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

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Abstract

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 (Δ) $\log_{10}$(IQ) or IIP and percent of subjects with plasma HIV-1 RNA below 50 copies/mL at week 48 was determined for antiretroviral drugs compared in 17 randomized clinical trials. The Δ $\log_{10}(IQ_{min})$, $\log_{10}(IQ_{max})$, IIP_{min}, IIP_{max} $\log_{10}(IQ_{12})$, $\log_{10}(IQ_{24})$, IIP_{12} and IIP_{24} for comparative drugs were correlated with Δ percent of subjects with HIV < 50 copies/mL in each trial. $\text{Log}_{10}(IQ_{24})$, $\log_{10}(IQ_{12})$, IIP_{24} and IIP_{12} were calculated using published median effect model slope values, and $t_{1/2}$ values; r^2 values from linear regression and Spearman correlation coefficients were calculated for each analysis and correlations coefficients were compared between Log_{10}(IQ) and IIP.

Results—The r^2 values were greatest for the $\Delta\log_{10}(IQ_{12})$ and $\Delta\log_{10}(IQ_{24})$ comparisons using ITT outcomes from the 17 trials. Differences in r^2 values between $\Delta\log_{10}(IQ_{24})$ and ΔIIP_{24}, and between $\Delta\log_{10}(IQ_{12})$ and ΔIIP_{12} 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 $\Delta\log_{10}(IQ_{max})$ and ΔIIP_{max}; the $\Delta\log_{10}(IQ_{max})$ correlation was significantly stronger than the ΔIIP_{max} correlation.

Conclusions—The IIP was not substantially better than log(IQ) in describing the modest relationship between antiviral activity, pharmacokinetics and virologic outcomes for antiretroviral drugs.

Keywords

HIV infection; antiviral therapy; pharmacology; inhibitory quotient; instantaneous inhibitory potential

INTRODUCTION

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

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to quantify antiviral activity include the IC_{50} (amount of drug required to inhibit 50 percent of viral activity *in vitro*) 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}'s due to 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 Equation 1:

$$\mathrm{IIP}_{Ct} = \log\left(1/f_{uCt}\right) = \log\left(1+(C_t/IC_{50})^m\right) \quad (1)$$

in which f_u represents the fraction of viruses in a single-round infectivity assay unaffected by drug, C_t represents antiviral concentrations at specific time (t), and m represents the slope from the median effect model of mass action.

The IIP has been proposed as a better predictor of antiviral activity *in vivo* than IQ because it takes into account the intrinsic antiviral potency of a drug and potentially the cooperativity of drugs used in combination [3,7-8]. It was also proposed that the slope parameter of the IIP is class-specific and define intrinsic limitations on antiviral activity in some classes [3]. However, the IIP has not been compared rigorously to traditional pharmacologic measures such as the IQ, and it is unclear that IIP is a better indicator of virologic response. Correlating *in vitro* antiviral activity with virologic outcomes has been challenging given the diverse ways in which virologic response data are analyzed and the complexities of extrapolating antiviral activity to predict outcome measures. To test the hypothesis that IIP provides a better measure of clinical outcome than previous pharmacodynamic metrics, we compared the correlation between differences in IIP or IQ and differences in virologic response between pairs of antiretroviral agents using 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 HIV-1 RNA below 50 copies/mL at 48 weeks or one year (with the exception of ACTG A5142, which reported HIV-1 RNA at 96 weeks) and if the pharmacokinetic data required to calculate IQs and IIPs were available [9-28]. 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 [9-27].

Results of intention-to-treat (ITT) analyses of virologic outcomes were used in the primary analysis; if several analyses were reported, data from the switch or discontinuation equals failure analysis were used, 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 between $\log_{10}$(IQ) or IIP values for the drugs being compared in a particular trial ($\Delta\log_{10}$[IQ] or ΔIIP, respectively). Separate analyses were performed using

minimum and maximum steady-state drug concentrations to calculate $\Delta\log_{10}(IQ_{min})$ and ΔIIP_{min}, or $\Delta\log_{10}(IQ_{max})$ and ΔIIP_{max}, respectively. In addition, $\Delta\log_{10}(IQ_{12})$ and $\Delta\log_{10}(IQ_{24})$ were compared with ΔIIP_{12} andΔIIP_{24}, respectively, using drug concentrations 12 and 24 hours after C_{max}. For trials included in the analysis by Shen *et al.*, IQ_{min}, IQ_{max}, IIP_{min} and IIP_{max} values were based on those reported in their paper, as were values for slope (*m*) and IC_{50} [3]. For the remaining trials, IQ_{24}, IQ_{12}, IIP_{24} and IIP_{12} were calculated based on published virologic and pharmacokinetic data or data from the FDA-approved prescribing information (package insert). Drug concentrations 12 and 24 hours after C_{max} were calculated using the classic decay equation (formula 2) [3]:

$$C_t = C_{max} e^{-kt} \quad (2)$$

where $k = \ln(2)/t_{1/2}$, and t is the time after C_{max}.

