Effect of selection bias due to lack of resistance in the study population on virco®TYPE clinical cutoff estimates for new drugs

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Background:

- New drug:
  - limited clinical data available
  - few patients resistant to the new drug

- Issue:
  - clinical cutoffs estimates need to be applicable to populations resistant to the new drug.

- Objective:
  - to evaluate clinical cutoff estimates in populations with different ratios of resistant/sensitive patients

Methods:

• A sigmoid Emax model was fitted to the clinical data of the RESIST studies (1 and 2), evaluating the change in VL at week 8 as a function of baseline fold change in IC50 (FC) for tipranavir (TPV).

• This model was used to generate three populations:

1. a population with mostly low FC values for TPV (pop. 1),
2. a population with mostly high FC values (pop. 2)
3. a population with FC equally distributed over the dynamic range of the virco®TYPE HIV-1 assay (pop. 3).

• For each of these populations, TPV clinical cut-offs were calculated (20 and 80% loss of wild type response for CCO1 and CCO2 respectively). Cutoffs were compared to assess their dependence on the selected population.

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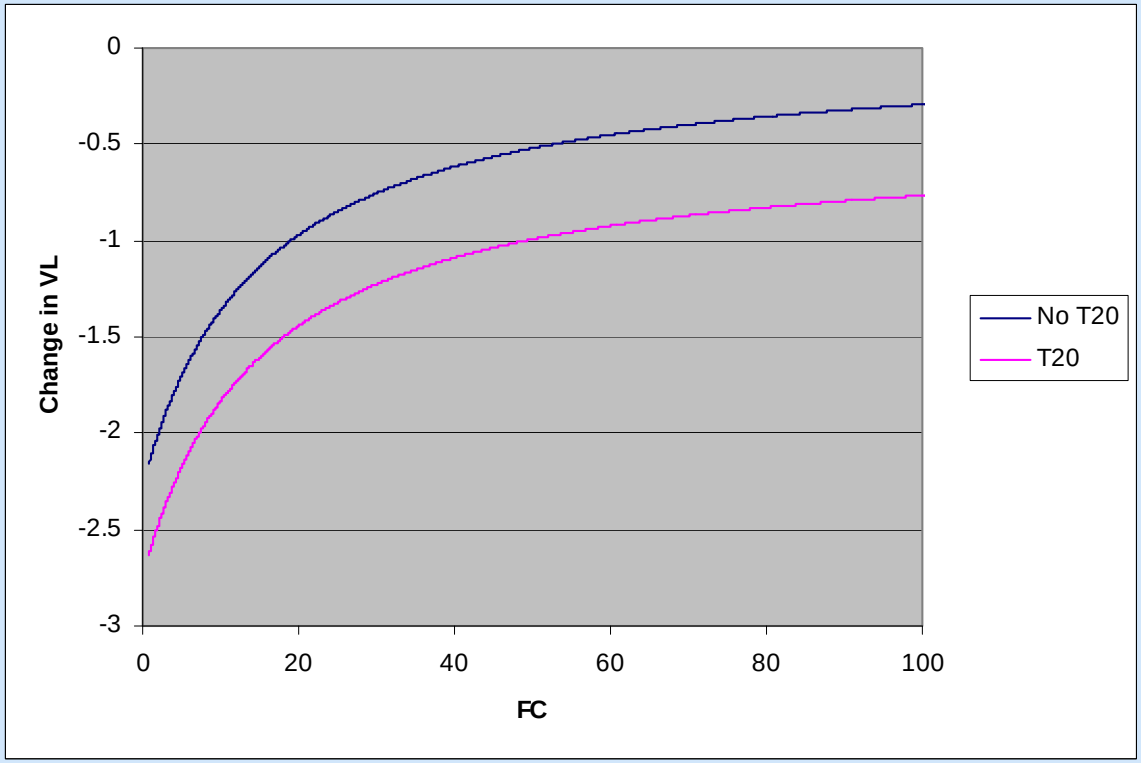
Fitting the Emax Model

$$\Delta VL_i = \alpha * T20 + \frac{\theta_1 * \exp(\varepsilon_{1i}) * (FC)^{\omega}}{\theta_2 + (FC)^{\omega}} + \varepsilon_2$$

, with $\varepsilon_{1i} \sim N(0,\sigma_1^2)$ and $\varepsilon_{2i} \sim N(0,\sigma_2^2)$



