Where does rilpivirine fit in?

Francois Venter

March 2018

Thanks Michelle Moorhouse
90% of all living with HIV will know their HIV status

90% of all living with HIV will receive sustained antiretroviral therapy

90% of all receiving antiretroviral therapy will have durable viral suppression
SA Snapshot

- 4.2 million 1\textsuperscript{st} line end 2017 ($110/year)
- 170,000 2\textsuperscript{nd} line ($350/year)
- 1300 3\textsuperscript{rd} line (roughly $1500/year, depends on regimen ($2000 if DRV/DTG/ETR))

- **Bill 2014/2015: $350 million**
- Sept 2016: Test and treat – theoretically doubling numbers
- SA drives the global market [SA=PEPFAR=Global Fund by ART volume]
How has ART changed?
The Evolving HIV Treatment Paradigm

- 3TC=lamivudine; ZDV=zidovudine

1983 HIV-1 discovered

1987 ZDV monotherapy

1995 ZDV/3TC

1996 Triple-Drug Therapy

2006 Single-Tablet Regimens

2012–2013 The Integrase Era

2017 Long Acting Injectable?

2020

WITS RHI

AbbVie Group Consultancy, Johannesburg, South Africa | September 17, 2016 | Company Confidential © 2016
Current ART in SA

- **Tenofovir**
- **XTC**
- **Efavirenz**
- **AZT** (zidovudine)
- **3TC**
- **Protease/r** (LPV or ATV)

**Failure**

**XTC, other nukes**

- **Darunavir**
- **Dolutegravir**
- **Etravirine**
First-line...

TDF + XTC + EFV

Desirable Property | EFV/TDF/FTC
--- | ---
High resistance barrier | No
Well tolerated | Not initially
No lab tox monitoring | TDF creat
Safe in pregnancy | Yes
Low pill burden | Yes FDC
Once a day | Yes
Use with TB (rif) | Yes

Toxicity driver
Pill size
Low genetic barrier
Cost
Efavirenz’s side effects...

- **Neuropsychiatric**
  - Suicide
  - Late encephalopathy

- **Metabolic**
  - Bone mineral density

- **DILI**

- **Suicide**

- **Late encephalopathy**
  - JAIDS 2017

- **DILI**
  - Sonderup AIDS 2016

- **Metabolic**
  - Dave PLoS ONE 10(12): e0144286.

- **Neuropsychiatric**
  - Ann Intern Med. 2005;143:714
  - PLoSMed 2004;1:e19
  - JAIDS 2012;60:33
  - Lancet Infect Dis 2012;12:111
  - Clin Infect Dis 2006;42:273
  - Lancet 2009; 374: 796
  - AIDS 2014;28(10):145
  - JAIDS 2011;57:2841
  - Karamchand Medicine 2016

- **DILI**
  - JAIDS 2011;57:2841
  - Lancet 2009; 374: 796

- **Metabolic**
  - Ann Intern Med. 2005;143:714
What are the “third drug” options?
Alternatives...

• Protease inhibitors – toxic, expensive, not discussed
• Integrase inhibitors
• Rilprivine
What about: Dolutegravir

- Wunderkind of the moment
- 50 mg once-daily (in naïve patients)
- Very good efficacy
- Minimal toxicity
- Pregnancy category B
- Superior to EFV at 48 weeks in naïve patients—SINGLE study (compared ABC/3TC/DTG with TDF/FTC/EFV.) – but safer, not virologically better
- Potential to be low cost and co-formulated
- Some concerns about resistance claims, creat clearance
- CHOICE of DoH!
In US and EU, DTG-based regimens have become the top prescribed ARVs, affirming DTG’s clinically superior profile.

**Source:** GILD and GSK earnings. Note: Graph depicts single tablet regimen plus core agent market.

- In Feb **2013**, the **US** Health and Human Services Guidelines on ARVs recommends **INSTI-based regimens as the preferred** for ART-naïve patients.
  - EFV no longer included in DHHS guidelines

- As of 2Q16, DTG treatment volume of >21,000 patients weekly, with nearly **1 in 5 patients on a DTG regimen in the US**

- DTG now leads US/EU markets:
  - US: #1 core agent in treatment share and volume
  - EU: #2 prescribed regimen in treatment-naïve patients

The US and EU has long moved on from EFV-based treatment

**Source:** GILD and GSK earnings.
**Note:** Graph depicts single tablet regimen plus core agent market.
Significant technical/programmatic work is required for full transition to TLD in 2018

