Evidence-based design of fixed-dose combinations – principles and application to pediatric anti-tuberculosis therapy

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Background and objective: Fixed-dose combination (FDC) formulations, where more than one compound is combined in one pill, are important for the implementation of multidrug therapies. The selection of optimal dose ratios and tablet content of FDCs and the design of individualized dosing regimens requires multiple simultaneous considerations. In this work, a methodology for rational design of FDCs was developed and applied to the case of a three-drug pediatric anti-tuberculosis formulation, individualized on body weight.

Methods: The optimization methodology included information on relevant covariates (and their covariance) of intended use population, pharmacokinetics and therapeutic targets of each of the drugs, and practical constraints, such as number of weight-bands for treatment individualization. A utility function was used to penalize deviations from the therapeutic targets and a sequential estimation procedure was developed for stable estimation of break-points for individualized dosing. The suggested optimized pediatric anti-TB FDC was compared to the recently launched WHO endorsed formulation (WHO-FDC).

Results: The optimization methodology estimated doses of rifampicin, isoniazid and pyrazinamide to be 15%, 36% and 16%, higher than the WHO-FDC, respectively. Predictions of percentage of underexposed children (exposure < ½ of therapeutic target) was much higher for WHO-FDC compared to the optimized FDCs, especially for the low-weight (low-age) group of children (figure 1).

Conclusions: The development of this design tool can aid implementation of evidence based formulations, integrating available knowledge and practical considerations, to optimize drug exposures and thereby treatment outcomes. A pediatric anti-tuberculosis fixed-dose combination was designed as a motivating example, and compared with a WHO-endorsed product currently in clinical trials.

![Figure 1. Proportion of children with significant underexposure (< ½ of target exposure)](image_url)