Implementation of a highly nonlinear, multi-scaled and long-term HIV dynamic model with treatment interruptions and non-static BQL data for population analysis

Shuhua Hu*, Kevin Feng, Bob Leary, Mike Dunlavey, Bill Poland
Certara/Pharsight, Cary, NC

Objectives: The goal is to apply QRPEM estimation in Phoenix® NLME™ (Pharsight/Certara) to a highly nonlinear, multi-scaled and long-term HIV dynamic model [1] for population analysis with clinical data [1] including treatment interruptions, total CD4+ T-cells and non-static BQL viral load. A simpler model was considered in [2] for population analysis using SAEM and does not incorporate some important features including HIV-specific CD8+ T-cells and another possible source of latency. Here we do not try to compare QRPEM with methods used in other software but rather show the capability of QRPEM in implementing such a complex model.

Methods: Due to the complexity of the problem, this model cannot be directly implemented in Phoenix® NLME™. For example, model states may become unrealistically negative in numerically solving it due to round-off error caused by large-scale differences among model states and parameters. Moreover, ODE solvers often failed due to some unrealistic parameter values obtained during the optimization process. To alleviate the first difficulty, we converted the model by log-transformation of all model states and parameters. To avoid obtaining unrealistic parameter values, we imposed lower and upper bounds on posthoc parameters and modified Mu-model for QRPEM estimation. To incorporate treatment interruptions, we added treatment as a time-varying covariate using a linear-interpolation approach.

Results: Through proposed methods, we successfully implemented this model and obtained reasonable goodness of fit for all patients (Figure 1 shows fitting results for one patient).

Conclusions: Numerical results demonstrate the capability of QRPEM in analyzing a complex dynamic model with complicated data. In the future, we plan to investigate a hierarchical structure of this model or other disease models and then use these models to design adaptive dosing regimens via the Phoenix modeling language engine.

References: