest that treatment for both TB and HIV should be started concomitantly and earlier in the course of both diseases. The limitations of concomitant use of HAART and rifamycin-based anti-tuberculosis regimens can be overcome by prescribing EFV-containing HAART when clinical and virologic characteristics allow its use.

Acknowledgments

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References

1. World Health Organization. WHO report 2010. Global Tuberculosis Control 2010. WHO/HTM/TB/2010.7. Geneva, Switzerland: WHO; 2011. http://www.doh.state.3.us/disease_ctrl/tb/Trends-Stats/Fact-Sheets/US-Global/WHO_Report2010_Global_TB_Control.pdf
2. Kwam CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011; 24:351–376. [PubMed: 21482729]
3. Miranda A, Morgan M, Jamal L, et al. Impact of antiretroviral therapy on the incidence of tuberculosis, 1995–2001. PLoS ONE. 2007; 9:1–9.
4. Santoro-Lopes G, Pinho AMF, Harrison LH, et al. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodefficiency virus treated with highly active anti-retroviral therapy. Clin Infec Dis. 2002; 34:543–546. [PubMed: 11797184]
5. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence population in sub-Saharan Africa. AIDS. 2001; 13:143–152. [PubMed: 11216921]
6. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active anti-retroviral therapy. AIDS. 2002; 16:75–83. [PubMed: 11741165]
7. Manabe YC, Campbell JC, Sydnor E, et al. Immune reconstitution inflammatory syndrome: risk factors and treatment implications. J Acquir Immune Defic Syndr. 2007; 46:456– 462. [PubMed: 18077835]
8. McIlleron H, Meintjes G, Burman WJ, et al. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. J Infect Dis. 2007; 196 (Suppl 1):S63–S75. [PubMed: 17624828]
9. Ministério da Saúde do Brasil. Boletim Epidemiológico AIDS e DST 2007. Brasilia, Brazil: Ministério da Saúde do Brasil; 2008. http://www.aids.gov.br [Accessed October 2012. [Portuguese]]
10. Pozniak AL, Miller R, Ormerod P. The treatment of tuberculosis in HIV-infected persons. AIDS. 1999; 13:435– 445. [PubMed: 10197371]
11. Rolla VC, Vieira MAS, Pinto DP, et al. Safety, efficacy and pharmacokinetics of ritonavir 400 mg/saquinavir 400 mg twice daily plus rifampicin combined therapy in HIV patients with tuberculosis. Clin Drug Invest. 2006; 26:469– 479.
12. Pedral-Sampaio DB, Alves CR, Netto EM, et al. Efficacy and safety of efavirenz in HIV patients on rifampin for tuberculosis. Braz J Infec Dis. 2004; 8:211–216. [PubMed: 15476053]
13. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodefficiency virus-related tuberculosis. Clin Infect Dis. 1999; 28:419–430. [PubMed: 10194057]
14. Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. Int J Tuberc Lung Dis. 2005; 9:248–257. [PubMed: 15786886]

