Instantaneous Inhibitory Potential Is Similar to Inhibitory Quotient at Predicting HIV-1 Response to Antiretroviral Therapy

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(See the editorial commentary by MacArthur, on pages 99–100.)

Background. The instantaneous inhibitory potential (IIP), a measure of antiviral activity that incorporates the slope of the dose-response curve, has been proposed as a better predictor of clinical efficacy than the inhibitory quotient (IQ). However, there are no quantitative analyses supporting this hypothesis.

Methods. The correlation between differences in \( \log_{10}(IQ) \) or differences in IIP (\( \Delta \text{IIP} \)) and the differences in percentage of subjects with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels <50 copies/mL at week 48 was determined for antiretroviral drugs compared in 17 randomized clinical trials. The \( \Delta \log_{10}(IQ_{\text{min}}) \), \( \Delta \log_{10}(IQ_{\text{max}}) \), \( \Delta \text{IIP}_{\text{min}} \), \( \Delta \text{IIP}_{\text{max}} \), \( \Delta \log_{10}(IQ_{10}) \), \( \Delta \log_{10}(IQ_{24}) \), \( \Delta \text{IIP}_{10} \), and \( \Delta \text{IIP}_{24} \) for comparative drugs were correlated with differences in percentage of subjects with HIV-1 RNA levels <50 copies/mL in each trial. \( \log_{10}(IQ_{10}) \), \( \log_{10}(IQ_{24}) \), IIP 10, and IIP 24 were calculated using published median effect model slope values and \( \log_{10}(IQ) \) values; values from linear regression and Spearman correlation coefficients were calculated for each analysis; and correlation coefficients were compared between \( \log_{10}(IQ) \) and IIP.

Results. \( r^2 \) values were greatest for the \( \Delta \log_{10}(IQ_{10}) \) and \( \Delta \log_{10}(IQ_{24}) \) comparisons using intention-to-treat outcomes from the 17 trials. Differences in \( r^2 \) values between \( \Delta \log_{10}(IQ_{10}) \) and \( \Delta \text{IIP}_{24} \) and between \( \Delta \log_{10}(IQ_{24}) \) and \( \Delta \text{IIP}_{24} \) were 0.05 and 0.18, respectively. Differences in Spearman rank correlation coefficients between \( \log_{10}(IQ) \) and IIP at each drug concentration were not significantly different, with the exception of \( \Delta \log_{10}(IQ_{\text{max}}) \) and \( \Delta \text{IIP}_{\text{max}} \); the \( \Delta \log_{10}(IQ_{\text{max}}) \) correlation was significantly stronger than the \( \Delta \text{IIP}_{\text{max}} \) correlation.

Conclusions. IIP was not substantially better than \( \log_{10}(IQ) \) in describing the modest relationship between antiviral activity, pharmacokinetics, and virologic outcomes for antiretroviral drugs.

Reliable laboratory and mathematical models to predict the antiretroviral activity of candidate drugs could aid the selection of novel agents for clinical development. Widely used measures to quantify antiviral activity include the amount of drug required to inhibit 50% of viral activity in vitro (\( IC_{50} \)) and the inhibitory quotient (IQ), which is the trough drug concentration divided by the \( IC_{50} \). The IQ shows a modest correlation with clinical outcome [1, 2], but outcomes can vary in relation to relatively minor changes in maximum inhibition that are not reflected in the IQ. Moreover, the shape of the dose-response curve can vary substantially between drugs with similar \( IC_{50} \) values because of differences in slope. There has been interest in designing and implementing new laboratory measures that overcome existing limitations. A recent study described an index for comparing antiviral activity of different drugs using classic dose-response relationships that incorporate the slope of the inhibition curve, or Hill coefficient, for each drug [3]. The Hill coefficient was first used to describe cooperative binding in hemoglobin [4] and has a role in modeling synergy between different drugs [3, 5, 6]. This index, termed the instantaneous inhibitory potential (IIP), is defined by the following equation:

\[
\text{IIP}_{\text{c}_i} = \log\left(\frac{1}{f_{\text{IC}_{50}}}\right) = \log\left[1 + \left(\frac{C_i}{\text{IC}_{50}}\right)^m\right],
\]

where \( f_{\text{IC}_{50}} \) is the fractional drug concentration at \( IC_{50} \), \( C_i \) is the drug concentration, and \( m \) is the Hill coefficient.
Table 1. Differences in Inhibitory Quotient (IQ), Instantaneous Inhibitory Potential (IIP), and Percentage of Subjects with Viral Load (VL) <50 Copies/mL at 48 Weeks for Trials Included in the Analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs compared</th>
<th>First regimen</th>
<th>Δlog10(IQ24)a</th>
<th>ΔIIP24a</th>
<th>ΔPercentage of subjects with VL &lt;50 copies/mLb</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK934c [9]</td>
<td>TDF vs. AZT</td>
<td>Yes</td>
<td>0.1</td>
<td>0.2</td>
<td>9</td>
</tr>
<tr>
<td>GSK903c [10]</td>
<td>D4T vs. TDF</td>
<td>Yes</td>
<td>−2.1</td>
<td>−0.7</td>
<td>3</td>
</tr>
<tr>
<td>ACTG A5095 [11]</td>
<td>EFV vs. ABC</td>
<td>Yes</td>
<td>1.0</td>
<td>3.3</td>
<td>22</td>
</tr>
<tr>
<td>BMS034 [12]</td>
<td>EFV vs. ATV</td>
<td>Yes</td>
<td>1.8</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>2NN [13]</td>
<td>EFV vs. NVP</td>
<td>Yes</td>
<td>1.0</td>
<td>2.0</td>
<td>5a</td>
</tr>
<tr>
<td>Dupont 006 [14]</td>
<td>EFV vs. IDV</td>
<td>Noa</td>
<td>5.1</td>
<td>5.4</td>
<td>21</td>
</tr>
<tr>
<td>ACTG A5142c [15]</td>
<td>EFV vs. LPV/r</td>
<td>Yes</td>
<td>1.3</td>
<td>1.4</td>
<td>12</td>
</tr>
<tr>
<td>NEAT [16]</td>
<td>fAMP vs. NFP</td>
<td>Yes</td>
<td>1.0</td>
<td>1.5</td>
<td>14</td>
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<tr>
<td>KLEAN [17]</td>
<td>DRV/r vs. LPV/r</td>
<td>Yes</td>
<td>−0.9</td>
<td>−1.8</td>
<td>1</td>
</tr>
<tr>
<td>ARTEMIS [18]</td>
<td>DRV/r vs. LPV/r</td>
<td>Yes</td>
<td>0.4</td>
<td>4.4</td>
<td>6</td>
</tr>
<tr>
<td>TITAN [19]</td>
<td>DRV/r vs. LPV/r</td>
<td>No</td>
<td>0.4</td>
<td>4.4</td>
<td>11</td>
</tr>
<tr>
<td>M96-863 [20]</td>
<td>LPV/r vs. NFP</td>
<td>Yes</td>
<td>2.1</td>
<td>3.8</td>
<td>15</td>
</tr>
<tr>
<td>CASTLE [21]</td>
<td>ATV/r vs. LPV/r</td>
<td>Yes</td>
<td>−0.1</td>
<td>0.9</td>
<td>2</td>
</tr>
<tr>
<td>GEMINIc [22]</td>
<td>SQV/r vs. LPV/r</td>
<td>Yes</td>
<td>−1.2</td>
<td>−1.1</td>
<td>1</td>
</tr>
<tr>
<td>MaxCmin1c [23, 24]</td>
<td>SQV/r vs. IDV/r</td>
<td>No</td>
<td>0.7</td>
<td>2.4</td>
<td>11</td>
</tr>
<tr>
<td>MaxCmin2c [24, 25]</td>
<td>LPV/r vs. SQV/r</td>
<td>No</td>
<td>1.1</td>
<td>1.1</td>
<td>7</td>
</tr>
<tr>
<td>STARTMRKc [26]</td>
<td>RAL vs. EFV</td>
<td>Yes</td>
<td>−1.5</td>
<td>−3.5</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE.** IQ, and IIP, were calculated from concentrations 24 h after Cm, Δ, Difference in values for antivirals compared; ABC, abacavir; ACTG, AIDS Clinical Trial Group; ATV, atazanavir; AZT, zidovudine; BMS, Bristol-Myers Squibb; DRV, darunavir; D4T, stavudine; EFV, efavirenz; fAMP fosamprenavir; GSK, GlaxoSmithKline; IDV, indinavir; LPV, lopinavir; NVP, nevirapine; NFV, nevirapine-boosted protease inhibitor; RAL, raltegravir; SQV, saquinavir; TDF, tenofovir.

Table 1 lists the clinical trials included in the analysis. Published phase 2b or phase 3 randomized trials were included for analysis if they reported the proportion of subjects with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels <50 copies/mL at 48 weeks or 1 year (with the exception of AIDS Clinical Trial Group [ACTG] A5142, which reported HIV-1 RNA levels at 96 weeks) and if the pharmacokinetic data required to calculate the IQ and IIP were available [9–27]. Our analysis incorporated data from 17 randomized clinical trials of antiretroviral drugs.

**METHODS**

**Data source.** Table 1 lists the clinical trials included in the analysis. Published phase 2b or phase 3 randomized trials were included for analysis if they reported the proportion of subjects with plasma human immunodeficiency virus type 1 (HIV-1) RNA levels <50 copies/mL at 48 weeks or 1 year (with the exception of AIDS Clinical Trial Group [ACTG] A5142, which reported HIV-1 RNA levels at 96 weeks) and if the pharmacokinetic data required to calculate the IQ and IIP were available [9–27]. Our analysis incorporated data from 11 clinical trials originally addressed by Shen et al [3], as well as data from 6 additional trials that compared antiretroviral drugs from various classes [9–14, 16–27].
Results of intention-to-treat (ITT) analyses of virologic outcomes were used in the primary analysis; if several analyses were reported, data were used from the analysis in which switch or discontinuation of treatment equaled failure, whenever possible. Data from ITT analyses were reported most consistently and were similar to those presented in the original description of the IIP [3].

**Study design.** The difference in the percentage of study subjects achieving virologic suppression was plotted against the difference in log₁₀(IQ) values (Δlog₁₀(IQ)) or the difference in IIP values (ΔIIP) for the drugs being compared in a particular trial. Separate analyses were performed using minimum and maximum steady-state drug concentrations to calculate Δlog₁₀(IQ<sub>min</sub>) and ΔIIP<sub>min</sub> and to calculate Δlog₁₀(IQ<sub>max</sub>) and ΔIIP<sub>max</sub> respectively. In addition, Δlog₁₀(IQ<sub>12</sub>) and Δlog₁₀(IQ<sub>24</sub>) were compared with ΔIIP<sub>12</sub> and ΔIIP<sub>24</sub> respectively, using drug concentrations 12 and 24 h after C<sub>max</sub>. For trials included in the analysis by Shen et al [3], IIP<sub>max</sub>, IIP<sub>10</sub>, ΔIIP<sub>min</sub>, and ΔIIP<sub>max</sub> values were based on those reported in their article, as were values for slope (m) and IC₅₀. For the remaining trials, IIP<sub>12</sub>, IIP<sub>24</sub>, IIP<sub>max</sub> and IIP<sub>min</sub> were calculated on the basis of published virologic and pharmacokinetic data or data from the US Food and Drug Administration–approved prescribing information (package insert). Drug concentrations 12 and 24 h after C<sub>max</sub> were calculated using the classic decay equation [3]:

\[ C_t = C_{\text{max}} e^{-kt}, \]

where \( k = \frac{\ln(2)}{t_{1/2}} \) and \( t \) is the time after C<sub>max</sub>.