- Revision processes for programmatic guidelines, STG and EML inclusion
- Tender extension to align with expected MCC registration timelines
- SA HIV Clinicians Society, clinicians, community groups etc. to communicate transition plans
- Updates to RSA Supplier Performance Database and Visual Analytics Network (VAN) to create modules for collection and analysis of demander data; providing visibility into consumption and stock availability

**From Dec 2016:**
Supplier communication on phase-in plans to accelerate product registrations

Develop tender forecast and documentation – tender date TBC

Supply security analysis ongoing; Monitoring MCC registration; Communication of transition to provinces and validation of forecast at province level will be required

Rollout plan to be developed
Elvitegravir

- Integrase inhibitor
- Requires boosting
  - ritonavir
  - cobicistat
- Co-formulated with a booster, TDF and FTC
- Renal monitoring, drug interactions

- QUAD-Stribild
Raltegravir

• Integrase inhibitor, very well tolerated, price dropping
• Very heavily studied
• TB friendly
• Expensive, no co-formulations, low resistance barrier
What about: Rilpivirine
NNRTI history and rilpivirine

• Rilpivirine licenced by FDA in 2011 (including as a single (Edurant), fixed dose combination (Complera, with TDF/FTC)
• TAF/FTC/rilpivirine (Odefsey) licenced in 2016
• Injectables being explored
• Dolutegravir/rilpivirine (Juluca) Nov 2017 – for switch
• Only the single in SA at the moment
What are the considerations?

• Once/day
• Higher resistance barrier than first generation NNRTIs
• Indicated > age 12, >35kg
• Pregnancy category B (although few exposures in pregnancy registry)
• Very cheap
ART discontinuation for AE

Better than efavirenz re side effects (ECHO and THRIVE)

<table>
<thead>
<tr>
<th>TABLE 3. Summary of Treatment-Emergent AEs and Laboratory Abnormalities at the Time of the Week-48 Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Median (range) treatment duration (wks)</td>
</tr>
<tr>
<td>AE, n (%)</td>
</tr>
<tr>
<td>Any AE</td>
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<tr>
<td>Any treatment-related AE ≥ grade 2</td>
</tr>
<tr>
<td>AE leading to permanent discontinuation</td>
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<tr>
<td>Any serious AE (including death)</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Most common treatment-related AEs ≥ grade 2 and occurring in ≥2% of patients in either group†</td>
</tr>
<tr>
<td>Rash‡</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Abnormal dreams/nightmares</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Most common treatment-related AEs of interest (all grades) occurring in ≥10% of patients in either group‡,§</td>
</tr>
<tr>
<td>Any neurologic AE</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Any psychiatric AE¶</td>
</tr>
<tr>
<td>Abnormal dreams/nightmares</td>
</tr>
<tr>
<td>Rash‡</td>
</tr>
<tr>
<td>Treatment-emergent grade 2-4 laboratory abnormalities occurring in ≥5% of patients in either group, n (%)</td>
</tr>
<tr>
<td>Any grade 2-4 laboratory abnormality</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
</tr>
<tr>
<td>Increased pancreatic amylase</td>
</tr>
<tr>
<td>Hyperglycemia (fasted)</td>
</tr>
<tr>
<td>Grade 2-3 increased LDL-cholesterol (fasted)††</td>
</tr>
<tr>
<td>Grade 2-3 increased total cholesterol (fasted)</td>
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<tr>
<td>Increased aspartate amino transferase</td>
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<tr>
<td>Increased alanine amino transferase</td>
</tr>
</tbody>
</table>
Depression

- **Efavirenz** (6%) - 2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)

Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study

#O315 Wednesday 5 November
C. Smith; L. Ryom; A. d’Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

Dolutegravir: discontinuation due to AE

Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE

Factors associated with DTG discontinuation

<table>
<thead>
<tr>
<th></th>
<th>RH</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.81</td>
<td>1.46–5.41</td>
<td>0.002</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.88</td>
<td>1.56–5.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.63</td>
<td>1.61–4.29</td>
<td>0.0001</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>8.93</td>
<td>3.76–21.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neuropsychiatric AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.64</td>
<td>1.23–5.65</td>
<td>0.01</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.86</td>
<td>1.42–5.77</td>
<td>0.003</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.42</td>
<td>1.38–4.24</td>
<td>0.002</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>11.36</td>
<td>4.31–29.41</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Log rank test, P < 0.0001

Hoffman et al. HIV Medicine (2017), 18, 56-63
Libre et al.CROI 2017 abstract# 651
Hsu et al CROI 2017 abstract #664
Why isn’t it used everywhere???