Statistical analyses

Linear regression curve-fitting was performed using Graphpad v5 (Graphpad Software, CA). Slopes, 95% confidence intervals (CI) for the slope, r^2 values and 95% CI for the regression line from best-fit values were calculated. Spearman (rank based) correlation coefficients and P values were also calculated using Graphpad v5. Dependent inter-correlation comparisons using t-tests were performed using SISA. The nominal level of significance was defined as p = 0.05.

RESULTS

Table 1 lists the antiviral drugs compared in each trial, along with $\Delta\log_{10}(IQ_{24})$ and ΔIIP_{24} 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 DMP006 trial was open to patients with prior NRTI treatment [except lamivudine], but excluded patients previously treated with any NNRTI or PI) [21]. Figure 1 shows scatter plots and linear regressions of the difference in virologic outcome versus the $\Delta\log_{10}(IQ)$, or ΔIIP at C_{min}, C_{max} C_{12}, and C_{24}. Each plot yielded a modest positive correlation between $\Delta\log_{10}(IQ)$ or ΔIIP and the difference in virologic outcome between treatment arms with the exception of ΔIIP_{max} (ΔIIP at C_{max}). The highest r^2 values were obtained for correlations between the difference in virologic outcome and $\Delta\log_{10}(IQ_{12})$, $\Delta\log_{10}(IQ_{24})$, and $\Delta\log_{10}(IQ_{min})$, respectively. Differences in r^2 values between analyses using $\Delta\log_{10}(IQ_{24})$ and ΔIIP_{24}, or between $\Delta\log_{10}(IQ_{12})$ and ΔIIP_{12} were 0.05 and 0.18, respectively and slopes for these correlations had overlapping 95% confidence limits (Figure 1).

Results of Spearman (rank based) correlation analyses were consistent with those of the linear regression models. All of the comparisons revealed modest, statistically significant correlations between differences in virologic outcome and $\Delta\log_{10}(IQ)$ or ΔIIP with the exception of ΔIIP_{max}. The correlation coefficients are listed in Table 2. There were no significant differences between correlation coefficients for $\Delta\log_{10}(IQ)$ and ΔIIP at each drug concentration (*e.g.* $\Delta\log_{10}[IQ_{12}]$ and ΔIIP_{12}) with the exception of C_{max} (P = 0.03). The $\Delta\log_{10}(IQ_{max})$ correlation was significantly stronger than that of the ΔIIP_{max}. Sample size for these comparisons was relatively small (N=17).

DISCUSSION

In this study, we explored the correlation between the instantaneous inhibitory potential of antiretroviral drugs and their virologic efficacy, and sought to determine whether differences

in IIP might predict the outcome of randomized clinical trials comparing two antiretroviral regimens better than differences in the inhibitory quotient. 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 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 IIP between drugs did show a modest correlation with differences in virologic outcome, but that these correlations were not significantly stronger than the correlations obtained using the IQ. The strongest correlations between difference in pharmacokinetic variables and difference in percent virologic suppression from linear regression modeling were for $\Delta\log_{10}(IQ_{12})$, $\Delta\log_{10}(IQ_{24})$, and $\Delta\log_{10}(IQ_{min})$, respectively, whereas the strongest Spearman correlations were for $\Delta\log_{10}(IQ_{24})$, $\Delta IIP_{24,}$ and $\Delta\log_{10}(IQ_{12})$. Differences between analyses were modest and Spearman correlations were not significantly different between $\Delta\log_{10}(IQ_{12})$ and ΔIIP_{12}, and $\Delta\log_{10}(IQ_{24})$ and ΔIIP_{24}; 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 $\Delta\log_{10}(IQ)$ or ΔIIP overall, 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 IIP or IQ between the comparator drugs; conversely, in other studies significant differences in outcome were observed despite modest differences in 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 overall clinical effectiveness of a drug or regimen. The predictive capacity of both IIP and 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 [3]), but efavirenz is more effective than indinavir due to its longer half-life and better tolerability [21]. Likewise, lopinavir and nelfinavir have similar slope values [3], but comparative trials show that lopinavir/ritonavir is superior to nelfinavir [24]. The generally similar correlation between IIP and IQ with virologic outcome in the trials we studied suggests that drug susceptibility (as measured by IC_{50}), pharmacokinetic parameters (as measured by Cmin, Cmax, $t_{½}$ etc.), which are common to IIP and IQ, dominate the slope in determining drug efficacy.

