# Semi-mechanistic pharmacokinetic/pharmacodynamics modeling of aztreonam-avibactam combination against multidrug resistant Gram(-) organisms

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## INTRODUCTION

- Aztreonam-avibactam (ATM-AVI) is a promising combination to treat serious infections caused by multi-drug resistant (MDR) pathogens including those producing metallo-β-lactamases (MBLs).
- Sy et al. developed a semi-mechanistic PK/PD model for ATM-AVI combination in which 3 effects for AVI were characterized : inhibition of ATM degradation; enhancement of ATM bactericidal activity and bactericidal effect.
- The aims of this study were to apply this PK/PD model for 4 new MDR strains with different β-lactamase profiles and to investigate the individual contribution of each of the 3 AVI PD effects.

## METHODS

- 4 *Enterobacteriaceae* strains (1 *E. coli*, 1 *C. freundii* and 2 *E. cloacae*) expressing MBLs and other β-lactamases were evaluated in *in vitro* static time-kill studies using wide concentration ranges of ATM and AVI alone and in combination.
- A common structural model with 2 sub-populations, slightly different from the one developed by Sy et al., was applied for all strains (Fig 1).
  - ✓ ATM degradation by β-lactamases was taken into account by measuring the actual concentrations of ATM by LC-MS/MS and was modeled depending on the bacteria density (S+R), remaining ATM in the system and AVI concentration (inhibitory effect).
  - ✓ ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations with a higher $EC_{50}$ for the resistant state. Whereas AVI bactericidal effect was incorporated in the model only for the susceptible subpopulation.
  - ✓ The enhancing effect of AVI was characterized by a reduction of the ATM $EC_{50}$ in a concentration-dependent manner.

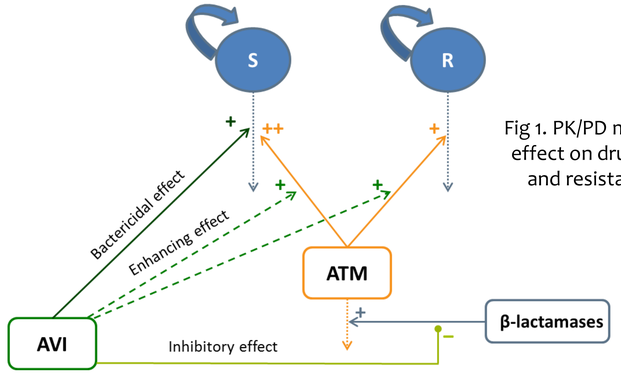


Fig 1. PK/PD model for ATM-AVI effect on drug-susceptible (S) and resistant (R) bacteria.

- Final model was used to simulate the 3 AVI effects separately in order to evaluate the impact of each effect at clinical ATM and AVI concentrations (25 and 4.5 µg/mL respectively, corresponding to a dose regimen of 2g and 0.5g in human[2,3]).

## RESULTS

- All strains were resistant to ATM alone with MICs ranging from 32 to 512 µg/mL. The susceptibility was restored in the presence of 4 µg/mL of AVI with corresponding ATM MICs ranging from 0.125 to 4 µg/mL.
- The PK/PD model succeeded in capturing the bacterial growth, regrowth and killing kinetics and ATM degradation profiles for all strains as shown in Fig 2, using *E. cloacae* 1318536 as an example.
- Interestingly, no ATM degradation, even in the absence of AVI, was observed for *E. coli* 1266865 (Fig 3). Thus, for this strain, only the bactericidal and the enhancing effects of AVI could be characterized.

