Different Methods to Calculate the Inhibitory Quotient of Boosted Single Protease Inhibitors and Their Association With Virological Response

To the Editor:

In individuals with incomplete suppression of HIV replication, a major clinical challenge is to establish which agents retain significant antiviral activity. Measurements of both plasma concentration and resistance of selected antiretroviral agents are widely available. Clinical studies have shown short-term virologic benefit associated with the use of resistance testing in drug-experienced patients; however, no clinical benefit has been observed with the use of plasma drug concentration monitoring in treated individuals.[1]

Inhibitory quotient (IQ), a measure of plasma drug exposure corrected by the degree of resistance, may enhance the result of HIV resistance tests by correcting for plasma drug exposure. Several methods to calculate IQ have been proposed including genotypic IQ (GIQ), virtual IQ (VIQ), and normalized IQ (NIQ), where the ratio of plasma drug exposure to a measure of genotypic resistance, virtual phenotypic resistance, or a calculated population IQ are calculated, respectively. Significant associations have been described between virologic response and the GIQ, VIQ, and NIQ.[2–6] Despite these studies, there is a lack of standardization in the calculation of IQ, and there are no data on the benefit of 1 calculation compared with another which limits their use in clinical practice.

The aim of this study was to assess the association between virologic response in a cohort of HIV-1 treatment-experienced patients changing antiretroviral therapy because of virologic failure or intolerance within a prospective cohort and a range of covariates including the GIQ, VIQ, and NIQ.

The Therapeutic Drug Monitoring (TDM) Study is an ongoing prospective study assessing the usefulness of measuring protease inhibitor (PI) and nonnucleoside reverse transcriptase inhibitor trough plasma concentrations (C_{trough}) in HIV-1 positive patients commencing new antiretroviral regimens at the Chelsea and Westminster Hospital, London, United Kingdom. Subjects recruited for the study underwent blood sampling to assess plasma PI and nonnucleoside reverse transcriptase inhibitor C_{trough} at 4, 24, and 48 weeks. As part of a planned 24-week analysis, all antiretroviral-exposed subjects who had commenced a new ritonavir-boosted single PI regimen who enrolled in the TDM study were included in the current analysis.

All subjects had an HIV resistance test before commencing antiretroviral therapy and when changing therapy because of virologic failure. For the purpose of this analysis, the most recent HIV resistance test within 6 weeks of changing antiretroviral therapy was used. Fold change (FC) for each PI was determined from the predicted FC virtual phenotype report.

The C_{trough} of the selected PI was determined using a validated high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) assay.[7] The IQs were calculated as the ratio of the TDM study week 4 PI C_{trough} to the following: (1) the number of major PI mutations for major genotypic IQ (majGIQ), (2) the number of total PI mutations (both major and minor mutations) for total genotypic IQ (totGIQ), (3) the virtual phenotype FC for VIQ, (4) the VIQ divided by population IQ for NIQ. For the calculation of both totGIQ and majGIQ, major and minor mutations in HIV protease on genotypic sequencing were considered significant as per International AIDS Society guidelines.[8] A value of 1 was added to the number of PI mutations present to allow the subjects with no mutations to be included in the analysis. The FC to calculate VIQ for each PI was determined from the virtual phenotype result (Virco Type HIV-1 reports). The recently described 80% clinical cutoff[9] and published population C_{trough}[10] levels were used to calculate population IQ for the correction of VIQ to NIQ.

Predictors of time-weighted change in HIV RNA for 48 weeks were determined using linear regression modeling. To allow comparisons of C_{trough}, majGIQ, totGIQ, and VIQ for different PIs, these parameters were reported as the normal standard deviate (z transformation).

Between June 2004 and August 2005, 98 patients were enrolled in the TDM study. Fifty-three subjects were changing therapy to a ritonavir-boosted single PI regimen. Of the 53 patients, plasma HIV RNA was below 50 copies/mL in 18 (34%) and 3.68 $\log_{10}$ copies/mL (median) in the remaining patients. Mean number of previous antiretroviral regimens in this cohort was 5 (range, 4–8). The new PI is composed of atazanavir, amprenavir, fosamprenavir, lopinavir, and saquinavir in 18 (34%), 5 (9%), 4 (8%), 15 (28%), and 11 (21%) patients, respectively. No patient included in this analysis underwent any changes to antiretroviral therapy since enrollment or had withdrawn from the study at the time of analysis.

Despite the 32 patients (60%) in this cohort being exposed to PIs, the number of major and total PI mutations were low (median, 1; range, 0–8).

Mean time-weighted change in HIV RNA for 48 weeks was −1.82 $\log_{10}$ copies/mL. Factors associated with time-weighted change in HIV RNA are shown in Table 1. In a multivariate analysis, only baseline HIV RNA and NIQ were significantly associated with time-weighted change in HIV RNA.

In this cohort of treatment-exposed HIV-1 patients changing antiretroviral therapy to a boosted single PI regimen, baseline HIV RNA and NIQ were significantly associated with virologic response; whereas C_{trough}, majGIQ, totGIQ, and VIQ were not significantly associated.

