Full Title: Comorbidities and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis

Short Title: Treatment outcomes in MDR/XDRTB

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Registration: Protocol Registered in Prospero:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016039866

Conflicts of Interest: No authors have any relevant conflict of interests.

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Appendix:

Search Strategy: We will conduct the following searches for each of the listed databases.

MEDLINE via OVID SP

1. Exp Tuberculosis, Multidrug-Resistant/
2. MDRTB.mp.
3. MDR TB.mp.
4. MDR-TB.mp.
5. MDR Tuberculosis.mp.
6. Multi*drug resistan* TB.mp.
7. Multi*drug resistan* Tuberculosis.mp.
8. (tuberculosis adj10 multi* drug resistan*).mp.
9. (tuberculosis adj10 MDR).mp.
10. (TB adj10 MDR).mp.
11. (TB adj10 multi* drug resistan*).mp.
12. extensive* drug resistan* tuberculosis.mp.
13. extensive* drug resistan* TB.mp.
14. XDR Tuberculosis.mp.
15. XDR TB.mp.
16. XDR-TB.mp.
17. XDRTB.mp.
18. (tuberculosis adj10 extensive* drug resistan*).mp.
19. (tuberculosis adj10 XDR).mp.
20. (TB adj10 XDR).mp.
21. (TB adj10 extensive* drug resistan*).mp.
22. exp Extensively Drug-Resistant Tuberculosis/
23. exp Treatment Outcome/
24. outcom*.mp.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
26. 23 or 24
27. 25 AND 26
28. limit 27 to English, French or Spanish language, Humans and 1980-2016

EMBASE via OVID SP

1. exp multidrug resistant Tuberculosis/
2. MDRTB.mp.
3. MDR TB.mp.
4. MDR-TB.mp.
5. Multi*drug resistan* TB.mp.
6. Multi*drug resistan* Tuberculosis.mp.
7. MDR Tuberculosis.mp.

8. (tuberculosis adj10 MDR).mp.
9. (tuberculosis adj10 multi* drug resistan*).mp.
10. (TB adj10 MDR).mp.
11. (TB adj10 multi* drug resistan*).mp.
12. exp extensively drug resistant tuberculosis/
13. extensive* drug resistan* TB.mp.
14. extensive* drug resistan* Tuberculosis.mp.
15. XDR Tuberculosis.mp.
16. XDRTB.mp.
17. XDR TB.mp.
18. XDR-TB.mp.
19. (tuberculosis adj10 extensive* drug resistan*).mp.
20. (tuberculosis adj10 XDR).mp.
21. (TB adj10 extensive* drug resistan*).mp.
22. (TB adj10 XDR).mp.
23. exp Treatment outcome/
24. outcom*.mp.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
26. 23 or 24
27. 25 AND 26
28. Limit 27 to English, French or Spanish language, Humans and 1980-2016

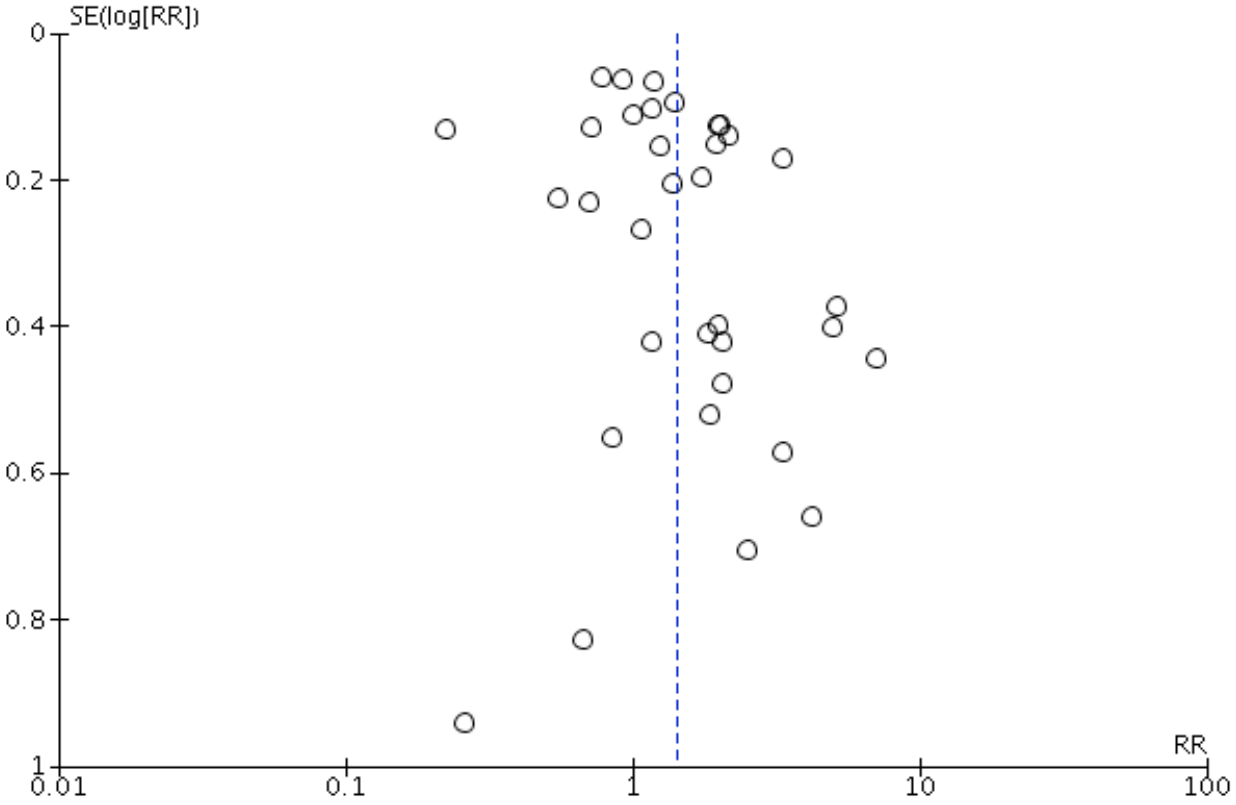
Cochrane Database of Systematic reviews via OVID

1. Multi*drug resistan* tuberculosis.mp.
2. Extensive* drug resistan* tuberculosis.mp.
3. XDR-TB.mp.
4. XDR TB.mp.
5. MDR TB.mp.
6. MDR-TB.mp.
7. (tuberculosis adj10 MDR).mp.
8. (tuberculosis adj10 multi* drug resistan*).mp.
9. (TB adj10 multi* drug resistan*).mp.
10. (TB adj10 MDR).mp.
11. (tuberculosis adj10 XDR).mp.
12. (tuberculosis adj10 extensive* drug resistan*).mp.
13. (TB adj10 XDR).mp.
14. (TB adj10 extensive* drug resistan*).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