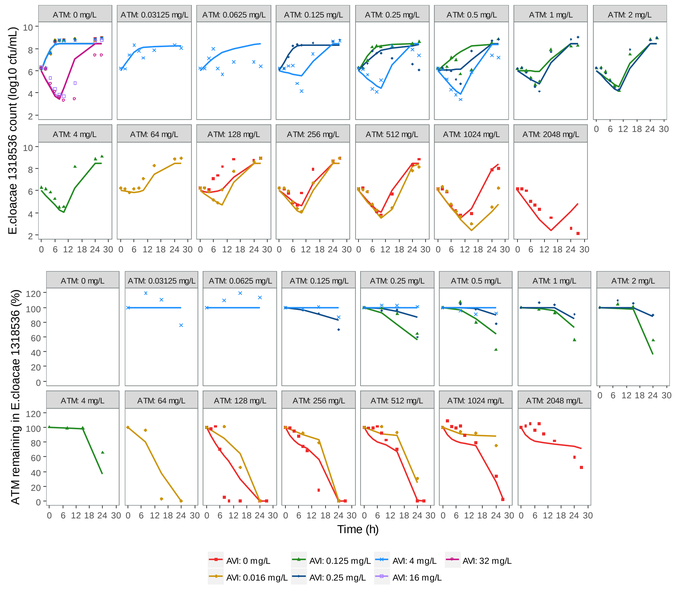


Fig 2. Model-prediction and observed static time-kill curves of ATM and AVI against *E. cloacae* 1318536 (top) and ATM concentration remaining in the system (bottom). The points show the experimental data and the lines the predictions from the model.

- AVI can avoid ATM degradation although this effect alone is not able to explain the bacterial killing due to the drug combination (Fig 3, light green triangles).
- When killing is observed, ATM degradation rate is lower due to a lower number of bacteria (Fig 3, green squares).
- Among the 3 AVI effects, the enhancing effect is the most important.
- The way that the AVI effects are affected by different ATM-AVI concentrations within a clinical range was investigated. The inhibitory and bactericidal effects of AVI contribute to a faster killing rate only at high concentration.

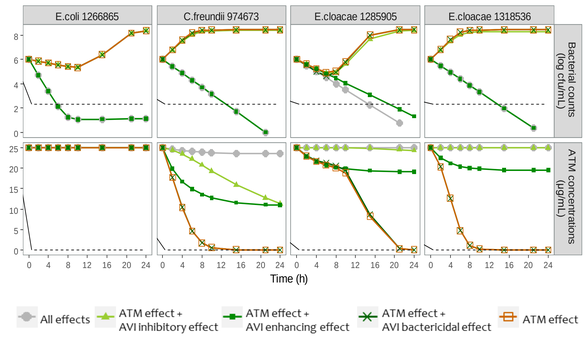


Fig 3. Model simulations of static time-kill curves and ATM concentrations for ATM-AVI combination of 25-4.5 µg/mL. Each color represents the simulated profile for the different effects of AVI and ATM against the 4 investigated strains. Dashed lines correspond to the limit of quantification.

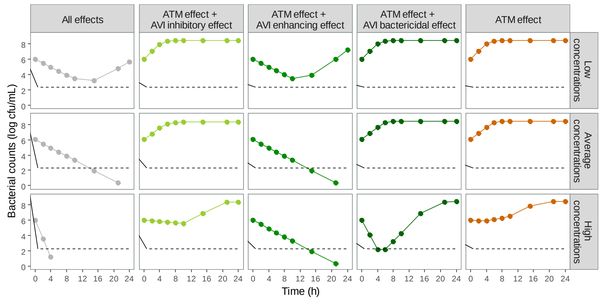


Fig 4. Evaluation of the different effects of AVI and ATM against E. cloacae 1318536 in response to different levels of ATM-AVI: low concentrations (5-0.9 µg/mL), average concentrations (25-4.5 µg/mL) and high concentrations (125-22.5 µg/mL). Dashed lines correspond to the limit of quantification.

## CONCLUSIONS

- The 3 previously reported effects of AVI could be well characterized by the PK/PD model for the new MDR strains evaluated in this study.
- However, within the clinical range of ATM and AVI concentrations, even though AVI could avoid ATM degradation, the combined bactericidal activity was mostly explained by AVI enhancing effect.

**References:**

[1]Sy, SKB et al., CPT Pharmacometrics Syst. Pharmacol., 2016 ; [2]Vinks, AA et al., AAC, 2007 ; [3]Merdjan, H et al., Clin. Drug Investig., 2015

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