Mortality in Adults HIV/MDR-TB by ART Use: Individual Patient Data Meta Analysis

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BACKGROUND

HIV-infection is associated with increased mortality during multidrug-resistant tuberculosis (MDR-TB – defined as resistance to rifampin and isoniazid) treatment, but factors affecting this risk are unclear. ***We examined how HIV, the use of anti-retroviral therapy (ART) and TB medications modify MDR-TB mortality.***

METHODS

- **Design and Population:** We conducted an **individual patient data meta-analysis** including adults ≥18 years with MDR-TB initiating TB treatment between 1993 and 2016. XDR- and pre-XDR-TB patients were also included. Search strategy available upon request.
- **Data:** Data included age, sex, HIV status, ART use (ever during TB treatment), antitubercular drugs used during MDR-TB treatment, drug resistance profile at baseline, World Bank Income category of treatment country, MDR-TB treatment year, AFB smear status, use of directly observed therapy (DOT), previous TB treatment, and use of TB medications during MDR-TB treatment grouped according to World Health Organization (WHO) effectiveness categorizations. Group A drugs are levo/moxifloxacin, bedaquiline, and linezolid.
- The **primary outcome** was death during MDR-TB treatment and was assessed among those not lost to follow-up. Multiple imputation addressed missing data.
- **Analyses** used logistic regression after ***exact matching*** on country World Bank Income level and drug resistance and ***propensity-score matching*** on age, sex, geographic site, MDR-TB treatment year, previous TB treatment, DOT, and AFB status.
- **Secondary analyses included:**
  - Analyses among those with HIV-infection
  - Survival analyses

Among nearly 10,000 patients with MDR-, pre-XDR-, and XDR-TB, HIV-infected patients were at increased risk of death during treatment, but ART use substantially decreased this risk. Use of WHO Group A Drugs - bedaquiline, linezolid and moxifloxacin/levofloxacin - also reduced the risk of death.

Table 2. Associations Between HIV, ART and Death during MDR-TB treatment

Adjusted Odds Ratios with 95% CIs	HIV-infected vs HIV-uninfected	HIV-infected on ART vs HIV-uninfected	HIV-infected not on ART vs HIV-uninfected
	aOR = 2.2 (1.8, 2.6)	1.7 (1.3, 2.0)	4.1 (2.8, 6.0)

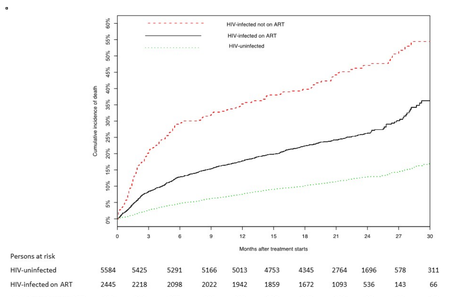
All aORs are exactly and propensity score matched as described in Methods. In addition, all estimates are adjusted for the number of effective drugs in the regimen AND the number of effective Group A drugs

RESULTS

- Individual patient data came from ***52 studies from 37 countries*** and regions including 11,920 patients with MDR-TB, 3,883 (33%) and 2,997 (25%) of whom were HIV-infected and HIV-infected on ART, respectively. The largest data set was from South Africa (n=3,474 patients).
- 1,749 (15%) had XDR-TB. 16 (0.1%) had RR-TB.
- Nearly all (11,437, 96%) had pulmonary disease only.
- Patient and treatment characteristics differed by HIV and ART status (**See *Table 1*; all p<0.001**).
- **Among 9,905 not lost to follow-up, 1,853 (19%) patients died, 971 (52%) of whom were HIV-infected.**
- **Associations with death are shown in *Table 2*, above.**
- **Associations of TB drugs with death among only those with HIV are shown in *Table 3*. Associations were similar for those on ART (not shown).**
- **Survival differed by ART status (*Figure*; p<0.001)**

