Efavirenz as a first-line drug

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Southern African HIV Clinicians Society

Topics to be covered

- History of EFV
- Important considerations
- Strategies for management of EFV toxicities
- Will this still work? (resistance in the community)

History of EFV

- Registered by the FDA in 1998
- Registered by the MCC in 2004
- Fixed dose combination registered in Feb 2011 with tenofovir and FTC
- A number of generic followed with either FTC or 3TC
- Currently almost 4 million South Africans take this combination

Important considerations (1)

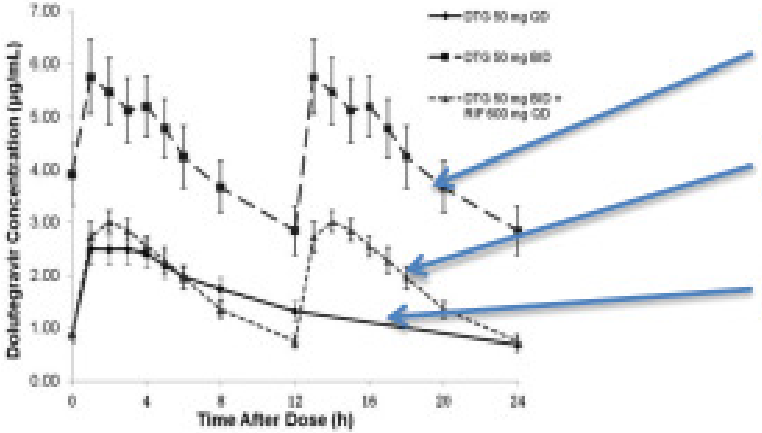
- The use of EFV in pregnancy
  - An accumulation of evidence indicating that EFV has superior efficacy and tolerability compared with NVP
  - Substantial reductions in the price of EFV, and increased availability as part of once-daily fixed dose combinations
  - Updated data suggesting a low risk of birth defects associated with EFV use during the first trimester of pregnancy
  - Programmatic experience highlighting the complications associated with switching HIV-positive pregnant women and those who may become pregnant from EFV to NVP.

Important considerations (2)

- The use of EFV with Rif containing TB regimen
  - Most common infection associated with HIV
  - Rifampicin effect on EFV PK
  - PK studies in patients with TB show no significant effect
    - Spain
    - South African adults (2 studies) & children
    - India
  - Package insert says AUC reduced 26% (n=12, no P value given)
  - Retrospective TDM database found significant reduction in EFV concentrations
  - Clin Pharmacokinet 2002;41:681 JAC 2006;58:1299 Cohen K Antivir Ther in press JAIDS 2009;50:439 AAC 2009;53:863 Antivir Ther 2008;13:675

Use of DTG in TB

- Rifampicin reduces dolutegravir concentrations – Induces UGT1A1, CYP3A4 and P-glycoprotein
- In healthy volunteers, 12 hourly dosing compensated for this



Dolutegravir 50mg bd

Dolutegravir 50mg bd + Rifampicin

Dolutegravir 50mg daily

Dooley, JAIDS 2013

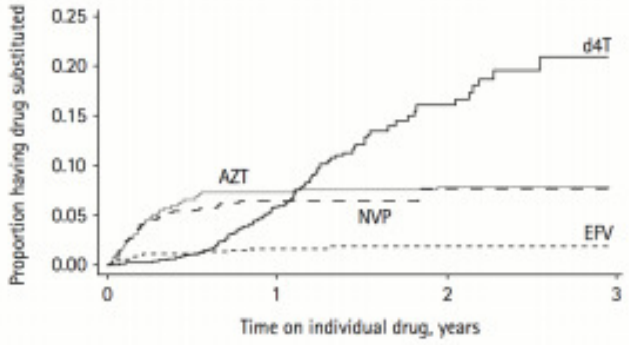
Comes close to a one size fits all

Antiviral Therapy 12:753–760

Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort

Andrew Boulle[1,], Catherine Orrell[2], Richard Kaplan[3], Gilles Van Cutsem[4], Matthew McNally[3], Katherine Hilderbrand[1,4], Landon Myer[1], Matthias Egger[5], David Coetzee[1,3], Gary Maartens[6] and Robin Wood[2] for the International Epidemiological Databases to Evaluate Aids in Southern Africa (IeDEASA) Collaboration*

