Background

Optimal adherence is critical for virological suppression for both 1\textsuperscript{st} and 2\textsuperscript{nd} line ART regimen.

In LMICs, poor adherence has been associated with high rates of virological failure to 2\textsuperscript{nd} line regimen.

4.8 What ART regimen to switch to (second- and third-line ART)

Table 4.15. Preferred second-line ART regimens for adults, adolescents, pregnant women and children

<table>
<thead>
<tr>
<th>Population</th>
<th>Failing first-line regimen</th>
<th>Preferred second-line regimen</th>
<th>Alternative second-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents</td>
<td>2 NRTIs + EFV (or NVP)</td>
<td>2 NRTIs + ATV/r or LPV/r</td>
<td>2 NRTIs + DRV/r</td>
</tr>
<tr>
<td>Pregnant or breastfeeding women</td>
<td>2 NRTIs + EFV (or NVP)</td>
<td>2 NRTIs + ATV/r or LPV/r</td>
<td>2 NRTIs + DRV/r</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 3 years</td>
<td>2 NRTIs + LPV/r</td>
<td>2 NRTIs + RAL</td>
<td>Maintain the failing LPV/r-based regimen and switch to 2 NRTIs + EFV at 3 years of age</td>
</tr>
<tr>
<td>3 years to less than 10 years</td>
<td>2 NRTIs + NVP</td>
<td>2 NRTIs + LPV/r</td>
<td>2 NRTIs + RAL</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs + LPV/r</td>
<td>2 NRTIs + EFV</td>
<td>2 NRTIs + RAL</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs + EFV (or NVP)</td>
<td>2 NRTIs + LPV/r</td>
<td>2 NRTIs + ATV/r</td>
</tr>
</tbody>
</table>

- Prohibitive cost of viral load testing and resistance testing
- Identifying the non-adherence is crucial for reaching the 3rd “90” target.
Challenge in measuring adherence

• Adherence changes over time

• Some ART are forgiving (including boosted PIs)
  • Shuter, J. Antimicrobial Chemotherapy (2008)

• Adherence threshold for maintaining durable suppression

• Self reported – bias and over-estimation

Background

Untimed plasma concentration of PIs

• Predict resistance in LPV/R based ART

• Undetectable plasma concentration predict virological failure in low level viraemia
Background

The SECOND-LINE main study**

- Adults ≥16 years old
- Confirmed virological failure of NNRTI+2N(t)RTIs (pVL >500 copies/mL)
- No prior PI or INI exposure
- Stratified by site and baseline pVL >100,000 c/mL


Background

The SECOND-LINE resistance study**

Virological failure in the SECOND-LINE trial was associated with:

- Self-reported non-adherence
- Higher baseline gGSS
- Higher baseline VL >100,000 copies/mL
- Ethnicity

Hypothesis

- Untimed plasma lopinavir concentration (UPLC) measured at week 12 would predict virological failure at 48 weeks in the SECOND-LINE Study

- Does ethnicity really matter?

Primary Objective

To investigate the association between untimed detectable lopinavir concentration (LPV≥25 μg/L) or undetectable (LPV<25 μg/L) LPV plasma levels at week 12 and virological failure at week 48 (VL ≥ 200 copies/mL).
Secondary Objectives

• To investigate the association between UPLC at week 12 and time to loss of virological response [TLOVR] over 48 weeks.

Methods

• “Untimed” WK 12 plasma LPV concentration using stored patient samples from the SECOND-LINE study.
• HPLC - LLD of 25 µg/L
• UPLC categorized as (using LLD and DHHS guidelines)
  i. Detectable (≥25 µg/L)
  ii. Undetectable (u-UPLC) (<25 µg/L)

• Detectable was further categorized as
  (a) detectable and optimal (o-UPLC) (≥1000 µg/L)
  (b) detectable but sub-optimal (s-UPLC) (≥25 to <1000 µg/L)
Methods

• A chi-square - association between UPLC and virological outcome at week 48

• Regression - association between VF at week 48, UPLC and other predictors of virologic outcome** (age, BMI, sex, ethnicity, duration of HIV infection, HIV stage, duration of ART, randomized arm, baseline VL, nadir CD4, baseline CD4, baseline CD8, baseline CD4/CD8 ratio, adherence at week 4, adherence at week 48, baseline resistance (genotypic sensitivity score (GSS)) and HIV subtype).

• Cox regression - relationship between UPLC and TLOVR

Results

Baseline characteristics:

• N=517
• Median age38(32,44) years,
• 54% males,
• 50% RAL+LPV/r, 50% N(t)RTIs+LPV/r
• At week 12, 32/517 (6%) had undetectable UPLC, and 485/517 (94%) had detectable UPLC
• Ethnicity (Asian 46.9%, Hispanic 15.6%, African 28.1% Caucasian9.4%)
Results

Significant association between UPLC and virological outcome

<table>
<thead>
<tr>
<th>UPLC (µg/L)</th>
<th>Virological failure N (%)</th>
<th>Viral suppression N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>15(22.1)</td>
<td>17(3.8)</td>
<td>32(6.19)</td>
</tr>
<tr>
<td>Detectable</td>
<td>53(77.9)</td>
<td>432(96.2)</td>
<td>485(93.8)</td>
</tr>
<tr>
<td>Total</td>
<td>68(100)</td>
<td>449(100)</td>
<td>517(100)</td>
</tr>
</tbody>
</table>

\[ X^2 (1) = 18.51 \quad p < 0.001 \]

Results

Undetectable UPLC was associated with higher rate of virological failure over 48 weeks.
Undetectable UPLC independently predicted virological failure at week 48

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&gt;0.019</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&gt;0.043</td>
</tr>
<tr>
<td>Baseline Viral load</td>
<td></td>
</tr>
<tr>
<td>&lt;100,000 copies/mL</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td>Randomized arm</td>
<td></td>
</tr>
<tr>
<td>N(0)RTI</td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td></td>
</tr>
<tr>
<td>Week 48 Adherence**</td>
<td></td>
</tr>
<tr>
<td>Took all pills</td>
<td>&gt;0.065</td>
</tr>
<tr>
<td>Took less than all pills</td>
<td></td>
</tr>
<tr>
<td>Baseline GSS score*</td>
<td></td>
</tr>
<tr>
<td>Low score (0 - 3.5)</td>
<td></td>
</tr>
<tr>
<td>Medium score (3.75 - 4.25)</td>
<td>&gt;0.003</td>
</tr>
<tr>
<td>High score (4.75 - 8)</td>
<td></td>
</tr>
<tr>
<td>LPV Concentration</td>
<td></td>
</tr>
<tr>
<td>Detectable (LPV ≥25 μg/L)</td>
<td></td>
</tr>
<tr>
<td>Undetectable (LPV &lt;25 μg/L)</td>
<td>&lt;0.0002</td>
</tr>
</tbody>
</table>

**Conclusion**

Untimed plasma concentration in LMCIs

- Early and objective identification of non-adherence
- Ethnicity on its own is not predictive
- Optimize 2nd line treatment outcome through adherence stewardship
- Sustainability of ART treatment programs
- 90 – 90 -90 targets
Acknowledgements

• We thank the SECOND-LINE Study participants and their partners, families, and carers for participation in the study.

• We also thank all the staff from all centres participating in the trial and laboratory staff at HIV Immunovirology (Biobank) Laboratory, St Vincent’s Hospital Centre for Applied Medical Research, St Vincent’s Hospital, Sydney.

• We thank Gilead for study support through Gilead Australian Fellowship Grant 2015 awarded to Mark Boyd

• Thank you