Is there a role for bedaquiline in the treatment of nontuberculous mycobacterial diseases?

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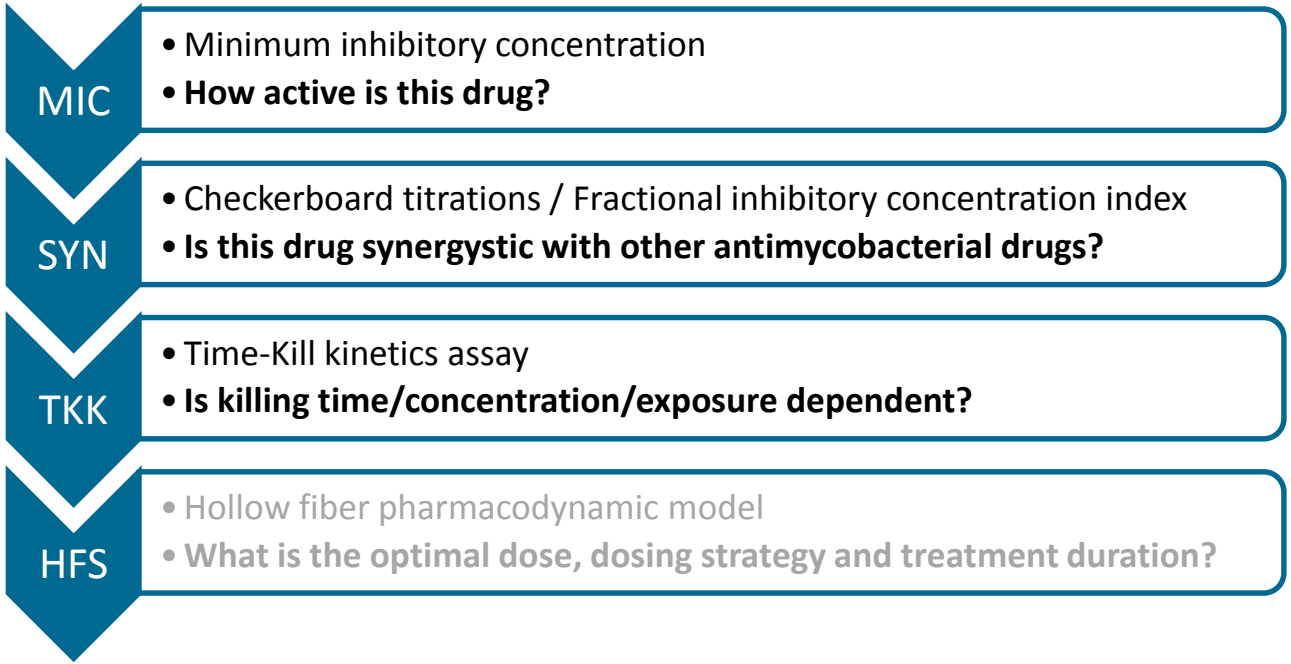
Disclosures

- This work was supported by a Dutch Ministry of Health grant
  - Veni (personal, to Jakko van Ingen)

- Bedaquiline was provided by Jansen Pharmaceuticals

The regimen development track

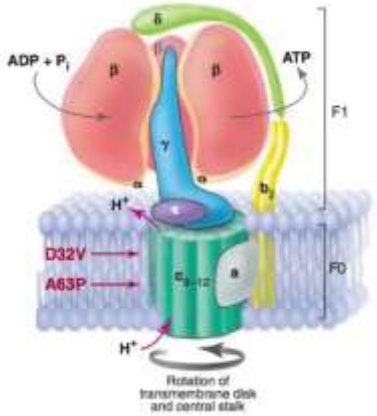


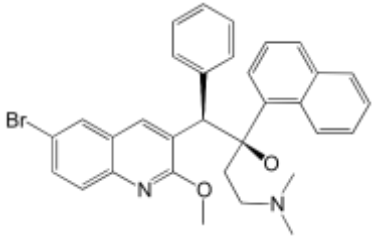
Bedaquiline

- Effective new drug for DR-TB
- Potential role in NTM disease?

