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 2nd 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 1st 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

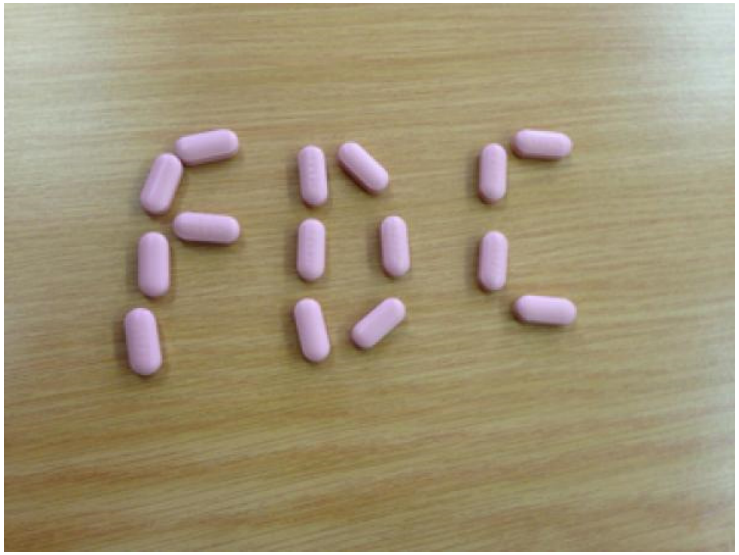
Initial antiretroviral therapy regimens for the previously untreated patient: HAART

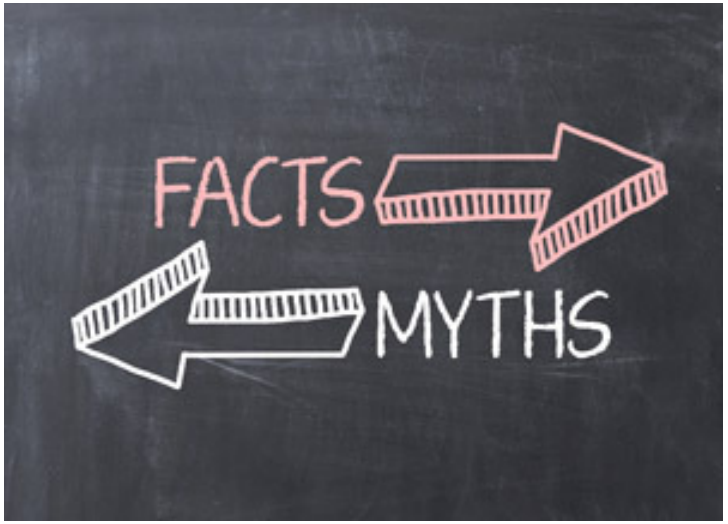
Options	Preferred	Alternative	One of
NRTI Backbone	TDF + FTC/3TC	ABC + 3TC	
		AZT + 3TC	
		d4T + 3TC	
3rd Drug			
			EFV
			RPV
			DTG

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

ECHO: Conclusions

“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

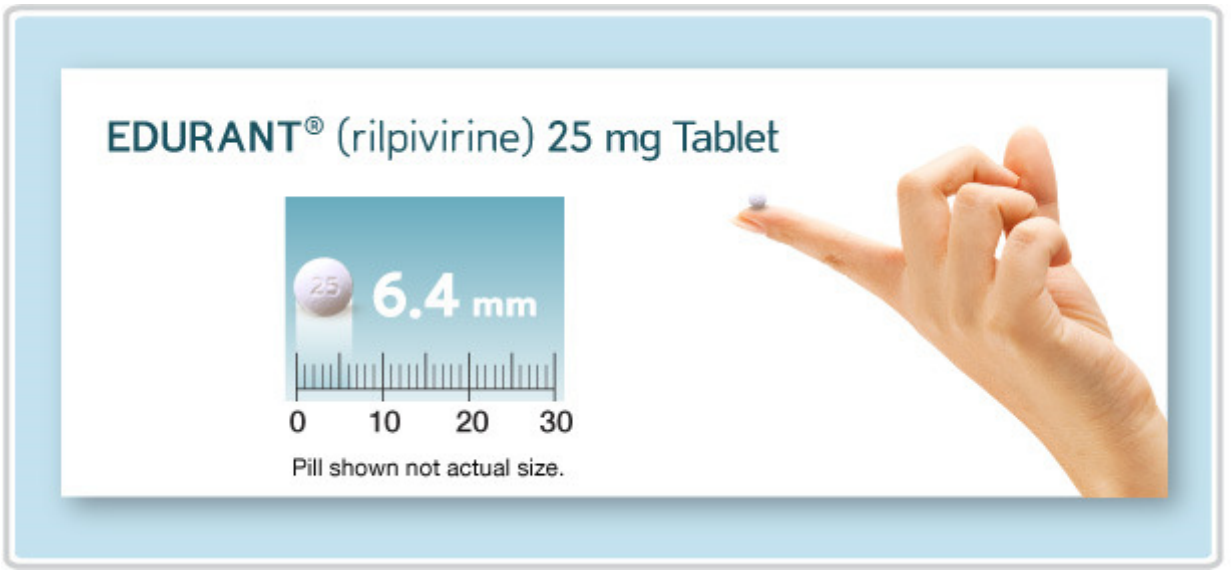
Rash, skin disorders

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?

Collective terms for doctors –Sanjay Pai *BMJ 2002*

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

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
6. Wikipedia
7. Paula Munderi et al AIDS 2016, Durban