**Statistical analyses.** Linear regression curve fitting was performed using Graphpad, version 5 (Graphpad Software). Slopes, 95% confidence intervals (CIs) for the slope, \( r^2 \) values, and 95% CIs for the regression line from best-fit values were calculated. Spearman (rank-based) correlation coefficients and \( P \) values were also calculated using Graphpad, version 5. Dependent intercorrelation comparisons using Student’s t tests were performed using SISA [28]. The nominal level of significance was defined as \( P = .05 \).

**RESULTS**

Table 1 lists the antiviral drugs compared in each trial, along with Δlog₁₀(IQ<sub>12</sub>) and ΔIIP<sub>24</sub> for the comparator drugs and differences in virologic suppression between the study arms. The ITT data were the most consistent among the trials compared. Thirteen of the 17 trials compared initial antiretroviral regimens in treatment-naïve patients (the Dupont 006 trial was open to patients who had received prior treatment with a nucleoside reverse-transcriptase inhibitor [except lamivudine] but excluded patients who previously received treatment with any nonnucleoside reverse-transcriptase inhibitor or protease inhibitor) [14]. Figure 1 shows scatter plots and linear regressions of the difference in virologic outcome versus Δlog₁₀(IQ) or ΔIIP at C<sub>min</sub>, C<sub>max</sub>, C<sub>12</sub>, and C<sub>24</sub>. Each plot yielded a modest positive correlation between Δlog₁₀(IQ) or ΔIIP and the difference in virologic outcome between treatment arms, with the exception of ΔIIP<sub>max</sub> (ie, ΔIIP at C<sub>max</sub>). The highest \( r^2 \) values were obtained for correlations between the difference in virologic outcome and Δlog₁₀(IQ<sub>12</sub>), Δlog₁₀(IQ<sub>24</sub>), and Δlog₁₀(IQ<sub>min</sub>). Differences in \( r^2 \) values between analyses using Δlog₁₀(IQ<sub>12</sub>) and ΔIIP<sub>24</sub> or between analyses using Δlog₁₀(IQ<sub>24</sub>) and ΔIIP<sub>12</sub> were 0.05 and 0.18, respectively, and slopes for these correlations had overlapping 95% CIs (Figure 1).

Results of Spearman (rank-based) correlation analyses were consistent with those of the linear regression models. All the comparisons revealed modest, statistically significant correlations between differences in virologic outcome and Δlog₁₀(IQ) or ΔIIP, with the exception of ΔIIP<sub>max</sub>. The correlation coefficients are listed in Table 2. There were no significant differences between correlation coefficients for Δlog₁₀(IQ) and ΔIIP at each drug concentration (eg, Δlog₁₀(IQ<sub>12</sub>) and ΔIIP<sub>12</sub>), with the exception of C<sub>max</sub> (\( P = .03 \)). The Δlog₁₀(IQ<sub>max</sub>) correlation was significantly stronger than was the ΔIIP<sub>max</sub> correlation. The sample size for these comparisons was relatively small (\( N = 17 \)).