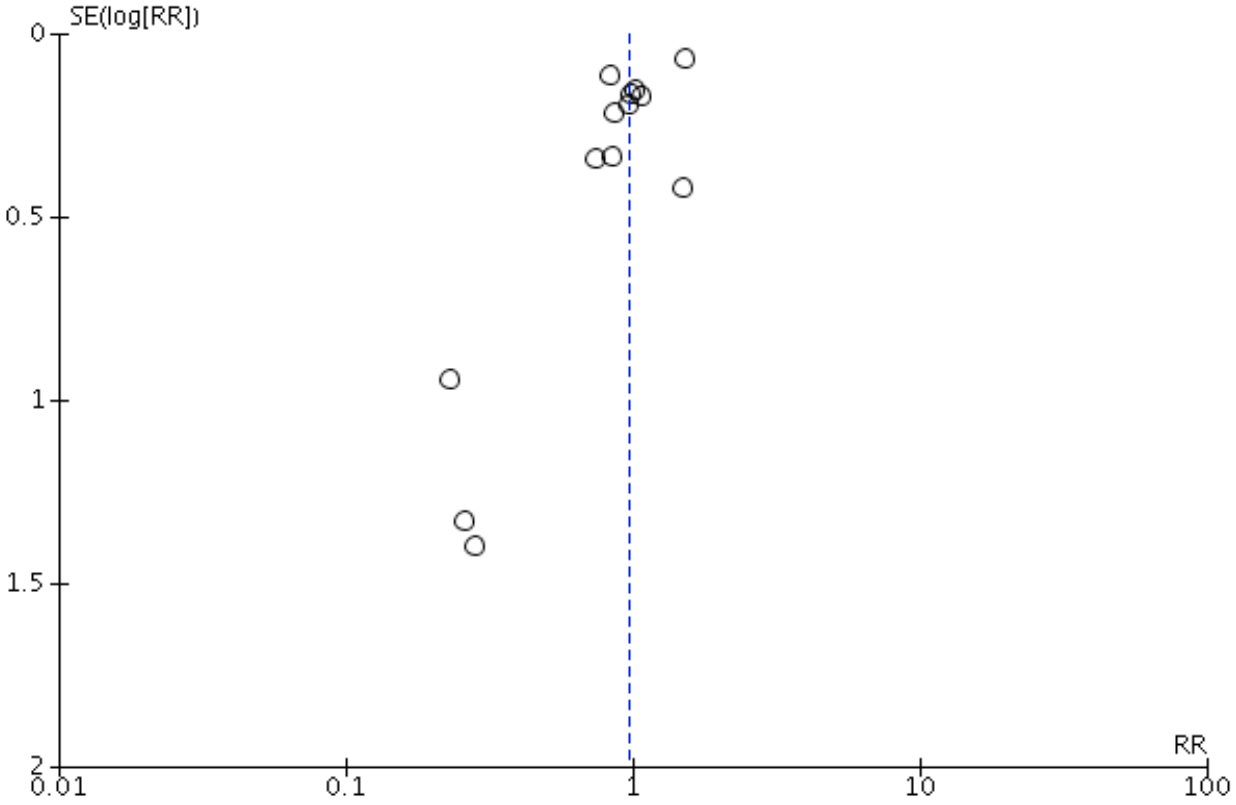
Cochrane Central Register of Controlled Trials via OVID

1. exp Tuberculosis, Multidrug-Resistant/
2. exp Extensively Drug-Resistant Tuberculosis/
3. extensive* drug resistan* Tuberculosis.mp.

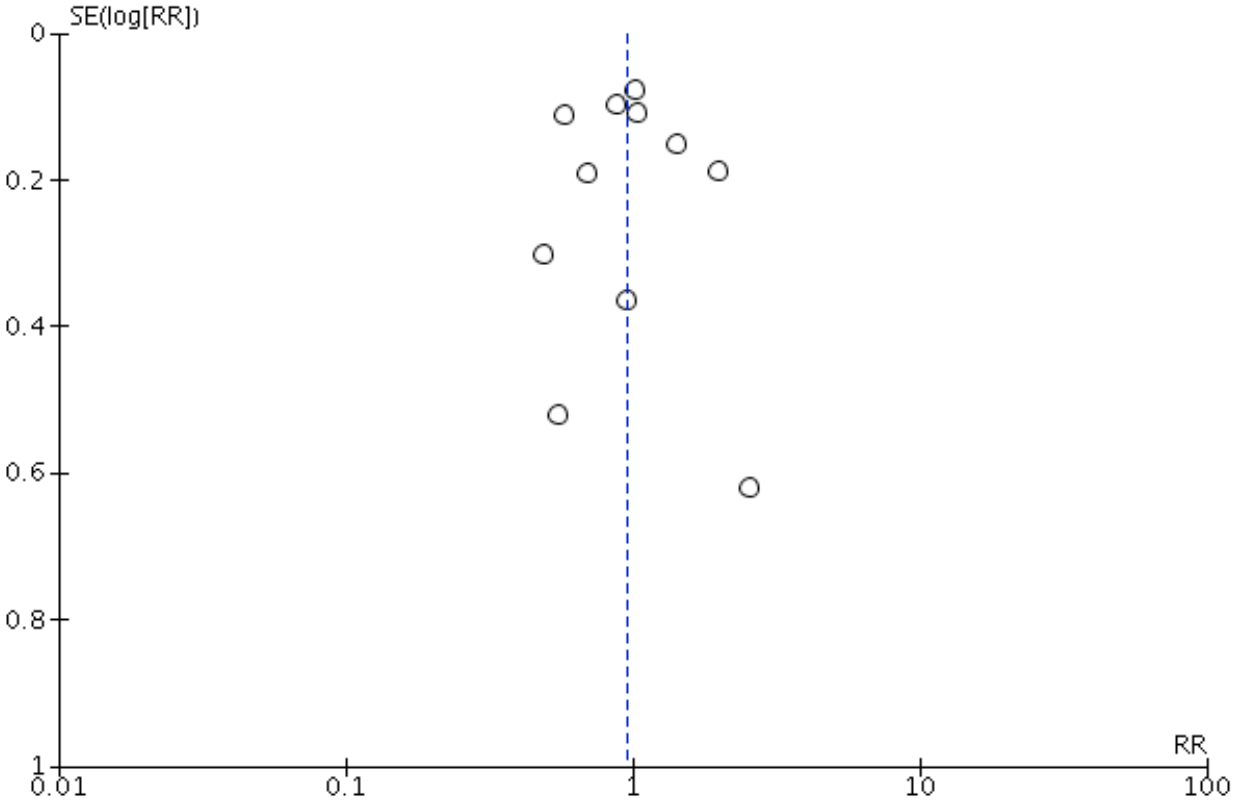
4. extensive* drug resistan* TB.mp.
5. XDRTB.mp.
6. XDR-TB.mp.
7. XDR TB.mp.
8. XDR Tuberculosis.mp.
9. MDRTB.mp.
10. MDR-TB.mp.
11. MDR TB.mp.
12. MDR Tuberculosis.mp.
13. Multi*drug resistan* Tuberculosis.mp.
14. Multi*drug resistan* TB.mp.
15. (tuberculosis adj10 extensive* drug resistan*).mp.
16. (tuberculosis adj10 XDR).mp.
17. (tuberculosis adj10 MDR).mp.
18. (tuberculosis adj10 multi* drug resistan*).mp.
19. (TB adj10 XDR).mp.
20. (TB adj10 extensive* drug resistan*).mp.
21. (TB adj10 multi* drug resistan*).mp.
22. (TB adj10 MDR).mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. Limit 19 to English, French or Spanish Languages and 1980-2016



