Southern African HIV Clinicians Society
3rd Biennial Conference
13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za
Impact of PIs on AIDS mortality

CDC.gov. Epidemiology of HIV infection.
Evolution of PIs

Many pills per day
Multiple doses necessary
High toxicity

SQV
RTV
IDV

Improved tolerability
Some boosted

SQV/r
IDV/r

ATV
ATV/r
DRV/r

1 pill per day (+ RTV and NRTIs)
Boosting gold standard
Manageable toxicity

Once-daily dosing
Coformulation
Some treatment-limiting toxicity

FPV/r
LPV/r

PAST

PRESENT

FUTURE
(FDA) Licensed PIs

Tipranavir

Darunavir

Amprenavir

Lopinavir

Atazanavir

Saquinavir

Indinavir

Ritonavir

Nelfinavir
Can we talk about safety and ignore efficacy?

Some day drugs will be perfect
If we try
Some day drugs will be perfect
And no one will ever die

Some day risk will be zero
My, oh my
Some day pills will be magic
And they'll taste of apple pie
PIs work

- CASTLE
  - ATV/r vs LPV/r
- ACTG 5202
  - ATV/r vs EFV
- GS-103
  - ATV/r vs E/C/T/F
- ARTEMIS
  - DRV/r vs LPV/r
Then came ACTG 5257

Comparing preferred and alternative first-line regimens

<table>
<thead>
<tr>
<th>GUIDELINES</th>
<th>NRTI BACKBONE</th>
<th>NNRTI</th>
<th>INSTI</th>
<th>PI</th>
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<tbody>
<tr>
<td></td>
<td>TDF/XTC</td>
<td>ABC/3TC</td>
<td>AZT/3TC</td>
<td>EFV</td>
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<tr>
<td>IAS (2014)</td>
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<td>DHHS (2015)</td>
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<td>WHO (2015)</td>
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<td>SAHIVCS</td>
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</tbody>
</table>

- **preferred**
- **alternative**
- **not recommended/ special situations**
Safety issues with PIs

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

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

DRV/r
- Rash
- GI upset
- Hepatitis
PIs require boosting

- PIs usually boosted with RTV
- RTV inhibits CYP3A4 in the liver, increasing PI exposure and t1/2\(^1\)
- Less frequent dosing and lower daily dose
- RTV associated with diarrhoea and nausea, increased lipids, drug interactions\(^2\)

Drug interactions

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
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<td>Carbamazepine</td>
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<td>Phenobarbital (Phenobarbitone)</td>
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<td>Valproate (Divalproex)</td>
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</tbody>
</table>
Drug interactions with RTV

**Exposures Increase With RTV**
- Maraviroc
- Antiarrhythmics
- Anticancer agents
- Anticonvulsants (some)
- Antidepressants (some)
- Beta-blockers
- Calcium channel blockers
- Colchicine
- Digoxin
- Erectile dysfunction drugs
- Glucocorticoids
- Methamphetamine
- Rifabutin
- Sedatives/hypnotics
- Statins (some)

**Exposures Decrease With RTV**
- Anticonvulsants (some)
- Antidepressants (some)
- Bupropion
- Ethinyl oestradiol
- Methadone
- Theophylline
- Rifampicin
Interactions with TB medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>LPV/r</th>
<th>ATV/r</th>
<th>DRV/r</th>
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### What about pregnancy?

<table>
<thead>
<tr>
<th>Guideline Categorization</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>INSTI</th>
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<tr>
<td>Preferred</td>
<td>ABC/3TC*&lt;br&gt; TDF/FTC or 3TC†&lt;br&gt; ZDV/3TC‡</td>
<td>EFV§</td>
<td>LPV/RTV¶&lt;br&gt; ATV/RTV</td>
<td></td>
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<tr>
<td>Alternative</td>
<td>NVP‖</td>
<td>DRV/RTV&lt;br&gt; SQV/RTV**</td>
<td>RAL+++</td>
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<tr>
<td>Insufficient data</td>
<td>RPV</td>
<td>FPV/RTV</td>
<td>DTG&lt;br&gt; EVG/COBI</td>
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<tr>
<td>Not recommended††</td>
<td>ABC/3TC/ZDV&lt;br&gt; d4T&lt;br&gt; ddl</td>
<td>ETR</td>
<td>IDV/RTV&lt;br&gt; NFV&lt;br&gt; RTV&lt;br&gt; TPV</td>
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</table>

What about pregnancy?

