Francois Venter

October 2018

Low dose darunavir

Thanks DoH, WHO, PEPFAR, CHAI, UCT, Michelle Moorhouse, Celicia Serenata, Polly Clayden
Optimize

- Led by Wits RHI, the PEPFAR-supported, USAID-managed OPTIMIZE consortium focuses on accelerating access to PEPFAR’s priority first- and second-line treatment products. OPTIMIZE, formed through an innovative co-formulation effort, partners with five leading private and public sector organizations and leverages co-funding from Unitaid, SAMRC and pharma.
- Supporting PEPFAR’s TLD Transition & Global ART Optimization
- Coordinates with several countries for TLD introduction
- Close coordination in SA with Pretoria office – critical for TLD
- ADVANCE and the low-dose darunavir study (052 are two studies in OPTIMIZE (with several related and sub-studies)
Optimizing Drug Regimens
Major Strategies

- Co-formulation (use FDCs or co-blister pack)
- Reformulation (use extended release formulation; improve drug bioavailability)
- Dose adjustment (improve toxicity, reduce pill burden/size)
- New drugs (substitution to improve toxicity or increase efficacy)
- New strategies (eg: induction-maintenance; intensification)
- Drug manufacturing process (improve API route synthesis and reduce cost)
Drug Interactions will be greater as patients age.

WHO regimens 2018/soon

Tenofovir + XTC + Efavirenz

AZT + Lamivudine + Darunavir, DTG, doravirine, other

XTC, other nukes + Darunavir, Dolutegravir, Etravirine

Failure
Efficacy of LPV/r-Based Therapy in Second-Line ART

- **EARNEST**: Hakim J, et al. CROI 2015; Poster 552
- **ACTG 5273**: La Rosa AM, et al. CROI 2016; Abstract 30

### Percentage Suppressed

<table>
<thead>
<tr>
<th>Study</th>
<th>Week</th>
<th>&lt;400 c/mL</th>
<th>&lt;200 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARNEST</td>
<td>144</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td>SECOND-LINE</td>
<td>96</td>
<td>76%</td>
<td>80%</td>
</tr>
<tr>
<td>ACTG 5273</td>
<td>48</td>
<td>90%</td>
<td>92%</td>
</tr>
</tbody>
</table>

EARNEST: <400 c/mL
SECOND-LINE: <200 c/mL
ACTG 5273: <400 c/mL

For more information, see:
- EARNEST: Hakim J, et al. CROI 2015; Poster 552
- ACTG 5273: La Rosa AM, et al. CROI 2016; Abstract 30
Randomized Comparison of 3 Second-Line ART Regimens in Africa: The 2Lady/ANRS/EDCTP Study

- A 48-week, randomized, open label, non-inferiority trial in 3 African cities—Yaoundé (Cameroun), Bobo-Dioulasso (Burkina Faso), Dakar (Senegal)—comparing efficacy and safety of 3 second-line regimens from Jan 2010 to Oct 2012:

N= 454
- >18 years old
- Failed first-line NNRTI-based ART (confirmed VL ≥1000 cpm)
- Good adherence (≥80%)

Baseline characteristics:
- 72% women
- Median duration on ART — 49 months (IQR 33–69)
- Median CD4 count of 183 cell/mm³ (IQR 87–290)
- Median VL of 4.5 Log_{10} (IQR 4–5.1).
- ~99% had resistance to at least 1 first-line drug and 95% to 2 classes

Primary efficacy endpoint:
- HIV-1 RNA <50 c/mL at 48 weeks
  (ITT and per protocol; non inferiority margin of 15%)

Arm A: LPV/r + TDF/FTC n=152
Arm B: LPV/r + ABC + ddi n=145
Arm C: DRV/r + TDF/FTC n=154

ITT: Proportion in Each Arm of Patients With VL <50 Copies/mL With CI 95%

![Graph showing proportion of patients with VL <50 Copies/mL over time.](image-url)
The 2Lady/ANRS/EDCTP Study: Results

• In multivariate analysis, VL ≤100,000 copies/mL at baseline was an independent predictor of viral suppression

• No difference among arms was observed in:
  • Median CD4 gain (+127 cells/μL)
  • Mortality
  • Severe adverse events

