DISCUSSION/CONCLUSIONS

- Standardization of the assay to measure protein-binding adjusted IC50 improves consistency in assessment of IQ. This enables IQ to better quantify the relative potencies of PIs in vivo.
- LPV/r 400/100 mg BID and 800/200 mg QD provided the highest estimated IQ of all PIs included in this assessment.
- ATV had the highest estimated IQ of the non-boosted PIs included in this assessment.
- One potential limitation of this investigation is that not all Cmin values were obtained from HIV-infected individuals.
- A second potential limitation is that regimens with different dosing frequencies (i.e., BID and QD) were compared. The relationship of IQ and clinical response with respect to this parameter has not been explored.
- The predictive value of IQ as a metric of antiretroviral response needs further validation in prospective, randomized, controlled clinical trials (e.g., ACTG 5126) since therapeutic outcome is a consequence of many factors, not just drug potency and pharmacokinetics.

REFERENCES


RESULTS

Potency of PIs based on measured in vitro IC50 (means±SD µg/mL): were ampranavir (APV) 0.49±0.12; atazanavir (ATV) 0.016±0.005; indinavir (IDV) 0.071±0.028; lopinavir (LPV) 0.082±0.019; nelfinavir (NFV) 0.761±0.159; saquinavir (SQV) 0.456±0.114; and tipranavir (TPV) 4.7±0.8. Published mean (95% CI) Cmin values were from 0.5 to 5.05 µg/mL in healthy volunteers (BI 1182.5). 9th CROI, 2002, Abst 434.

Table 1. IQ and Virologic Response

<table>
<thead>
<tr>
<th>PI</th>
<th>N</th>
<th>Virologic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV 400 QD</td>
<td>14</td>
<td>IQ &gt; 1 associated with significant response</td>
</tr>
<tr>
<td>LPV/r 800/200 QD</td>
<td>24</td>
<td>IQ &gt; 15 associated with virologic response</td>
</tr>
<tr>
<td>NFV/SQV 1250/100 QD</td>
<td>27</td>
<td>v10 ≥ 2 for DRV best predictor of virologic response (P = 0.001)</td>
</tr>
<tr>
<td>ATV 400 QD</td>
<td>13.8–46.4</td>
<td>NFV 1250 BID (1.0, 0.7–1.3)</td>
</tr>
<tr>
<td>SQV/r 1600/100 QD</td>
<td>27</td>
<td>ATV 400 QD (1.0, 0.6–1.3)</td>
</tr>
<tr>
<td>TPV/r 500/200 BID</td>
<td>4.2, na</td>
<td>NFV 1250 BID (1.3, 0.8–1.9)</td>
</tr>
</tbody>
</table>

The inhibitory quotient (IQ) has been shown to be a useful pharmacodynamic predictor of protease inhibitor (PI) potency in vivo. Adopted from the antibiotic literature, the IQ is best defined for PIs as the ratio of the minimum plasma drug concentration (Cmin) to the drug concentration necessary to inhibit virus replication by 50% (IC50). The clinical relevance of IQ in predicting virologic response has been demonstrated in several clinical studies using different PIs (Table 1 and Figure 1). 1–3

BACKGROUND

Studies have shown that IQ (Cmin/IC50) is associated with virologic response. This metric may have application in assessment of in vitro potency relative to achievable PI concentrations if determination of IC50 and method of protein binding correction are uniform.

METHODS

Anti-HIV activity was assessed against HIV wild-type (wt) pHN-4-3 strain in MT4 cells in media containing 10% fetal calf serum supplemented with 50% human serum. Protein-binding adjusted IC50 values for PIs were determined in at least two sets of triplicate measurements. Steady-state Cmin values from published reports was used to calculate IQ.

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ABSTRACT

Inhibitory Protease of Quatrate Inhibitors

Using a Standardized Determination of IC50

RC Stevens, TN Kakuda, R Bertz, H Mo, A Molla, R Rode, D Kempf; Abbott Laboratories, Abbott Park, IL, USA

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Assuming that pharmacokinetic (C\text{min}) and \textit{in vitro} antivarian (IC\text{min}) parameters are independent random variables, the point estimate (mean) and variance for IQ were derived using first-order Taylor approximations. In particular, the point estimate and variance for IQ are given by:

$$\text{Mean} = \frac{\mu_X}{\mu_Y}$$

where $\mu_X$ represents point estimates for C\text{min} and IC\text{min}, respectively. In addition, Var X and Var Y represent variance estimates for C\text{min} and IC\text{min}, respectively. The lower (LL) and upper (UL) 95% confidence limits for IQ are then given by:

$$\text{LL} = \text{Mean} - 1.96 \times \left(\frac{\text{Var X}}{\mu_Y^2}\right)$$

and

$$\text{UL} = \text{Mean} + 1.96 \times \left(\frac{\text{Var Y}}{\mu_X^2}\right)$$