A significant reduction in virologic response has been described in patients harboring viral isolates with more than 6 PI-associated mutations to lopinavir[2] and amprenavir[3] and with more than 4 mutations to saquinavir[4] when subjects were treated with these PIs boosted with ritonavir. In our study, we have not observed significant associations between majGIQ and virologic response. These differences may be explained by differences in PI resistance patterns between our cohort and other reports. Our cohort, although highly treatment-experienced (previous regimens median, 5), had lower number of patients with viral isolates harboring PI-associated mutations with only 10 (19%) and 24 (45%)

TABLE 1. Associations Between Time-Weighted Change in Plasma HIV RNA for 48 Weeks

	Univariate Analysis		Multivariate Analysis	
Parameter	***P***	**95% CI Change**	***P***	**95% CI Change**
Baseline CD4 lymphocyte count	<0.001	0.003 to 0.008	0.137	0.000 to 0.002
Baseline HIV RNA	<0.001	−2.03 to −1.56	<0.001	−1.97 to −1.53
No. previous antiretroviral regimens (above or below median)	0.900	−1.64 to 1.45	—	—
Choice of new PI	0.227		—	
atazanavir		Reference		—
amprenavir		−4.66 to 1.41		—
fosamprenavir		−0.78 to 4.77		—
lopinavir		−3.40 to 0.54		—
saquinavir		−0.26 to 1.60		—
Trough plasma PI concentration	0.698	−0.26 to 0.17	—	—
Presence of PI mutations (major)	0.671	−1.50 to 2.30	—	—
Presence of PI mutations (total)	0.258	−0.66 to 2.40	—	—
Mean Fold Change	0.823	−0.06 to 0.52	—	—
GIQ (major mutations)	0.225	−0.35 to 0.09	—	—
GIQ (all mutations)	0.098	−0.40 to 0.04	0.072	−0.17 to 0.008
VIQ	0.241	−0.34 to 0.09	—	—
NIQ	0.112	−0.027 to 0.003	0.026	−0.013 to −0.01

CI indicates confidence interval.

patients with isolates carrying major or any PI mutations, respectively. Indeed, many subjects in our cohort had no PI-associated resistance observed. This may explain the lack of association between GIQ and VIQ with virologic response.

Our cohort is representative of patients undergoing changes in antiretroviral therapy because of intolerance or virologic failure and currently attending for care in a large UK HIV treatment center, and the associations observed in our cohort between different calculations for the IQ and virologic response may be representative of patients changing therapy in a real life situation rather than in clinical trials.

The NIQ may be a more sensitive marker in our cohort because of the correction of the IQ using the 80% clinical cutoffs FC based on clinical outcome. The recently described 80% clinical cutoffs are the FC associated with an 80% reduction in expected virologic response from wild type based on the results of more than 13,000 viral isolates.

Being corrected by population parameters, NIQ can be compared across several PIs without mathematical correction, whereas other IQ calculations require correction before comparisons can be made (normal standard deviate used in our study).

In summary, we have found NIQ to be associated with virologic response in treatment-exposed patients commencing single-boosted PI regimen within a clinical setting, whereas other parameters used to calculate the IQ were not significantly associated. Further prospective studies assessing the use of NIQ are warranted.

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Response to Rapatski BL, Suppe F, Yorke JA. HIV Epidemics Driven by Late Disease Stage Transmission

To the Editor:

Using 7 annual infection rates in the San Francisco City Clinic Cohort (SFCCC) of gay males from 1978 through 1984 as data points, Rapatski et al[1] have estimated the transmission probabilities for primary, latent, and late infection at 0.024, 0.002, and 0.299, respectively. This translates to 1.3% of all transmission potential occurring during primary infection and 97.2% during late infection.

In contrast, Wawer et al[4] more directly estimated heterosexual transmission to monogamous uninfected partners in prospectively followed discordant couples in Africa. Wawer et al[4] found peak transmission probabilities during the first stage that were 11.7 times those of the long latent stage and 2–2.7 times those of late infection. Transmission occurred to 57% of partners over the course of early stage infection but only to 37% of partners over the course of late stage infection.

If the estimates of Rapatski et al[1] are correct, then identifying HIV-seropositive individuals using current strategies should control transmission and a vaccine that eliminates the primary infection peak will be of little use. If, on the other hand, early infection plays a key role in transmission dynamics, as speculated by Koopman et al[2] using transmission probabilities similar to those found by Wawer et al,[4] then a strategy like that of North Carolina[3] is needed and vaccines that only reduce primary infection transmissibility will be useful.

We believe the transmission probability inferences of Rapatski et al[1] are not robust to realistic violation of the following simplifying assumptions in their analysis:

1. The SFCCC is representative of the actual transmission system.
2. Individual pairings are random with
   a. no ongoing relationships between individuals;
   b. no greater likelihood that the contacts of one person form a partnership than for any other individuals;
   c. no clustering of contacts by geography, class, race, risk behavior, sex act preferences, or any other factor; and
   d. the population mixes thoroughly after each pairing.
3. Individual contact rates do not fluctuate and are not influenced by illness, death, changing fortunes in finding permanent partners, or social maturation.

Other issues affecting the Rapatski et al[1] estimates are biases and variance in the data. The SFCCC does not represent a uniformly followed cohort. The initial recruitment was to find hepatitis B serology-negative individuals. Originally, recruited hepatitis B-seropositive individuals were followed up at later times and inferences had to be made about when they might have been infected. The biases likely to have arisen in this process could have especially affected the crucial "lull" in infection rates seen in the 1981 data point. The robustness of the inferences should be assessed with regard to these potential biases.

From their analysis, Rapatski et al[1] conclude that Africa has extremely high reproduction numbers that require great behavioral changes to overcome. To make that inference, all of the above assumptions must also apply to Africa. Here, the assumptions seem even more unrealistic and will have even greater effects. A better way to make inferences about the African situation is to take the estimates of Wawer et al[4] and apply them in a model that specifies the nature of ongoing relationships and contact patterns in realistic African situations. We hypothesize that such an analysis would support the inference that transmission during primary infection plays a central role in sustaining HIV circulation, even in mature epidemics.

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