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

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Efavirenz as first-line therapy
"We combined all your medications into ONE convenient dose."
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-reviewed journals.
- 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.
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
4. Avert