Summary statistics for C\text{min} were computed on the arithmetic scale for all PIs with the exception of amprenavir and fosamprenavir, which were computed on the logarithmic scale and then converted (transformed) to the arithmetic scale. Given that summary statistics for amprenavir and fosamprenavir were computed on a different measurement scale than the other PIs, 95% confidence limits for the IQ of amprenavir and fosamprenavir have not been reported.
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LL = \text{Mean} - 1.96 \times \left(\text{Variance} \right)^{1/2} \quad \text{and} \quad UL = \text{Mean} + 1.96 \times \left(\text{Variance} \right)^{1/2}
\]

estimates for C_{min} and IC_{50}, respectively. The lower (LL) and upper (UL) 95% confidence limits for IQ are then given by:

Mean = \frac{\mu_x}{\mu_y} and Variance = \frac{\left(1 / \mu_y^2\right) \times \text{Var} X} {\left(\mu_x^2/ \mu_y^4\right) \times \text{Var} Y},

where \(\mu_x\) and \(\mu_y\) represent point estimates for \(C_{min}\) and IC\(_{50}\), respectively. The lower (LL) and upper (UL) 95% confidence limits for IQ are then given by:

\[
\text{LL} = \text{Mean} - 1.96 \times \text{(Variance)}^{1/2} \hspace{1cm} \text{and} \hspace{1cm} \text{UL} = \text{Mean} + 1.96 \times \text{(Variance)}^{1/2}
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\textbf{MATERIALS AND METHODS}

\textbf{Protease Inhibitors}

- Amprenavir (APV), atazanavir (ATV), fosamprenavir (fos-APV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), saquinavir (SQV), and tipranavir (TPV). If used in combination with ritonavir, the "boosted" PI is identified using the modifier "r".
- ATV and TPV were synthesized according to published methods.

\textbf{Determination of Protein-Binding Adjusted IC}_{50}

- Anti-HIV activity was assessed against the pH4-3 strain of wild-type HIV in MT4 cells in media containing 10% fetal calf serum (FCS) supplemented with 50% human serum (HS) using methodology described previously by Molla et al. Briefly, the methodology used to determine anti-HIV activity can be summarized as follows:
  - Inhibition of HIV-induced cytopathic effect over a range of PI drug concentrations was monitored by uptake of MTT.
  - Protein-binding adjusted IC\(_{50}\) values for the PIs were determined in at least two sets of triplicate measurements.
  - Kempf et al. have demonstrated that the attenuation of activity by 10% FCS supplemented with 50% HS approximates that predicted with 100% HS.

\textbf{Inhibitory Quotient}

\[
IQ = \frac{\text{mean } C_{min}}{\text{mean protein-binding adjusted IC}_{50}}\hspace{1cm}(\text{of HIV})
\]

\textbf{Statistical Analysis}

IQ is typically reported as a point estimate. However, pharmacokinetic and in vitro antiviral parameters are measured with some degree of variability. As such, we report corresponding confidence limits for IQ. Assuming that pharmacokinetic (C\(_{min}\)) and in vitro antiviral (IC\(_{50}\)) parameters are independent random variables, the point estimate (mean) and variance for IQ were derived using first-order Taylor approximations. In particular, the point estimate and variance for IQ are given by:

\[
\text{Mean} = \mu_x/\mu_y \quad \text{and} \quad \text{Variance} = \left(1/\mu_y^2\right) \times \text{Var} X \div \left(\mu_x^2/\mu_y^4\right) \times \text{Var} Y
\]

where \(\mu_x\) and \(\mu_y\) represent point estimates for \(C_{min}\) and IC\(_{50}\), respectively. The lower (LL) and upper (UL) 95% confidence limits for IQ are then given by:

\[
\text{LL} = \text{Mean} - 1.96 \times \text{(Variance)}^{1/2} \hspace{1cm} \text{and} \hspace{1cm} \text{UL} = \text{Mean} + 1.96 \times \text{(Variance)}^{1/2}
\]

\text{.website:} would you like to know more about the IQ and its calculation? Make sure to check out our comprehensive guide, which covers all the latest research and practical applications in the field. With our detailed explanations, you’ll have a clear understanding of how to calculate IQ accurately and effectively. Stay tuned for our upcoming webinar series, where our experts will delve deeper into the nuances of IQ computation and its implications in real-world scenarios.