Table 3. TB drug use and death among HIV-infected

Number of effective Group A drugs used[2]	Adjusted OR of death (95% CI)
0	Reference
1	**0.53 (0.37, 0.74)**
2 or more	**0.26 (0.18, 0.38)**
Moxifloxacin or levofloxacin use[3]	
Not used or used but resistant	Reference
Used and sensitive	**0.58 (0.45, 0.75)**
Bedaquiline & linezolid use[3]	
Neither used	Reference
Used linezolid but not bedaquiline	0.87 (0.44, 1.70)
Used bedaquiline but not linezolid	**0.53 (0.38, 0.74)**
Used both linezolid and bedaquiline	**0.34 (0.25, 0.46)**



CONCLUSIONS

- HIV infection is associated with an increased risk of death, but ART use reduces this risk substantially.
- Use of WHO Group A TB drugs also reduces the risk of death among those with HIV.
- Availability of Group A drugs and ART for those with HIV and MDR-TB remains heterogenous.
- Access to these core components of MDR-TB care should be urgently increased.
- Missing data and residual confounding are limitations.

Table 1: Patient Characteristic

	HIV-uninfected (N=8037)	HIV-infected (N=3883)	HIV-infected, on ART (N=2997)	HIV-infected, not known to be on ART (N=886)[3]
Age, mean (range)	38.6 (1894)	36.01 (18;76)	36.5 (18;94)	34.4 (18;73)
Sex, n (%)[4]				
Male	5314 (66%)	2020 (52%)	1564 (52%)	456 (51%)
Female	2722 (34%)	1862 (48%)	1432 (48%)	430 (49%)
Acid-fast bacilli smear status, n (%)				
Positive	4770 (59%)	2303 (59%)	1950 (65%)	353 (40%)
Negative	1583 (20%)	1168 (30%)	1016 (34%)	152 (17%)
Unknown	1684 (21%)	412 (11%)	31 (1%)	381 (43%)
Year of MDR-TB treatment initiation, median (IQR)	2008 (2006; 2012)	2015 (2008; 2015)	2015 (2015; 2016)	2006 (2002; 2008)
World Bank Income classification level, n (%)				
Low and low-middle	2421 (30%)	130 (3%)	115 (4%)	15 (2%)
Upper-middle	3244 (40%)	3585 (92%)	2786 (93%)	799 (90%)
High	2372 (30%)	168 (4%)	96 (3%)	72 (8%)
Drug resistance profile, n (%)[5]				
MDR, without fluoroquinolone or second-line injectable resistance	4863 (63%)	2542 (67%)	1921 (65%)	621 (74%)
MDR, fluoroquinolone susceptible but with any second-line injectable resistance	985 (13%)	301 (8%)	255 (9%)	46 (5%)
MDR, fluoroquinolone resistant but without any second-line injectable resistance	809 (11%)	230 (6%)	209 (8%)	21 (2%)
XDR, with both fluoroquinolone and any second-line injectable resistance	1031 (13%)	718 (19%)	564 (19%)	154 (18%)
Number of effective Group A drugs used, n (%)[6]				
0	3012 (37%)	1201 (31%)	515(17%)	686 (77%)
1	3929 (49%)	1800 (46%)	1629 (54%)	171 (19%)
2 or more	1096 (14%)	882 (23%)	853 (28%)	29 (3%)
Fluoroquinolone use, n (%)				
Used ofloxacin or ciprofloxacin	2543 (32%)	772 (20%)	203 (7%)	569 (64%)
Used moxifloxacin or levofloxacin[8]	5014 (62%)	2790 (72%)	2579 (86%)	211 (24%)
No fluoroquinolone used	480 (6%)	321 (8%)	215 (7%)	106 (12%)
Bedaquiline & linezolid use, n (%)				
Neither used	6273 (78%)	2854 (73%)	2015 (67%)	839 (95%)
Used linezolid but not bedaquiline	656 (8%)	74 (2%)	66 (2%)	8 (1%)
Used bedaquiline but not linezolid	475 (6%)	365 (9%)	344 (11%)	21 (2%)
Used both linezolid and bedaquiline	633 (8%)	590 (15%)	572 (19%)	18(2%)

1. All p-values <0.001. 2. Because of rounding, percentages might not add to 100%. 3. WHO classification: Group A drugs are bedaquiline, moxifloxacin, levofloxacin and linezolid. Efficacy was estimated based on imputed drug susceptibility testing results.

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