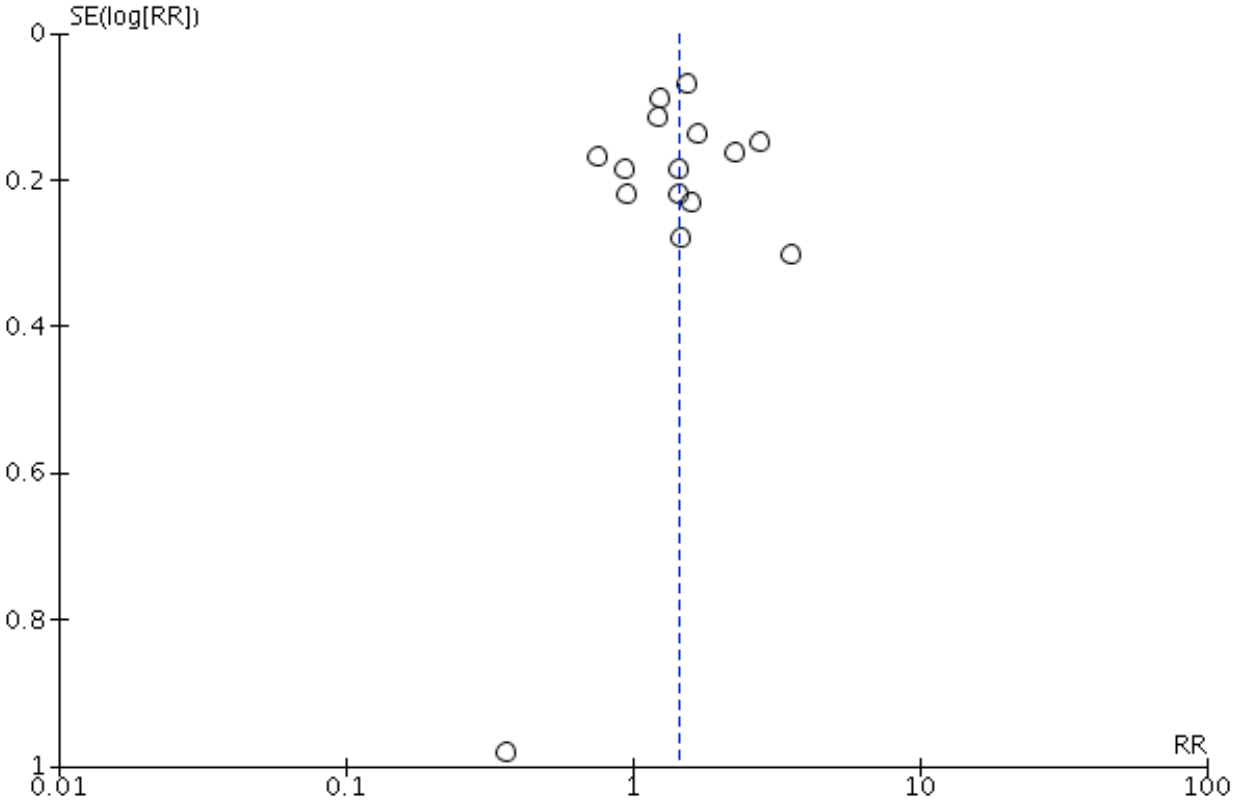
Supp. Fig. 1: Funnel plot for the effect of HIV on the primary outcome in MDR/XDRTB.



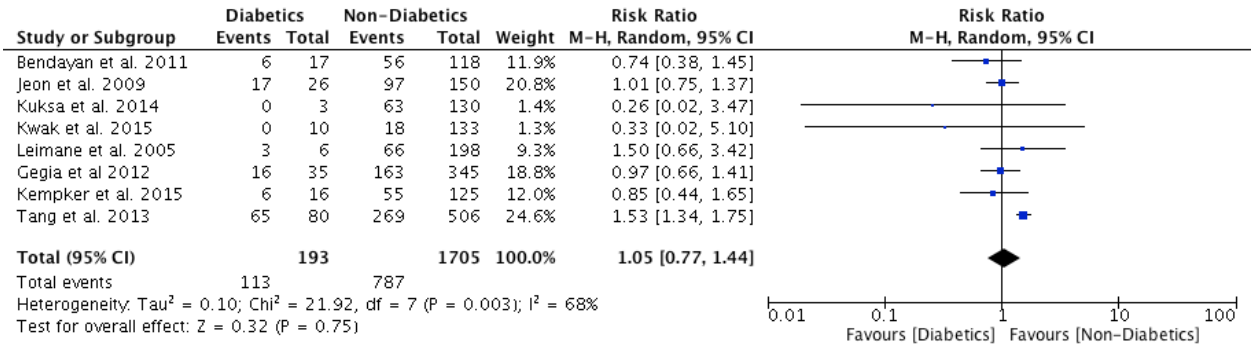
Supp. Fig. 2: Funnel plot for the effect of DM on the primary outcome in MDR/XDRTB.



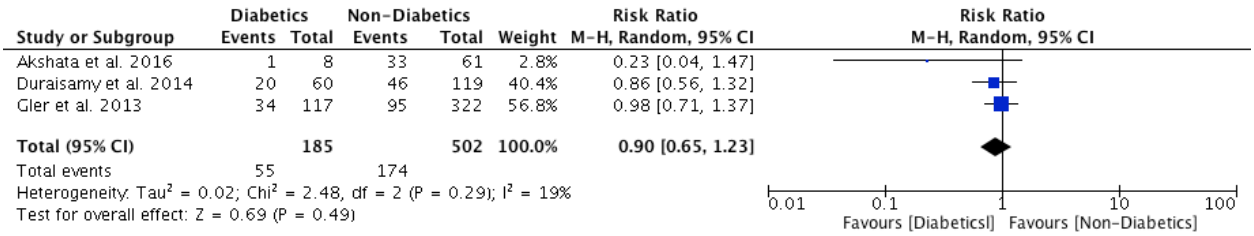
Supp. Fig. 3: Funnel plot for the effect of smoking on the primary outcome in MDR/XDRTB.



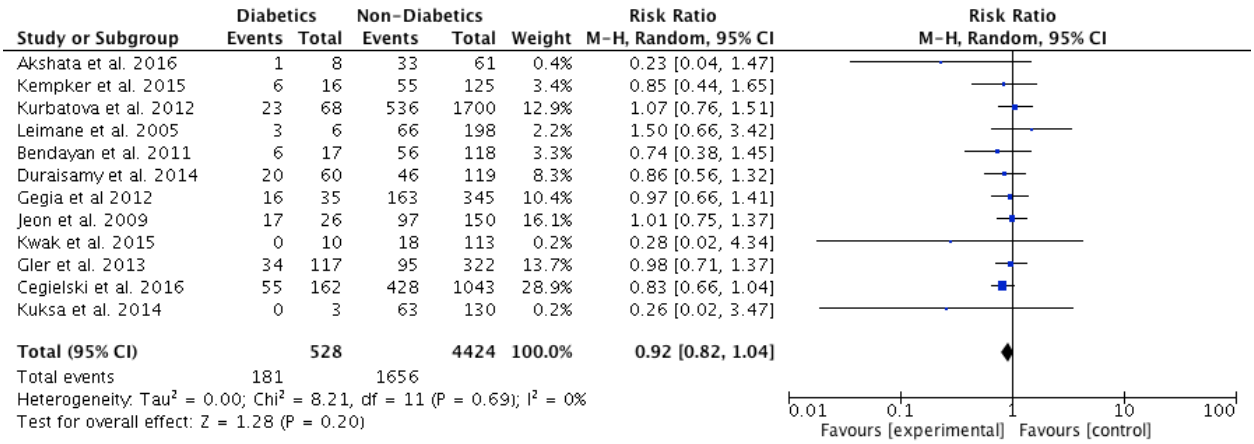
Supp. Fig. 4: Funnel plot showing the effect of alcohol misuse on the primary outcome in MDR/XDRTB.



