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Assignment 4

Paper 2

Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection

1. Describe the motivating question / novelty of the paper.

2. Describe the discrete mathematical model/ framework used, and interpretation of any model terms, along with parameters and units.

   The only model really talked about in the paper is the following:

   Before drug administration, the change in viral load with time can be expressed by the differential equation:

   $$\frac{dV}{dt} = P - cV$$

   P: viral production rate
   c: the viral clearance rate constant
   V: the number of plasma virions

   During the pretreatment steady state, $\frac{dV}{dt} = 0$ and hence $P = cV$.

   Based on the data, the authors were not able to determine whether the rise was linear or strictly exponential.

   It also says in the paper that the authors also tested more intricate models, in which the viral decay is governed by two or three exponential rates, namely the viral clearance rate, the decay rate of virus producing cells, and the decay rate of latently infected cells.

   The paper also talks about irrespective of the model, on a log plot, $S = \frac{-d(lnV)}{dt} = c - \frac{P}{V}$. If drug inhibition is complete and virus producing cells are rapidly lost ($P = 0$), then $S = c$.

3. List key assumptions.

   The authors made the following assumptions:

   (a) that ABT-538 administration does not affect viral clearance.
   (b) that there exists a steady state and hence the calculated clearance rate is equal to the minimum virion production rate before drug therapy.

4. BRIEFLY describe the author's approach (methods, analysis, etc), and their results/ conclusions.

   The authors administered 600 - 1200 mg of ABT-538 orally daily to twenty HIV-1 infected patients. Post treatment CD4 lymphocyte counts were monitored sequentially, as were copy numbers of particle associated HIV-1 RNA in plasma, using an ultrasensitive assay based on a modification of the branched DNA signal application technique.
   Following treatment every patient had a rapid and dramatic decline in plasma viraemia over the first two weeks. The initial decline was always exponential which was demonstrated by a straight-line fit to the data on a log plot.
   In Table 1, the viral decay slopes varied from -0.21 to -0.54 per day, with a mean of -0.34 ± 0.06 per day; correspondingly, $t_{1/2}$ varied from 1.3 to 3.3 days with a mean of 2.1 ± 0.4 days.
   The authors' observations strongly suggest that the viral clearance rate constant is not dependent on the stage of HIV-1 infection. Instead they indicate that viral load is largely a function of viral production, because clearance rate constants vary by about 2.5 fold whereas the initial loads vary by almost 40 fold.

5. List at least one criticism of the work presented in the manuscript.

   One criticism is that it was hard to understand the paper unless you had knowledge of the biology behind HIV-1. I had to do research to fully understand the paper. Also, it would have been nice if more attention was paid to the mathematical model. I almost missed it and did not even see the model at first.

6. Name at least one extension, improvement, related question or assumption that could be relaxed that could/should be done as future work.
   The patients had a wide variety of baseline values. It would be interesting to do the study on a group with very similar baseline values to see if the results are consistent from one patient to another or if they vary greatly.