<table>
<thead>
<tr>
<th>Guideline Categorization</th>
<th>NRTI</th>
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<tr>
<td>Preferred</td>
<td>ABC/3TC*</td>
<td>EFV§</td>
<td>LPV/RTV[</td>
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<tr>
<td></td>
<td>TDF/FTC or 3TC†</td>
<td></td>
<td>ATV/RTV]</td>
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<tr>
<td></td>
<td>ZDV/3TC‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td>NVP[</td>
<td>DRV/RTV]</td>
<td>RAL[††</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SQV/RTV**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient data</td>
<td>ABC/3TC/ZDV d4Tddl</td>
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</table>

Not recommended\[‡‡

<table>
<thead>
<tr>
<th>Drug</th>
<th>Defects/Live Births, n (&gt; 200 First Trimester Exposures)</th>
<th>Prevalence, % (95% CI)</th>
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<tbody>
<tr>
<td>PIs</td>
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<tr>
<td>ATV</td>
<td>19/878</td>
<td>2.2 (1.3-3.4)</td>
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<tr>
<td>DRV</td>
<td>5/212</td>
<td>2.4 (0.8-5.4)</td>
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<tr>
<td>LPV</td>
<td>26/1125</td>
<td>2.3 (1.5-3.4)</td>
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<td>NFV</td>
<td>47/1211</td>
<td>3.9 (2.9-5.1)</td>
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<tr>
<td>RTV</td>
<td>52/2260</td>
<td>2.3 (1.7-3.0)</td>
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DHHS Perinatal Guidelines. March 2014

HOW DO WE MAKE PROTEASE INHIBITORS SAFER?
New molecules

• Optimise chemical structure to avoid side effects
  – Eg ATV does not cause dylipidaemia to same extent as other PIs

• Modify available HIV protease inhibitors
  – Structural similarity
  – Eg DRV (APV); LPV (RTV)
New molecules

- Optimise chemical structure to avoid side effects
  - Eg ATV does not cause dyslipidaemia to same extent as other PIs
- Modify available HIV protease inhibitors
  - Structural similarity
    - Eg DRV (APV); LPV (RTV)
Prodrugs of current PIs

FosAPV is phosphate ester prodrug of APV

• FosAPV metabolised to APV
• Increases duration of action
• Improved the safety profile (KLEAN)
New formulations of existing PIs
### New PK boosters

<table>
<thead>
<tr>
<th></th>
<th>Cobicistat</th>
<th>Ritonavir</th>
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<tbody>
<tr>
<td>HIV replication</td>
<td>No activity</td>
<td>PI activity</td>
</tr>
<tr>
<td>CYP 3A4</td>
<td>Potent inhibitor</td>
<td>Potent inhibitor</td>
</tr>
<tr>
<td>Other CYPs</td>
<td>CYP 2D6, minimal effect</td>
<td>CYP 2D6, CYP 2B6</td>
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<tr>
<td></td>
<td>CYP 2B6</td>
<td></td>
</tr>
<tr>
<td>P-gp</td>
<td>Minimal</td>
<td>Weak to moderate</td>
</tr>
<tr>
<td>Glucuronidation</td>
<td>Low</td>
<td>Inducer</td>
</tr>
<tr>
<td><strong>Effect on lipids</strong></td>
<td><strong>Minimal</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>Renal transporters</td>
<td><strong>Creatinine</strong> effect</td>
<td></td>
</tr>
</tbody>
</table>
Cobicistat versus ritonavir

**ATV**
- ATVc (300/150) and ATVr (300/100) were bioequivalent
- RCT (N=692) powered for non-inferiority showed comparable efficacy through 48w

  Significant (but modest) differences in effect on eGFR by w8 (P<0.001)
  No differences in other renal adverse events, hyperbilirubinaemia, nausea

  Deeks Drugs 2014 74:195–206
  Gallant J Infect Dis. 2013

**DRV**
- DRV AUC and Cmax were bioequivalent
- DRV Cmin 25-30% lower (DRV/c 800/150 OD vs DRV/r 800/100 OD) - not considered clinically relevant.
- A non-inferiority trial has not been conducted.

Kakuda, J Clin Pharm 2014
Drug interactions with cobicistat

**Exposure Increased With COBI**
- Antacids
- Antiarrhythmics
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Erectile dysfunction drugs
- Inhaled/injectable corticosteroids
- OCPs (norgestimate)
- Statins

**Increase COBI Exposure**
- Azole antifungals
- Clarithromycin

**Decrease COBI Exposure**
- Rifabutin
- Carbamazepine
- Phenytoin
Use existing PIs in different ways: Lower doses

Atazanavir/ritonavir 200/100 mg is non-inferior to atazanavir/ritonavir 300/100 mg in virologic suppressed HIV-infected Thai adults: a multicentre, randomized, open-label trial: LASA

Conclusions: Higher dose ATV was associated with higher rates of treatment discontinuation.
Lower doses

100 HIV+ adults
On 2 NRTIs + DRV 800mg qd > 4 weeks
HIV-1 RNA < 50 c/mL > 3 months
No history of prior virologic failure to PI-based ART

Randomisation
1 : 1
Open-label

N = 50
DRV/r 800/100 mg QD + 2 NRTIs

N = 50
DRV/r 600/100 mg QD + 2 NRTIs

Reduced Darunavir Dose Is as Effective in Maintaining HIV Suppression as the Standard Dose in Virologically Suppressed HIV-Infected Patients. The DRV600 Study.

