First line ART: Efavirenz

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Outline: EFV as first-line therapy

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

A walk down memory lane…

- Non-nucleoside reverse transcriptase inhibitor NNRTI that stops HIV from replicating within cells by binding near reverse transcriptase's active site and inhibiting polymerase activity
- Developed by Du Pont Pharma and approved for HIV treatment in the USA in 1998
- Marketed by BMS / MSD
- Numerous generics available
- Most commonly used in fixed-dose combination with NRTI

A walk down memory lane…

- Efavirenz is part of the first once-daily tablet containing a complete HIV treatment regimen approved in 2006
- Proven to reduce HIV-1 viral load to below 400 copies/ml within 6 months in 60 to 80% of people who have not previously taken any HIV treatments
- Efavirenz is not active against HIV-2
- Recommended as a component of first-line antiretroviral treatment since 2002

A walk down memory lane…

- Dose - 600mg tablet once a day (400mg daily for those < 40kg)
- Should be taken on an empty stomach before going to bed to reduce the risk of side-effects
- Taking the drug with food may increase drug levels in some people by up to 50%
- High-fat meals may increase the absorption of efavirenz
- Efavirenz is also available as a solution for use in children and people who cannot take the tablets or capsules

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; ie**. 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

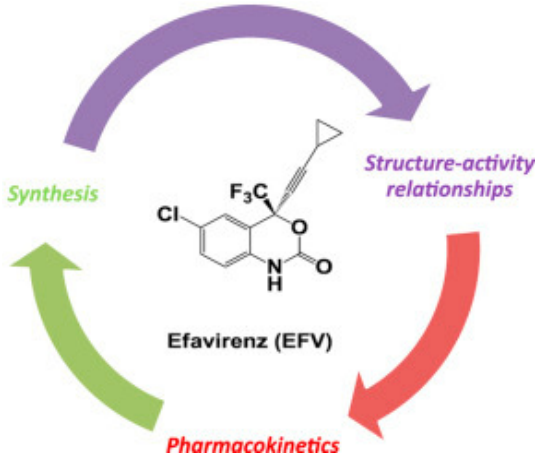
Key principles

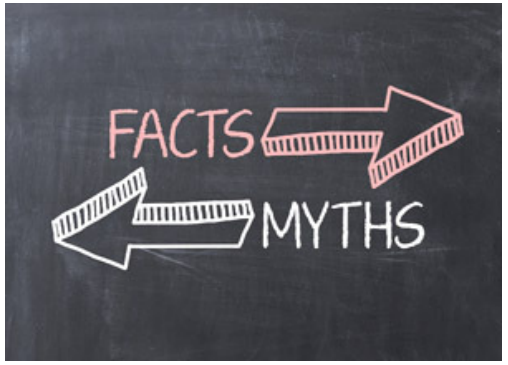
- The choice of first-line therapy is determined by various considerations including
  - Severity of infection
  - Drug tolerability
  - Presence of drug-resistant mutations in non-treated populations
  - Co-morbidities
  - Pregnancy
  - Availability of drugs
  - Cost
- The many studies evaluating ARV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

Efavirenz as first-line therapy






"We combined all your medications into ONE convenient dose."
NICKEL

Efficacy and Safety

- The efficacy and safety of efavirenz were assessed in numerous head-to-head randomized controlled trials (RCTs)
- In a meta-analysis of Efavirenz-based regimens in naive HIV-Infected Patients –34 studies were reviewed, with 26 trials being suitable for analysis
- Electronic databases searched up to Dec 2013 for RTCs in peer-reviewedjournals
- Efavirenz compared with drugs from 4 different classes: NNRTIs (nevirapine or rilpivirine), integrase strand transfer inhibitors (InSTIs),ritonavir-boosted protease inhibitors (bPI) and receptor (CCR5) antagonists (maraviroc), all of them were added to the background regimen, 2NRTIs

Safety and Efficacy

Results:

- Showed efavirenz-based regimens were equally effective as other recommended regimens based on NNRTI, InSTI,boosted PI or CCR5 antagonists in terms of efficacy outcomes
  - Disease progression and/or death
  - Plasma viral HIV RNA <50 copies/ml

