Therapeutic Drug Monitoring of Lopinavir in HIV-infected Children on Second-line ART

Background

- Failure rates of second-line boosted protease inhibitor (PI) regimens in children in resource-limited settings are expected to rise over time.
- Known risk factors for antiretroviral treatment (ART) failure include high baseline viral load, low baseline CD4 cell count, inadequate drug concentrations and non-adherence.
- There is no single standard method to measure treatment adherence; therapeutic drug monitoring can contribute to assessments of adherence and inform decisions to conduct resistance testing.
- According to the US Department of Health and Human Services (DHHS) guidelines (version February 12, 2014), the suggested minimum target trough concentration of lopinavir (LPV) in patients with drug-susceptible HIV virus is 1 mg/L.
- A study among adults in South Africa supported that a LPV plasma level of 1 mg/mL was the threshold concentration that maximized the sensitivity and specificity for predicting virologic failure.
- We aimed to explore whether this recommendation was applicable to children and adolescents in Asia.

Study objectives

1. To explore whether the target trough concentration of LPV recommended by the DHHS is able to predict virologic failure (VF) in HIV-infected Asian children and adolescents receiving LPV as a part of second-line ART.
2. To determine whether therapeutic drug monitoring (TDM) of LPV would be useful as a proxy for adherence and/or justification for genotypic resistance testing in children and adolescents on second-line ART in the TASER-Pediatrics cohort.

Methodology

- This is a week 24 sub-analysis of TASER-Pediatrics (ClinicalTrials.gov identifier: NCT01788891), which is a longitudinal observational cohort study to monitor treatment failure while on second-line ART in Asian children.
- Data were analyzed from study participants in Indonesia, Thailand, and Vietnam receiving second-line LPV-based ART and followed for ≥24 weeks.
- Random plasma and/or trough LPV concentrations (Ctrough) and HIV RNA level were tested in all participants at 24 weeks after enrollment; HIV RNA was repeated every 24 weeks, while samples for TDM were collected and held for future testing depending on HIV RNA results.
- Those with HPV (HIV RNA<1000 copies/mL) had genotypic resistance testing and plasma LPV levels.
- Mutations were interpreted using the Stanford University HIV Drug Resistance Database.

Results

Cohort characteristics

Participant characteristics are shown in Table 1. At the time of the study, 219 (95%) acquired HIV infection perinatally.

Table 1 Characteristics of 223 participants on LPV-based regimens

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All of study (n=223)</th>
<th>At the time of study (n=223)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>7 (5-12.5)</td>
<td>7 (5-12.5)</td>
</tr>
<tr>
<td>CD4 count (cells/L)</td>
<td>818 (675-1013)</td>
<td>818 (675-1013)</td>
</tr>
<tr>
<td>HIV RNA (copies/mL)</td>
<td>276 (133-586)</td>
<td>276 (133-586)</td>
</tr>
<tr>
<td>Ctrough (%)</td>
<td>0 (0-9.5)</td>
<td>0 (0-9.5)</td>
</tr>
<tr>
<td>Duration on LPV-based ART (years)</td>
<td>2.5 (1.3-4.2)</td>
<td>2.5 (1.3-4.2)</td>
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</tbody>
</table>

At week 24

- 23 of 223 participants had VF at week 24; of these, 3 had LPV trough available.
- Using LPV trough in predicting VF at week 24 had a sensitivity of 67% and specificity of 96% (Table 2).
- The sensitivity and specificity were lower when random LPV concentrations from all 23 participants were included (Figure 2).
- 21 of 23 participants with HIV RNA>1000 copies/mL at study week 24 had resistance results available. Of these, 7 (33%) had major PI mutations (Table 2) and had been taking LPV for 1.7 positive days, while pill count revealed 100% adherence. Only 2 reported missed doses in the 3 days prior to the clinic visit, while the genotypic resistance results showed susceptibility to LPV.
- Pill count revealed 100% adherence in 2, 96% adherence in 2, and were not available in the remaining participant.

Conclusions

- Our data support that the target LPV trough recommended by DHHS predicts treatment failure, but not the major risk of LPV mutations in HIV-infected Asian children and adolescents receiving LPV as a part of second-line ART.
- Children with LPV concentrations <1 mg/mL and CD4 ≤20% were at greater risk for VF.
- Therapeutic drug monitoring of LPV may be used as a proxy for adherence and/or justification for genotypic resistance testing in this population.

After week 24

- Fourteen additional children developed VF after study week 24.
- Their duration on LPV ranged from 0.8-5.8 years.
- 21/4 (14%) had major PI mutations (NATMIL, V83A); both had LPV >1 mg/mL.
- 5/14 (36%) children with VF had LPV plasma concentrations below the 1 mg/mL cut-off.
- At 5 mg/mL no missed doses in the 3 days prior to the clinic visit, while the genotypic resistance results showed susceptibility to LPV.
- Pill count revealed 100% adherence in 2, 96% adherence in 2, and were not available in the remaining participant.

Factors associated with virologic failure

- LPV concentrations <1 mg/mL (OR 6.47, 95% CI 2.15-19.50, P=0.001) and CD4 <20% (OR 2.83, 95% CI 1.01-7.9, P=0.05) were associated with VF.
- Age, duration on LPV, WHO staging, and adherence as assessed by pill count or VAS were not associated with VF.
- No factors predicted major LPV resistance mutations.