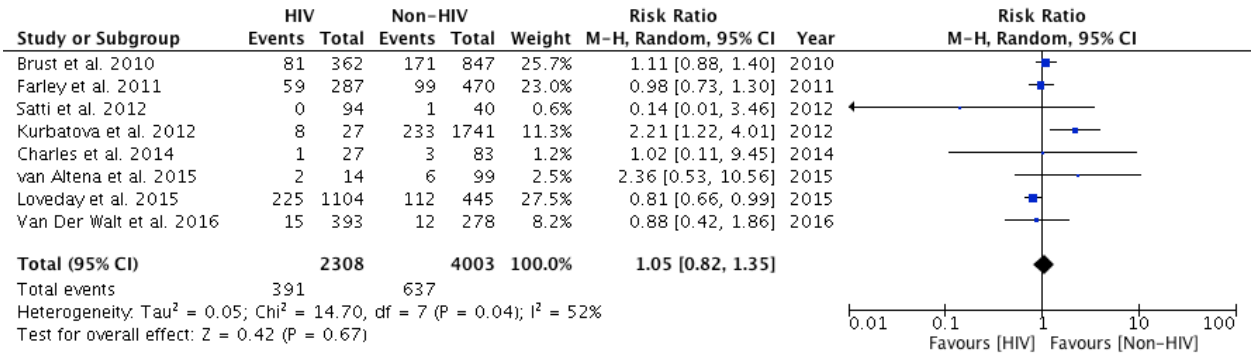
Supp. Fig. 5: Relative Risk of the primary outcome in MDR/XDRTB in those with and without DM in high GDP Countries.



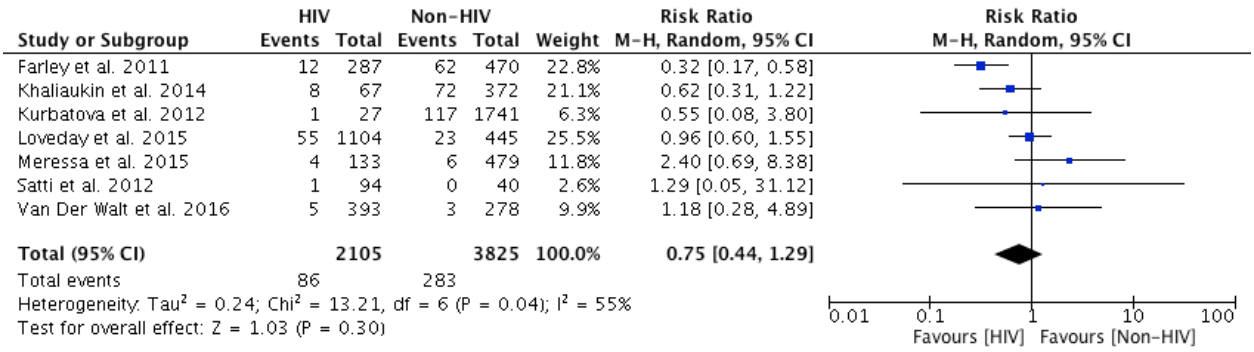
Supp. Fig. 6: Relative Risk of the primary outcome in MDR/XDRTB in those with and without DM in low GDP Countries.



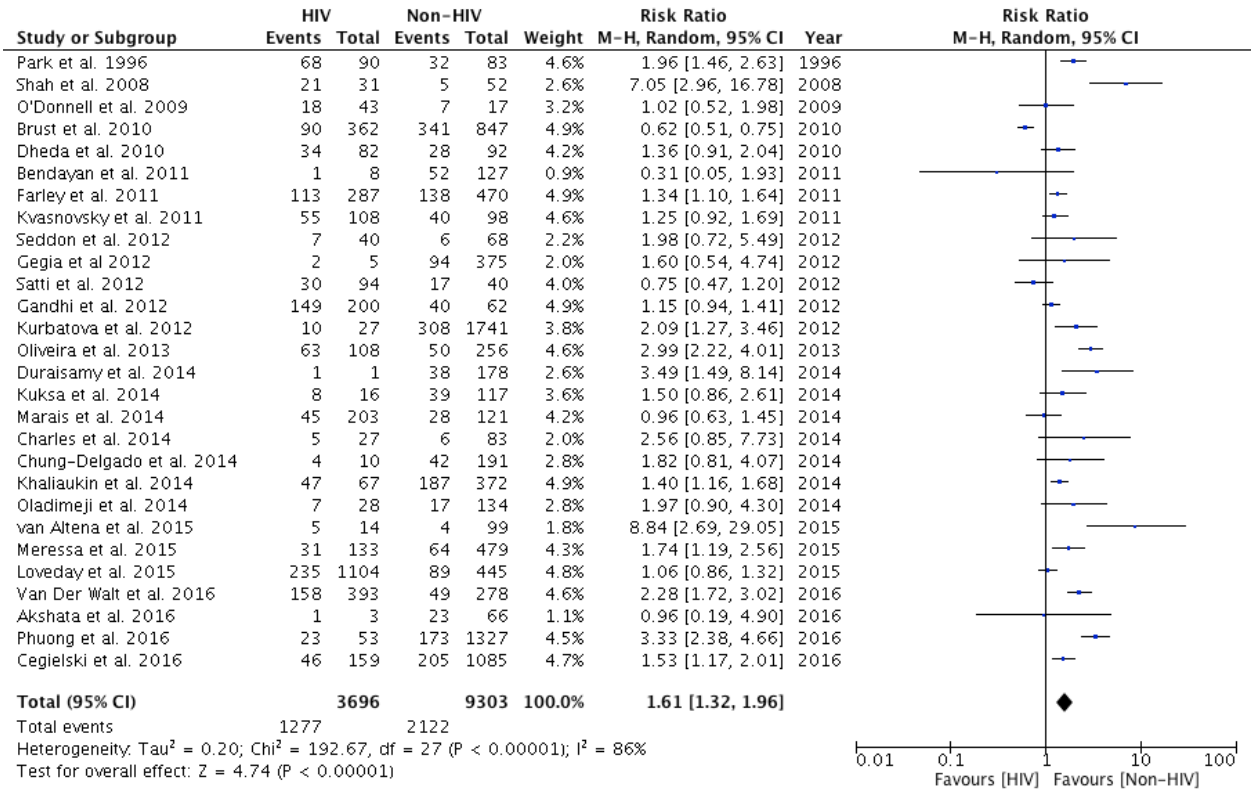
Supp. Fig. 7: Relative Risk of the primary outcome in MDR/XDRTB in those with and without DM from low to high quality study.



