Original Article

Survival of HIV patients with tuberculosis started on simultaneous or deferred HAART in the THRio cohort, Rio de Janeiro, Brazil

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\textbf{ABSTRACT}

\textbf{Background:} The timing of highly active antiretroviral therapy (HAART) after a tuberculosis diagnosis in HIV-infected patients can affect clinical outcomes and survival. We compared survival after tuberculosis diagnosis in HIV-infected adults who initiated HAART and tuberculosis therapy simultaneously to those who delayed the start of HAART for at least two months.

\textbf{Methods:} The THRio cohort includes 17,983 patients receiving HIV care in 29 public clinics in Rio de Janeiro, Brazil. HAART-naïve patients at the time of a new TB diagnosis between September 2003 and June 2008 were included. Survival was measured in days from diagnosis of TB. We compared survival among patients who initiated HAART within 60 days of TB treatment (simultaneous – ST) to those who started HAART >60 days of TB treatment or never started (deferred – DT). Kaplan–Meier plots and Cox proportional hazards regression analyses were conducted.

\textbf{Results:} Of 947 patients diagnosed with TB, 572 (60\%) were HAART naïve at the time of TB diagnosis; 135 were excluded because of missing CD4 count results. Among the remaining 437 TB patients, 56 (13\%) died during follow-up: 25 (10\%) among ST patients and 31 (16\%) in DT group (p = 0.08). ST patients had lower median CD4 counts at TB diagnosis than DT patients (106 vs. 278, p < 0.001). Cox proportional hazards utilizing propensity score analysis showed that DT patients were more likely to die (adjusted HR = 1.89; 95\% CI: 1.05–3.40; p = 0.03).

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Conclusion: HAART administered simultaneously with TB therapy was associated with improved survival after TB diagnosis. HAART should be given to patients with HIV-related TB as soon as clinically feasible.
Table 1 – Predictors of mortality in HIV/TB co-infected patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 437)</th>
<th>Mortality</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Died (n = 56)</td>
<td>Survived (n = 381)</td>
<td></td>
</tr>
<tr>
<td>Median age (years; IQR)</td>
<td>36 (29–43)</td>
<td>36 (29–45)</td>
<td>36 (29–42)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>306 (70%)</td>
<td>46 (82%)</td>
<td>260 (68%)</td>
</tr>
<tr>
<td>Median CD4 at TB diagnosis (IQR)</td>
<td>150 (67–294)</td>
<td>157 (72–243)</td>
<td>150 (63–300)</td>
</tr>
<tr>
<td>HAART &gt;60 days after TB treatment start (θ, %)</td>
<td>194 (44%)</td>
<td>31 (55%)</td>
<td>163 (43%)</td>
</tr>
</tbody>
</table>

Descriptive statistics were performed using t-tests for continuous variables and Fisher’s exact test for categorical variables. Survival curves were examined using the Kaplan–Meier method, and the log rank test was used to assess differences in survival functions by group.

Propensity scores were calculated as follows: a logistic regression model was run having DT/ST as the response variable and gender, age, and CD4 counts as co-variables. Predicted probabilities from the model were used to construct quintiles, which were included in the model as a stratifying variable. Cox proportional hazards regression analyses were conducted and propensity scores for HAART initiation by 60 days post-TB diagnosis were used to stratify the baseline hazard function in order to minimize bias from treatment by indication.

The THRio study was approved by the Research Ethics Committee of the Municipal Secretary of Health and Civil Defense of the Municipality of Rio de Janeiro, Brazil, and the Johns Hopkins Medicine Institutional Review Board. The study received a waiver of informed consent, as no direct contact with patients was undertaken by study staff and all data were deidentified prior to analysis.

Results

There were 17,983 subjects in the THRio cohort for this analysis. Between September 2003 and June 2008, 947 cases of TB were diagnosed, of whom 572 had no history of exposure to HAART for greater than 60 days at TB diagnosis. One hundred thirty-five patients were excluded from the analysis because they did not have a CD4 count result available within four months of their TB diagnosis. Of the 437 TB/HIV patients in the current analysis, 78% of the cases were male, the median age was 36 years (IQ range: 29–43 years) and the median CD4 cell count at TB diagnosis was 150 cells/mm³ (IQ range: 67–294 cells). Of the 389 (89%) who started HAART at or after TB treatment start date, 125 started HAART >60 days and ≤365 days after TB treatment start date (DT), 21 started HAART >365 days after TB treatment start date and were censored at HAART start date (DT). Forty-eight patients never started HAART in the study period (DT) and were censored as described. ST patients did not differ from DT patients in age, gender or RNA viral load at the time of TB diagnosis (Table 2). ST patients had lower median CD4 cell counts at the time of TB diagnosis (106 vs. 278 cell/mm³, p < 0.001). Fifty-six patients (13%) died during a median of 2.1 years of follow-up (2212 person-years), at a mortality rate of 7.6 deaths per 100 person-years. The median time to death was 338 days. Subjects who died had similar baseline CD4 counts and HIV viral loads at time of TB diagnosis as those who survived (Table 1).