\textbf{RESULTS}

- Table 2 lists the IC\(_{50}\) values for various PIs determined in a standardized in vitro assay using the pH4-3 wild-type strain of HIV in MT4 cells in media containing 10% FCS supplemented with 50% HS.
- The free fractions of the PI drug concentrations under these conditions are similar to the free fractions in human plasma.
- In this assay, the in vitro IC\(_{50}\) values ranged by more than 100-fold from 0.16 (ATV) to 4.7 (TPV) µg/mL.

\begin{table}
<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Mean ± SD IC(_{50}) (µg/mL)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV</td>
<td>0.016 ± 0.005</td>
<td>Wood et al.</td>
</tr>
<tr>
<td>IDV</td>
<td>0.071 ± 0.028</td>
<td>O’Mara et al.</td>
</tr>
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<td>LPV</td>
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<td>SQV</td>
<td>0.456 ± 0.114</td>
<td>Wite et al.</td>
</tr>
<tr>
<td>APV</td>
<td>0.468 ± 0.121</td>
<td>Bertz et al.</td>
</tr>
<tr>
<td>NFV</td>
<td>0.761 ± 0.159</td>
<td>Kurowski et al.</td>
</tr>
<tr>
<td>TPV</td>
<td>4.7 ± 0.8</td>
<td>Mara et al.</td>
</tr>
</tbody>
</table>

\textbf{OBJECTIVE}

- To assess the IQ of PI drugs accounting for variance in both the observed plasma C\(_{min}\) and in vitro potency based on a standardized method of determining the protein-binding adjusted IC\(_{50}\) values.

\textbf{CONCLUSION}

The standardized IC\(_{50}\) values (Table 2) were combined with C\(_{min}\) values from the literature (Table 3) to provide mean IQ estimates for various ritonavir-boostered and non-boostered PI regimens as shown in Figure 2.

- Mean IQ estimates ranged from 0.7 to 67.4 with LPV/r (400/100 mg BID) providing the highest estimated IQ of all PIs assessed and ATV (400 mg QD) providing the highest estimated IQ for the non-boosted PIs assessed.

\textbf{Table 3. Steady-State C\(_{min}\) Values Used to Estimate IQ}

<table>
<thead>
<tr>
<th>PI Regimen</th>
<th>Subjects* (n)</th>
<th>Mean C(_{min}) (95% CI) (µg/mL)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV 0.016 ± 0.005</td>
<td>HIV+ (15)</td>
<td>1.39 (1.21–1.57)</td>
<td>Wood et al.</td>
</tr>
<tr>
<td>IDV 0.071 ± 0.028</td>
<td>HIV+ (12)</td>
<td>1.32 (1.02–1.68)</td>
<td>O’Mara et al.</td>
</tr>
<tr>
<td>LPV 0.082 ± 0.016</td>
<td>HIV+ (22)</td>
<td>1.05 (0.78–1.32)</td>
<td>Wite et al.</td>
</tr>
<tr>
<td>SQV 0.456 ± 0.114</td>
<td>HIV+ (24)</td>
<td>2.12 (1.77–2.45)</td>
<td>Wite et al.</td>
</tr>
<tr>
<td>APV 0.468 ± 0.121</td>
<td>HIV+ (28)</td>
<td>0.16 (0.01–0.21)</td>
<td>Bertz et al.</td>
</tr>
<tr>
<td>NFV 0.761 ± 0.159</td>
<td>HIV+ (24)</td>
<td>0.61 (0.37–0.84)</td>
<td>Kurowski et al.</td>
</tr>
</tbody>
</table>

\textbf{Figure 2. Estimated Mean IQ for Protease Inhibitors}

- The wide confidence bands observed in the high IQ region were a function of smaller number of samples with IQ in that range (e.g., sample sizes for IQ ranges of <4, 4–15 and >15 were 21, 15 and 16, respectively).

- The use of this pharmacodynamic parameter in comparing the potencies of the various PIs. These factors include: whether inhibitory concentrations were measured in the presence of human serum and the concentrations of serum used; the specific cell line and strain of virus used to measure IC\(_{50}\); whether C\(_{min}\) was calculated or measured in healthy volunteers versus HIV-infected individuals; and the dosing regimen of the drug (or agent) used to assess C\(_{min}\). The authors concluded that to make valid comparisons between the PI drugs, it is necessary to compare data obtained using the same methodology.
**DISCUSSION/ CONCLUSIONS**

- Standardization of the assay to measure protein-binding adjusted IC\(_{50}\) improves consistency in assessment of IQ. This enables IQ to better quantify the relative potencies of PIs in vivo.
- LPV/r 400/100 mg BID and 800/200 mg QD provided the highest estimated IQ of all PIs included in this assessment.
- AVT had the highest estimated IQ of the non-boosted PIs included in this assessment.
- One potential limitation of this investigation is that not all C\(_{\text{min}}\) values were obtained from HIV-infected individuals.
- A second potential limitation is that regimens with different dosing frequencies (i.e., BID and QD) were compared. The relationship of IQ and clinical response with respect to this parameter has not been explored.
- The predictive value of IQ as a metric of antiretroviral response needs further validation in prospective, randomized, controlled clinical trials (e.g., ACTG 5126) since therapeutic outcome is a consequence of many factors, not just drug potency and pharmacokinetics.