**DISCUSSION**

In this study, we explored the correlation between the IIP of antiretroviral drugs and their virologic efficacy and sought to determine whether differences in the IIP might predict the outcome of randomized clinical trials comparing 2 antiretroviral regimens better than would differences in the IQ. A previous study suggested that, by incorporating the slope, or steepness, of the drug inhibition curve, the IIP represented a more accurate pharmacodynamic measure of in vivo antiviral activity than did traditional parameters and may play a major role in determining virologic outcomes [3]. This new measure has generated a great deal of interest since its introduction, especially because it has been purported to predict differences in potency of different antiviral classes; the IIP has also been proposed as a tool for selecting new drugs for clinical development [3, 7, 8]. Our analysis of data from 17 randomized clinical trials of antiretroviral drugs (ITT analysis) found that differences in the IIP between drugs did show a modest correlation with differences in virologic outcome but that these correlations were not significantly stronger than were the correlations obtained using the IQ. The strongest correlations between difference in pharmacokinetic variables and difference in percentage with virologic suppression from linear regression modeling were for Δlog₁₀(IQ<sub>12</sub>), Δlog₁₀(IQ<sub>24</sub>), and Δlog₁₀(IQ<sub>min</sub>), whereas the strongest Spearman correlations were for Δlog₁₀(IQ<sub>12</sub>), ΔIIP<sub>12</sub> and Δlog₁₀(IQ<sub>12</sub>). Differences between analyses were...
Figure 1. Scatter plots of difference in (Δ) percentage of patients in intention-to-treat analysis who demonstrated viral load (VL) <50 copies/mL at week 48 (week 96 for AIDS Clinical Trial Group A5142) versus Δlog_{10}(IQ) and ΔIIP at different concentrations. Linear regression lines and 95% confidence intervals are shown. $r^2$ and slope (m) with 95% confidence intervals in parentheses are also shown. IQ, inhibitory quotient; min, minimum steady-state antiviral concentration; max, maximum steady-state antiviral concentration.

modest, and Spearman correlations were not significantly different between Δlog_{10}(IQ) and ΔIIP, and Δlog_{10}(IQ) and ΔIIP max; these results are not surprising, given the relatively small sample size used in the correlation analysis.

Despite positive correlations between the difference in virologic outcome and Δlog_{10}(IQ) or ΔIIP overall, the correlation in many individual studies fell well outside the 95% confidence limits of the linear regression plots. In some cases, small differences in treatment outcome between arms were observed despite substantial differences in the IIP or IQ between the comparator drugs; conversely, in other studies, significant differences in outcome were observed despite modest differences in the IIP or IQ. Although this finding may reflect the uncertainty in the estimated difference in both virologic and pharmacokinetic effect sizes, it suggests that variables other than intrinsic drug activity and pharmacokinetics, such as adherence,
tolerability, dosing convenience, and emergence of resistance, are important contributors to the overall clinical effectiveness of a drug or regimen. The predictive capacity of both the IIP and the IQ are therefore inherently limited by the complex factors encountered during the extrapolation of in vitro measures to virologic outcome in clinical trials.

While it is tempting to conclude that molecules with a steeper dose-response curve make better drugs, clinical experience suggests that other properties, such as the pharmacokinetic profile, tolerability and dosing convenience, may be more important determinants of drug efficacy. For example, the slope of the inhibition curve for indinavir is substantially greater than that for efavirenz (Figure 1d and Supplementary Table 1 in the article by Shen et al [3]), but efavirenz is more effective than indinavir because of its longer half-life and better tolerability [14]. Likewise, lopinavir and nelfinavir have similar slope values [3], but comparative trials show that lopinavir/ritonavir is superior to nelfinavir [20]. The generally similar correlation between the IIP and IQ with virologic outcome in the trials we studied suggests that drug susceptibility (as measured by IC_{50}) and pharmacokinetic parameters (as measured by C_{max}, t_{1/2}, etc), which are common to the IIP and IQ, dominate the slope in determining drug efficacy.

The 48-week end point (ITT analysis; switch or noncomple- tion of treatment equals failure, when available) was chosen for primary analysis for 3 major reasons: (1) similar data were used in the original description of the IIP [3], (2) it was the primary end point of most of the studies incorporated in our analysis, and (3) there are limitations to publicly available as-treated data or data from earlier time points. Factors such as drug toxicity, tolerability, baseline drug resistance, variations in background antiviral therapies, and loss to follow-up do not contribute to overall regimen efficacy but are not captured by either the IIP or the IQ. However, the aim of this exploratory analysis was to provide a quantitative estimate of the association between pharmacodynamic properties of different drugs and virologic outcomes and was consistent with the approach taken in the original report on the IIP. However, that report did not formally test the relative strength of association of the IIP and other traditional pharmacodynamic metrics with virologic outcomes in clinical trials [3], making it difficult to infer superiority of one laboratory measure over another.