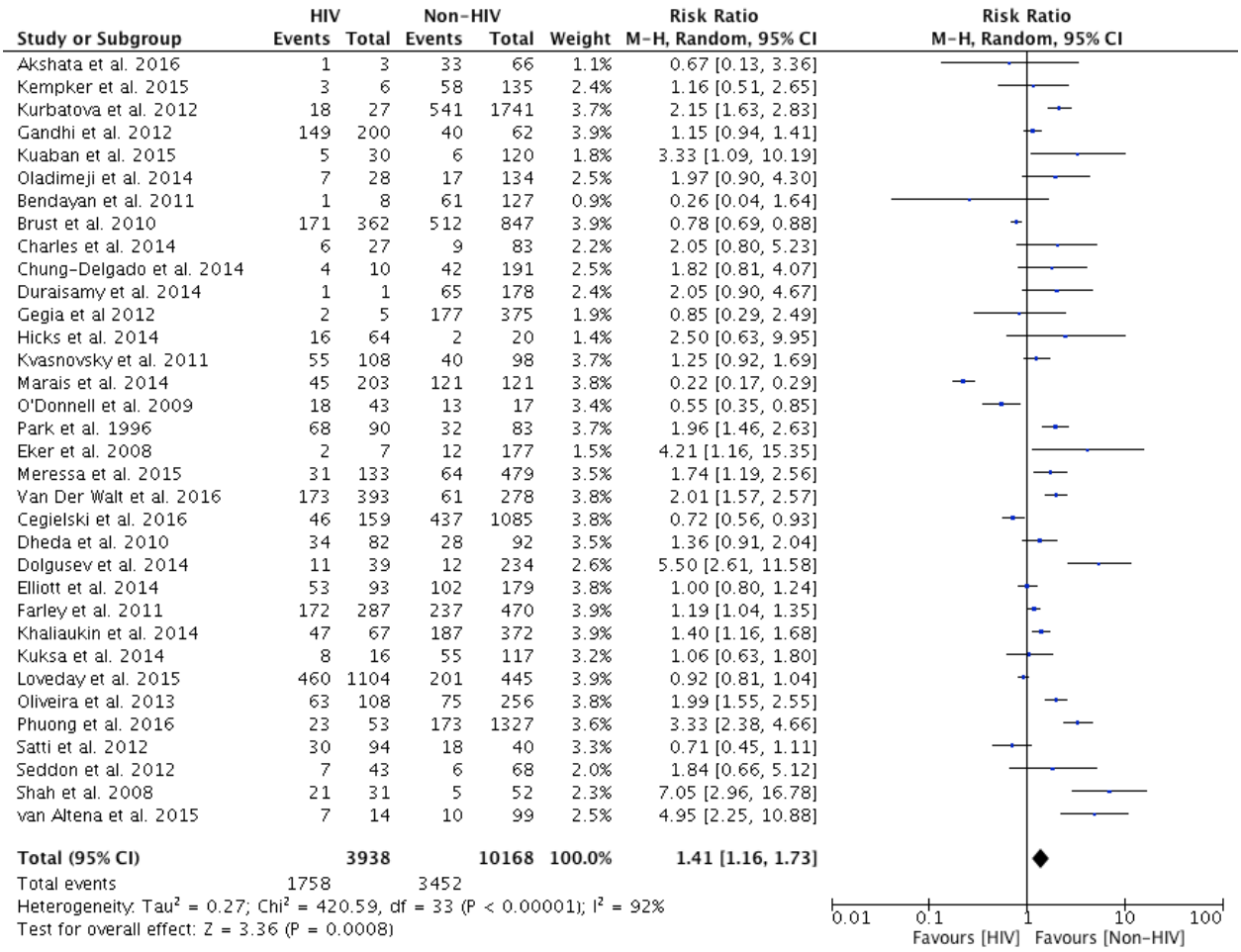
Supp. Fig. 8: Relative Risk of Default in MDR/XDRTB in those with HIV compared to those without HIV.



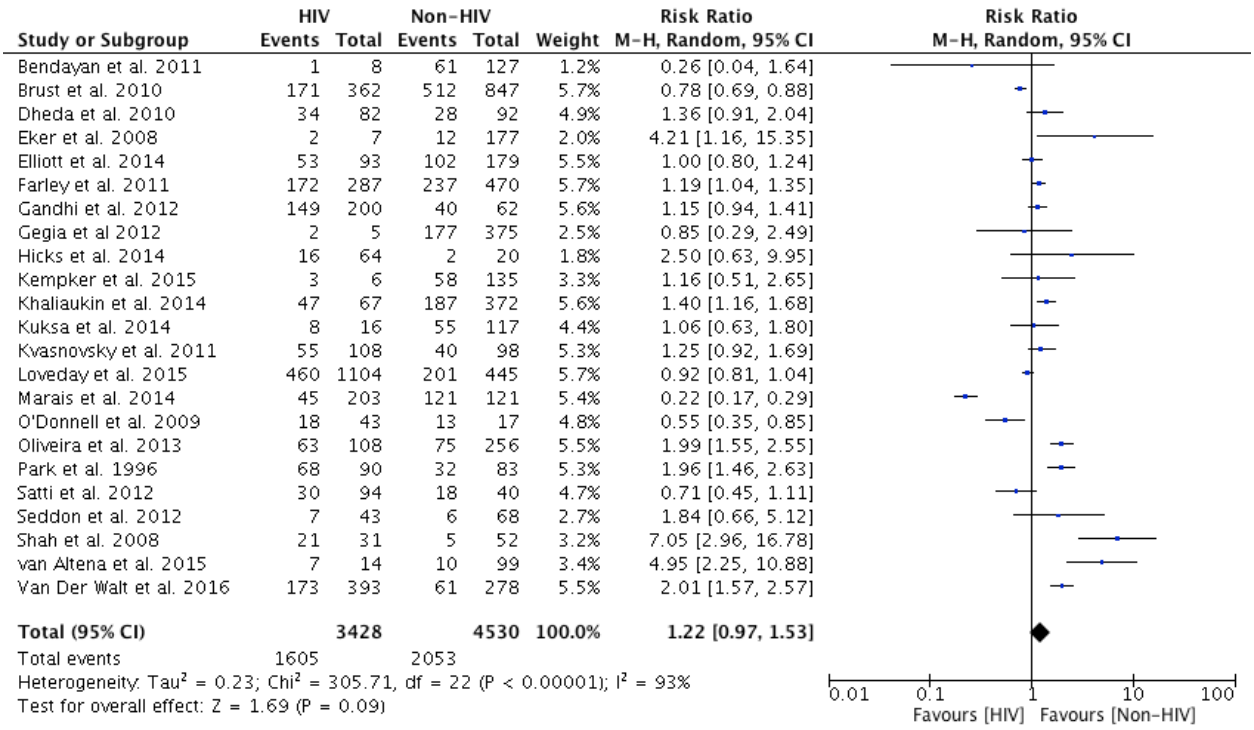
Supp. Fig. 9: Relative Risk of Treatment Failure in MDR/XDRTB among those with HIV compared to those without HIV.



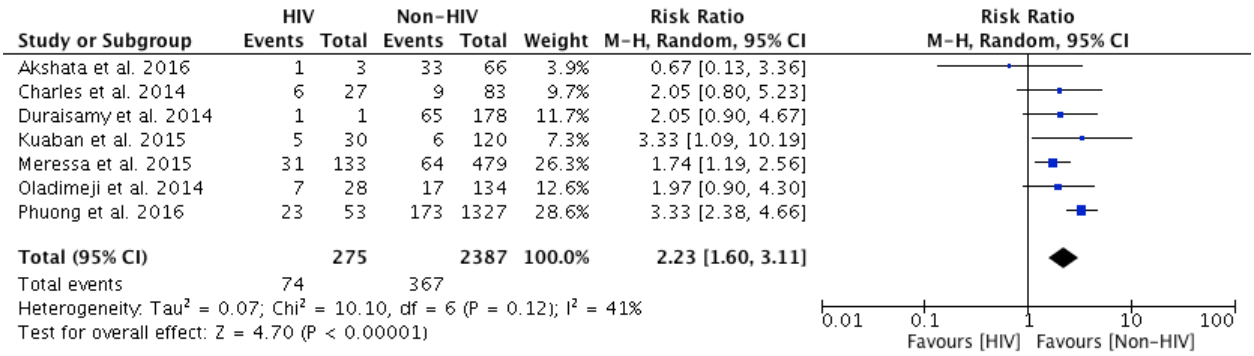
Supp. Fig. 10: Relative Risk of Death/Failure in MDR/XDRTB in those with HIV compared those with and without HIV.