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Generating new populations from the Emax model

$$\mu = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \sigma_1 \\ \sigma_2 \\ \omega \\ \alpha \end{bmatrix} = \begin{bmatrix} -3.1252 \\ 1.2353 \\ 0.0090 \\ 1.0874 \\ -0.7302 \\ -0.7429 \end{bmatrix} \qquad \Sigma = \begin{bmatrix} 2.2057 & -1.6206 & 0.0014 & -0.0022 & -0.3527 & -0.0142 \\ & 1.1968 & -0.007 & 0.0011 & 0.2607 & 0.0075 \\ & & 0.0049 & -0.0080 & 0.0000 & -0.0010 \\ & & & 0.0164 & -0.0000 & 0.0015 \\ & & & & 0.0652 & 0.0037 \\ & & & & & 0.0100 \end{bmatrix}$$

The following steps were repeated 1000 times:

- Generate a new set of parameters based on the multivariate normal distribution.
- For each set of parameters, generate 10000 viral load drops over the entire dynamic range of the assay.
- Create 3 populations as described in the methods section.

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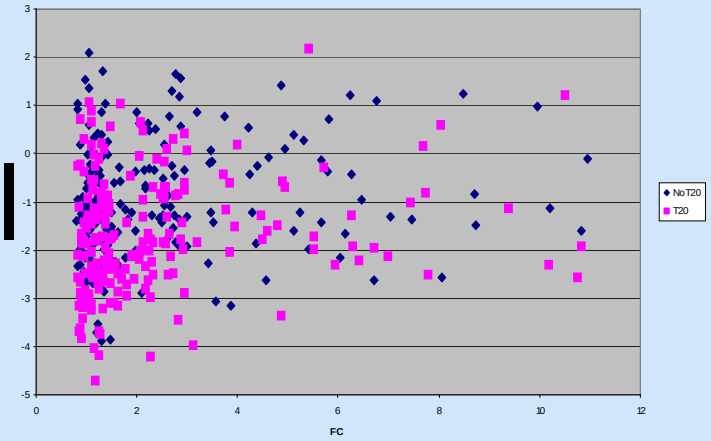
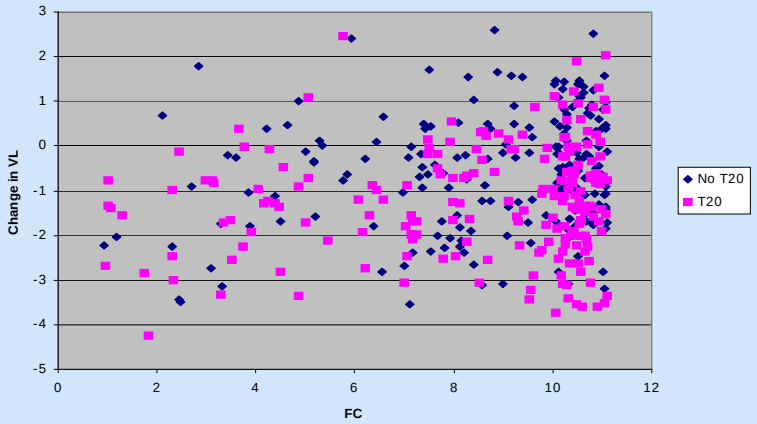
Example