**REFERENCES**

6. Wood R et al. Amprenavir (APV) 600 mg BID or APV 1200 mg QD given in combination with abacavir and lamivudine maintains virologic response has been demonstrated in several clinical studies using different PIs (Table 1 and Figure 1).2–4

**RESULTS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Protease Inhibitors</th>
<th>N</th>
<th>Virologic Response</th>
</tr>
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<tbody>
<tr>
<td>Casado et al.</td>
<td>IDV/RVT 800/100 mg BID</td>
<td>14</td>
<td>IQ &gt; 1 associated with significant response</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>IDV 400/400 mg QD</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Shultman et al.</td>
<td>NFV/SV 1250/100 mg BID</td>
<td>27</td>
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<td>LPV/r 400/100 mg BID</td>
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(After vIQ = virtual IQ, which is a function of baseline phenotypic resistance estimated by virtual phenotype, and the plasma-protein concentrations. Drug abbreviations of the PIs are defined in the Methods.)

**BACKGROUND**

Studies have shown that IQ (C\(_{\text{min}}\)/IC\(_{50}\)) is associated with virologic response. This metric may have application in assessment of in vitro potency relative to achievable PI concentrations if determination of IC\(_{50}\) and method of protein binding correction are uniform.

**METHODS**

- Anti-HIV activity was assessed against HIV wild-type (wt) pNL4-3 strain in MT4 cells in media containing 10% fetal calf serum supplemented with 50% human serum. Protein-binding adjusted IC\(_{50}\) values for PIs were determined in at least two sets of triplicate measurements. Steady-state C\(_{\text{min}}\) from published reports was used to calculate IQ.

**RESULTS**

- Potency of PIs based on measured in vitro IC\(_{50}\) (means±SD mg/L) were: amprenavir (APV) 0.49±0.12; atazanavir (ATV) 0.01±0.005; indinavir (IDV) 0.071±0.028; lopinavir (LPV) 0.08±0.019; nelfinavir (NFV) 0.76±0.159; saquinavir (SQV) 0.45±0.114; and tipranavir (TPV) 4.7±0.8. Published mean (95% CI) C\(_{\text{min}}\) mg/L values were: (ritonavir represented by r): APV 1200/200 mg QD, 1.36 (1.12–1.67); and 600/100 mg BID, 1.12 (1.01–1.26); fos-APV 1395 mg BID, median 0.325 (ns); fos-APV 1395/200 mg QD, 1.45 (1.16–1.81); and 700/100 mg BID, 2.12 (1.77–2.54); IDV 800/100 mg BID, 0.99 (0.58–1.40); LPV 800/200 mg QD, 2.46 (1.13–3.81); and 400/100 mg BID, 5.51 (4.26–6.80); NFV 1250 mg BID, 0.76 (0.61–0.92); SQV 160/100 mg QD, 0.61 (0.37–0.84); and TPV 500/200 mg BID, median 19.51, range, 0.43–42.83. Estimated mean and 95% CI for IQ were: APV 1200/200 QD [2.7, na] and 600/100 BID [2.7, na]; ATV 400 QD [10.0, 6.9–13.1]; fos-APV 1395 mg BID [7.7, na]; fos-APV 1395/200 QD [9.7, na] and 700/100 BID [4.3, na]; IDV 800/100 BID [13.9, 6.6–21.2]; LPV 400/100 BID [67.4, 48.1–86.7] and 800/200 BID [30.1, 13.8–46.4]; NFV 1250 mg BID [1.0, 0.7–1.3]; SQV 1600/100 QD [1.3, 0.8–1.9]; and TPV 200/200 BID [4.2, na].

Conclusions: Standardization of the assay to measure protein-binding adjusted IC\(_{50}\) improves consistency in assessment of IQ. This enables IQ to provide better quantification of the relative potencies of PIs in vivo. This metric is being validated in ongoing clinical trials evaluating IQ and antiretroviral response.

**THE INHIBITORY QUOTIENT IQ**

The inhibitory quotient (IQ) has been shown to be a useful pharmacodynamic predictor of protease inhibitor (PI) potency in vivo. Adopted from the antibiotic literature,1 the IQ is best defined for PIs as the ratio of the minimum plasma concentration (C\(_{\text{min}}\)) to the drug concentration necessary to inhibit virus replication by 50% in vitro (IC\(_{50}\)). The clinical relevance of IQ in predicting virologic response has been demonstrated in several clinical studies using different PIs (Table 1 and Figure 1).2–4