• No protease mutations were observed in patients failing second-line therapy

Conclusions:
• Despite multiple NRTI mutations, PI/b-based second-line regimens showed satisfactory results
• However, results for patients with high VL at switch to second-line are of special concern
• The WHO recommended regimen (LPV/r + 2NRTIs) remains a valid option
Safety issues with PIs and AZT

- AZT associated with gastrointestinal upset, anaemia, long term lipoatrophy, lactic acidosis
- LOTS of tablets twice daily

**LPV/r**
- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

**ATV/r**
- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

**DRV/r**
- Rash
- GI upset
- Hepatitis
Safety issues with Pis and AZT

AZT associated with gastrointestinal upsets, anaemia, long term lipoatrophy, lactic acidosis

Switching to second line is a big deal!
## WHO Guidelines – Dec 2015

<table>
<thead>
<tr>
<th>Options</th>
<th>First-Line</th>
<th>Second-Line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong>*</td>
<td>• TDF + 3TC (or FTC) + EFV</td>
<td>• 2 NRTIs + ATV/r or LPV/r</td>
</tr>
</tbody>
</table>
| **Alternative** | • AZT + 3TC + EFV  
• AZT + 3TC + NVP  
• TDF + 3TC (or FTC) + NVP | • 2 NRTIs + DRV/r  
• TDF + 3TC (or FTC) + DTG†  
• TDF + 3TC (or FTC) + EFV\(_{400}\)†  
• LPV/r + RAL |
## WHO technical update and 2018 guidelines

<table>
<thead>
<tr>
<th>Population</th>
<th>First-line regimens</th>
<th>Second-line regimens</th>
<th>Third-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (incl. women of childbearing potential and pregnant women)</td>
<td>Two NRTIs + DTG</td>
<td>Two NRTIs + (ATV/r or LPV/r)</td>
<td>DRV/r + DTG + 1–2 NRTIs (if possible, consider optimisation using genotyping)</td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + EFV</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + LPV/r</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + NNRTI</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
<tr>
<td>Children (0–10 years)</td>
<td>Two NRTIs + DTG</td>
<td>Two NRTIs + (ATV/r or LPV/r)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + LPV/r</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two NRTIs + NNRTI</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
</tbody>
</table>

- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR\(^1\)
  - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10% 

SA guidelines (state)

Third-line antiretroviral therapy programme in the South African public sector: cohort description and virological outcomes

Michelle Moorhouse MBCh (Wits), DA (SA), FRSPH, Gary Maartens, MBChB, MMed, Willem Daniel Francois Venter, MBCh, MMed, FCP (SA), DTM&H, Din HIV Man (SA)
Current recommendations re DRV dosing:
SAHCSA

• ATV/r 300/100 mg preferred PI/r for second-line ART
• “When the appropriate dose tablet becomes available, the [DRV/r] 800/100 mg daily dose will be a feasible option in second-line ART, with fewer side effects than the twice-daily dosing” – now available
• If on PI and VL LDL – switch to 800/100
• DRV/r 600/100 mg bd third-line - switch to 800/100 if no baseline VL
Using DRV/r 800/100 mg in third-line ART

- Currently patients on DRV in third-line receive DRV/r 600/100 mg bid
- A small proportion of third-line patients have no DRV RAMs, and in such patients it may be possible to use DRV/r 800/100 mg daily instead of DRV/r 600/100 mg bid to, reducing pill burden, dosing frequency and side effects
- Patients initiating third-line ART: if DRV score (Stanford) is zero on all genotypes, may initiate DRV 800/100 mg daily
- Switching patients already on third-line: the patient’s VL must be LDL, AND the DRV score (Stanford) MUST be zero on all genotypes the patient has had done
So why low dose DRV?

- Most drugs titrated against toxicity – THEN think about efficacy (VL) – and dose stopped once they harmonise
- Little impetus to lower dose further
- Lots of examples of dose reduction - AZT, d4T, EFV, ATV
- DRV registration studies mainly in treatment experienced patients
- Lots of excitement in 2012 – “red pill then blue pill” – TDF/3TC/EFV400 then DRV/DTG
Pill "A" to Pill "B" – two single tablet regimens?

