The terminal velocity calculations in the table produced by Snelling and colleagues assume a unit density for clostridial spores. In fact, the reported dry density for clostridial spores is 1.42 g/mL [4]. This means that the terminal velocities should be multiplied by 1.42 and the settling time divided by 1.42. For example, the terminal velocity for 1.99-μm particles should be 0.185 mm/s, and the time to deposit 1 m reduced to 1.5 h.

Validation work conducted at the Health Protection Agency’s Centre for Emergency Preparedness and Response (A. Bennett, personal communication) determined the extent of deposition on the (12 mm in diameter) inner surfaces of the tubing used during our air sampling. Only 0.14%–15.9% of particles measuring 0.7–17.6 μm (expressed in Bacillus subtilis colony-forming units) were trapped on the inner surfaces of the tubing. Thus, such loss had a minimal effect on the airborne C. difficile counts we measured in situ [3].

Last, we emphasize that air movements in the clinical setting are extremely difficult to predict. Environmental sampling of sites beyond the reach of routine cleaning clearly show that C. difficile is frequently deposited on a variety of surfaces in clinical areas, likely exacerbated by aggregation with organic matter, as discussed above [5].

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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 nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors relative to the nucleoside analogue reverse-transcriptase inhibitors. The superior activity of the NNRTIs and protease inhibitors, a well-accepted concept that is incorporated into human immunodeficiency virus (HIV) treatment guidelines [6], is not explained by standard measures, such as IC50 or inhibitory quotient. In this regard, the integrase strand transfer inhibitors (ISTIs) represent a special case, which is discussed below.

Henrich et al [1] examined the relationship between the pharmacologic measures IIP and inhibitory quotient and the outcomes of clinical trials of antiretroviral drugs. Not surprisingly, neither parameter showed a particularly strong correlation with outcome as measured according to the fraction of patients who had an undetectable level of 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, toxic effects, adherence, drug interactions, and barriers to resistance. Henrich and colleagues 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 provides a perfect illustration of how slope influences antiviral activity. Indinavir has a steep slope, which means that small increases in drug concentration produce large increases in antiviral activity. Missing from the analysis by Henrich and colleagues is an appreciation of the fact that a steep slope can also have negative consequences for drug action, because for drugs with a steep slope, small decreases in drug concentration cause large decreases in activity. For drugs with a steep 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 during 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 5 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 IC50 and slope; (2) the change in the concentration of the drug over time (ie, pharmacokinetics); (3) factors such as convenience and toxic effects 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 cases in which suppression is suboptimal. The superior performance of protease inhibitors such as darunavir is largely a result of the first factor [2, 3], whereas for the ISTIs, the fourth factor is of particular importance (B. Jilek, M. Sampah, L. Shen, and R. Siliciano, unpublished data, 2010). Our hope is that a quantitative analysis of all 5 factors will eventually allow a more rational choice of treatment regimens, particularly in patients with resistance.

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References


Response to Shen and Siliciano

In their letter regarding our article comparing the instantaneous inhibitory potential (IIP) and the inhibitory quotient as predictors of antiretroviral efficacy [1], Shen and Siliciano [2] propose that understanding the efficacy of antiretroviral drugs requires consideration of 5 factors: intrinsic antiviral activity, pharmacokinetics, convenience and tolerability, drug-drug interactions, and the genetic barrier to resistance. We agree. In our view, the examples of efavirenz and indinavir illustrate the point that pharmacokinetics may trump intrinsic activity in determining relative efficacy. Comparative trials involving treatment-naive patients have generally not revealed superior efficacy when drugs with higher IIPs have been tested against drugs with lower IIPs (ie, efavirenz vs nevirapine [3], efavirenz vs atazanavir [4], darunavir-ritonavir vs lopinavir-ritonavir [5], lopinavir-ritonavir vs fosamprenavir-ritonavir [6], and saquinavir-ritonavir vs lopinavir-ritonavir [7]). It will be interesting to see whether the higher intrinsic activity and IIP of darunavir-ritonavir (IIP, 8.46 [2]) translates into superior efficacy,