- Mouse models
  - Monotherapy bacteriostatic (*M. avium*)
  - Synergistic with clofazimine (*M. abscessus*)

- 13 patients treated, most failed
  - Resistance emerges, by increased efflux

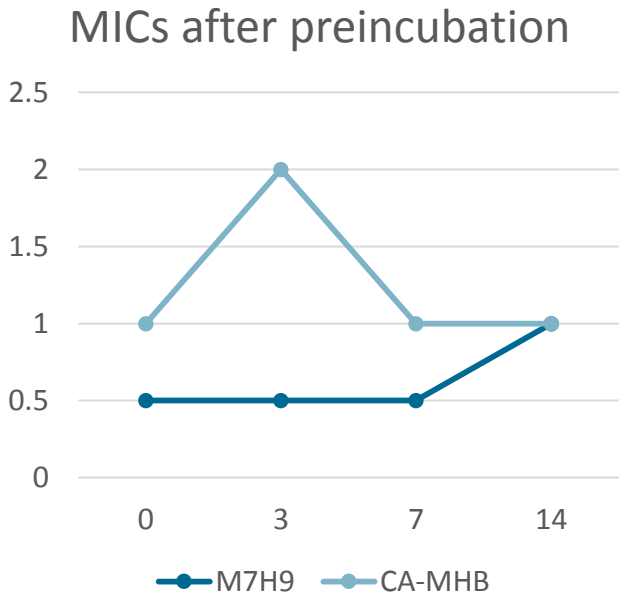




Philley JV, et al. Chest 2015 ; Alexander DC et al., J Clin Microbiol 2017
Lounis N, et al., Antimicrob Agents Chemother 2009

Stability

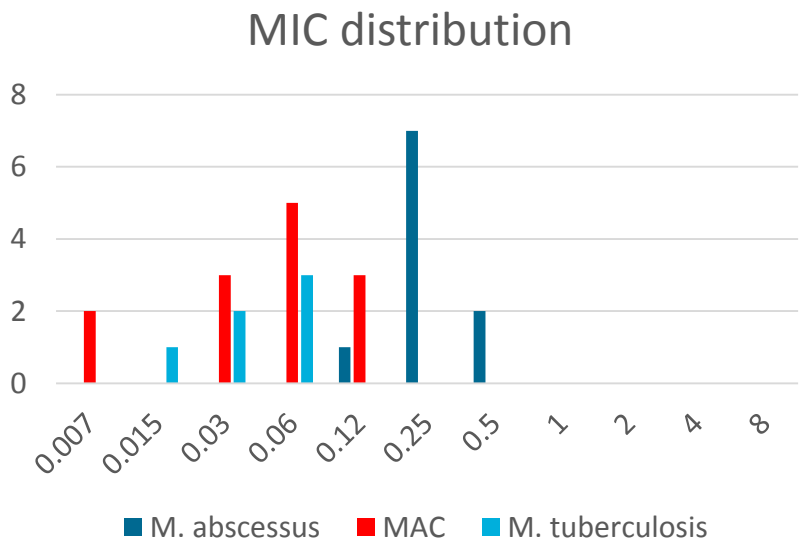
- Determine MIC of *M. abscessus*
- After pre-incubation of plates
  - 3 days
  - 7 days
  - 14 days
- Remained within a single 2-fold dilution
- Stable in both Middlebrook 7H9 and cation-adjusted Mueller Hinton broth



Step 1: MIC

- Broth microdilution in CA-MH
- *M. tuberculosis*: microdil. in 7H9

NTM species	Median BDQ MIC
M. abscessus	0.25 mg/l
M. fortuitum	0.125 mg/l
M. avium complex	0.06 mg/l
M. malmoense	0.06 mg/l
M. kansasii	0.06 mg/l
M. simiae	0.06 mg/l
M. xenopi	4 mg/l



Synergy testing, checkerboards

- Fractional inhibitory concentration index (FICI)
- FICI = FICa + FICb = (MICa combination/MICa alone) + (MICb combination/MICb alone)
  - Bedaquiline as drug ‘a’ and other as drug ‘b’ in the combination

- FICI interpretation:
  - synergy (FICI ≤ 0.5)
  - no interaction (FICI 0.5-4)
  - antagonism (FICI ≥ 4.0)

