INTRODUCTION

Treating HIV infection is challenged by the rapid turnover and high reverse transcription errors of HIV viruses. A significant proportion of patients eventually fail to control viral replication and develop resistant viruses during treatment with most of the highly potent antiretroviral therapies (HAART). However, no primary or active site mutation/resistance to protease has been noted to date in Phase II and III antiretroviral (ARV)-naive adult and pediatric subjects treated with lopinavir/ritonavir (LPV/r, or Kaletra®) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) [1–4]. In particular, in an Abbott Phase III trial with 653 patients randomized to receiving LPV/r or nelfinavir
(NFV) with two NRTIs, d4T and 3TC, 123/327 subjects receiving NFV had HIV RNA >400 copies/mL during the week 24-108 period. Ninety-six of the 123 subjects with viral rebound had genotype data; 45% of these (43/96) developed primary mutation to protease, 82% (79/96) had 3TC resistance, and 9% (9/96) had d4T resistance [1]. In the same study, 74/326 subjects receiving LPV/r also had HIV RNA >400 copies/mL and 51 of the 74 subjects with viral rebound had genotype data. Interestingly, none of these developed primary mutations to protease or d4T resistance, and only 37% (19/51) had 3TC resistance. It is important to note that adherence rates were similar between the two study regimens. The absence of resistance to protease inhibitors (PIs) in the treatment-naive patient population treated with LPV/r motivated this analysis.

HYPOTHESIS

The absence of resistance emergence to LPV/r in the treatment-naive patient population is hypothesized to be due to the following reasons.

1. The median inhibitory quotients \( IQ = \frac{C_{trough}}{IC_{50}} \) in PI-naive patients receiving LPV/r and NFV are substantially different, being 91 (N=30) and 3.3 (N=91), respectively, based on protein-binding corrected \( IC_{50} \) values [5,6]. However, resistance develops to drugs with even higher IQ values, such as efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) [7]. Thus, the lack of resistance to LPV/r cannot be fully explained by high IQ values.

2. Multiple steps of mutations are probably required to develop resistance to PIs with high IQ values, such as LPV/r [1,6,8,9]. Literature data show that clinical isolates from patients treated with (NNRTIs, such as EFV, and some NRTIs, such as 3TC, often have large increases in \( IC_{50} \) values (i.e., large resistance step sizes), while isolates from patients treated with PIs tend to show smaller, incremental increases in \( IC_{50} \) values (i.e., small resistance step sizes) [1,7, 8, 9–12]. In the absence of data on resistance development in LPV/r-treated patients, results from \textit{in vitro} experiments suggest that mutation step sizes for LPV likely are 2-3 fold [1,8,9].

3. Additionally, the terminal-phase elimination of LPV/r is very rapid when given alone or during missed doses, which theoretically can reduce the time during which a patient is exposed to sub-therapeutic concentrations and high selection pressure after missing doses.