15. Piscitelli SC, Flexner C, Minor JR, et al. Drug interactions in patients infected with human immunodefficiency virus. Clin Infect Dis. 1996; 23:685–693. [PubMed: 8909827]
16. Breen RAM, Miller RF, Gorsuch T, et al. Virological response to highly active antiretroviral therapy is unaffected by anti-tuberculosis therapy. J Infect Dis. 2006; 193:1437–1440. [PubMed: 16619192]
17. Dheda K, Lampe FC, Johnson MA, et al. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. J Infect Dis. 2004; 190:1670–1676. [PubMed: 15478074]
18. Girardi E, Palmieri F, Cingolani A, et al. Changing clinical presentation and survival in HIV-associated tuberculosis after highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2001; 26:326–331. [PubMed: 11317073]
19. Karim SSA, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010; 362:697–706. [PubMed: 20181971]
20. Franke MF, Robins JM, Mugabo J, et al. Effectiveness of early antiretroviral therapy initiation to improve survival among HIV-infected adults with tuberculosis: a retrospective cohort study. PLoS Med. 2011; 8:1–9.
21. Ministério da Saúde. Tuberculose: guia de vigilância epidemiológica. 1. Brasília, DF, Brazil: Fundação Nacional de Saúde, Ministério da Saúde; 2002. [Portuguese]
22. Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). Radiology. 1994; 193:115–119. [PubMed: 7916467]
23. Mello FCQ, Lacerda APM, Gounder C, et al. The impact of institution of HAART in the co-infection tuberculosis and HIV in a reference hospital for AIDS in Rio de Janeiro, Brazil. Am J Respir Crit Care Med. 2001; 163:A496.
24. Hung CC, Chen MY, Hsiao CF, et al. Improved outcomes of HIV-1 infected adults with tuberculosis in the era of highly active antiretroviral therapy. AIDS. 2003; 17:2615–2622. [PubMed: 14685055]
25. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. Am J Respir Crit Care Med. 2007; 175:1199–1206. [PubMed: 17290042]
26. Straetemans M, Bierrenbach AL, Naegelkere N, et al. The effect of tuberculosis on mortality in HIV positive people: a meta analysis. PLoS ONE. 2010; 5:1–10.
27. Small PM, Schecter GF, Goodman PC, et al. Treatment of tuberculosis in patients with advanced human immunodefficiency virus infection. N Engl J Med. 1991; 324:289–294. [PubMed: 1898769]
28. Johnson JL, Okwera A, Nsubuga P, et al. Efficacy of an unsupervised 8-month rifampicin-containing regimen for the treatment of pulmonary tuberculosis in HIV-infected adults. Int J Tuberc Lung Dis. 2000; 4:1032–1040. [PubMed: 11092715]
29. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. AIDS. 2006; 20:131–132. [PubMed: 16327334]
30. Patel A, Patel K, Patel J, et al. Safety and antiretroviral effectiveness of concomitant use of rifampicin and efavirenz for antiretroviral-naïve patients in India who are co-infected with tuberculosis and HIV-1. J Aquir Immune Defic Syndr. 2004; 37:1166–1169.
31. Secretaria de Vigilância em Saúde, Programa Nacional de DST e AIDS. Ministério da Saúde. Recomendações para terapia anti-retroviral em adultos infectados pelo HIV 2007/2008: documento preliminar. Brasilia, Brazil: Secretaria de Vigilância em Saúde; 2008. http://www.aids.gov.br [Accessed October 2012. [Portuguese]]
32. Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. J Acquir Immune Defic Syndr. 2007; 44:229–234. [PubMed: 17159657]
33. Badri M, Wood R. Usefulness of total lymphocyte count in monitoring highly active antiretroviral therapy in resource-limited settings. AIDS. 2003; 17:541–545. [PubMed: 12598774]
34. Bedell R, Heath KV, Hogg RS, et al. Total lymphocyte count as a surrogate of CD4 cell count to prioritize eligibility for antiretroviral therapy among HIV-infected individuals in resource-limited settings. Antivir Ther. 2003; 8:379–384. [PubMed: 14640384]

35. Liu FR, Guo F, Ye JJ, et al. Correlation analysis on total lymphocyte count and CD4 count of HIV-infected patients. Int J Clin Pract. 2008; 62:955–960. [PubMed: 17983435]

36. Mahajan AP, Hogan JW, Snyder B, et al. Changes in total lymphocyte count as a surrogate for changes in CD4 count following initiation of HAART: implications for monitoring in resource-limited settings. J Acquir Immune Defic Syndr. 2004; 36:567–575. [PubMed: 15097299]

