Thi Huyen Tram NGUYEN, 27 October 2014, « Handling of data below the quantification limit in viral kinetic modeling for model evaluation and prediction of treatment outcome».

**Abstract**

Viral kinetic (VK) models are useful tools to understand the lifecycle of hepatitis C virus and the mechanisms of action of antiviral agents. The understanding of virologic response can be improved by including pharmacokinetic (PK) information. VK model might also be useful to predict individual treatment outcome and support treatment personalization. One common problem in VK modeling is data below the quantification limit (BQL). However the impact of these data on model evaluation and treatment response prediction and how to properly handle them in these steps are still in question.

We extended prediction discrepancies (pd) and normalized prediction distribution errors (npde) to handle BQL data and evaluated them in a simulation study. The extended metrics have better performance with satisfactory type I errors and powers, compared to the methods omitting BQL data. We developed a PK-VK model to characterize the VK to alisporivir, a cyclophillin inhibitor, given in with or without peg-IFN. The model provided good predictions for the virologic responses (BQL data fraction and SVR rate) for different combinations and doses of alisporivir in another study. We also studied by simulation the use of VK model to predict individual treatment outcome and evaluated several factors that can impact this prediction: methods for handling BQL data, design and *a priori* information on population parameters. We showed that Bayesian estimation of individual parameters can give good predictions for treatment outcome from only few early responses, provided that BQL data are correctly handled and correct *a priori* information is available.

Key words: Nonlinear mixed effect models, data below quantification limit, model evaluation, viral kinetic modeling, hepatitis C infection, treatment outcome prediction