Prevalent Tuberculosis (TB) at HIV diagnosis in Rio de Janeiro, Brazil: The TB/HIV in Rio (THRio) Cohort

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Abstract

Background—Although Brazil has model HIV care programs, many patients continue to present late to care. We studied the frequency of tuberculosis (TB) diagnosed at HIV diagnosis in Rio de Janeiro, Brazil, in order to quantify missed opportunities for TB prevention.

Methods—People living with HIV (PLHIV) and enrolled in the TB/HIV in Rio (THRio) study between 1 September 2005 and 31 August 2009 were included. Prevalent TB was defined as TB diagnosed within 60 days of HIV diagnosis or HIV diagnosis during TB therapy. Survival was measured from HIV diagnosis. We conducted Kaplan-Meier survival plots and Cox regression analyses.

Results—4,548 newly diagnosed PLHIV were enrolled; 476 (10.5%) with prevalent TB. Prevalent TB cases were older, had lower CD4 counts and higher viral loads than those without TB. Median time to receiving highly active antiretroviral therapy (HAART) in prevalent TB cases was 99 days (IQR=58–191) vs. 126 days (IQR=63–301) in those without TB (p=0.021). Among prevalent TB cases, 17% died during follow-up compared to 8% among non-TB cases (p<0.001). After adjustment for sex, age, baseline CD4 and baseline viral load, risk of death remained significantly higher among prevalent TB cases [aHR=1.72 (CI 95% 1.19–2.48)].

Conclusions—More than 10% of newly PLHIV in our study presented to care with concurrent active TB disease and thus missed the opportunity for TB preventive therapy. Despite initiating
HAART more quickly, these were at significantly greater risk of death. Earlier HIV diagnosis is necessary to provide earlier initiation of HAART and TB preventive therapy to reduce morbidity and mortality in PLHIV.

Introduction

Although Brazil has been recognized as having model HIV/AIDS care programs, many patients continue to present late to care, thus, missing opportunities for preventive interventions and prolonging survival. In the early era of HIV/AIDS, co-trimoxazole prophylaxis became widely adopted as an effective measure to prevent Pneumocystis jirovecii pneumonia, and subsequently was shown to reduce morbidity and mortality in people living with HIV (PLHIV) in developing countries. Tuberculosis (TB) is now the leading killer of PLHIV, and highly active antiretroviral therapy (HAART) is the most effective way to reduce the risk of TB among them. However, mounting scientific evidence shows that isoniazid preventive therapy (IPT) reduces the risk of active TB and may reduce the risk of death in PLHIV with latent tuberculosis infection (LTBI). In Brazil, studies of IPT in PLHIV demonstrate reduced incidence of active TB and improved survival that is additive to the impact of HAART. Brazil has a high burden of TB in PLHIV, with most recent estimates stating that 9% of HIV deaths are due to TB. Brazilian guidelines recommending tuberculin skin tests and isoniazid preventive therapy for PLHIV have existed since 1995 and recent recommendations from the World Health Organization restate the need for IPT for PLHIV, though evidence in Brazil suggests that physicians do not adhere strictly to these guidelines.

Persons diagnosed with both HIV and TB simultaneously are missed opportunities for TB prevention. We report the frequency of TB at the time of HIV diagnosis in new patients entering the TB/HIV in Rio (THRio) study to quantify missed opportunities for TB prevention and to measure the impact on survival of newly diagnosed PLHIV co-infected with active TB disease in this population.

Methods

The THRio study was a cluster-randomized trial assessing the impact of implementing TB screening and IPT in public HIV clinics. THRio followed over 19,000 PLHIV receiving care in 29 public HIV clinics in Rio de Janeiro. Trained data collectors routinely abstracted clinical and laboratory data from clinic medical records in a standardized manner. TB in Brazil is commonly diagnosed without microbiological confirmation, thus for purposes of this analysis, we included TB diagnosed either through microbiological confirmation or clinical suspicion based on symptoms and chest radiographic findings as recorded in the medical records. Anti-tuberculosis therapy is only available through the public sector in Brazil and must be reported, thus we supplemented our case detection through linkage of THRio patients with the Brazilian Health System for Mandatory Reporting Diseases (SINAN). Deaths were ascertained through linkage to the Brazilian Health Information Systems for Death (SIM), as described elsewhere.
In this analysis, PLHIV entering care between 01 September 2005 and 31 August 2009 were included and followed until death (primary outcome of interest) or administratively censored at 31 December 2009. Prevalent TB was defined as TB diagnosed within 60 days following an HIV diagnosis, or a new HIV diagnosis made during the 180 days of standard TB therapy. All patients diagnosed with HIV should be screened for TB, thus we allowed for 60 days following HIV diagnosis for screening and laboratory results to be conducted and a TB diagnosis to be made. All patients diagnosed with TB should be screened for HIV; however, this screening is often delayed. Thus, we allowed for HIV results to be conducted during TB treatment and assumed that a positive HIV diagnosis during these 6 months meant that the patient had HIV at time of TB diagnosis. Thus, these two definitions were both considered to be prevalent TB in this analysis. Patients diagnosed with TB more than 180 days prior to HIV diagnosis were excluded from this analysis.

