HIV Viral Dynamics of Lopinavir/ritonavir Monotherapy as Second-Line Treatment in a Resource-Limited Setting

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Introduction & Background
• Access to antiretroviral treatment (ART) is increasing worldwide in response to need and expanding treatment guidelines.
• Rates of failure of first-line therapy (NRTI + NRTI) have been reported as high as 32%[1]; efficacious and cost-effective second-line regimens are needed.
• NRTI backbones in second-line regimens may provide minimal benefit at the cost of significant toxicities. Boosted protease inhibitor (PI) monotherapy may offer effective treatment with minimalization of toxicity.
• Prior trials of boosted protease inhibitor monotherapy (e.g., Kaletra, Kalcit, Microl, BOI-MONO) in naive patients or first-line drug-intensification trials have achieved treatment efficacies ranging from 40% to 80%.[2]
• Second-line treatment trials have demonstrated general treatment efficacy rates of 60-65%.[3] The ACTG trial demonstrated efficacy of 87% at 24 weeks, and the ENNIT trial showed only 55% efficacy of LPIV/r monotherapy de-intensification second-line treatment in resource-limited settings.[4]
• Boosted PI trials to date have only intermittently monitored viral load, with rates of virologic ranging from 0.24% to 0.14%.[5] We report the viral dynamics of HIV in the setting of boosted PI monotherapy as second-line treatment in hopes of improving our understanding of treatment responses in resource-limited settings.

Methods
• Study Design: Prospective, single arm, non-randomized, open label, proof of concept study evaluating viral load and efficacy of boosted LPIV/r (LPV/r) monotherapy over 48 weeks conducted at 27 treatment centers in 18 nations (South Africa, India, Asia, and Latin America) in adult and children patients with clinical, virologic evidence of treatment failure and confirmed by culture or PCR. Eligible patients were aged 18 years and older, with prior ART exposure, CD4 cell counts measured as ≤100 cells/μL, ≥100 cells/μL to ≤350 cells/μL, ≥350 cells/μL to ≤500 cells/μL, and ≥500 cells/μL at baseline. LPIV/r was administered as a once-daily regimen (LPV/r 400 mg/ritonavir 100 mg, twice daily for 4 weeks then once daily for 44 weeks). No concomitant antiretroviral or non-antiretroviral medications were allowed except for lopinavir/ritonavir (LPV/r) monotherapy (200 mg/100 mg twice daily). Patients were excluded if they were pregnant, allergic to lopinavir/ritonavir, or had a history of intolerance to protease inhibitors. Patients were monitored every 8 weeks for 48 weeks. Data were analyzed using the intention-to-treat principle and the per-protocol analysis for comparison. The primary endpoint was virologic success at 48 weeks, defined as undetectable viral load at week 48. Secondary endpoints included virologic success at 24 weeks, on-treatment virologic success, and treatment success at 48 weeks.

Key Findings
• By strict ITT criteria, LPV/r monotherapy succeeded in maintaining sustained viral suppression in only 9% (52/585) patients after achieving viral suppression with NRTI + NRTI therapy.[6]
• However, at 48-weeks, 14 (47%) patients had viral suppression (<400 copies/mL) on LPV/r monotherapy. Low to moderate viroemia was prevalent in 96% of patients.[7]
• Blips (defined as a detectable VL, preceded and followed by an undetectable VL) were common, over half of patients experienced at least one blip on LPV/r.[8]

Conclusions
• Viremia was pervasive on LPV/r monotherapy in the treated population and more frequent than previously described, with 96% of patients experiencing viroemia or viricemic blips after initial suppression.
• Possible factors leading to viroemia in this study include non-adherence, immune activation, pharmacokinetics, and activity of PI monotherapy only in the activated pool of cells.
• Due to significant risk of low-level viremia and unpredictable viral suppression, LPV/r monotherapy cannot be recommended as a routine second-line therapy but may have a role in certain patients intolerable to NRTIs.[9]
• Patients that are virologically suppressed at 24 weeks (6 months) are likely to remain suppressed on LPV/r monotherapy.