Synergy testing, checkerboard results

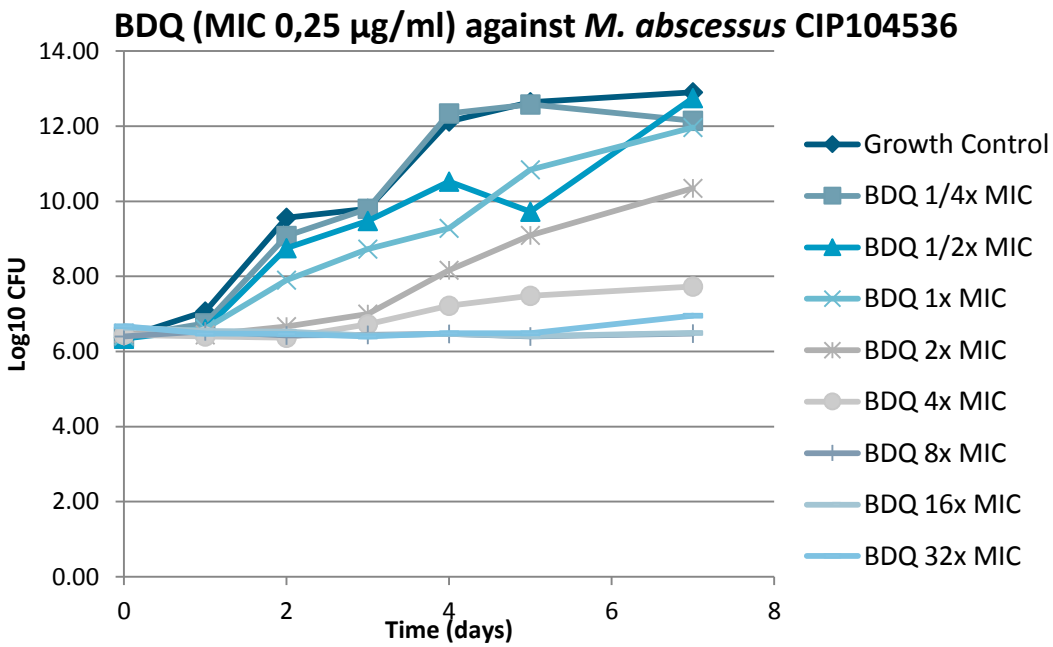
- 10 isolates per species
- No evident synergy
- … no antagonism, too
- BDQ-clofazimine looks best

FICIs for *M. abscessus*			
Antibiotic combination	Average FICI	Range FICI	Interaction
Bedaquiline - amikacin	0,98	0,73 - 2	additive
Bedaquiline - tigecycline	1,10	0,98 - 2	additive
Bedaquiline - clarithromycin	1,27	0,75 - 2	additive
Bedaquiline - clofazimine	0,79	0,62 - 1	additive
Bedaquiline - cefoxitin	1,95	1,0 - 3,0	additive

FICIs for *M. avium* complex			
Antibiotic combination	Average FICI	Range FICI	Interaction
Bedaquiline - amikacin	1,81	0,73 - 3,08	additive
Bedaquiline - rifampicin	1,10	0,98 – 2	additive
Bedaquiline - clarithromycin	1,63	0,5 – 2	additive
Bedaquiline - clofazimine	0,69	0,5 – 1	**Syn/add**
Bedaquiline - ethambutol	1,43	0,73 – 2	additive