- Pill "A": TDF/3TC/EFV400, $100
- Pill "B": DRV400/r/DTG, $250

- Two pills, used in sequence
- Simple treatment rule – task shifting
- No overlapping drug resistance
- Mass generic production
- Low cost: $100 and $250 per person-year
The approved dose DRV/r is 800/100 mg once daily for PI-naïve patients.

DRV/r is the most highly recommended PI in international treatment guidelines.

However, DRV/r is rarely used in sub-Saharan Africa, because of high treatment costs.

Results from several pilot studies and PK/PD analyses suggest that DRV/r 400/100 mg once daily shows equivalent efficacy to the standard dose.

Therefore the WHRI 052 study was designed to evaluate efficacy and safety of DRV/r 400/100 mg once daily as a switch option.
POWER trials: % HIV RNA > 1 log reduction at Week 24, by dose and baseline DRV resistance

<table>
<thead>
<tr>
<th>DRV/r dose group</th>
<th>DRV FC &lt; 4 (sensitive)</th>
<th>DRV FC &gt; 4 (resistant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD 400/100</td>
<td>80%</td>
<td>10%</td>
</tr>
<tr>
<td>OD 800/100</td>
<td>80%</td>
<td>10%</td>
</tr>
<tr>
<td>BID 400/100</td>
<td>80%</td>
<td>10%</td>
</tr>
<tr>
<td>BID 600/100</td>
<td>80%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Haubrich et al. AIDS 2007, 21: F11-F18

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]
Non-inferior efficacy for darunavir/ritonavir 400/100 mg once daily versus lopinavir/ritonavir, for patients with HIV RNA below 50 copies/mL in South Africa: The 48-week WRHI 052 study

Francois Venter\textsuperscript{1}, Michelle Moorhouse\textsuperscript{1}, Ellisha Maharaj\textsuperscript{1}, Godspower Akpomiemie\textsuperscript{1}, Bryony Simmons\textsuperscript{2}, Ambar Qavi\textsuperscript{2}, Celicia Serenata\textsuperscript{1}, Simiso Sokhela\textsuperscript{1}, Andrew Hill\textsuperscript{3}

\textsuperscript{1}University of Witwatersrand, WITS Reproductive Health and HIV Institute, Johannesburg, South Africa; \textsuperscript{2}Imperial College, Faculty of Medicine, London, United Kingdom; \textsuperscript{3}Liverpool University, Pharmacology, Liverpool, United Kingdom

\textsuperscript{22nd} International AIDS Conference, Amsterdam, the Netherlands, July 2018

Session B35: Regimen simplification and switch studies [TUAB0107LB]
WRHI 052 study: Trial design

Inclusion criteria:

- On a LPV/r-containing regimen for > 6 months with no history of other PI use
- HIV-1 RNA level < 50 copies/mL in the last 60 days

300 subjects

2NRTI + DRV/r 400/100 mg QD
n = 148

2NRTI + LPV/r
n = 152

48 Weeks

Open-label, 48 week study in Johannesburg, South Africa

Study visits at Baseline, Week 12, 24, 36 and 48

Resistance testing for samples with HIV RNA > 200 copies/mL on study

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]
Main efficacy endpoint: FDA SNAPSHOT: Switch equals failure analysis

If a patient shows a confirmed elevation in HIV RNA > 50 copies/mL at Week 48, this is a failure. Change in randomised treatment or missing data is also a failure.

Secondary endpoint: ITT: Switch included analysis

This analysis also includes the HIV RNA levels at Week 48, after changes in treatment. Missing data is failure.

New FDA non-inferiority margin for switch studies = -4%

The trial was originally powered for a -12% NI margin, but the -4% margin was added to the analysis plan after consultation with the trial DSMB.
**Study disposition**

- **300 Subjects**
  - **DRV/r + NRTIs**
    - n = 148
    - 4 subjects withdrawn
      - Adverse event: 2 (1%)
      - Withdrew consent: 1 (1%)
      - Protocol deviation*: 0 (0%)
      - Dead: 1 (1%)
  - **LPV/r + NRTIs**
    - n = 152
    - 3 subjects withdrawn
      - Adverse event: 1 (1%)
      - Withdrew consent: 1 (1%)
      - Protocol deviation: 1 (1%)
      - Dead: 0 (0%)