The 48 week endpoint (ITT, switch or non-completion = 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 endpoint of most of the studies incorporated in our analysis, and 3) there are limitations to publically available as-treated data or from earlier time-points. Factors such as drug toxicity, tolerability, baseline drug resistance, variations in background antiviral therapies and loss to follow-up no doubt contributed to overall regimen efficacy, but are not captured by either the IIP or 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 IIP report. 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 utilizing 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 endpoint in which subjects are censored at treatment discontinuation, which would be informative in our comparison between 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 inadequate virologic outcome and leads to informative censoring. Although a method for carrying forward the last HIV-1 RNA level to subsequent time-points of 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 discontinuations 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 endpoint 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 as 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 $\log_{10}$IQ, IIP, and virologic outcome. Our analysis shows that the insights 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.

Summary: Article we compares the correlation between differences in IIP or IQ and differences in virologic response between pairs of antiretroviral agents in order to test the hypothesis that IIP provides a better measure of clinical outcome than previous pharmacodynamic metrics.

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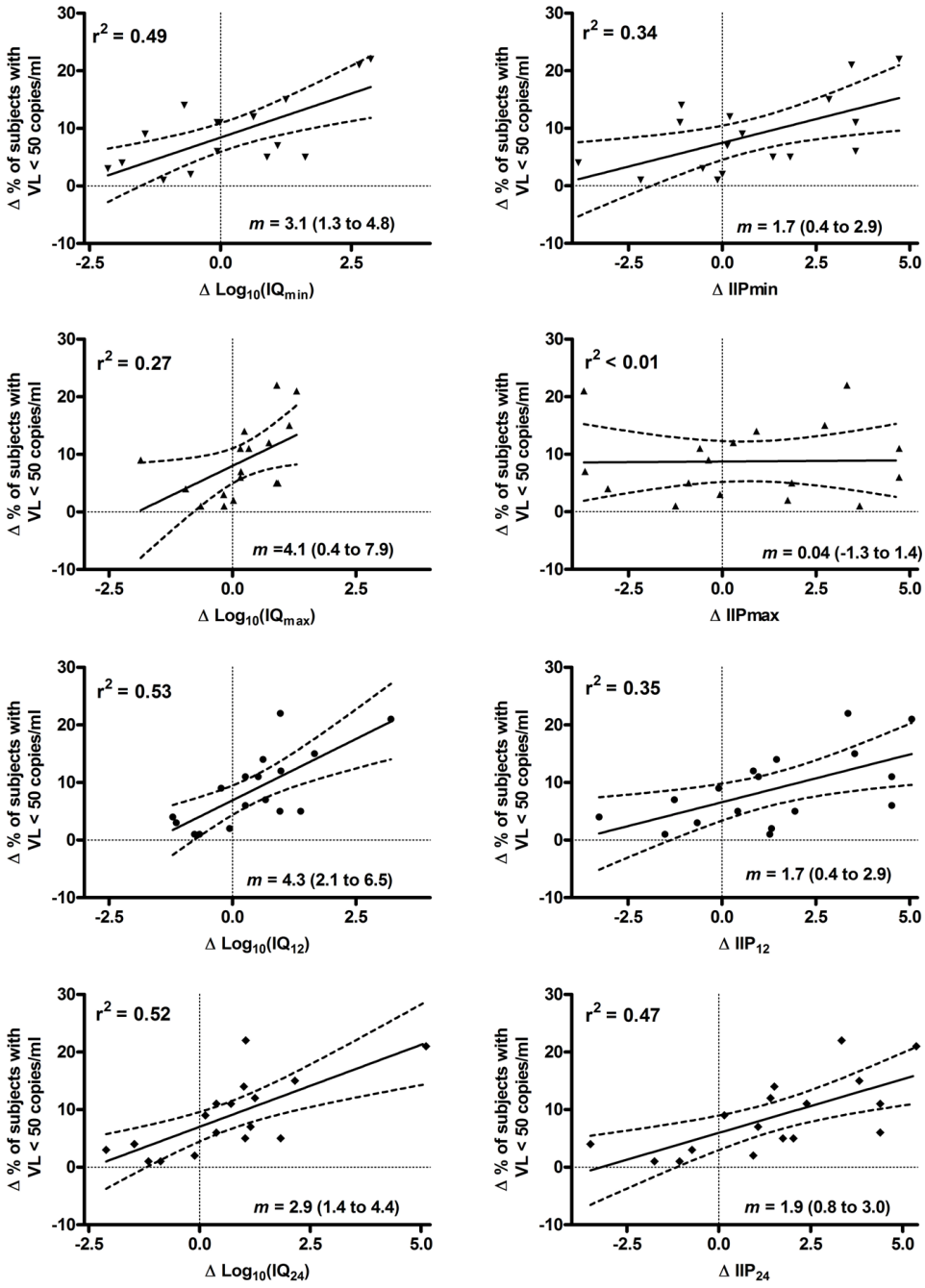

FIGURE 1.