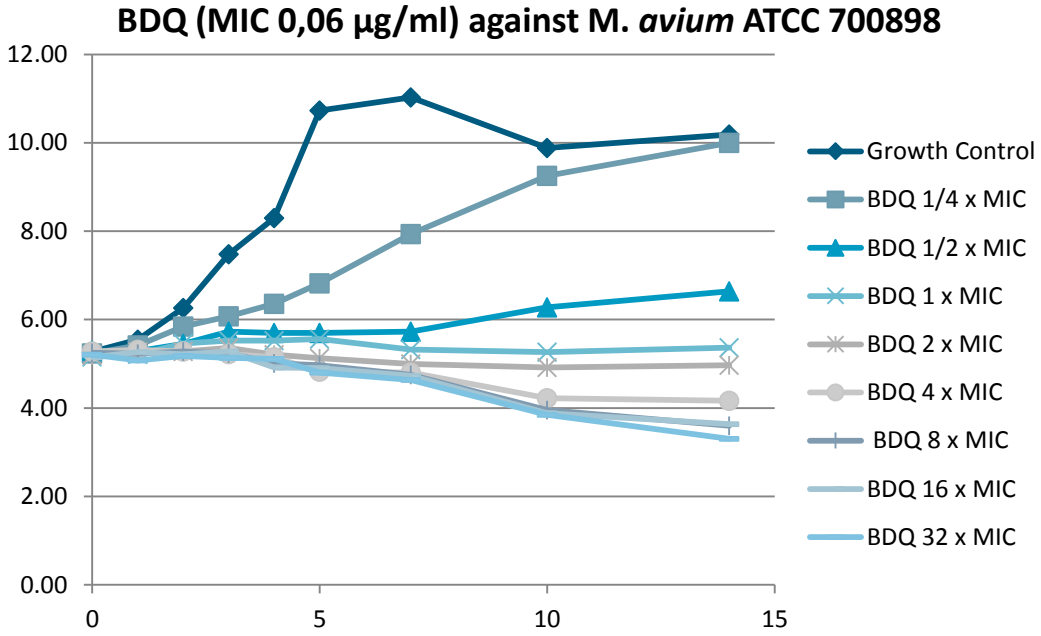
Time-Kill: BDQ mono vs *M. abscessus*

- Bacteriostatic at >2x MIC
- Concentration-dependent
- Stasis only, no killing



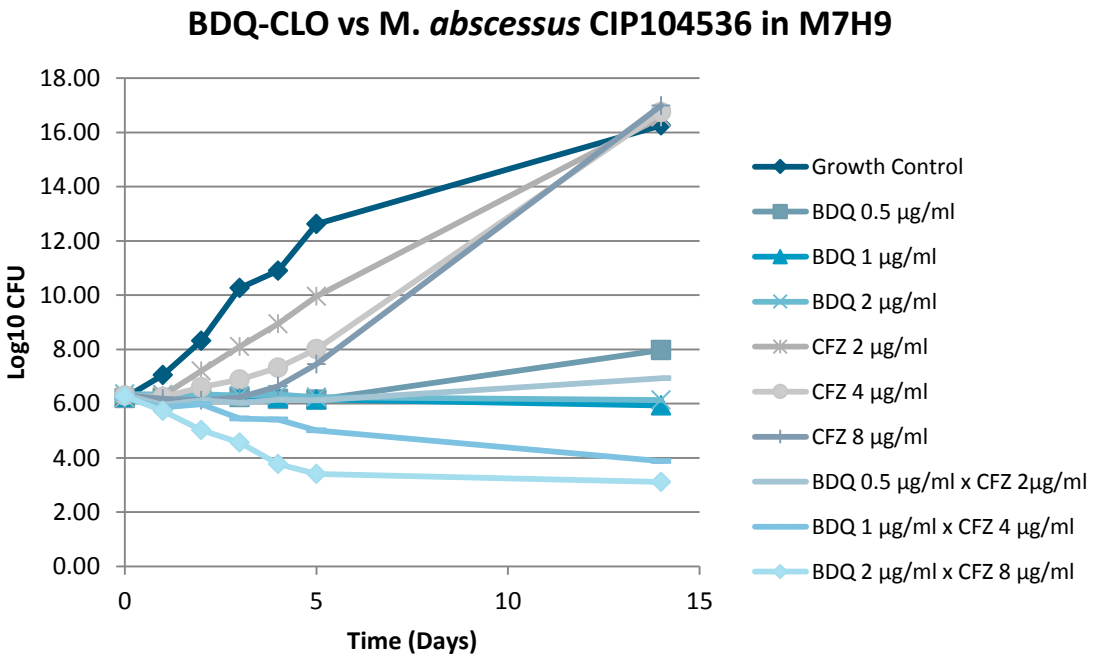
Time-Kill: BDQ mono vs *M. avium*

- Bacteriostatic at >0.5x MIC
- Concentration-dependent
- 2 logs kill at 32x MIC



Sneak peak: BDQ-CLO vs *M. abscessus*

- Synergy!
  - Enhanced killing
  - Slower R-emergence



Currently ongoing:

- BDQ-CLO vs *M. avium*
- R-mutants emergence

Conclusions to date

- Bedaquiline is a concentration-dependent, bacteriostatic drug

- Less active against NTM than against *M. tuberculosis*
- More active against MAC than against *M. abscessus*

- Synergistic only with clofazimine

- Clofazimine-bedaquiline containing regimens warrant further study
  - Dynamic models (hollow fiber model)
  - Clinical trials

Thank you for your attention

Radboudumc NTM team
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