Survival was measured from HIV diagnosis date, comparing those with prevalent TB to those who entered the cohort TB-free (not prevalent or not concurrent TB). Only death or administrative censoring ended follow-up; thus other opportunistic infections, including TB, were not censoring variables. Patient demographics and other characteristics related to HIV care were compared between prevalent and TB-free cases using the chi-square test and t-test. We generated Nelson-Aalen cumulative hazard plots and we conducted Cox proportional hazards regression analyses. All analyses were performed using STATA statistical package (version 11; College Station, Texas).

Results

In the study period, 4,548 patients entered care with newly diagnosed HIV, of whom 476 (10.5%) were diagnosed with prevalent TB. There were 168 patients who were diagnosed with HIV during TB therapy and 308 patients diagnosed with TB within the first 60 days following HIV diagnosis. These two groups were similar regarding sex, age, baseline viral load, and days from HIV diagnosis until HAART began, and death, however, the group with TB diagnosed first had higher baseline CD4 (206 vs 133; p=0.041). There were 162 (3.6%) patients who had a TB diagnosis more than 180 days before their HIV diagnosis date and were excluded from the present analysis.

Prevalent TB patients were more likely to be male and slightly older than non-prevalent TB patients (Table 1). Prevalent TB patients had significantly lower CD4 counts (median: 162 cells/mm$^3$ (interquartile range (IQR: 62–297) vs. 315 cells/mm$^3$ (IQR: 148–511), p<0.001) at HIV diagnosis and slightly higher viral loads (median: 4.4 log (IQR: 2.3–5.1) vs. 4.1 log (IQR: 3.0–4.8), p=0.34) than those without TB. The median time to initiation of HAART after HIV diagnosis in prevalent TB cases was 99 days (IQR=58–191) compared to 126 days (IQR=63–301) in those without TB (p=0.02); 75% of the prevalent TB cases ever started HAART compared to 60% among non-prevalent TB patients (p<0.001).

Among prevalent TB patients, 81 (17%) died during follow-up versus 317 (8%) among TB-free patients (p<0.0001) and the hazard of death among prevalent TB cases was significantly greater (log-rank test, p<0.001; Figure 1). Among prevalent TB patients, those who died were less likely to initiate HAART than those who survived (65% vs. 77%, p=0.02) and
received HAART for a shorter median period of time (181 (IQR: 29 – 376) vs. 828 days (IQR: 451 – 1,157), p=0.02). Prevalent TB patients who died were less likely to have a CD4 count (52% vs. 92%; p<0.001) or a viral load (46% vs. 87%; p<0.001) assay performed at baseline than those who survived (Table 2).

Cox proportional hazards regression analysis showed that prevalent TB patients had a greater risk of death versus patients without prevalent TB [HR=2.33 (95% CI 1.82–2.97) p<0.001]. After adjustment for sex, age, baseline CD4 cell count and baseline viral load, the hazard of death remained significantly greater for prevalent TB cases [aHR=1.72 (CI 95% 1.19–2.48)] (Table 3). Risk of death was inversely associated with baseline CD4 cell count.

Discussion

In this cohort of newly diagnosed PLHIV, a concurrent TB diagnosis was detected in 10.5% of patients and these patients had a significantly greater risk of death despite receiving HAART earlier than newly diagnosed PLHIV without TB. PLHIV are at great risk for TB and though effective preventive therapy is available\textsuperscript{10}, patients newly diagnosed with TB at the time of HIV diagnosis represent missed opportunities for prevention. These patients, in addition to the 3.6% of the population with a prior TB diagnosis at time of HIV diagnosis, suggest that HIV diagnoses are not being made early enough in Brazil.

Late diagnosis of HIV in Brazil has been well documented\textsuperscript{21,22}, with over 40% of patients considered late entries into care\textsuperscript{22}. In our study, patients with prevalent TB at HIV diagnosis entered care later than expected, as evidenced by lower median CD4 cell counts (162 cells/mm\textsuperscript{3}) than the TB-free population (315 cells/mm\textsuperscript{3}) at time of HIV diagnosis. In Brazil, access to HIV care and universal provision of antiretroviral therapy should prompt earlier HIV diagnosis, thus providing PLHIV more opportunities for prevention of opportunistic infections\textsuperscript{21}. Access to antiretroviral therapy has been shown to improve survival since the early days of combined antiretroviral therapy\textsuperscript{22}, and in a scenario of universal access to HAART like Brazil, a reduction of 43% in mortality has been shown\textsuperscript{2}, comparable to outcomes in the developed world\textsuperscript{23}. Research in Brazil suggests that late entry into HIV care is likely greatest in regions of lower economic development where there are barriers to accessing health care\textsuperscript{22}. Thus, our data adds to the evidence that despite free access to HIV diagnosis and testing in Brazil, uptake is poor.