Lower doses

100 HIV+ adults
On 2 NRTIs + DRV 800mg qd > 4 weeks
HIV-1 RNA < 50 c/mL > 3 months
No history of prior virologic failure to PI-based ART

Randomisation 1 : 1 Open-label

N = 50

DRV/r 800/100 mg QD + 2 NRTIs

N = 50

DRV/r 600/100 mg QD + 2 NRTIs

Drug-related AEs

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<thead>
<tr>
<th></th>
<th>DRV 800 n=12</th>
<th>DRV 600 n=7</th>
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<td>Gastrointestinal disturbances</td>
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<td>4</td>
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<tr>
<td>Dislipidemia</td>
<td>5</td>
<td>-</td>
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<tr>
<td>Other &lt;5%</td>
<td>1</td>
<td>3</td>
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Different combinations
Nuc-sparing or “nuc-lite” regimens

<table>
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<tr>
<th>Regimen</th>
<th>Results</th>
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<tbody>
<tr>
<td>DRV/r + <strong>RAL</strong> (ACTG 5262)<strong>[1]</strong></td>
<td>Poor performance at high VL</td>
</tr>
<tr>
<td>DRV/r + <strong>RAL</strong> (NEAT)<strong>[2]</strong></td>
<td>Less effective at high VL, low CD4</td>
</tr>
<tr>
<td>DRV/r + <strong>MVC</strong> (MODERN)<strong>[3]</strong></td>
<td>Less effective than standard ART</td>
</tr>
<tr>
<td>ATV/r + <strong>RAL</strong> (HARNESS – switch)<strong>[4]</strong></td>
<td>Less effective than standard ART</td>
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<tr>
<td>LPV/r + <strong>RAL</strong> (PROGRESS)<strong>[5]</strong></td>
<td>Small study; few pts with high VL</td>
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<tr>
<td>LPV/r + <strong>EFV</strong> (ACTG 5142)<strong>[6]</strong></td>
<td>Poorly tolerated but effective</td>
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<tr>
<td>LPV/r + <strong>3TC</strong> (GARDEL)<strong>[7]</strong></td>
<td>As effective as standard ART</td>
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<tr>
<td>LPV/r + <strong>XTC</strong> (OLE – switch)<strong>[8]</strong></td>
<td>As effective as standard ART</td>
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<tr>
<td>ATV/r + <strong>3TC</strong> (SALT – switch)<strong>[9]</strong></td>
<td>As effective as standard ART</td>
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</table>

GARDEL: Dual ART vs Triple ART

- Randomised, open-label phase III noninferiority trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL (ITT-e, FDA snapshot analysis)
- Pts with virologic response at Week 48 offered extension to Week 96

**Stratified by HIV-1 RNA (≤ vs > 100,000 c/mL)**

**Wk 48 primary analysis**
- Lopinavir/Ritonavir 400/100 mg BID + Lamivudine 150 mg BID
  - (n = 217)

**Wk 96 extension analysis**
- Lopinavir/Ritonavir 400/100 mg BID + Investigator-Selected NRTIs in FDC*
  - (n = 209)

**Wk 24 interim analysis**
- ART-naive pts with HIV-1 RNA > 1000 copies/mL; no NRTI/PI resistance; HBsAg negative
  - (N = 426)

*ZDV/3TC: 54%; TDF/FTC: 37%; ABC/3TC: 9%

GARDEL: Dual ART Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms

Virologic Success
- Wk 48 difference: +4.6%
  (95% CI: -2.2 to 11.8; \( P = .171 \))
- Wk 96 difference: +5.9%
  (95% CI: -2.3 to 14.1; \( P = .165 \))

Virologic Nonresponse

D/C due to AE or Death

D/C for Other Reasons

GARDEL: Dual ART Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms

Virologic Success
- Wk 48 difference: +4.6% (95% CI: -2.2 to 11.8; P = .171)
- Wk 96 difference: +5.9% (95% CI: -2.3 to 14.1; P = .165)

Virologic Nonresponse

D/C due to AE or Death

D/C for Other Reasons

Is 2 years long enough?

Evolution of PIs

Many pills per day
Multiple doses necessary
High toxicity

SQV
RTV
IDV

Improved tolerability
Some boosted

SQV/r
IDV/r

ATV
ATV/r
DRV/r

1 pill per day (+ RTV and NRTIs)
Boosting gold standard
Manageable toxicity

More coformulations
Single-tablet regimens

ATV/COBI
DRV/COBI
DRV/COBI/TAF/FTC

Once-daily dosing
Coformulation
Some treatment-limiting toxicity

FPV/r
LPV/r

PAST

PRESENT

(Not-too-distant)
FUTURE

In summary

• Not much new in PIs
• Look at using what we have better
  – Dosing
  – Combinations
  – Sequencing
Acknowledgements

• Francois Venter
• Saye Khoo
• Polly Clayden
• CCO
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