Supplementary Information File 2

Alternative viral dynamic models including immune effectors

We assumed that the immune responses could have various effects in our viral dynamic model and tested whether those alterative models could better describe the data. Based on the cytokines measured in the 31 infected cynomolgus macaques, we explored the correlations between the are under the cytokine curve and the viral load AUC predicted by the model without immune response and used it to build the novel models. Correlations showing a p-value<0.1 were implemented in the model as regressor values instead of describing the cytokine kinetics. In addition, we considered 4 models involving the IFN-⍺ concentrations as usually admitted to drive immune effects in viral dynamic modelsmodels, even though it showed no correlation with model parameters. Data fitting was performed using Monolix software (<http://lixoft.com/products/monolix>) and models were compared based on the Bayesian information criteria (BIC): the lower the BIC, the better the model. However, an absolute difference of less than 5 was not sufficient to distinguish the models. A comparison of all models tested is provided Table S1.

For each model, we assumed the same fixed parameters as the model without any immune response and supposed no inter-individual variability for the parameter .

Model 1: IFN-⍺ reduces infectivity

We explored a model where concentrations of IFN-⍺ led to a reduction of the infectivity rates.1,2 This yields to the following system of ODEs (1):

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|  | (1) |

where is the concentration of IFN-⍺.

Model 2: IFN-⍺ prevents target cells from infection

Here we assumed that IFN-⍺ could favor the formation of refractory cells i.e. target cells protected from infection.3 We supposed that this state is permanent and cells could not return to their infectious-sensitive status. The following ODEs (2) describe the model.

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|  |  |
|  | (2) |

where is the concentration of IFN-⍺.

Model 3: IFN-⍺ increases loss of infected cells

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|  |  |
|  | (3) |

where is the concentration of IFN-⍺.

Model 4: IFN-⍺ lowers the viral production rate

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|  |  |
|  | (4) |

where is the concentration of IFN-⍺.

Models comparison

Alternative models 1-4 described above were compared to the best fitting model presented in the main text i.e. without immune response. The BICs obtained after fitting are presented in Table S1. None of the models incorporating an immune response provided an improvement > 5 points. Thus, none was considered performing better than the reference model. Although models 1 and 2 have a BIC within 5 points difference compared to the best model, the addition of one parameter () makes parameter identifiabitilty harder. Thus, we favored the model without any immune response, as it allowed to well describe the data with fewer but identifiable parameters. Parameters estimates and individual fits of models 1 and 2 are shown in tables S2-S3 and figures S1-S2.

**Table S1:** Bayesian information criteria of the alternative tested models

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Description** | **BIC** | **σN** | **σT** |
| **Reference model** | Absence of immune response | 1253.8 | 1.06 | 1.19 |
| **Model 1** | IFN-α reduces infectivity | 1248.6 | 1.06 | 1.19 |
| **Model 2** | IFN-α prevents target cells from infection | 1249.3 | 1.07 | 1.20 |
| **Model 3** | IFN-α increases loss of infected cells | 1256.6 | 1.06 | 1.20 |
| **Model 4** | IFN-α lowers viral production | 1257.4 | 1.06 | 1.19 |

**Table S2:** Model 1 - Population parameter estimates

|  |  |  |
| --- | --- | --- |
| **Parameters (units)** | **Fixed effects (RSE%)** | **SD of random effects (RSE%)** |
| **βT (mL/copie/d)** | 3.410-4 (26) | 0.2 (65) |
| **βN (mL/copie/d)** | 2.710-5 (58) |
| **pT (copies/d)** | 1.4104 (37) | 0.9 (27) |
| **pN (copies/d)** | 5.4104 (38) |
| **VT0 (copies)** | 1.7107 (22) | - |
| **VN0 (copies)** | 1.9106 (22) | - |
| **δ (1/d)** | 1.75 (8) | 0.2 (27) |
| **φ (mL/pg)** | 0.11 (130) | - |
| **c (1/d)** | 10 (fixed) | - |
| **k (1/d)** | 3 (fixed) | - |
| **TT (t=0) (cells)** | 2.25104 (fixed) | - |
| **TT (t=0) (cells)** | 1.25105 (fixed) |  |
| **σT** | 1.06 (6) | - |
| **σN** | 1.19 (6) | - |

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**Figure S1**: Nasopharyngeal (blue) and tracheal (red) individual predicted viral loads **obtained with model 1** (decrease of the infectivity rate β with IFN-⍺ concentrations)

**Table S3:** Model 2 - Population parameter estimates

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| --- | --- | --- |
| **Parameters (units)** | **Fixed effects (RSE%)** | **SD of random effects (RSE%)** |
| **βT (mL/copie/d)** | 1.110-3 (32) | 0.3 (75) |
| **βN (mL/copie/d)** | 5.210-5 (50) |
| **pT (copies/d)** | 1.1104 (34) | 0.9 (26) |
| **pN (copies/d)** | 4.8104 (28) |
| **VT0 (copies)** | 4.7107 (18) | - |
| **VN0 (copies)** | 5.2106 (18) | - |
| **δ (1/d)** | 1.88 (9) | 0.2 (24) |
| **φ (mL/pg)** | 2.091017 (>100) | - |
| **c (1/d)** | 10 (fixed) | - |
| **k (1/d)** | 3 (fixed) | - |
| **TT (t=0) (cells)** | 2.25104 (fixed) | - |
| **TT (t=0) (cells)** | 1.25105 (fixed) |  |
| **σT** | 1.07 (6) | - |
| **σN** | 1.20 (6) | - |

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Figure S2: Nasopharyngeal (blue) and tracheal (red) individual predicted viral loads obtained with model 2 (IFN-⍺ prevents target cells from infection)