Do the pharmacokinetic and pharmacodynamic graphs warrant additional explanation?

Avaneesh Kumar Pandey[a], Navjot Kaur[b,1], and Nusrat Shafiq[a]

We read with great interest the article by Kudalkar et al. (1), in which the authors identify and conduct substantial work for a promising novel long-acting nonnucleoside reverse transcriptase inhibitor (NNRTI) molecule. We commend the authors for addressing an urgent, unmet global need. Such studies are particularly relevant for developing countries like India, where the reported prevalence of any drug-resistant mutations to the NNRTI group of drugs is more than 70% (2). However, we would like to share our concerns and understand the presented work in greater depth.

Our first and foremost concern is the data presented in their figure 6C. We fail to understand why there was a fall in the plasma viral loads after day 19 in the control group (i.e., the group not given any intervention). Furthermore, not only was the fall in the plasma viral load significant (to below the limit of detection; <150 copies per milliliter) but also it was more rapid (showing a steeper decline) compared with the treated groups by day 32. If the viral loads are decreasing so rapidly and significantly in the noninterventional (control group), can we draw conclusions about the efficacy of interventional arms?

Second, it would be interesting to know the possible reasons for the steep increase in the serum concentrations of compound I (group 1; green circles) when dosed continuously (at a dose of 100 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ until day 32) after day 16 until day 25 as depicted in their figure 5B. Had the drug accumulation been due to saturation of elimination processes, we would have expected a further increase in concentrations even after day 25 until the day of last measurement, that is, day 32. We fail to understand the mechanism underlying the initial steep rise followed by the fall in drug concentrations despite continued dosing of free compound I at the same dose level for 32 d.

1 Kudalkar SN, et al. (2018) From in silico hit to long-acting late-stage preclinical candidate to combat HIV-1 infection. *Proc Natl Acad Sci USA* 115:E802–E811.

2 Karade S, et al. (2018) HIV drug resistance following a decade of the free antiretroviral therapy programme in India: A review. *Int J Infect Dis* 66:33–41.

[a]Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India; and [b]Department of Pharmacology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi 110029, India

Author contributions: A.K.P., N.K., and N.S. analyzed data; and N.K. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. Email: drnavjotpharma@gmail.com.

Published online August 10, 2018.