Published in final edited form as:
Clin Infect Dis. 2010 November 1; 51(9): 1105–1107. doi:10.1086/656688.

Achieving a Quantitative Understanding of Antiretroviral Drug Efficacy

Lin Shen[1] and **Robert F. Siliciano**[1,2]

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore MD 21204

[2]Howard Hughes Medical Institute, Baltimore MD 21204

Keywords

antiretroviral therapy; dose-response curve; slope; IIP; inhibitory quotient

We are writing to expand upon some issues raised in a recent article by Henrich et al. [1] regarding the Instantaneous Inhibitory Potential (IIP), a novel index of antiviral activity developed by Shen et al. [2, 3]. IIP is the log reduction in single round infection events produced by a drug at clinically relevant concentrations. Because IIP takes into account the shape (slope) of the dose response curve, we have argued that it is a more accurate representation of intrinsic antiviral activity than conventional pharmacodynamic measures such as IC_{50} or inhibitory quotient (IQ, the ratio of clinical drug concentration to IC_{50}). Importantly, the slope parameter is included in all of the fundamental equations of pharmacology including the Hill equation [3], the sigmoidal E_{max} model [4], and the Chou Talalay median effect equation [5]. Thus a true understanding of the dose effect relationship cannot be obtained achieved without inclusion of this parameter. It had been largely ignored in studies of antiretroviral drugs until our study showed that the slope parameter varies dramatically and in a class specific way for antiretroviral drugs[2, 3]. Indeed, we showed that differences in the slope parameter explain the higher antiviral activity of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) relative to the nucleoside analogue reverse transcriptase inhibitors (NRTIs). The superior activity of the NNRTIs and PIs, a well accepted concept that is incorporated into HIV treatment guidelines [6], is not explained by standard measures like IC_{50} or IQ. In this regard, the integrase strand transfer inhibitors (ISTIs) represent a special case discussed below.

Henrich et al. [1] examined the relationship between the pharmacologic measures IIP and IQ and the outcomes of clinical trials of antiretroviral drugs. Not surprisingly, neither parameter showed a particularly strong correlation with outcome as measured by the fraction of patients who had undetectable HIV RNA after 48 weeks of treatment. It is important to note that IIP was developed to predict antiviral activity at a given drug concentration, not clinical outcome. As we pointed out in our original article [2, 3], clinical outcome is determined by many factors in addition to antiviral activity including pharmacokinetics, distribution, toxicity, adherence, drug interactions, and barriers to resistance. Henrich et al. suggest that these factors dominate the slope in determining drug efficacy and cite the superior clinical performance of efavirenz over indinavir as an example. Interestingly, this comparison

Reprints or correspondence: Dr. Robert F. Siliciano, Deparment of Medicine, Johns Hopkins University School of Medicine, 879 Broadway Research Building, 733 N. Broadway, Baltimore MD 21205, Phone 410-955-2958, Fax 443-287-6218, rsiliciano@jhmi.edu.

Potential conflicts of interest: All authors: no conflicts

provides a perfect illustration of how slope influences antiviral activity. Indinavir has a high slope which means that small increases in drug concentration give large increases in antiviral activity. Missing from the analysis by Henrich et al. is an appreciation of the fact that a high slope is can also have negative consequences for drug action because for drugs with a high slope, small decreases in drug concentration cause large decreases in activity. For drugs with a high slope and a short half life, the IIP falls dramatically during the dosing interval. As we pointed out [2, 3], when this effect is taken into account, efavirenz shows superior activity over the dosing interval, consistent with the clinical data. Thus we feel that it is important to avoid viewing the role of the slope parameter in an overly simplistic way.

We believe that a true understanding of the efficacy of antiviral drugs requires consideration of five factors: (1) the intrinsic antiviral activity of a drug at a given concentration, which, according to fundamental laws of pharmacology, is a function of both IC_{50} and slope, (2) the change in the concentration of the drug over time, i.e pharmacokinetic, (3) factors such as convenience and toxicity that determine whether the patient will actually take the drug, (4) interactions with other drugs in the regimen, and (5) genetic barriers to resistance in the setting of suboptimal suppression. The superior performance of PIs like darunavir is largely a result of the first factor [2, 3] whereas for the ISTIs, the fourth factor is of particular importance (B. Jilek et al, manuscript in preparation). Our hope is that a quantitative analysis of all five factors will eventually allow a more rational choice of treatment regimens, particularly in patients with resistance.

Acknowledgments

This work was supported by NIH grant AI081600 and the Howard Hughes Medical Institute

References

1. Henrich TJ, Ribaudo HJ, Kuritzkes DR. Instantaneous inhibitory potential is similar to inhibitory quotient at predicting HIV-1 response to antiretroviral therapy. Clin Infect Dis. 2010; 51:93–98. [PubMed: 20504163]
2. Shen L, Peterson S, Sedaghat AR, et al. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. Nat Med. 2008; 14:762–766. [PubMed: 18552857]
3. Hill AV. The possible effects of the aggregation of the molecules of huemoglobin on its dissociation curves. J Physiol (London). 1910; 40:iv–vii.
4. Holford NH, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet. 1981; 6:429–453. [PubMed: 7032803]
5. Chou TC. Derivation and properties of Michaelis-Menten type and Hill type equations for reference ligands. J Theor Biol. 1976; 59:253–276. [PubMed: 957690]
6. Hammer SM, Eron JJ Jr, Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA. 2008; 300:555–570. [PubMed: 18677028]