What is treatment non-adherence?

- When participants do not receive their allocated regimen as planned (missed doses)
- Common in trials ⇨ potential to bias estimates of efficacy

How can treatment non-adherence be handled?

- In NI trials, intention-to-treat (ITT) and per-protocol (PP) analyses advocated
- If treatment non-adherence occurs ⇨ possible for these analyses to be biased in same direction

More sophisticated statistical methods are available[1], but it is unclear how well they perform in NI trials comparing two active drugs

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Simulation study based on REMoxTB trial for drug-sensitive TB[1]

	6-month control regimen (CON) 4-month experimental regimen (EXP)

[1] Gillespie SH, Crook AM, McHugh TD, et al. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis. New England Journal of Medicine. 2014;371(17):1577-1587

The following variables were simulated based on the REMoxTB dataset:

1) Age, smoking status, and HIV status

2) Random allocation 1:1 to CON or EXP

3) The overall percentage of doses received (adherence)

4) Unfavourable outcomes simulated so that those who were older (≥30 years), ever smokers, HIV positive, and received <100% of doses had a higher risk

1) ITT analysis

2) PP analysis

   Excluding non-adherent participants.

   Three different definitions applied based on less than 100%, 90% and 80% of doses being received (denoted PP100, PP90 and PP80)

3) Adjusted ITT analysis

   Observed levels of treatment adherence included as a covariate

4) Multiple imputation (MI) of outcomes

   Imputing the outcomes of non-adherent participants as if they had been fully adherent

5) Inverse-probability-of-treatment weighting (IPTW)

   Upweighting the outcomes of fully adherent participants to create a pseudo-population where all participants receive 100% of doses

6) Doubly-robust (DR) estimator

   Combining properties of the MI and IPTW methods