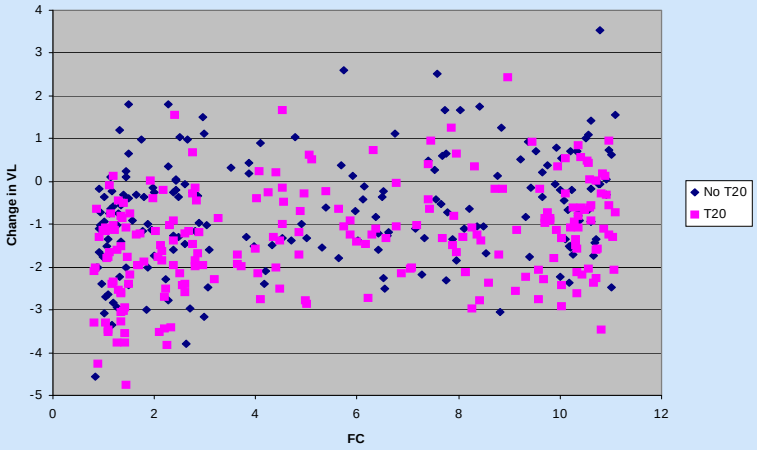
Population 1



Population 2



Population 3



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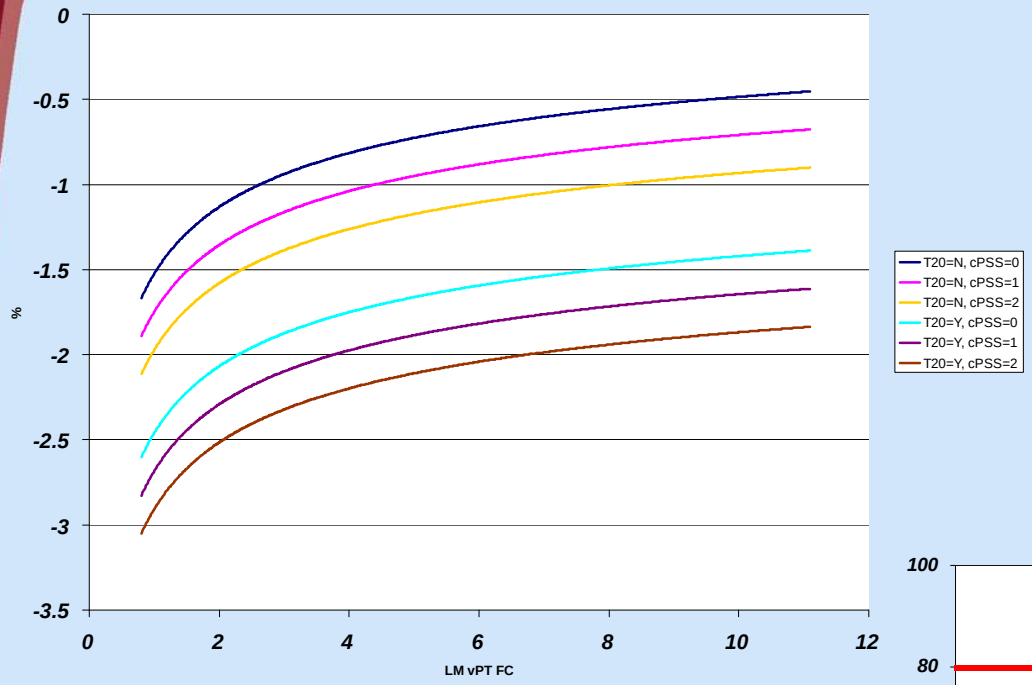
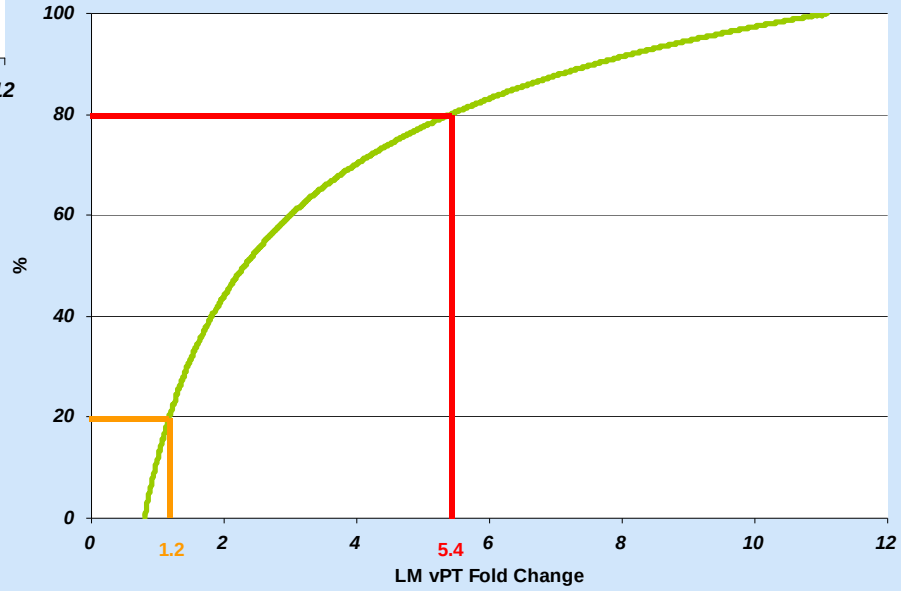
Determining the clinical cutoffs



1. Linear regression of VL drop as a function of baseline fold change

2. Rescale the predicted VL drops to a % loss of wild type response.

3. Clinical cutoffs are the fold changes corresponding to 20 and 80% loss.



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Results

	Population 1		*Population 2*		*Population 3*	
	Low	***High***	***Low***	***High***	***Low***	***High***
N	1000		1000		1000	
Mean	1.4	5.4	1.6	5.8	1.4	5.7
SD	0.6	2.3	0.7	2.6	0.6	2.2
Median	1.2	5.4	1.2	5.8	1.2	5.4
(Q1;Q3)	(1.0;1.5)	(3.4;7.2)	(1.0;2.3)	(3.4;8.5)	(1.0;1.6)	(4.0;7.6)

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Conclusions

• The mean/median of the clinical cutoffs estimates were not dramatically affected by the baseline FC distribution of the study population.

• The variability of the clinical cutoff estimates was slightly higher in the population with mostly high fold changes.

• The outcome of this analysis will be reevaluated when more clinical outcome will be available.

• The model used to generate the 3 populations will be refined further, in particular with respect of T20 use.