Scatter plots of Δ percent patients in ITT analysis that demonstrated HIV viral load <50 copies/ml at week 48 (week 96 for ACTG A5142) versus $\Delta\log_{10}$(IQ) and IIP at different concentrations. Linear regression lines and 95% confidence intervals are shown. R^2 and slope (*m*) with 95% confidence intervals are also shown. Min, max = minimum and maximum steady-state antiviral concentrations; IQ_{12}, IIP_{12}, and IQ_{24}, IIP_{24} calculated from concentrations 12 and 24 hours after C_{max} respectively.

TABLE 1

Differences in $\log_{10}(IQ_{24})$, IIP_{24}, and differences in percent of subjects with VL < 50 copies/ml at 48 weeks for trials included in analysis[a]

Trial	Drugs Compared	First Regimen	$\Delta\text{Log}_{10}(IQ_{24})$ [b]	ΔIIP_{24} [b]	Δ % Subjects with VL < 50 copies/ml[c]
GSK934[d] [12]	TDF vs. AZT	Yes	0.1	0.2	9
GSK903[d] [13]	D4T vs. TDF	Yes	−2.1	−0.7	3
ACTG A5095 [14]	EFV vs. ABC	Yes	1.0	3.3	22
BMS034 [20]	EFV vs. ATV	Yes	1.8	1.7	5
2NN [22]	EFV vs. NVP	Yes	1.0	2.0	5[e]
DMP006 [21]	EFV vs. IDV	No[f]	5.1	5.4	21
A5142 [a] [28]	EFV vs. LPV/r	Yes	1.3	1.4	12
NEAT [19]	fAMP vs. NFV	Yes	1.0	1.5	14
KLEAN [11]	fAMP/r vs. LPV/r	Yes	−0.9	−1.8	1
ARTEMIS [18]	DRV/r vs. LPV/r	Yes	0.4	4.4	6
TITAN [16]	DRV/r vs. LPV/r	No	0.4	4.4	11
M96-863 [24]	LPV/r vs. NFV	Yes	2.1	3.8	15
CASTLE [17]	ATV/r vs. LPV/r	Yes	−0.1	0.9	2
GEMINI[d] [23]	SQV/r vs. LPV/r	Yes	−1.2	−1.1	1
MaxCmin1[d] [9,25]	SQV/r vs. IDV/r	No	0.7	2.4	11
MaxCmin2[d] [10,25]	LPV/r vs. SQV/r	No	1.1	1.1	7
STARTMRK[d] [26]	RAL vs. EFV	Yes	−1.5	−3.5	4

NOTE: VL = viral load, r = ritonavir boosted protease inhibitor, Δ = difference between values for antivirals compared, TDF = tenofovir, AZT = zidovudine, D4T = stavudine, EFV = efavirenz, NVP = nevirapine, ABC = abacavir, ATV = atazanavir, IDV = indinavir, LPV = lopinavir, fAMP = fosamprenavir, DRV = darunavir, NFV = nelfinavir, SQV = saquinavir, RAL = raltegravir

[a] ACTG 5142 VL data from 96 week time-point

[b] Rounded to nearest decimal

[c] Outcomes based on intent to treat analyses (switch/discontinuation/non-completion = failure, when available), rounded to nearest integer

[d] Trial not included in original analysis by Shen *et al.*[3]

[e] difference in viral load calculated from results of twice-daily NVP dosing

[f] Subject were excluded from this trial if any prior exposure to lamivudine or any NNRTI or PI

TABLE 2

Spearman rank correlations of differences in percent of subjects demonstrating VL < 50 copies/ml for trials included in analysis and differences in $\log_{10}$(IQ) and IIP[a]

	Spearman Correlation Coefficient	P
$\Delta\text{Log}_{10}(\text{IQ}_{\text{min}})$	0.63	0.007
$\Delta\text{IIP}_{\text{min}}$	0.54	0.025
$\Delta\text{Log}_{10}(\text{IQ}_{\text{max}})$	0.67	0.004
$\Delta\text{IIP}_{\text{max}}$	0.07	0.802
$\Delta\text{Log}_{10}(\text{IQ}_{12})$	0.72	0.001
ΔIIP_{12}	0.56	0.020
$\Delta\text{Log}_{10}(\text{IQ}_{24})$	0.73	0.001
ΔIIP_{24}	0.72	0.001

NOTE: VL = viral load, Δ = difference between values for antivirals compared

[a]Virologic outcomes from intent to treat analysis