Does the risk of bias affect the results in HIV treatment adherence intervention trials?

A systematic review and meta-analysis of randomized controlled trials

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Background

• Randomized controlled trials (RCTs) can provide the strongest causal evidence for the efficacy of interventions

• Various types of bias (systematic errors in results or inferences) can threaten this internal validity

• Systematic reviewers examine the risk of bias (RoB) to judge the validity of RCTs and weigh the quality of evidence

• Yet, very little empirical evidence showing impact RoB on outcomes in (meta-analysis of) behaviour change RCTs

1 Higgins, Altman, & Sterne (2011). Cochrane handbook (Chapter 8)
Objective

- Given the ...:
  - .. number of systematic reviews continuously conducted
  - .. widespread use of RoB tools in grading the evidence
  - .. impact of systematic reviews on policy and practice
  - .. little empirical support for these RoB criteria

.. to conduct a systematic review of behaviour change RCTs, code RoB, and examine the relationship between RoB and effect sizes using meta-analysis

- Domain: Interventions to promote adherence to antiretroviral medication among people with HIV
Methods: search strategy

• Search strategy:
  – Developed and conducted by 2 experienced librarians
  – Automated search in MEDLINE, EMBASE, PsycINFO, CINAHL
  – Manual search in 20 key journals to identify new studies that were not yet indexed
  – Reference lists and listserves were reviewed
  – Date: May 2012
Methods: study selection

• Study selection:
  – Published or in press from 01-01-1996 to 01-05-2012
  – Interventions targeting adherence among adult HIV patients
  – RCT design
  – Data on at least 1 of the 2 relevant outcomes: Medication adherence or Viral load

• Exclusion:
  – Directly observed therapy (not autonomous behaviour)
Methods: data extraction

• Independent coding by 2 trained reviewers, and discrepancies resolved with a 3rd reviewer
  – Primary articles and other study articles referenced
  – Study characteristics (e.g., location, dates)
  – Sample characteristics (e.g., target population, ethnicity)
  – Outcome information for adherence and viral load (e.g., assessment time, instrument used, viral load cut-off point)
  – Risk of bias

• Authors were contacted in case insufficient information was given to compute an effect size
Methods: RoB

• Cochrane tool:
  – Selection, performance, detection, attrition and reporting bias
  – Blinding of patients and health care personnel to treatment assignment not coded (blinding not possible)

• Other: participant incentives, a-priori power calculations, subjective versus objective measurement dependent, appropriate analyses in cluster-RCTs

• For analysis: low versus high/unknown risk of bias

Methods: analysis

• Analysis
  – Natural logarithm of OR [ln(OR)] calculated for each trial
  – A fixed effects model was used
  – Separate analyses conducted for adherence and viral load

  – Step 1: Stratified analyses of single variables, i.e., RoB and potential confounders (study, participant, measurement)

  – Step 2: Meta-regression analyses including RoB predictors and potential confounders with p < .10 in Step 1
Results: studies included

• Screened at title and abstract: N = 16,235 citations
• N = 80 unique studies included in quantitative synthesis

• Most trial conducted in USA (k=58, 62%)
• 1/3 published between 2010-2012 (k=26, 32%)
• Average sample size 186 at baseline and 146 at follow-up
• 75 trials reported adherence, and 59 viral load outcomes
• Majority used subjective adherence measures (k=42, 56%)
• 1/3 trials targeted patients starting treatment (k=29, 36%)
Results: risk of bias for adherence
Results: risk of bias for viral load
Results: adherence efficacy

• Overall efficacy
  – Adherence: OR=1.43; 95% CI=1.31, 1.56; k=75

• Variables p <.10* or p <.05** in stratified analyses
  – More recent study enrolment date (yes: more effective)**
  – Majority study sample of colour (yes: less effective)**
  – Random sequence generation sound (yes, larger effect)**
  – Overall attrition ≤30% (yes: larger effect)*
  – Differential attrition ≤ 10% (yes: larger effect)**
Results: adherence meta-regression

- Meta-regression of adherence on predictors

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Adherence$^b$</th>
<th>$\beta$</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Study enrollment date</td>
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<td>0.0950</td>
<td>0.433</td>
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<tr>
<td>% persons of color in study sample</td>
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<tr>
<td>Random sequence generation (High/unclear risk vs low risk)</td>
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<td>Overall attrition (High/unclear risk vs low risk)</td>
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<tr>
<td>Differential attrition (High/unclear risk vs low risk)</td>
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<td>-0.3402</td>
<td>0.035*</td>
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</table>
Results: viral load efficacy

• Overall efficacy
  – Viral load: OR=1.20; 95% CI=1.09, 1.32; k=59

• Variables p <.10* or p <.05** in stratified analyses
  – Cut-off viral load test ≤50 c/ml blood (yes: larger effects)*
  – Overall attrition ≤30% (yes: larger effects)*
  – Intent-to-treat analysis (yes: larger effects)*
Results: viral load meta-regression

- Meta-regression of viral load on predictors

<table>
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<tr>
<th>Predictor variable</th>
<th>HIV viral load</th>
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<td>Measurement type/Cutoff (binary, using cutoff greater than 50 copies/ml; reference=continuous)</td>
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<td>Measurement type/Cutoff (binary, using cutoff of ≤50 copies/ml; reference=continuous)</td>
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<td>Overall incomplete data (High/unclear risk vs low risk)</td>
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<td>Intent-to-treat analysis (High/unclear risk vs low risk)</td>
<td>-0.0996</td>
<td>0.566</td>
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</tbody>
</table>
Results: other

• Other:
  – No evidence of publication bias (funnel plot and Egger’s regression intercept test)
  – All other single RoB scores, and the total number of high RoB scores were unrelated to effect sizes
Discussion

• About 60% RoB scores low, 20% Unknown and 20% High

• Stratified and meta-regression analyses: mainly evidence for attrition bias on adherence effect sizes

• Objective outcomes (here: viral load) known to be less sensitive to bias\(^1\)

• Note the direction of effects: higher RoB, less efficacious

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Conclusion

• Individual trials may be affected by several sources of bias, yet little evidence of their impact on total evidence-base.

• Should we downgrade the quality of the evidence base in this field based on all RoB scores, or just discriminate on attrition bias for adherence?

• Recommendations:
  – More experimental and meta-analysis evidence to gather empirical evidence on RoB in behaviour change trials
  – When grading the quality of the evidence-base, first examine whether it is actually affected by the criteria applied?
For questions, please contact

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