First line ART
Rilpirivine
A New NNRTI

Chris Jack
Physician, Durdoc Centre
eThekwini
Overview: Rilpirivine an option for ARV Naïve patients

- History
- Current guidelines
- Efficacy and Safety
- Tolerability / side effects
- Co-morbidities / pregnancy
- Cost
- Conclusions
Background...

• When viral RNA enters the CD4 cell it is transcribed into DNA by the reverse transcriptase enzyme – a process inhibited by NNRTI

• Rilpivirine is a 2\textsuperscript{nd} generation non-nucleoside reverse transcriptase inhibitor with a unique structure that allows for greater flexibility when binding to RT enzyme and this is thought to preserve its potency in the presence of mutations that affect 1\textsuperscript{st} generation agents

• Developed by Tibotec, subsidiary of Janssen

• No generics available in SA
Rilpivirine

- Approval:
  - FDA - May, 2011
  - MCC – Aug, 2014
- Indication: in combination with other ARVs for treatment-naïve adults
- FDA Approved Dose/Formulation: 25 mg tablet (with a meal)
- No generic available
Rilpivirine

- Co-Formulation
  - Tenofovir-Emtricitabine-Rilpivirine (Complera)
  - TAF-Emtricitabine-Rilpivirine (Odefsey)
  - DTG-Rilpivirine (Juluca)
  - Not available in South Africa

- Metabolism: primarily in liver via cytochrome P450 (CYP 3A4) enzymes
Evidence-based Medicine

• Modern medicine influenced by 2 paradigms: ‘evidence-based medicine (EBM)’ and ‘patient-centered medicine (PCM)’

• Both affect clinical decision making

• EBM (1990s) - offers clinicians best available evidence about most adequate treatment

• PCM - focus on patient participation in clinical decisions and tuning medical care to patients’ needs and preferences
Key Principles

• There are many ART guidelines all encompassing the same basic evidence-based principles but each written to address issues relevant to the specific region.

• Locally these are
  • Variations between middle income and low-income countries - affordability
  • Only available treatment and diagnostic options
  • Synergy in treatment recommendations between public and private sector programmes
  • Acknowledging the differences of healthcare services in South Africa hence the need for a wider range of therapeutic/diagnostic options
Key Principles

- The choice of first-line therapy is determined by various considerations including:
  - Severity of infection
  - Drug tolerability
  - Presence of drug-resistant mutations in non-treated populations
  - Co-morbidities
  - Pregnancy
  - Availability of drugs
  - Cost

- The many studies evaluating ARV regimens reflect the difficulties in finding the optimal treatment option which would provide optimal efficacy, durability, tolerability and convenient dosing schedules.

- Among the initial regimens, the most preferred is a backbone combination of two NRTIs—TDF / FTC (or 3TC) + an active drug from one of the following classes: NNRTI, PI, or InSTI.
### Initial antiretroviral therapy regimens for the previously untreated patient: HAART

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<thead>
<tr>
<th>Options</th>
<th>Preferred</th>
<th>Alternative</th>
<th>One of</th>
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<tbody>
<tr>
<td>NRTI Backbone</td>
<td>TDF + FTC/3TC</td>
<td>ABC + 3TC</td>
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<td>AZT + 3TC</td>
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<td>d4T + 3TC</td>
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<td>EFV, RPV, DTG</td>
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Features of a New Drug

• Effective
• Safe
• Well tolerated
• Little to no drug interactions
• Well priced
Rilpirivine as first-line therapy
Pharmacokinetics

3 Trials in HIV infected and non-infected volunteers

- Rapid absorption with long half-life (34 – 55 hours) supporting once daily dosing
- Taken with a meal (acidic environment)
- No dose adjustments for mild renal / hepatic impairment
Drug Interactions

• Extensively metabolised primarily in liver via cytochrome P450 (CYP 3A4) enzymes

• Not clinically significant
  • PI, TDF

• Clinically significant
  • Rifampicin, Rifabutin
  • PPI, H2 Antagonists, Antacids
Clinical Trials

ARV Naïve

- Phase 2b Trial
  - C204 Dose Ranging Study: Rilpivirine versus Efavirenz

- Phase 3 Trials
  - ECHO (TMC278-C209): Rilpivirine versus Efavirenz
  - THRIVE (TMC278-C215): Rilpivirine versus Efavirenz

