Supplemental Methods

Count variables: The model building approach and final models were similar for all MRI counts, therefore these will be described jointly here, with all important differences highlighted.

As a starting point for this analysis, a Poisson model which assumes that the mean value of individual observations and their variance are equal was used to describe the placebo data. The basic model parameter is LAMBDA (λ) representing mean count of HIV RNA within an individual. The probability of observing certain response (i.e. HIV RNA count) is described by the Poisson distribution:

$$P(Y_i = n) = \frac{e^{-\lambda} \cdot \lambda^n}{n!}, \quad \lambda \geq 0, \quad n \in \mathrm{N}_0 \mathrm{P}(\mathrm{Y_i} = \mathrm{n}) = \frac{\mathrm{e}^{-\lambda} \times \lambda^{\mathrm{n}}}{\mathrm{n!}}, \lambda \geq 0, \mathrm{n} \in \mathrm{N}_0 \qquad \text{Equation 1a}$$

$$E(Y_i) = Var(Y_i) = \lambda \qquad \text{Equation 1b}$$

where n is actual observation, $n!$ is the factorial function and λ the mean.

The validity of the assumption that the individual mean is equal to the individual variance was evaluated by plotting the mean values of observed data versus its variance, and after inspecting this plot, other models, which account for cases when zero count is in excess and the variance is larger than the mean, were also evaluated. These models include zero-inflated Poisson model, Generalized Poisson model and Negative binomial model. The basic model parameters for Zero-inflated Poisson model are λ and P0 (probability of having zero count) (Ette and Williams 2007, Troconiz, Plan et al. 2008) and the general model is shown by Equation 2. Observed variable (DV) is represented with n in Equations 2-6.

$$P(Y_i = n) = \begin{cases} \mathrm{P}_0 + (1 - \mathrm{P}_0) \cdot e^{-\lambda}; n = 0 \\ (1 - \mathrm{P}_0) \cdot \dfrac{e^{-\lambda} \cdot \lambda^n}{n!}; n > 0 \end{cases}, \lambda \geq 0, n \in N_o \qquad \text{Equation 2}$$

The basic parameters for Generalized Poisson model are λ and dispersion parameter (δ) which can account for the fact that the variance may be either larger or smaller than the mean (Equation 3).

$$P(Y=n)=\frac{\lambda\cdot(\lambda+n\cdot\delta)^{n-1}\cdot e^{-\lambda-n\cdot\delta}}{n!},\quad \lambda\geq 0,\quad n\in \mathrm{N}_0 \qquad \text{Equation 3}$$

The basic parameters for the negative binomial model are λ and over-dispersion parameter (*OVDP*) which accounts for the fact that the variance is larger than the mean (Equation 4).

$$P(Y_i=n)=\left[\frac{\Gamma\left(n+\frac{1}{OVDP}\right)}{n!\cdot\Gamma\left(\frac{1}{OVDP}\right)}\right]\cdot\left(\frac{1}{1+OVDP\cdot\lambda}\right)^{\frac{1}{OVDP}}\cdot\left(\frac{\lambda}{\frac{1}{OVDP}+\lambda}\right)^{n}; \qquad \text{Equation 4}$$

$$\lambda, OVDP\geq 0,\quad n\in \mathrm{N}_0$$

In order to incorporate these models into the NONMEM code, the numerical approximation for factorial function as well as for gamma function (Γ) was needed. For that purpose, improved version of Stirling's formula was employed (Equation 5 and 6) (Abramowitz and Stegun 2002, Osterberg, Savic et al. 2006, Nemes 2010).

$$n!\approx\sqrt{2\pi}\cdot n^{n+\frac{1}{2}}\cdot e^{-n}\cdot\left(1+\frac{1}{12n}\right) \qquad \text{Equation 5}$$

$$\Gamma(n)\approx\sqrt{2\pi}\cdot n^{n-\frac{1}{2}}\cdot e^{-n}\cdot\left(1+\frac{1}{12n}\right) \qquad \text{Equation 6}$$

Where λ is a function of drug exposure using

$$\lambda_{trt}=\lambda_{base}\times(\,1+[E_{max}\times\exp(\eta_{4i})]\frac{(A_i)^{Gamma}}{[AUC_{50}\times\exp\,(\eta_{3i}\,)]^{Gamma}+\,(A_i)^{Gamma}})$$

where η_{3i} and η_{4i} are the random effects (individual perturbations) for AUC_{50} and E_{max}, and λ_{trt} = the calculated mean count of HIV-1 RNA during treatment. The variance of the counts is calculated using

Equation 4 above, which utilizes λ and OVDP.

References

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