Mathematical Analysis of the Model

In this paper, we generalized a previous model of HBV infection and treatment (1), by including proliferation of uninfected hepatocytes, T, and infected hepatocytes, I. The equations describing the model are

$$\begin{aligned}\frac{dT}{dt} &= s + r_T T(1-\frac{T+I}{T_{\max}}) - d_T T - (1-\eta)\beta VT + \rho I \\ \frac{dI}{dt} &= (1-\eta)\beta VT + r_I I(1-\frac{T+I}{T_{\max}}) - (\delta+\rho)I \\ \frac{dV}{dt} &= (1-\varepsilon)pI - cV\end{aligned} \qquad (1)$$

This model is described in detail in the main text. Here we derive the steady state solutions and outline how the expression for the critical drug efficacy is obtained (see also (2)).

Note that in order to have $\bar{T}_0 \le T_{\max}$, s must satisfy $s \le dT_{\max}$. We also assume $r_T > d_T$, as a liver rapidly regenerates via proliferation if its size is reduced, as in living donor transplantation, and that the rate of noncytolytic cure, ρ, is small. With these assumptions, model (1) admits two steady states: an uninfected steady state with $I=V=0$ and total number of uninfected hepatocytes equal to

$$\bar{T}_0 = \frac{T_{\max}}{2r_T}\left[r_T - d_T + \sqrt{(r_T - d_T)^2 + \frac{4r_T s}{T_{\max}}} \right], \qquad (2)$$

and an infected steady state with

$$\bar{V} = \frac{(1-\varepsilon)p\bar{I}}{c} \ , \ \bar{I} = \bar{T}(\frac{A}{r_I} - 1) + T_{\max}(1-B) \quad , \qquad (3)$$

where $B = \frac{\delta + \rho}{r_I}$. Here $\overline{T}$ is the steady state value of T defined as the solution of the quadratic equation

$$\frac{A\,D}{T_{\max} r_I}\,\overline{T}^2 - (\delta + \rho - d_T + \frac{\delta + 2\rho}{r_I} D - A - \rho\frac{r_T}{r_I})\overline{T} - [s + T_{\max}\rho(1 - \frac{\delta + \rho}{r_I})] = 0 \qquad (4)$$

where

$$A = \frac{(1-\varepsilon_{tot})\,p\beta T_{\max}}{c}\ , \quad D = A + r_T - r_I\ ,$$

and ε_{tot}= (1-ε)(1-η) as in the main text. The coefficient of $\overline{T}^2$ is positive since $\varepsilon_{tot} < 1$. For small enough ρ the constant term in the polynomial is negative. Thus by Decartes' rule of signs there is only one positive root of equation (4).

The local stability of the two steady states is determined by examining the eigenvalues of the Jacobian of equation (1) evaluated at the steady state solutions. At the uninfected steady state, the Jacobian, *J*, is

$$\begin{bmatrix} -d_T + r_T - \frac{2r_T\overline{T}_0}{T_{\max}} & -\frac{r_T\overline{T}_0}{T_{\max}} + \rho & -(1-\eta)\beta\overline{T}_0 \\ 0 & r_I - \frac{r_I\overline{T}_0}{T_{\max}} - \delta - \rho & (1-\eta)\beta\overline{T}_0 \\ 0 & (1-\varepsilon)p & -c \end{bmatrix}. \qquad (5)$$

Solving the characteristic equation, $J-\lambda I=0$, the three eigenvalues, λ, for the system are given by

$$
\begin{aligned}
&-\sqrt{(r_T - d_T)^2 + \frac{4r_T s}{T_{\max}}} \\
&-\frac{1}{2T_{\max}}\left(W + \sqrt{W^2 - \frac{4}{p\beta\bar{T}_0}(\varepsilon_{tot} - \varepsilon_c)}\right), \\
&-\frac{1}{2T_{\max}}\left(W - \sqrt{W^2 - \frac{4}{p\beta\bar{T}_0}(\varepsilon_{tot} - \varepsilon_c)}\right)
\end{aligned}
\tag{6}
$$

where $W = (1-\varepsilon_c)p\beta T_{\max}\bar{T}_0 / c + cT_{\max}$ and

$$
\varepsilon_c = 1 - \frac{c((\delta+\rho)T_{\max} + r_I(\bar{T}_0 - T_{\max}))}{p\beta T_{\max}\bar{T}_0} \ . \tag{7}
$$

For the uninfected state to be stable all three eigenvalues must be negative. It is straightforward to check that independently of the effectiveness of therapy (i.e., ε_{tot}) the two first eigenvalues are always negative. However, the sign of the third eigenvalue depends on ε_{tot}. When $\varepsilon_{tot}>\varepsilon_c$ the term in the square root is smaller than W and the third eigenvalue is also negative. Thus, in this case the uninfected steady state is stable, and treatment would lead to clearance of the virus. When $\varepsilon_{tot}<\varepsilon_c$, the term in the square root is larger than W and the eigenvalue is positive. Thus, the uninfected steady state is unstable and therapy could never lead to loss of virus. One can also show that when $\varepsilon_{tot}<\varepsilon_c$, the infected state is stable and that when $\varepsilon_{tot}>\varepsilon_c$ then infected steady state is unstable. We do not prove these last statements, because the algebra becomes ugly, although not difficult.

We also note that it can be shown that when $\varepsilon_{tot}=\varepsilon_c$, the expressions for both $\bar{I}$ and $\bar{V}$ in Eq. (3) are equal to zero, that is the infected steady state merges with the uninfected steady state. This again suggests that the effectiveness of therapy must be at least ε_c for viral clearance to be predicted by the model.

1. Lewin SR, Ribeiro RM, Walters T, Lau GK, Bowden S, Locarnini S, Perelson AS. Analysis of hepatitis B viral load decline under potent therapy: complex decay profiles observed. Hepatology 2001;34:1012-1020.

2. Dahari H, Lo A, Ribeiro RM, Perelson AS. Modeling hepatitis C virus dynamics: Liver regeneration and critical drug efficacy. J Theor Biol 2007;247:371-381.