In people with both TB and HIV diseases, HAART significantly improves survival when given within the first two months of TB therapy\textsuperscript{24–27}, but survival is still poorer after a TB episode\textsuperscript{27–29}. Late presentation to care among people living with HIV can reduce the odds of survival, and in Brazil late entry increased AIDS mortality probability in the first year in 36% of patients\textsuperscript{2}, and has impaired the outcome of people living with HIV in the US as well\textsuperscript{3}. Prevalent TB at baseline or soon after HIV diagnosis were strongly associated with elevated mortality risk in a recent South Africa study\textsuperscript{30}. In our study, death among patients presenting with prevalent TB was higher for those who never received HAART; the median time to HAART among the prevalent TB cases was 99 days, strongly suggesting that “unmasking TB” following HAART initiation was not a concern, as has been suggested by others\textsuperscript{31}.
Early provision of HAART is the primary benefit of early HIV diagnosis, though, given the high prevalence of TB at or immediately after HIV diagnosis in high TB incidence settings, the window of opportunity to provide IPT and prevent TB was closed for many as TB was present at time of HIV diagnosis. Scaling up of programs to implement IPT for PLHIV are expanding globally, but uptake remains low, particularly for patients presenting with advanced HIV infection. The THRio study aimed to implement IPT according to Brazilian guidelines and was successful in reducing both the time to tuberculin skin testing (TST) and to IPT after a positive TST, and reduced TB incidence and death in this population.

Active TB case finding among newly diagnosed PLHIV is a World Health Organization recommendation as part of the 3 I’s Initiative, which also strongly recommends IPT preventive therapy. In our study population, TB diagnosis led to an HIV diagnosis in 168 patients, and TB was diagnosed in the first 60 days after the HIV diagnosis in 308 patients. Delays in diagnosing PLHIV are life-threatening, and the prognosis for HIV-infected patients with prevalent TB is poor compared to those who are TB free. Efforts to increase HIV testing are necessary, as is further integration of HIV and TB services if progress in the battle against this dual epidemic is to be made.

Conclusion

More than 10% of newly diagnosed PLHIV in our study presented to care with concurrent active TB disease and thus missed the opportunity for TB preventive therapy. Despite initiating HAART more quickly, these patients were at significantly greater risk of death. Only achieving consistent and widely accessible early HIV diagnosis will lead to early initiation of HAART and IPT and corresponding reductions in morbidity and mortality in Brazil.

Acknowledgments

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References


Figure 1.
Cumulative hazard of death in newly HIV-diagnosed patients in the THRio cohort, prevalent TB versus no concurrent TB.
Table 1


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prevalent TB (n=476)</th>
<th>No concurrent TB (n=4,072)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>330 (69%)</td>
<td>2,552 (63%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (median; IQR)</td>
<td>37 (30–45)</td>
<td>35 (29–44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline CD4 (median; IQR, cells/mm³)</td>
<td>162 (62–297)</td>
<td>315 (148–511)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 assay performed (baseline)</td>
<td>85%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline viral load log (median; IQR)</td>
<td>4.4 (2.3–5.1)</td>
<td>4.1 (3.0–4.8)</td>
<td>0.338</td>
</tr>
<tr>
<td>HAART (ever)</td>
<td>75%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days to HAART (median; IQR)</td>
<td>99 (58–191)</td>
<td>126 (63–301)</td>
<td>0.021</td>
</tr>
<tr>
<td>Death</td>
<td>81 (17%)</td>
<td>317 (8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2

Characteristics of deceased and alive patients at the end of follow-up among those diagnosed with prevalent TB (n=476).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dead (n=81)</th>
<th>Not dead (n=395)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known CD4 at baseline</td>
<td>52%</td>
<td>92%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known viral load at baseline</td>
<td>46%</td>
<td>87%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAART ever</td>
<td>65%</td>
<td>77%</td>
<td>0.022</td>
</tr>
<tr>
<td>Median time on HAART (days)</td>
<td>181</td>
<td>828</td>
<td>0.021</td>
</tr>
<tr>
<td>Median survival time (days)</td>
<td>218</td>
<td>975</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table 3

Characteristics associated with death, multivariable Cox proportional hazards analysis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent TB</td>
<td>1.72</td>
<td>1.19 – 2.48</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.93</td>
<td>0.69 – 1.26</td>
<td>0.642</td>
</tr>
<tr>
<td>Age (10 years)</td>
<td>1.10</td>
<td>0.97 – 1.26</td>
<td>0.148</td>
</tr>
<tr>
<td>CD4 &lt; 200*</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 200 – 349*</td>
<td>0.46</td>
<td>0.31 – 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 350 – 499*</td>
<td>0.43</td>
<td>0.28 – 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 &gt;=500*</td>
<td>0.24</td>
<td>0.14 – 0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Viral load (log)</td>
<td>1.33</td>
<td>1.20 – 1.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* cells/mm$^3$