- Can’t use with rifampicin OR rifabutin
- Food restriction – need to take with a meal
- Lack of available co-formulation
- Appears to fail more often if VL>100 000 copies (vs. efavirenz) – 2-3x risk virological failure and resistance emerging
  - Does NOT apply if using as switch, if started >100 000 on original regimen
  - May be an issue with other NNRTIs too
  - Note: still works in majority (83%) of patients if VL>100 000
Other issues to consider

• Little data on ABC/3TC with rilpivirine
• CI if PPI; absorption generally an issue
• Is it an alternative to people who can’t tolerate efavirenz or dolutegravir? Excellent in SALIF
• Several studies suggesting good durability
• First line choice in a healthy person with low VL initiating ART? No study vs. dolutegravir yet (in fact, used in combination! Network analysis suggests dolutegravir superior)
• And an option for PEP (but ?benefit over FDC?)
A 48-week randomized, open-label study of RPV/TDF/FTC STR as an appropriate “switch” option for virologically suppressed HIV-1 infected patients in low- and middle income countries on stable NNRTI-based therapies.

**Key entry criteria:**
- On first-line ART with **EFV** or **NVP** for ≥1 year*
  - Plasma HIV-1 RNA <50 copies/mL
  - CD4 > 200 cells/mm$^3$
- No history of virologic or immunologic failure during ART
- No known primary N[t]RTI or NNRTI mutations

- Randomization stratified by NNRTI at screening (EFV or NVP)
- **Key exclusion** criteria:
  - TB requiring rifampicin based treatment or CrCl <50 mL/min

Randomization 1:1

**RPV/TDF/FTC STR**
(n=213)

**EFV/TDF/FTC STR**
(n=213)

48 weeks

*Switch from NVP to EFV allowed but not vice versa*
RPV/TDF/FTC as a switch option is non-inferior to EFV/TDF/FTC regardless of suppression cut-off of <400 or <50 copies/mL

1 confirmed virologic failure ≥400 copies/mL in each study arm (0.5%)

No ARV resistance observed - preserved future ARV options
# SALIF – Safety

**Number of Subjects with**

<table>
<thead>
<tr>
<th></th>
<th>RPV/TDF/FTC (n=213)</th>
<th>EFV/TDF/FTC (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>16 (7.5%)</td>
<td>11 (5.2%)</td>
</tr>
<tr>
<td>At least possibly related</td>
<td>3 (1.4%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Fatal SAE (MI, unrelated)*</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>AE, grade 3 or 4</td>
<td>40 (18.8%)</td>
<td>56 (26.5%)</td>
</tr>
<tr>
<td>At least possibly related</td>
<td>13 (6.1%)</td>
<td>4 (1.9%)</td>
</tr>
</tbody>
</table>

**AE of interest (all cause)**

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<th>EFV/TDF/FTC (n=211)</th>
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</thead>
<tbody>
<tr>
<td>Rash</td>
<td>32 (15.0%)</td>
<td>23 (10.9%)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>60 (28.2%)</td>
<td>63 (29.9%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>38 (17.8%)</td>
<td>29 (13.7%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (3.3%)</td>
<td>14 (6.6%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (4.7%)</td>
<td>6 (2.8%)</td>
</tr>
<tr>
<td>Nightmare/abnormal dreams</td>
<td>4 (1.9%)</td>
<td>10 (4.7%)</td>
</tr>
<tr>
<td>Potential QT prolongation</td>
<td>3 (1.4%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>AE leading to permanent stop study medication</td>
<td>8 (3.8%)†</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>
Finally, as an injectable....

- In combination with cabotegravir, 4-8 weekly
- Exciting for “difficult adherence groups” – long road ahead for registration, likely to be expensive, but exciting
- ? Role in PrEP!
Finally...

• Where does rilpivirine fall in an INSTI-dominated era?

• Tussle now re two and three drug regimens (DTG/3TC vs DTG/rilpivirine vs. TAF/FTC/BIC vs. ABC/3TC/DTG) in high income countries

• And between NRTI and non-NRTI regimens