



## W22 META-ANALYSES AND INDIRECT COMPARISONS FROM RCTS WITH SMALL PATIENT NUMBERS

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## Workshop outline



- Which **methodological preconditions** for indirect comparisons have to be met to provide valid and precise estimates of clinical effects?
- To what extent can **clinical evidence from indirect comparisons** be used as a substitute for evidence from **head-to-head comparison**?
- How do RCTs with **small patient numbers** affect the validity and precision of indirect comparisons?



## Why using external evidence to estimate a given treatment effect?



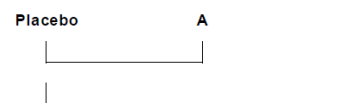
- Decision making in health care requires comparison of all relevant interventions
- New interventions are often compared to a common standard or placebo C but not against each other
- Indirect comparison and mixed treatment comparison meta-analyses are now frequently used in comparative effectiveness research and HTA



## Adjusted indirect comparison I



- x RCTs investigating a common condition
- i trials compare drug A vs C (control standard TX, placebo)
- k trials compare drug B vs C
- We are interested in the comparison of A vs B



HC Bucher et al, J Clin Epidemiol 1997



## Adjusted indirect comparison II

$$OR_{ind} = OR_{AvsC} / OR_{BvsC}$$

$$\ln(OR_{ind}) = \ln(OR_{AvsC}) - \ln(OR_{BvsC})$$

$$\text{Var}(OR_{ind}) = \text{Var}(OR_{AC}) + \text{Var}(OR_{BC})$$



$$LOR_{AB} = LOR_{AC} - LOR_{BC}$$

HC Bucher et al, J Clin Epidemiol 1997

## How reliable is evidence from indirect comparison: An example

Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials  
 Stefan Vandepol, Dennis Stedje, Matthias Egger, Yves Meyer, Martin Zwahlen, Catherine Chêne

BMJ (published 23 January 2004)

Initial highly-active antiretroviral therapy with a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor: discrepancies between direct and indirect meta-analyses

http://dx.doi.org/10.1136/bmj.328.7447.1015

Lancet 2004; 363: 1015-15

**Conclusions** Indirect evidence shows that protease inhibitor based triple regimens are superior to regimens based on the NRTI zidovudine and didanosine in patients with advanced immunodeficiency who have been exposed to NRTIs. Large trials with clinical end points are required.

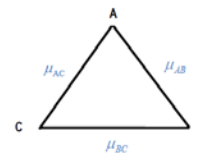
**Interpretation** Results from direct analyses suggested that NNRTI based HAART was more effective than PI based HAART in the absence of comparison and was superior to zidovudine based HAART. Indirect comparisons could be unreliable for complex and rapidly evolving interventions such as HAART.

## Methodological preconditions

### Assumptions in meta-analysis of indirect comparison I

- The effect AvB is measured using a common comparator C by contrasting the estimated effects of AvC & BvC
- Pairs of comparisons have to be independent
- All trials are measuring the same effect (fixed effect model)
- There are no important differences between the sets of trials (AvC & BvC) that could bias the estimated effect AvB (no interaction between covariates defining subgroups and the magnitude of the treatment effect of interest)

## Expanding indirect comparison with a common comparator to a three treatment network



There are three possible indirect comparisons:

$$\mu_{AB}^{indirect} = \mu_{AC} - \mu_{BC};$$

$$\mu_{AC}^{indirect} = \mu_{BC} - \mu_{AB};$$

$$\mu_{BC}^{indirect} = \mu_{AC} - \mu_{AB}$$

## Assumptions in meta-analysis of indirect comparison II

- The sets of trials that are constitutive of an indirect comparison or a network are exchangeable (any comparisons  $X_i$  and  $Y_j$  represented in the analysis are at random)
- To test the consistency assumption (null hypothesis of no difference between direct and indirect estimates)

$$Z_{XY} = \hat{\omega}_{XY} / \sqrt{\text{Var}(\hat{\omega}_{XY})}$$



## When is evidence from indirect comparisons reliable as a substitute for a head-to-head comparison

1. Model assumptions are not violated
  - If study or patient characteristics (co-medication, baseline risk) differ in trials of indirect comparison and are effect modifier of relative treatment effects the analysis is biased
  - Borrowing external evidence is clinically meaningful
    - Characteristics of common comparator (study and patients)
    - Margins of the network are defined
    - Expert and clinical judgment is needed
2. Insufficient data from non-randomised studies with sufficient control of confounding by indication (marginal structured models, g-estimation)



## Small trials and the validity and precision of indirect comparisons I

- Suppose that for a given trial from a set of trials investigating a condition has a treatment effect  $\theta$  and a variance  $\sigma^2 (= [\text{SE}(\theta)]^2)$
- For a meta-analysis of  $2k$  trials an inverse variance meta-analysis will provide an estimated variance for the treatment effect  $[\text{SE}(\theta_{[2k]})]^2 = \sigma^2/2k$ .
- The expected variance from an indirect comparison of  $k$  trials for each comparison is:

$$[\text{SE}(\theta_{\text{AR}[k]} - \theta_{\text{AC}[k]})]^2 = \frac{\sigma^2}{k} + \frac{\sigma^2}{k} = \frac{2\sigma^2}{k}$$

AM Glenny Health Technology Assessment 2005



## Small trials and the validity and precision of indirect comparisons II

- A direct comparison from 1 RCT is as precise as an indirect comparison from 4 RCTs (assuming equal variance of all paired comparisons, common underlying true treatment effect and same sample size)
- Fixed effect methods for indirect comparison will further underestimate  $\text{SE}(\theta)^2$  (in particular if heterogeneity is present)
- Indirect comparison of trials with small  $n$ 's are likely to be inefficient and render inconclusive summary estimates

AM Glenny Health Technology Assessment 2005, HC Bucher J Clin Epidemiol 1997



## Back to our example ...

What is better a protease inhibitor or a NNRTI when initiating antiretroviral therapy in HIV infection?

- If the comparison of interest is important to clinicians and patients a head to head comparison is needed!

**Protease Inhibitor** → **Analysis of Interest Medication** | **Comparative Research** ← **NNRTI**

**Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1**  
A Randomized Trial

**Conclusion:** Atazanavir plus ritonavir and efavirenz have similar antiviral activity when used with abacavir-lamivudine or tenofovir DF-embicicabine.

**Primary Funding Source:** National Institutes of Health.  
Ann Intern Med 2011;154:446-456. [www.annals.org](http://www.annals.org)

## Conclusions:

- Whenever possible summary estimates for evidence synthesis should be based on direct comparisons
- Indirect comparisons are likely to be biased and may lead to an over- or underestimation of a true treatment effect
- If indirect comparisons are used in evidence synthesis the critical exploration of bias (confounding, consistency) is fundamental besides an explicit justification of the comparator and trial network that form the base of the analysis