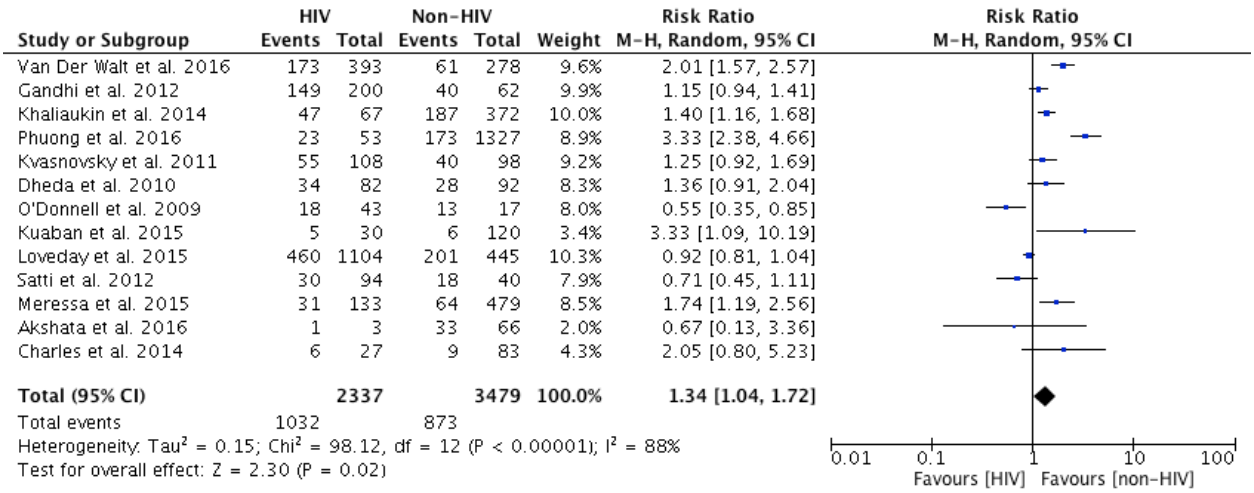
Supp. Fig. 11: Relative Risk of the primary outcome in MDR/XDRTB comparing those with and without HIV from low to high study quality.



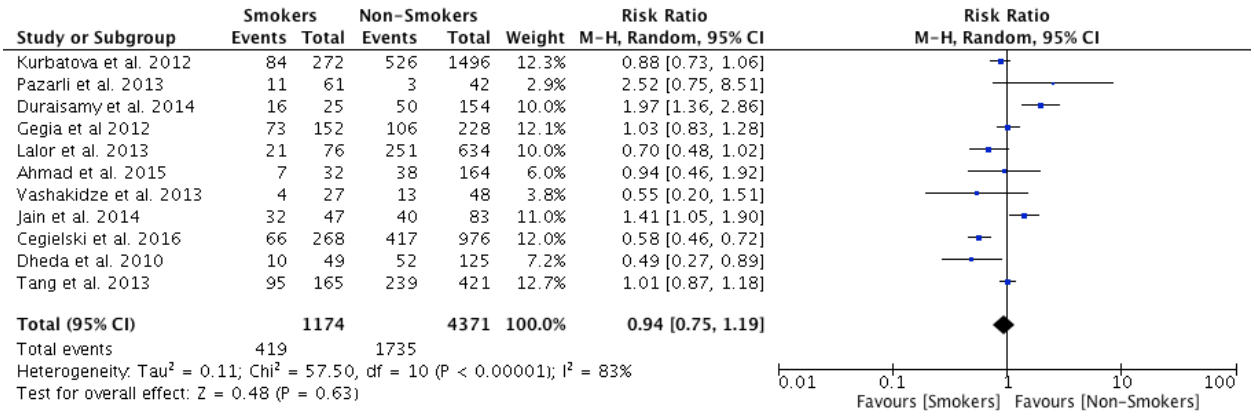
Supp. Fig. 12: Relative Risk of the primary outcome in MDR/XDRTB comparing those with and without HIV in high GDP countries.



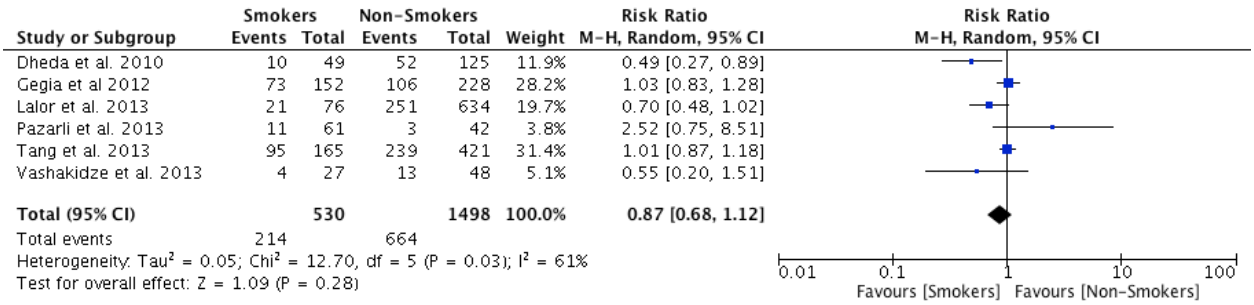
Supp. Fig. 13: Relative Risk of the primary outcome in MDR/XDRTB comparing those with and without HIV in low GDP countries.



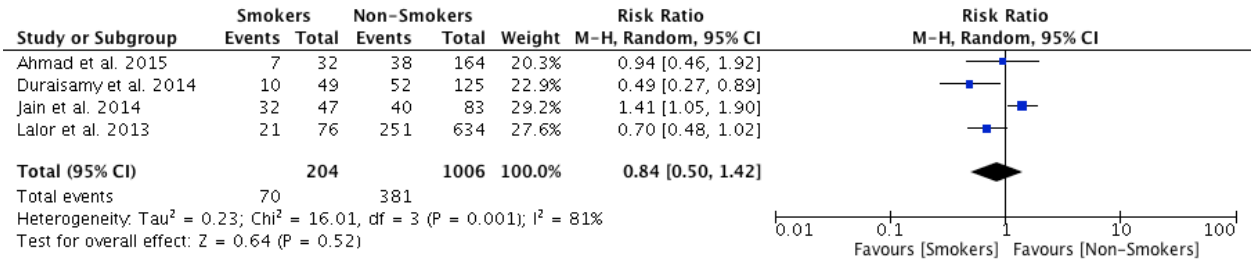
Supp. Fig. 14: Relative Risk of the primary outcome in MDR/XDRTB comparing those with and without HIV from lowest to highest ART use.



