Single Agent Therapy (SAT) with Lopinavir/ritonavir (LPV/r) Controls HIV-1 Viral Replication in the Female Genital Tract

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INTRODUCTION
- Lopinavir/ritonavir (LPV/r) as single agent therapy has demonstrated virologic suppression when used in a variety of treatment strategies.1-3
- We have previously shown that LPV/r single-agent therapy suppressed viral replication in the cervicobulbar fluid of 10 out of 11 antiretroviral-naïve subjects.4
- A separate study (MONARK) evaluated viral response in semen and showed undetectable HIV RNA in 5 out of 5 men on LPV/r single-agent therapy after 48 weeks of therapy, despite undetectable semen LPV and ritonavir (RTV) concentrations.5
- Use of combination antiretroviral therapy has been associated with decreased genital HIV RNA in men and women.6
- When used as part of combination therapy, LPV/r concentrations in cervicovaginal fluid (CVF) from direct aspiration were a median of 8% (interquartile range, 0.4%, 424%) of blood plasma.7
- No study to date has evaluated control of HIV replication and drug penetration into the female genital tract (FGT) with LPV/r single-agent therapy.

OBJECTIVES
- To assess viral load in the FGT after 24 weeks of LPV/r single-agent therapy in patients that have HIV RNA <75 copies/mL on at least 2 consecutive visits.
- To estimate LPV/r penetration into the FGT compared to blood plasma.

METHODS
- MANI-2 is an ongoing, prospective, open-label investigation of LPV/r single-agent therapy in 39 antiretroviral-naive, HIV-1-infected subjects administered as 400/100mg twice daily.
- This substudy was approved by the Institutional Review Board and all subjects provided written, informed consent.
- Inclusion criteria: All females at or at least 24 weeks of LPV/r with at least 2 consecutive plasma HIV RNA <75 copies/mL, by branched DNA assay at least 4 weeks apart and at the most recent evaluation were approached for enrollment.
- Exclusion criteria: not meeting inclusion criteria

IMANI-2 FGT Substudy Subject Disposition

<table>
<thead>
<tr>
<th>Women enrolled</th>
<th>Women at 24 weeks of study</th>
<th>Women met inclusion criteria</th>
<th>Women not met inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 women</td>
<td>8 women</td>
<td>5 women</td>
<td>7 women</td>
</tr>
</tbody>
</table>

- Paired blood plasma, FGT sampling.
- Genital tract sampling was performed within 14 days after end of menses in menstruating women. Prior to FGT sampling, women refrained from sexual intercourse, vaginal medications, and douching for at least 48 hours.
- Pelvic exams were performed by a board-certified obstetrician-gynecologist.
- Adherence over the previous week was based on 7-Pelvic exams were performed by a board-certified obstetrician-gynecologist.
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Table 3. Collection method: direct aspirate and CVL

<table>
<thead>
<tr>
<th>LPV/r Penetration</th>
<th>N = 7</th>
<th>Median [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r Plasma</td>
<td>449,996</td>
<td>[7044, 18811]</td>
</tr>
<tr>
<td>LPV/r CV</td>
<td>99,601</td>
<td>[2.3, 13.1]</td>
</tr>
</tbody>
</table>

- Drug Penetration
  - Direct cervicovaginal aspirate was able to be done in only 1 woman.
  - Cervicovaginal lavage (CVL) performed in all.

Table 4. LPV Concentrations in CVL-Plasma Pairs

<table>
<thead>
<tr>
<th>Time after dose (h)</th>
<th>Plasma LPV (ng/mL)</th>
<th>CVL LPV (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>449,996</td>
<td>99,601</td>
</tr>
<tr>
<td>1</td>
<td>292,453</td>
<td>14,496</td>
</tr>
<tr>
<td>6</td>
<td>224,284</td>
<td>12,600</td>
</tr>
</tbody>
</table>

- In all women, the main risk factor for HIV transmission was heterosexual intercourse. Median number of sexual partners in the past 6 months was 0 – 2.
- Four women were no longer menstruating: 3 with history of total abdominal hysterectomy, 1 with total vaginal hysterectomy.
- Pelvic exams and CVL sampling were performed at median of 61 [54 – 88] weeks after LPV/r initiation.

RESULTS

- All subjects achieved plasma HIV RNA suppression to <75 copies/mL by week 16 after LPV/r initiation. Median time of suppressed plasma HIV RNA at time of FGT sampling was 69 [50 – 84] weeks.
- All 7 subjects had viral load ≥102 copies/mL, and all 3 subjects with an intact cervix had cervical HIV RNA ≥400 copies/mL, at the time of sampling.

Table 2. Baseline CD4, Viral Load and Response

<table>
<thead>
<tr>
<th>Median [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma HIV RNA</td>
</tr>
<tr>
<td>CVL HIV RNA</td>
</tr>
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- When used as part of combination therapy, LPV/r concentrations in cervicovaginal fluid (CVF) from direct aspiration were a median of 8% (interquartile range, 0.4%, 424%) of blood plasma.
- No study to date has evaluated control of HIV replication and drug penetration into the female genital tract (FGT) with LPV/r single-agent therapy.

Table 1. Demographics

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<tr>
<th>Median [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
</tbody>
</table>

- Drug Penetration
  - Direct cervicovaginal aspirate was able to be done in only 1 woman.
  - Cervicovaginal lavage (CVL) performed in all.

DISCUSSION

- Control of HIV replication in blood plasma with LPV/r as single-agent therapy is associated with suppression of HIV replication in sanctuary sites of the peripheral nervous system and the male genital tract, but data in the FGT was previously unknown.
- This study is the first to show suppression of HIV replication in the FGT in a diverse cohort of women with undetectable HIV in plasma, despite low LPV concentrations in CVL.
- HIV RNA was undetectable (<400 copies/mL) in the cervicovaginal fluid of all 7 women studied.
- LPV concentration in cervicovaginal fluid exceeded the reference population median IC50 (1.9 ng/mL) in all but one sample, despite significant dilution of LPV/r single-agent therapy in plasma.
- Larger longitudinal investigations are warranted evaluating single-agent therapy on viral suppression and drug pharmacokinetics in sanctuary sites.

CONCLUSIONS

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- This study is the first to show suppression of HIV replication in the FGT in a diverse cohort of women with undetectable HIV in plasma, despite low LPV concentrations in CVL.
- HIV RNA was undetectable (<400 copies/mL) in the cervicovaginal fluid of all 7 women studied.
- LPV penetration into cervicovaginal fluid exceeded the reference population median IC50 (1.9 ng/mL) in all but one sample, despite significant dilution of LPV/r single-agent therapy in plasma.

REFERENCES

ACKNOWLEDGEMENTS
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