*Protocol deviation in LPV/r arm was due to non-compliance.*

97% completed Week 48 (n=144)
98% completed Week 48 (n=149)

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]
## Baseline characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>DRV/r + NRTIs (n=148)</th>
<th>LPV/r + NRTIs (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, years)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Male (%)</td>
<td>34%</td>
<td>30%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>66%</td>
<td>70%</td>
</tr>
<tr>
<td>Black (%)</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Weight (median, kg)</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL (%)</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Mean CD4+ cell count (cells/uL)</td>
<td>623</td>
<td>646</td>
</tr>
</tbody>
</table>
HIV RNA by study visit (observed data)

**DRV/r + NRTIs**
- N=148

**LPV/r + NRTIs**
- N=152

<table>
<thead>
<tr>
<th>Visit</th>
<th>&lt;50 copies/mL</th>
<th>50-199 copies/mL</th>
<th>200-999 copies/mL</th>
<th>1000+ copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 36</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]
HIV RNA < 50 copies/mL at Week 48
FDA Snapshot and ITT population

Switch=failure analysis (FDA Snapshot)
Difference = +1.9% (-3.7%, +6.5%)*

Switch included analysis (ITT)
Difference = +1.9% (-3.4%, +7.3%)*

* 95% confidence intervals from univariate analysis

22nd International AIDS Conference, Amsterdam, the Netherlands, July 2018 [TUAB0107LB]
Drug resistance

Genotypic resistance tests on samples with HIV RNA > 200 copies/mL at any visit to Week 48

<table>
<thead>
<tr>
<th>Resistance analysis</th>
<th>DRV/r +NRTIs (n=4)</th>
<th>LPV/r + NRTIs (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PI or NRTI mutations</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>1</td>
<td>4*</td>
</tr>
<tr>
<td>M184V</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>K219E</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K65R</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Y115E</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K70R</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*NRTI mutations may have been archived from prior virological failure on first-line treatment
**Summary of adverse events**

<table>
<thead>
<tr>
<th></th>
<th>DRV/r + NRTIs (n=148)</th>
<th>LPV/r + NRTIs (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event, n (%)</td>
<td>100 (68)</td>
<td>106 (70)</td>
</tr>
<tr>
<td>Most common AEs (≥ 4% in either arm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>31 (21)</td>
<td>34 (22)</td>
</tr>
<tr>
<td>Influenza</td>
<td>14 (9)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (2)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>8 (5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Backache</td>
<td>3 (2)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>7 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>30 (20)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>6 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Drug-related serious AEs**</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*1 Patient died from MI after week 12. ** DRV arm: all LFT elevations, 2 led to withdrawal
## Treatment emergent grade 3 or 4 laboratory abnormalities

<table>
<thead>
<tr>
<th></th>
<th>DRV/r Grade 3 or 4</th>
<th>LPV/r Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematology, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Clinical Chemistry, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AST</td>
<td>3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LDL</td>
<td>6 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
Conclusions

In this 300 patient study, DRV/r at the lower dose of 400/100 mg once daily showed non-inferior efficacy to LPV/r as a switch option for patients with HIV RNA < 50 copies/mL.

These results are consistent with pilot studies of low-dose DRV/r, which showed no difference in efficacy versus standard 800/100 mg once daily dosing for PI-naïve patients.

A lower dose of DRV/r would be better tolerated and cheaper to produce than the standard 800/100 mg dose, LPV/r or ATV/r.

This result needs to be confirmed in new studies where DRV/r 400/100 mg once daily is used in PI naïve patients – for example after failure of first-line treatment.
We would like to thank everyone who contributed to this study:

Participants and their families

Study coordinators and staff

Data Safety Monitoring Board

Country:
- South Africa: 197
- Zimbabwe: 87
- Malawi: 4
- Lesotho: 3
- Congo: 2
- Mozambique: 2
- Burundi: 1
- Nigeria: 1
- eSwatini: 1
- Uganda: 1
- Zambia: 1

n=300 Patients
Thank you…

- South African Medical Research Council and USAID for funding
- South African Department of Health
- OPTIMIZE Consortium, especially Andrew Hill and colleagues, Wits RHI staff and Clinton Health Access Initiative (CHAI)
- Scientific Advisory Committee
Now what?

- Article under review
- ?role of DTG