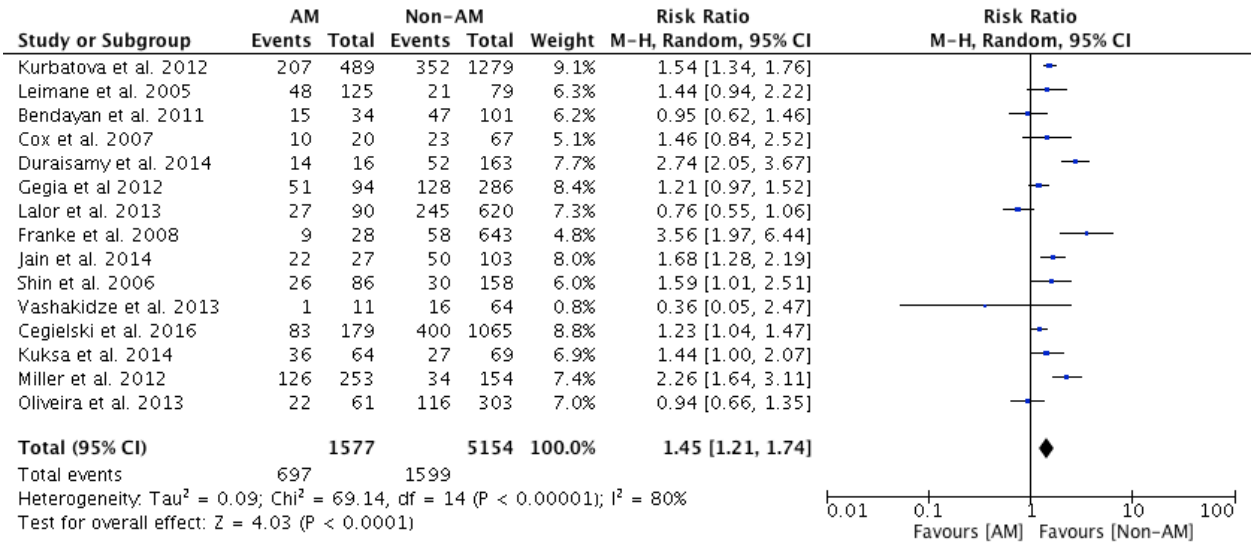
Supp. Fig. 15: Relative Risk of the primary outcome in MDR/XDRTB comparing smokers and non-smokers from low to high quality study.



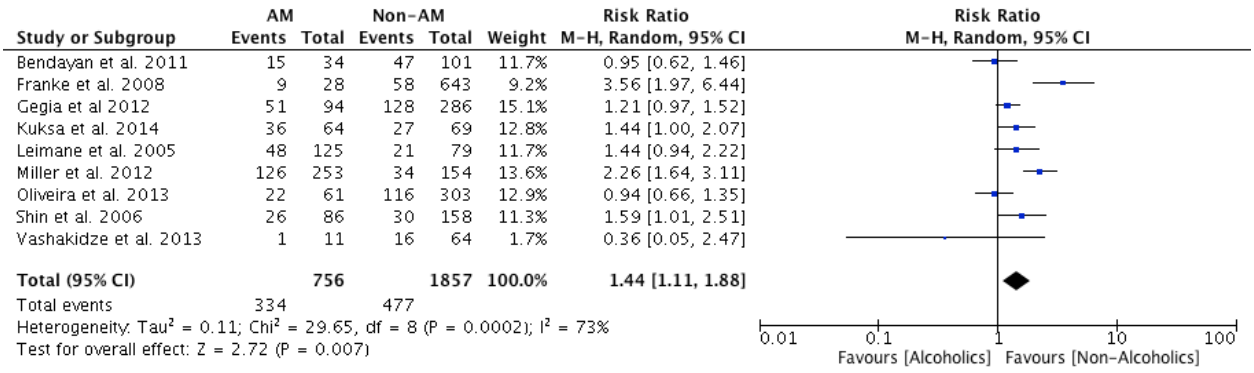
Supp. Fig. 16: Relative Risk of the primary outcome in MDR/XDRTB comparing smokers and non-smokers in high GDP countries.



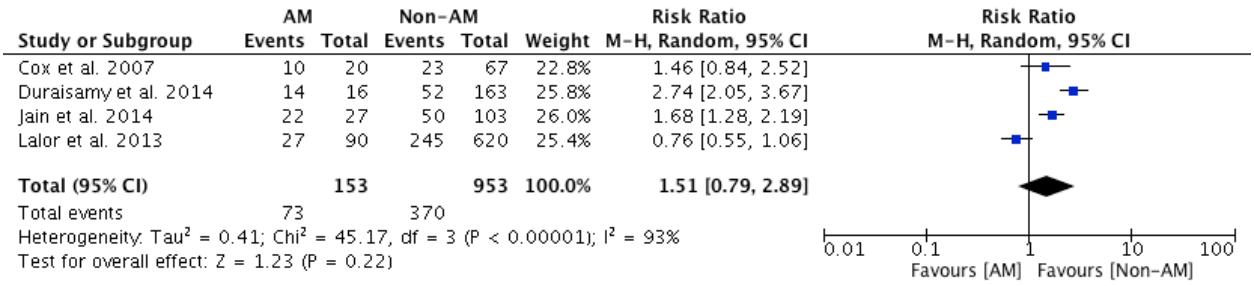
Supp. Fig. 17: Relative Risk of the primary outcome in MDR/XDRTB comparing smokers and non-smokers in low GDP countries.



Supp. Fig. 18: Relative Risk of the primary outcome in MDR/XDRTB in those with alcohol misuse (AM) compared to those without alcohol misuse from low to high study quality.



Supp. Fig. 19: Relative Risk of the primary outcome in MDR/XDRTB in those with alcohol misuse (AM) compared to those without alcohol misuse in high GDP countries.



Supp. Fig. 20: Relative Risk of the primary outcome in MDR/XDRTB in those with alcohol misuse (AM) compared to those without alcohol misuse in low GDP countries.

	Data Missing (default/data unaccounted for/lost to follow up/transfer out)
Akshata *et al.* 2016 [82]	N/A
Bendayan *et al.* 2011 [63]	N/A
Cegielski *et al.* 2016 [14]	0.19
Gegia *et al.* 2012 [45]	N/A
Gler *et al.* 2013 [80]	N/A
Jeon *et al.* 2009 [73]	0.23
Kempker *et al.* 2015 [44]	N/A
Kuksa *et al.* 2014 (XDR data only) [60]	N/A
Kurbatova *et al.* 2012 [68]	0.12
Kwak *et al.* 2015 [10]	N/A
Leimane *et al.* 2005 [28]	N/A

Supplemental Table 1: Proportion of data missing amongst participants with DM.

	Data Missing (default/data unaccounted for/lost to follow up/transfer out)
Park *et al.* 1996 [15]	0.16
Shah *et al.* 2008 [49]	0.03
Eker *et al.* 2008 [61]	N/A
O'Donnell *et al.* 2009 [55]	N/A
Brust *et al.* 2010 [53]	0.75
Dheda *et al.* 2010 [13]	N/A
Farley *et al.* 2011 [64]	0.21
Kvasnovsky *et al.* 2011 [48]	N/A
Bendayan *et al.* 2011 [63]	N/A
Kurbatova *et al.* 2012 [68]	0.30
Seddon *et al.* 2012 [11]	N/A
Satti *et al.* 2012 [65]	0.02
Gegia *et al.* 2012 [45]	N/A
Gandhi *et al.* 2012 [72]	N/A
Oliveira *et al.* 2013 [69]	N/A
Kuksa *et al.* 2014 [60]	N/A
Dolgusev *et al.* 2014 [66]	N/A
Hicks *et al.* 2014 [57]	N/A
Charles *et al.* 2014 [76]	0.04
Chung-Delgado *et al.* 2014 [81]	N/A
Khaliaukin *et al.* 2014 [67]	0.03
Elliott *et al.* 2014 [50]	N/A
Duraisamy *et al.* 2014 [12]	N/A
Marais *et al.* 2014 [78]	0.26
Oladimeji *et al.* 2014 [56]	N/A
Kuaban *et al.* 2015 [52]	N/A
Meressa *et al.* 2015 [43]	0.07
Kempker *et al.* 2015 [44]	N/A
Van Altena *et al. 2016 [54]*	0.14
Akshata *et al.* 2016 [82]	N/A
Phuong *et al.* 2016 [59]	N/A

Supplemental Table 2: Proportion of data missing amongst participants with HIV.