ARV Experienced

- Limited

- Switching At Low HIV-1 RNA Into Fixed Dose Combinations (SALIF) 48 weeks results
Rilpivirine vs. Efavirenz

TMC-278-C204 Dose-Ranging Study
Rilpivirine vs. Efavirenz in ARV-Naive Patients

- 368 patients
- Randomized and treated with once-daily TMC278
  - 25mg
  - 75mg
  - 150 mg
  - open-label, active control, efavirenz 600 mg once daily,
- With 2 NRTI
  - All TMC278 doses demonstrated potent and sustained efficacy comparable with efavirenz
  - TMC278 was well tolerated with lower incidences of neurological and psychiatric adverse events, rash and lower lipid elevations than those with efavirenz.
  - TMC278 25 mg once daily was selected for further clinical development
Rilpivirine vs. Efavirenz

ECHO and THRIVE Studies
ECHO

• Phase 3, randomised, double-blind study
• Treatment naïve patients > 18 with HIV-1
• Viral load ≥5000 copies per mL fully sensitive
• Patients were randomly assigned to
  • Once daily 25 mg rilpivirine
  • Once daily 600 mg efavirenz
• With tenofovir-disoproxil-fumarate and emtricitabine
“Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.”
THRIVE

- Phase 3, randomised, double-blind study
- Treatment naïve patients > 18 with HIV-1
- Viral load ≥5000 copies per mL fully sensitive
- Patients were randomly assigned to
  - Once daily 25 mg rilpivirine
  - Once daily 600 mg efavirenz
  - With
    - TDF + FTC
    - AZT + FTC
    - ABC + 3TC
THRIVE: Conclusions

• “Despite a slightly increased incidence of virological failures, a favourable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients infected with HIV-1.”
ARV Experienced Patients

- Limited data available
- Phase II open-labelled trial randomized 36 patients failing a PI-based regimen to 1 of 3 daily Rilpivirine doses (25, 50, or 150mg)
- 7 day trial
- Some reduction in VL – similar for a doses
- No conclusive comments
**SALIF:** Switching At Low HIV-1 RNA Into Fixed Dose Combinations

**Criteria**

- On first-line ART with **EFV** or **NVP** for ≥1 year*
- Plasma HIV-1 RNA <50 copies/mL
- CD4 >200 cells/mm³
- No history of virologic or immunologic failure during ART
- No known primary N[t]RTI or NNRTI mutations
SALIF: Summary and Conclusions

Non-inferior

- Virologic Failure rates were very low (0.5% per arm)
- No ARV resistance observed
- Comparable tolerability
- Consistent safety

Adherence was very high, with 412/426 (97%) subjects having >95% adherence overall in the treatment period

RPV/TDF/FTC could be an alternative treatment option in low- and middle-income countries in virologically suppressed first-line patients on EFV- or NVP-based therapies
Tolerability / Side Effects

CNS

- Headache
- Dizziness
- Insomnia, depressive / psychiatric disorders, vivid dreams

Rash, skin disorders

General

Pregnancy: category B
Price

- Efavirenz
  - 600mg ± R120.00 – R200.00
  - 200mg ± R90.00
  - 50mg ± R30.00

- Rilpirivine
  - R60.00

- Dolutegravir
  - ± R830.00
What does all this mean for us?
A pride of surgeons
A culture of microbiologists
A synapse of neurologists
A howl of paediatricians
A consolidation of respiratory care physicians
A rash of dermatologists
A stream of urologists
Benefits

• Effective
• Safe
• Well tolerated
• Good resistance profile
• Cost
Pitfalls

- Food
- High VL $>100\,000$
- Absence of FDC
- TB

Every second someone becomes infected with TB.
That’s more than 31 million people each year.
Personal Reflections

- Changing HIV landscape
- Evolving clients
- Managed health care
- Public v Private health systems
- Treatment goals
Acknowledgements

1. Posniak et al AIDS 2010
2. Jean-Michel Molina et al Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO)
3. Calvin J Cohen et al Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE)
4. Shafer et al Antiviral Therapy 2012; 17 1495-1502
5. SAHIV Clin Soc Guidelines 2017
7. Paula Munderi et al AIDS 2016, Durban