Among 243 TB patients in the ST group, 25 (10%) died during follow-up compared to 31 of 194 (16%) in the DT group (p = 0.085). Kaplan–Meier estimates of survival after TB diagnosis stratified by timing of HAART initiation are shown in Fig. 1. ST patients were significantly less likely to die over the follow-up period than DT patients (log-rank test p = 0.02). Univariate Cox analysis revealed that delaying therapy increased mortality risk 45% (HR = 1.45; 95% CI: 1.05–2.00). Adjusted Cox proportional hazards modeling revealed an 89% increased risk in mortality among DT patients compared to ST patients (RH = 1.89; 95% CI: 1.05–3.40; p = 0.03), taking the propensity score into account (Table 3). No other covariates were associated with increased mortality.

Discussion

In this cohort of 437 patients with HIV-related TB who were HAART naïve at the time of TB diagnosis, not receiving HAART within 60 days after TB diagnosis was associated with an 89% increased risk of mortality. Patients who received HAART early had significantly lower CD4 cell counts at the time of TB diagnosis but had better overall survival. New WHO guidelines state that HAART should be initiated as soon as possible in all patients with HIV and active tuberculosis, regardless of CD4 cell count.1 Our

Fig. 1 – Time from TB diagnosis to death of HAART-naïve HIV/TB co-infected patients with HAART deferred at least 60 days following initiation of TB therapy (DT) and patients starting HAART at the time of TB therapy initiation.
Table 2 – Patient characteristics by timing of HAART for TB/HIV co-infection.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Timing of HAART for HIV/TB co-infected patients</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST (n = 243)</td>
<td>DT (n = 194)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>35.8</td>
<td>36.0</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>70.8</td>
<td>69.1</td>
</tr>
<tr>
<td>Median CD4 at TB diagnosis</td>
<td>106</td>
<td>278</td>
</tr>
<tr>
<td>Median HIV VL at TB diagnosis</td>
<td>5.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Mortality at the end of follow-up (#, %)</td>
<td>25 (10.3)</td>
<td>31 (16.0)</td>
</tr>
</tbody>
</table>

Table 3 – Cox regression model, univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
<th>Adjusted HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.94 (0.68-1.30)</td>
<td>0.71</td>
<td>0.46 (0.21-1.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99 (0.98-1.01)</td>
<td>0.43</td>
<td>1.00 (0.97-1.04)</td>
<td>0.66</td>
</tr>
<tr>
<td>CD4 per 100 change HR (absolute)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.52</td>
<td>0.90 (0.66-1.22)</td>
<td>0.48</td>
</tr>
<tr>
<td>Deferred HAART</td>
<td>1.45 (1.05-2.00)</td>
<td>0.02</td>
<td>1.89 (1.05-3.40)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Stratified by propensity score quintile.

data strongly support the use of HAART in all patients with HIV-related TB as early after TB treatment as possible in Brazil, with a reduction in mortality that was even greater than what has been reported in recent clinical trials.4–7

HAART has been shown to decrease the incidence of TB in Africa,20,21 Brazil,22,23 and other developed and developing countries,24–26 and HAART strongly reduces mortality among patients co-infected with HIV and TB5,11 as seen in our study. The protection offered by HAART has been consistently seen across CD4 cell strata, but most markedly in patients with most advanced immunodeficiency.26,4–7 In our study, CD4 at the time of TB diagnosis did not independently impact survival among co-infected patients, though CD4 was significantly lower in patients starting HAART early. Most likely, the increase in the CD4 cell count explains most of the protection afforded by HAART, although other factors, such as HIV viral load and levels of other T cell subpopulations, may play a role.26 Patients who fail to increase their CD4 counts after HAART initiation are at higher risk of recurrent TB.27

Survival between the ST and DT groups did not begin to diverge until about 1.5 years following TB diagnosis, well after TB treatment had been completed. The SAPIt Trial in South Africa and the CAMELIA Trial also did not see a significant survival benefit until after six months of TB therapy.5,7

This clinical cohort study has some limitations. Our data were collected from patient medical records, and information on drug toxicity and IRIS was generally not available. Drug-related toxicity and IRIS events occur more commonly at lower CD4 counts and may affect morbidity, although clinical trials show no impact of IRIS on mortality. In addition, the THRio study is based on data abstracted from medical charts, and exposure to HAART was allocated at physicians’ discretion, based on the Brazilian Recommendations for Antiretroviral Therapy for Adults and Adolescents,19 which guides HIV care in Brazil. These guidelines have recently been updated stating that for patients with pulmonary TB with a cavitary lesion, a CD4 cell count should be conducted 30 days after starting TB treatment28 and that HAART should be started if CD4 count is less than 350 cells/mm³.

Conclusion

We showed that HAART initiated early after TB treatment in co-infected patients was associated with an 89% reduction in the risk of death compared to delayed HAART initiation. Thus, we provide further evidence of the importance of early HAART in increasing survival among HIV/TB co-infected patients. Strategies to promote the early diagnosis of HIV infection among TB patients and early initiation of HAART play important roles in improving the quality of care for patients co-infected with TB and HIV.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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