Figure 2. Estimates of cumulative regimen substitutions due to toxicity by individual drug over a 3-year period



	n				Changed by 36 months, % (95% CI)
AZT	676	469	295	126	7.8 (5.9–10.3)
EFV	1,613	858	334	74	1.9 (1.3–2.8)
NVP	1,062	376	75	44	7.6 (5.3–10.9)
d4T	1,996	782	137	15	20.8 (16.2–26.5)

Over 3 years:
2% substituted efavirenz

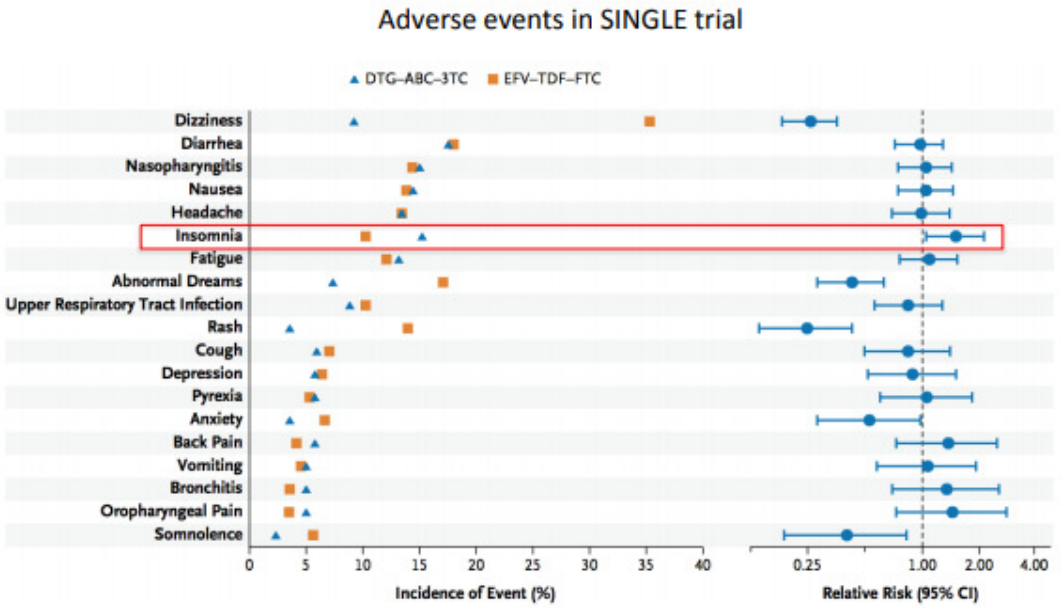
Use of RPV in TB

- Data on drug interactions of rifampicin and rifabutin with the NNRTI rilpivirine are limited
- Rifampicin decreases serum rilpivirine levels substantially

Side effects of EFV

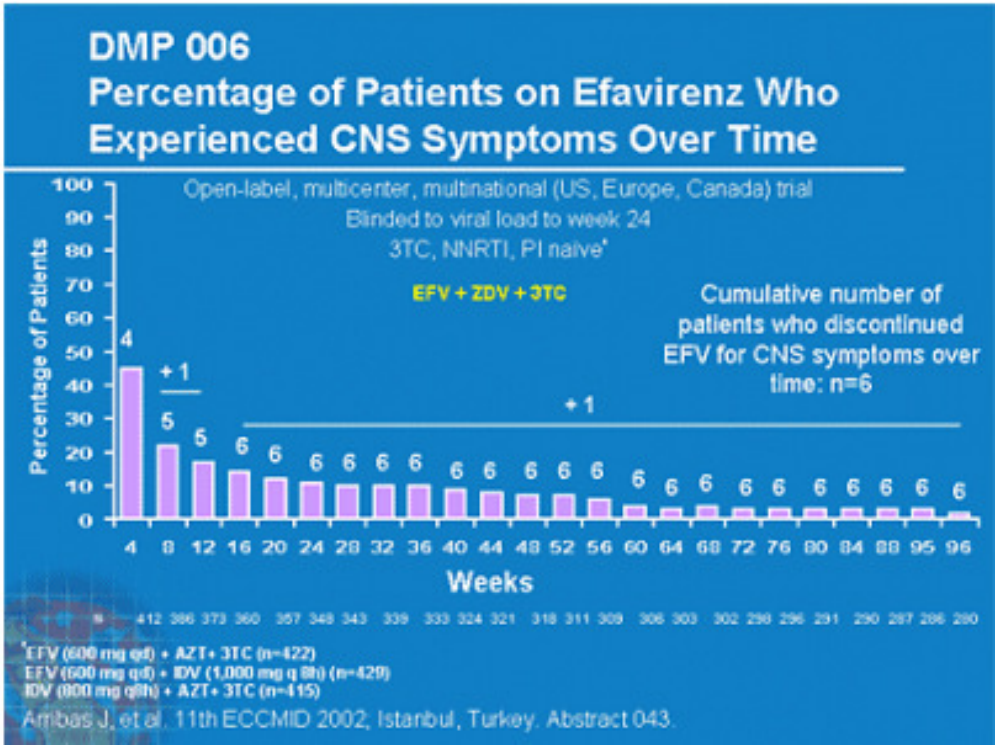
- Neuro-psychiatric side effects ranging from insomnia to over psychosis.