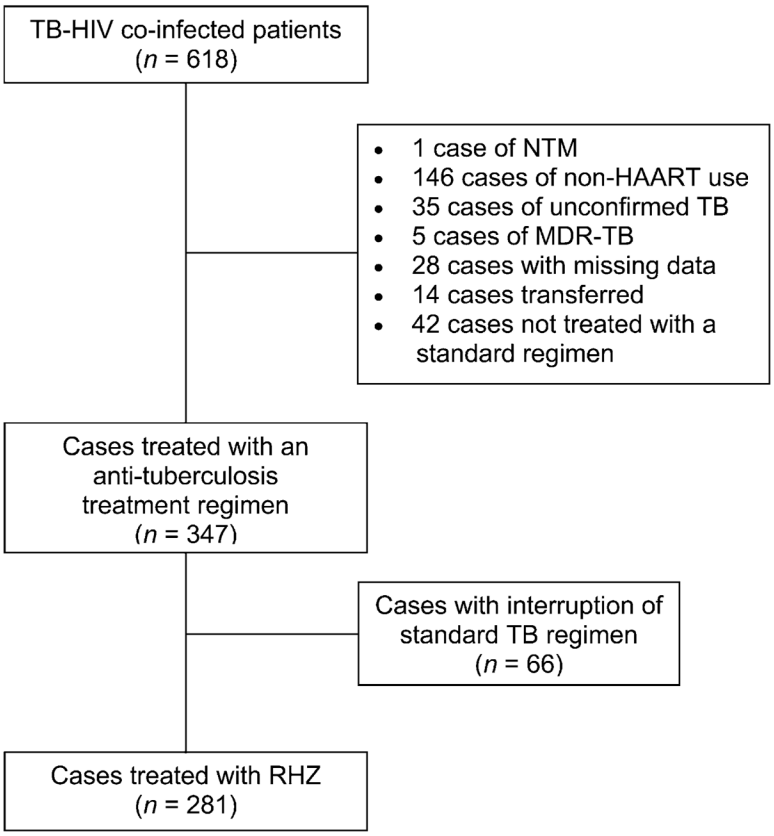

Figure 1.
Diagram of study population. TB = tuberculosis; HIV = human immunodeficiency virus; NTM = non-tuberculous mycobacteria; MDR-TB = multidrug-resistant TB; R = rifampin; H = isoniazid; Z = pyrazinamide.

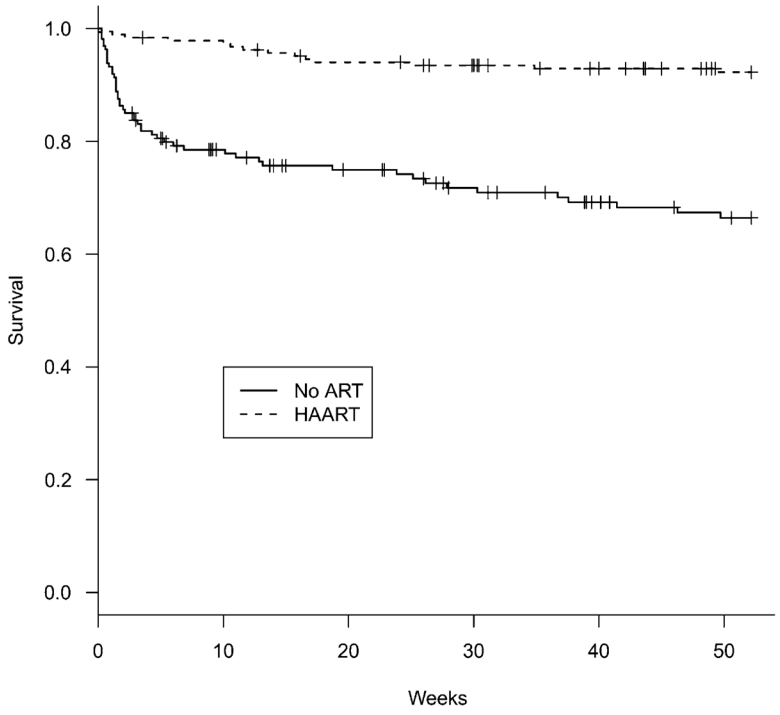

Figure 2.
Kaplan-Meier survival curves comparing deaths among patients with TB-HIV co-infection by ART regimen. ART = antiretroviral therapy; HAART = highly active ART; TB = tuberculosis; HIV = human immunodeficiency virus.