Although using as-treated or per-protocol data may partially control for potentially confounding factors, such as drug toxicity, tolerability, and medication cross-over, there are limitations with this potential approach. As-treated results may involve an end point in which subjects are censored at treatment discontinuation, which would be informative in our comparison between the IIP and IQ. However, many trials do not define early discontinuation of patients, and the as-treated results represent a cross-sectional analysis of patients still randomized at week 48. This analysis discounts early treatment discontinuation for adequate virologic outcome and leads to informative censoring. Although a method for carrying forward the last HIV-1 RNA level to subsequent time points for a patient who discontinues treatment early during a study protocol may overcome some of the informative censoring, this type of analysis is not possible without access to raw data for all trials. Furthermore, this manipulation does not necessarily overcome the problem of bias created by early discontinuation before a study subject has had a chance to have a response to medication.

A method of quantifying treatment differences for both a major clinical outcome and a surrogate marker and for measuring the strength of association between these values has been described [29]. This approach requires that measurements of the surrogate marker and the clinical end point come from one group of individuals or from a single study or requires an allowance of precision to be assessed for treatment differences across studies [29]. We could not apply this approach to our analysis, because it requires access to raw data from each of the respective clinical trials. Moreover, in the current analysis, the treatment effect was estimated across trials with different sample sizes and different degrees of precision, which were not taken into consideration. Furthermore, few of these studies included measurement of both pharmacokinetic parameters and longer-term clinical outcomes, which would be necessary for a more complete analysis. However, all the virologic studies included in our analysis were based on robust clinical trials with relatively large study populations. Spearman rank correlations were chosen to reduce emphasis on individual trial size and the strength of each correlation data point, as well as to compensate for potential lack of linearity between variables.

Despite these limitations, this study provides an in-depth, quantitative comparison of the relationship between the Δlog_{10} (IQ), IIP, and virologic outcome. Our analysis shows

Table 2. Spearman Rank Correlations between Differences in Percentage of Subjects Demonstrating Viral Load <50 Copies/mL for Trials Included in the Analysis and Differences in Inhibitory Quotient (IQ) and Instantaneous Inhibitory Potential (IIP).

<table>
<thead>
<tr>
<th>Value</th>
<th>Spearman correlation coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δlog_{10}(IQ_{max})</td>
<td>0.63</td>
<td>.007</td>
</tr>
<tr>
<td>ΔIIP_{min}</td>
<td>0.54</td>
<td>.025</td>
</tr>
<tr>
<td>Δlog_{10}(IQ_{max})</td>
<td>0.67</td>
<td>.004</td>
</tr>
<tr>
<td>ΔIIP_{max}</td>
<td>0.07</td>
<td>.802</td>
</tr>
<tr>
<td>Δlog_{10}(IQ_{12})</td>
<td>0.72</td>
<td>.001</td>
</tr>
<tr>
<td>ΔIIP_{12}</td>
<td>0.56</td>
<td>.020</td>
</tr>
<tr>
<td>Δlog_{10}(IQ_{24})</td>
<td>0.73</td>
<td>.001</td>
</tr>
<tr>
<td>ΔIIP_{24}</td>
<td>0.72</td>
<td>.001</td>
</tr>
</tbody>
</table>

NOTE. Virologic outcomes are from intention-to-treat analysis. IQ_{24} and IIP_{24} were calculated from concentrations 24 h after C_{max}; IQ_{12} and IIP_{12} from concentrations 24 h after C_{min}. Δ Difference in values for antivirals compared.
that the insights that the IIP provides into the kinetics of drug activity at the cellular and biochemical level do not translate into substantially better predictions of efficacy from primary outcomes of major clinical trials than traditional measures such as the IQ. The slope of the dose-response curve used in calculation of the IIP may be an important factor influencing in vivo antiviral activity, but better models are needed for predicting the relative efficacy of antiretroviral regimens that incorporate these additional pharmacokinetic and cooperative drug parameters.

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