Dolutegravir also has CNS side effects



Walmsley, NEJM 2013

Management of side effects of EFV



- Reduce the dose of EFV to 400mg

abstract
948

Unexpectedly High Rate of Intolerance for Dolutegravir in Real Life Setting

Guido van den Berk, Josephine Oryszczyn, Willem Blok, Narda van der Meche, Rosa Regez, Daoud Ait Moha, **Kees Brinkman**

dept internal medicin OLVG, Amsterdam, The Netherlands – k.brinkman@olvg.nl

- Large ART clinical service in Amsterdam
- Dolutegravir treatment stopped in 62/387 patients (16%)
- Reasons
  - Sleeping problems (n=19)
  - Gastro-intestinal problems (n=18)
  - Neuropsychiatric problems (n=12)
  - Fatigue (n=9)
  - Headache (n=8)

Efavirenz and suicidality

HIV TREATMENT BULLETIN

Suicide not associated with efavirenz use in the D:A:D cohort study

1 December 2014. Related: Antiretrovirals, Conference reports, Side effects, HIV 12 Glasgow 2014.

Simon Collins, HIV i-Base

An analysis from the D:A:D cohort study, presented as an oral abstract by Colette Smith at the 2014 HIV Drug Therapy Glasgow Congress, was notable for reporting no association between suicide in HIV positive people taking efavirenz in European cohorts. [1]

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USING REAL WORLD DATA TO ASSESS THE RISK OF SUICIDALITY AMONG PATIENTS INITIATING AN EFAVIRENZ-CONTAINING REGIMEN VERSUS AN EFAVIRENZ-FREE ANTIRETROVIRAL REGIMEN

Conclusion:

In this analysis of two large real world databases, HIV patients with depression and psychiatric conditions were less likely to be prescribed EFV. Despite PS-adjustment, we did not find conclusive evidence of an increased risk of suicidality or suicide attempt among patients initiating an EFV-containing regimen.

Neuronal toxicity of efavirenz: a systematic review

Eric H Decloedt[†] & Gary Maartens

[†]*Stellenbosch University, Faculty of Medicine and Health Sciences, Division of Clinical Pharmacology, Department of Medicine, Tygerberg, South Africa*

"The clinical evidence that efavirenz use may worsen neuro-cognitive impairment or be associated with less improvement in neurocognitive impairment than other antiretrovirals is weak."

"There is a need for large randomized controlled trials to determine if the neuronal toxicity induced by efavirenz results in clinically significant neurological impairment before any conclusions can be made about ongoing use of this widely used antiretroviral drug."

Expert Opinion on Drug Safety, 2013

Strategies for the management of EFV toxicity

- To stay within class
- Lower dose efavirenz (400mg nocte)
  - Would need to go to split out medications
  - Three tablets and not one
  - ENCORE1 showed this strategy to be effective but not to be used in pregnancy or TB
- Change to RPV

Resistance in the community

- Resistance testing in not recommended prior to starting treatment
- Not all patients are truly treatment naïve (sdNVP and may not admit to prior treatment)
- In one study done in KZN, 17% of patient “presenting for the first time” resistance mutations : predominantly K103N yet it did not an impact to the outcomes

Conclusions

- EFV has served us well for many years
- Safe in pregnancy and with rifampicin
- The alternatives are not squeaky clean either.