Tolerability / Side Effects

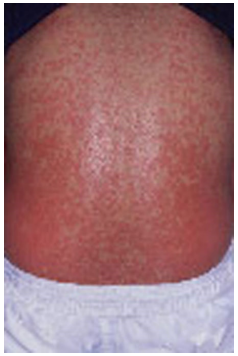
- The overall toxicity profile of efavirenz-based and other assessed regimens was comparable
- However, a significantly higher risk of the discontinuation of therapy due to adverse events was observed in the efavirenz group when compared with integrase inhibitors and CCR5 antagonists

Tolerability / Side Effects

Neuropsychiatric

- Early (2 – 6 weeks) as well as late
- Usually mild and transient
- Commonly - Vivid dreams, insomnia and mood changes ± 50%
- Include increased risk of suicidal ideation, encephalopathy, catatonia, psychosis and ataxia
- Low weight is a predisposing factor
- Other features: depression, psychosis, catatonia, encephalopathy or ataxia after the first few weeks of therapy
- Avoid EFV in patients with psychiatric disorders

Tolerability / Side Effects



- Rash
  - ± frequency ranging from 5- 34%
  - Usually occurs within the 1 to 3 weeks of initiation
  - From a mild diffuse, erythematous, maculopapular rash to severe lesions with associated blistering, desquamation or ulceration Grade 1 -4
  - Systemic symptoms such as fever, myalgia, transaminitis and fatigue
  - The incidence of severe rash such as erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome is 0.1%.
- Hepatotoxicity
  - Rare, usually as part of a hypersensitivity reaction
- Other: gynaecomastia
- Other medical causes must be excluded

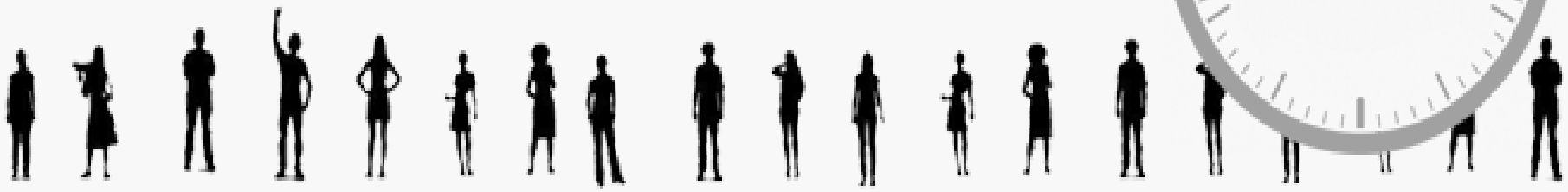
Co-morbidities

- Tuberculosis
- Pregnancy
  - Considered safe
- Hepatitis B, C
  - Considered safe but …
- Cardiovascular disease
  - Has been associated with alterations in lipid profile

Every second

someone becomes infected with TB.

That's more than **31 million** people each year.



Co-morbidities: TB

- The Department of Health reports that 60% of people with TB are HIV positive
- Also increasing incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB
- In 2015, 78% of people living with HIV who were also diagnosed with active tuberculosis were placed on ART
- The WHO recommends that treatments for common co-infections should be provided at the same time as treatment for HIV and the possibility of drug interactions needs to be managed

Cost for 30 tabs

- Efavirenz
  - 600mg ± R120.00 – R200.00
  - 200mg ± R90.00
  - 50mg ± R30.00
- Rilpirivine
  - R60.00
- Dolutegravir
  - ± R830.00

Summary

- Equally effective as other proposed first line agents
- Well tolerated
- Cost effective
- Safe to use in patients with co-morbidities
- Significant side effect profile

- **It's the drug we have the most experience with**

Acknowledgements

1. Nam AIDSmap
2. SAHIV Clinicians Society Guidelines 2017
3. Kryst J, Kawalec P, Pilc A (2015) Efavirenz-Based Regimens in Antiretroviral-Naive HIV-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS ONE 10(5):e0124279. doi:10.1371/journal.pone.0124279
4. Avert
5. Dheda M. Efavirenz and neuropsychiatric effects. S Afr J HIV Med. 2017;18(1), a741