Table 1

General descriptions of variables analyzed

		Adverse events			Death 1 year after TB		
Variable	**Total (*N* = 493) *n* (%)**	**Yes (*n* = 180) *n* (%)**	**No (*n* = 313) *n* (%)**	***P* value***	**Yes (*n* = 88) *n* (%)**	**No (*n* = 405) *n* (%)**	***P* value**
Male sex	343 (70)	119 (66)	224 (72)	0.22	54 (61)	289 (71)	0.07
Age <35 years	280 (57)	111 (62)	169 (54)	0.11	45 (51)	235 (58)	0.24
Married	184 (37)	63 (36)	121 (40)	0.44	32 (37)	152 (38)	0.90
History of alcoholism	117 (24)	45 (28)	72 (27)	0.82	17 (24)	100 (28)	0.56
History of smoking	229 (46)	83 (53)	146 (54)	0.84	39 (57)	190 (53)	0.60
Comorbidities							
Cancer	15 (3)	5 (3)	10 (3)	1	3 (3)	12 (3)	0.74
Diabetes	4 (1)	2 (1)	2 (1)	0.62	0	4 (1)	1
Viral hepatitis	59 (12)	25 (14)	34 (11)	0.32	6 (7)	53 (13)	0.14
Renal failure	8 (2)	5 (3)	3 (1)	0.15	1 (1)	398 (2)	1
Use of immunosuppressors	10 (2)	5 (3)	5 (2)	0.51	5 (6)	5 (1)	0.02
Lymphocyte count, cells/mm^3							
<1000	198 (40)	79 (57)	119 (53)	0.45	51 (71)	147 (50)	0.002
Clinical presentation of TB							
Pulmonary	217 (44)	64 (36)	153 (49)		41 (47)	176 (43)	
Extra-pulmonary	122 (25)	41 (23)	81 (26)	<0.001	16 (18)	106 (26)	0.28
Disseminated	154 (31)	75 (42)	79 (25)		31 (35)	123 (30)	
ART							
No ART	152 (31)	48 (27)	114 (36)		49 (56)	113 (28)	
Non HAART	150 (30)	43 (24)	103 (33)	<0.001	25 (28)	121 (30)	<0.001
HAART	191 (39)	89 (49)	96 (31)		14 (16)	171 (42)	

*Overall *P* values for Fisher's exact test for discrete variables.

TB = tuberculosis; aHR = adjusted HR; ART = antiretroviral therapy; HAART = highly active ART.

Table 2

Cox regression model analysis of variables associated with adverse events during anti-tuberculosis treatment in TB-HIV co-infected patients at the Clementino Fraga Filho University Hospital/Institute of Thoracic Diseases and Evandro Chagas Clinical Research Institute, Rio de Janeiro, Brazil, 1995–2003 (n = 347)

	Adverse events			
Variable	**HR (95%CI)**	***P* value**	**aHR (95%CI)**	***P* value**
ART				
HAART	1.89 (1.26–2.83)	0.002	2.08 (1.29–3.36)	0.002
No ART	1		1	
Sex				
Female	1.15 (0.79–1.66)	0.47	1.02 (0.65–1.62)	0.92
Male	1		1	
Age, years				
>35	0.79 (0.55–1.12)	0.18	0.91 (0.59–1.40)	0.68
<35	1		1	
Lymphocyte count, cells/mm^3				
>1000	0.67 (0.44–1.01)	0.06	0.83 (0.53–1.29)	0.39
<1000			1	
Clinical presentation of TB				
Extra-pulmonary	1.16 (0.73–1.84)	0.53	1.19 (0.69–2.09)	0.52
Disseminated	1.90 (1.26–2.87)	0.002	1.66 (1.00–2.77)	0.05
Pulmonary	1		1	

TB = tuberculosis; HIV = human immunodeficiency virus; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; ART = antiretroviral therapy; HAART = highly active ART.

Table 3

Cox regression model of variables associated with death during anti-tuberculosis treatment and death 1 year after TB in TB-HIV co-infected patients at the Clementino Fraga Filho University Hospital/Institute of Thoracic Diseases and Evandro Chagas Clinical Research Institute, Rio de Janeiro, Brazil, 1995–2003 (n = 347)

Variable	Death during anti-tuberculosis treatment aHR (95%CI)	Death 1 year after anti-tuberculosis treatment aHR (95%CI)
ART		
HAART	0.10 (0.03–0.29)	0.17 (0.09–0.32)
No ART	1	1
Sex		
Female	1.44 (0.65–3.18)	1.35 (0.76–2.41)
Male	1	1
Age, years		
>35	1.21 (0.57–2.62)	1.32 (0.76–2.30)
<35	1	1
Lymphocyte count, cells/mm^3		
>1000	0.29 (0.11–0.76)	0.38 (0.21–0.69)
<1000	1	1

TB = tuberculosis; HIV = human immunodeficiency virus; aHR = adjusted hazard ratio; CI = confidence interval; ART = antiretroviral therapy; HAART = highly active ART.