High Mortality From TB–Histoplasmosis Coinfection in HIV in Latin America and the Caribbean

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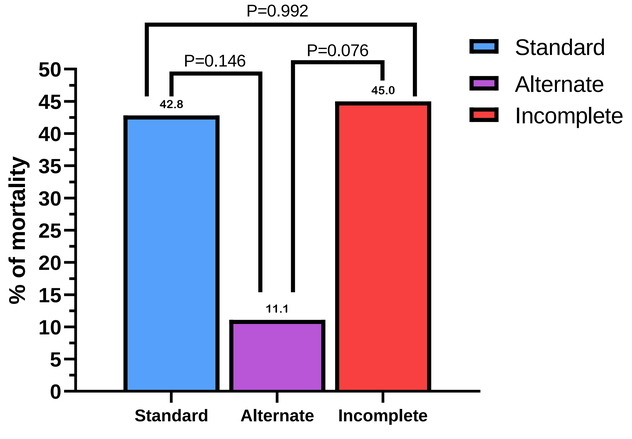
BACKGROUND

Tuberculosis (TB) and histoplasmosis are major opportunistic infections in people with advanced HIV (AHD) in Latin America and the Caribbean (LAC), with histoplasmosis occurring in 15–40% of TB cases and complicating treatment due to drug interactions and overlapping toxicities. Despite this, evidence on prevalence, outcomes, and optimal therapy remains limited, and as expanded AHD care increases diagnosis, stronger data are urgently needed to guide effective treatment.

METHODS

- Pooled data from 4 prospective implementation studies of rapid tests for OIs in people with AHD in LAC.
- Inclusion criteria: CD4 counts <200 cells/µL or symptoms suggestive of an opportunistic infection.
- TB and Histoplasmosis were diagnosed with either a positive rapid test (Abbott TB-LAM or Xpert for TB and IMMY EIA or Miravista LFA for Histoplasmosis) or standard microbiological methods (culture and histopathology).
- Univariate logistic regression for predictors of mortality among co-infected individuals at 365 days of follow-up.
- TB/Histoplasmosis treatment schemes were classified on:
  - Standard: H/R/Z/E for TB and Amphotericin followed by Itraconazole for Histoplasmosis
  - Alternative: those that replaced rifampicin by levofloxacin (or added it to the scheme) for TB or the substitution of itraconazole by fluconazole for histo.
  - Incomplete: missed treatment for TB and/or histo.
- Compared mortality at 365 days of follow-up between schemes using ANOVA with Bonferroni correction.

Figure 1. mortality comparison between treatment schemes



In people with advanced HIV disease TB–histoplasmosis co-infection causes a 4-fold higher mortality (compared to TB mono-infection).

RESULTS

- We included 1,282 individuals with AHD, 108 (8.4%) had histoplasmosis and 325 (25.3%) had TB.
- 46 of the 325 TB cases (14.1%) had histoplasmosis co-infection (median CD4 count 42 cells/mm³). Data on treatment available only for 43 of 46 cases (table 1).
- Mortality at 90 days: TB 7.8%, and TB/histoplasmosis co-infection 34.6%, no TB or histo 7.2%.
- Mortality at 365 days: TB monoinfection 9.3% and TB/histoplasmosis co-infection 41.9% (p<0.001).
- Mortality at 365 days only on individuals that received directed treatment for TB and/or histoplasmosis: TB monoinfection 5.2% and TB/histoplasmosis co-infection 25% (p=0.043).
- Severe histoplasmosis (OR 16.46, p<0.001), TB meningitis (OR 4.96, p=0.026), and lower CD4 counts (OR 0.97, p=0.014) were associated with increased mortality at 365 days.
- Schemes recieved: standard 7 (16.3%), alternative 9 (20.9%), incomplete (46.5%), only AMB 8 (18.6%).
- Receiving standard schemes showed no differences in mortality when compared with receiving schemes that excluded treatment for TB and/or histoplasmosis (42.8% vs. 45%, p=0.922) (Figure 1).
- All individuals that received histo schemes of only amphotericin B, died in the first 10 days of treatment.

Table 1. Treatment schemes for TB and histoplasmosis and mortality rates at 365 days

TB Tx \ Histo Tx	AMB+ITC	Alternative Histo Tx		No histo Tx	Total
		AMB+FLC	Only Amb		
H/R/Z/E	3/7 (42.8%)	1/5 (20%)	5/7 (71.4%)	0/2 (0%)	9/21 (42.8%)
Alternative TB Tx	0/4 (0%)	0 (0%)	0 (0%)	0/1 (0%)	0/5 (0%)
No TB Tx	1/2 (50%)	1/1 (100%)	1/1 (100%)	6/13 (46.1%)	9/17 (52.9%)
Total	4/13 (30.8%)	2/6 (33.3%)	6/8 (75%)	6/16 (37.5%)	18/43 (41.9%)

Absolute number of people treated with the regimen is shown in each cell as (individuals that died by 365-days follow-up/total individuals), and percentage of mortality at 365 days in parenthesis. Tx: treatment; AMB, Amphotericin B (either Deoxycholate or Liposomal); E, Ethambutol; FLC, Fluconazole; H, Isoniazid; ITC, Itraconazole; R, Rifampicin; Z, Pyrazinamide.

CONCLUSIONS

- In LAC, TB-histoplasmosis co-infection is frequent; among individuals with AHD.
- TB-histoplasmosis coinfection is associated with a 4-fold higher mortality compared to TB monoinfection.
- Several gaps in management still exist, with nearly half of all individuals receiving incomplete OI treatment.
- Standard treatments for TB-histoplasmosis seems no to have a better outcome compared to no treatment for TB, histoplasmosis or both.
- Evaluation of optimal treatment schemes for TB-histoplasmosis coinfection is an urgent priority.

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PLAIN LANGUAGE SUMMARY

In people with advanced HIV in Latin America, tuberculosis (TB) and histoplasmosis often occur together, yet this co-infection remains widely under-researched. We found that people with both infections were more than four times as likely to die, and that standard first-line treatments for each disease are not effectively reducing mortality. More research is urgently needed to identify better treatment options.