	Data Missing (default/data unaccounted for/lost to follow up/transfer out)
Ahmad *et al.* 2015 [58]	0.03
Cegielski *et al.* 2016 [14]	0.21
Dheda *et al.* 2010 [13]	N/A
Duraisamy *et al.* 2014 [12]	N/A
Gegia *et al.* 2012 [45]	N/A
Kurbatova *et al.* 2012 [68]	0.11
Lalor *et al.* 2013 [71]	0.28
Pazarli *et al.* 2013 [74]	N/A
Tang *et al.* 2013 [34]	N/A
Vashakidze *et al.* 2013 [51]	N/A

Supplemental Table 3: Proportion of data missing amongst participants that smoke.

	Data Missing (default/data unaccounted for/lost to follow up/transfer out)
Bendayan *et al.* 2011 [63]	N/A
Cegielski *et al.* 2016 [14]	0.22
Cox *et al.* 2007 [62]	0.35
Duraisamy *et al.* 2014 [12]	N/A
Franke *et al.* 2008 [70]	0.32
Gegia *et al.* 2012 [45]	N/A
Jain *et al.* 2014 [75]	N/A
Kuksa *et al.* 2014 [60]	N/A
Kurbatova *et al.* 2012 [68]	0.22
Lalor *et al.* 2013 [71]	0.30
Leimane *et al.* 2005 [28]	0.15
Miller *et al.* 2012 [46]	0.29
Oliveira *et al.* 2013 [69]	N/A
Shin *et al.* 2006 [77]	N/A
Vashakidze *et al.* 2013 [51]	N/A

Supplemental Table 4: Proportion of data missing amongst participants with alcohol misuse.

	ART proportion
Park *et al.* 1996 [15]	1
Shah *et al.* 2008 [49]	N/A
Eker *et al.* 2008 [61]	N/A
O'Donnell *et al.* 2009 [55]	N/A
Brust *et al.* 2010 [53]	1 (44% started pre TB tx)
Dheda *et al.* 2010 [13]	N/A
Farley *et al.* 2011 [64]	0.63
Kvasnovsky *et al.* 2011 [48]	N/A
Bendayan *et al.* 2011 [63]	N/A
Kurbatova *et al.* 2012 [68]	N/A
Seddon *et al.* 2012 [11]	N/A
Satti *et al.* 2012 [65]	N/A
Gegia *et al.* 2012 [45]	0.28
Gandhi *et al.* 2012 [72]	N/A
Oliveira *et al.* 2013 [69]	N/A
Kuksa *et al.* 2014 [60]	N/A
Dolgusev *et al.* 2014 [66]	0.40
Hicks *et al.* 2014 [57]	0.73
Charles *et al.* 2014 [76]	N/A
Chung-Delgado *et al.* 2014 [81]	N/A
Khaliaukin *et al.* 2014 [67]	0.55
Elliott *et al.* 2014 [50]	0.86
Duraisamy *et al.* 2014 [12]	N/A
Marais *et al.* 2014 [78]	0.98
Oladimeji *et al.* 2014 [56]	0.67
Kuaban *et al.* 2015 [52]	N/A
Meressa *et al.* 2015 [43]	N/A
Kempker *et al.* 2015 [44]	N/A
Van Altena *et al. 2016 [54]*	0.53
Akshata *et al.* 2016 [82]	0.96
Phuong *et al.* 2016 [59]	N/A
Park *et al.* 1996 [15]	N/A
Shah *et al.* 2008 [49]	N/A
Eker *et al.* 2008 [61]	0.24

Supplemental Table 5: Proportion of participants with HIV on ART.

	Current vs ever smoker
Ahmad *et al.* 2015 [58]	Ever
Cegielski *et al.* 2016 [14]	Ever
Dheda *et al.* 2010 [13]	Ever
Duraisamy *et al.* 2014 [12]	Ever
Gegia *et al.* 2012 [45]	Current
Kurbatova *et al.* 2012 [68]	Ever
Lalor *et al.* 2013 [71]	Ever
Pazarli *et al.* 2013 [74]	Ever
Tang *et al.* 2013 [34]	Ever
Vashakidze *et al.* 2013 [51]	Current

Supplemental Table 6: Definition of smoker used in study.

Diabetics	Unadjusted Effect Estimate	Adjusted Effect Estimate
Chung-Delgado *et al*. 2015 [32]	Hazard Ratio (HR): 4.1 (95%CI:2.15-7.85)	HR: 5.42 (95%CI:2.66-11.04)
Kendall *et al*. 2013 [26]	HR: 0.36 (95%CI:0.05-2.69)	N/A
Leimane *et al*. 2005 [28]	HR: 2.5 (95%CI:0.7-8.5)	N/A
Liu *et al*. 2011 [27]	OR: 0.65 (95%CI:0.37-1.14)-MDR data only	OR: 0.73 (95%CI:0.38-1.43) MDR data only
Tang *et al*. 2013 [34]	N/A	OR: 0.305 (95%CI: 0.140-0.663)

Supplemental Table 7: Effect estimates for combined negative treatment outcomes in participants with DM from studies that did not provide raw data.

HIV	Unadjusted Effect Estimate	Adjusted Effect Estimate
Mitnick *et al.* 2013 [25]	HR: 3.16 (95%CI: 1.29-7.74)	HR: 2.72 (95%CI: 1.03-7.24)
Pietersen *et al.* 2015 [30]	N/A	OR: 2.9 (95%CI: 1.34-6.3)
Kendall *et al.* 2013 [26]	HR: 0.61 (95%CI: 0.32-1.14)	N/A
Seung *et al.* 2009 [29]	OR: 1.9 (95%CI: 0.65-6.5)	N/A
Velasquez *et al.* 2014 [31]	HR: 1.7 (95%CI: 0.41-7.03)	HR: 3.4 (95%CI: 0.72-16.2)
Chung-Delgado *et al.* 2015 [32]	HR: 2.33 (95%CI: 0.83-6.51)	HR: 3.18 (95%CI: 1.05-9.69)
Kliiman *et al.* 2009 [33]	N/A	OR: 10.16 (95%CI: 1.17-88.4)

Supplemental Table 8: Effect estimates for combined negative treatment outcomes in participants with HIV from studies that did not provide raw data.

Smokers	Unadjusted Effect Estimate	Adjusted Effect Estimate
Kendall *et al*. 2013 [26]	HR: 2.02 (95%CI: 1.01-4.05)	N/A
Chung-Delgado *et al*. 2015 [32]	HR: 0.4 (95%CI: 0.12-1.29)	N/A

Supplemental Table 9: Effect estimates for combined negative treatment outcomes in participants that smoked from studies that did not provide raw data.

Alcohol Misuse	Unadjusted Effect Estimate	Adjusted Effect Estimate
Kendall *et al*. 2013 [26]	HR: 2.24 (95%CI: 1.22-4.13)	HR: 2.11 (95%CI: 1.11-4.02)
Chung-Delgado *et al*. 2015 [32]	N/A	HR: 0.51 (95%CI: 0.21-1.20)
Kliiman *et al*. 2009 [33]	OR: 2.42 (95%CI: 1.34-4.37)	OR: 1.94 (95%CI: 0.96-3.92)

Supplemental Table 10: Effect estimates combined negative treatment outcomes in participants with alcohol misuse from studies that did not provide raw