Exploring 1st Line ART Options: Efavirenz

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Introduction

- Cost, availability & acceptability drive ART use
- Major disadvantage of currently available NNRTIs
  - is prevalence of NNRTI resistance mutations in ART naïve patients
- High income countries no longer recommend EFV in 1st line
- Newer regimens are more effective

	NRTI	NNRTI	PI	Integrase inhibitor
1st line	TDF/FTC	Efavirenz Rilpivirine	-	Dolutegravir Raltegravir
2nd line	AZT/3TC	-	Atazanavir/r or Lopinavir/r	Raltegravir
3rd line	Guided by genotype	Possibly Etravirine	Darunavir/r	Raltegravir Dolutegravir

Switch from 2nd line to 3rd line only after genotype

In many instance there is compatibility between public and private sectors

First Line Regimen: TDF/FTC/EFV

Desirable Property	TDF FTC EFV
High Resistance Barrier	No
Well tolerated	Maybe
Safe in Pregnancy	Yes
Low pill burden	Yes FDC
Use with TB -Rif	Yes
No lab toxicity monitoring	TDF creat

J Antimicrob Chemother 2014; **69**: 1742–1747
doi:10.1093/jac/dku058 Advance Access publication 5 March 2014

Journal of Antimicrobial Chemotherapy

Has the time come to abandon efavirenz for first-line antiretroviral therapy?

Francois Raffi[1]*, Anton L. Pozniak[2] and Mark A. Wainberg[3]

Table 2. Neurological, psychiatric and cutaneous adverse events by week 48 in selected efavirenz-based randomized clinical trials performed in antiretroviral-naive patients

		ECHO[9]	THRIVE[10]	STaR[28]	STARTMRK[30]	SINGLE[25]
Neurological	comparator	16%	18%	30%	26%[a]	22%
	efavirenz	37%	39%	51%	59%[a]	47%
Psychiatric	comparator	15%	15%	16%	—	29%
	efavirenz	25%	20%	38%	—	38%
Rash	comparator	4%	3%	8%[b]	0%[c]	3%
	efavirenz	15%	13%	13%[b]	7%[c]	14%

Efavirenz- general & pharmacological characteristics

- EFV- crosses BBB, reaching concentration of 11.1-30 µg/l in CSF (0.4-1.2% plasma concentration)
- Metabolized mainly in liver (90%) via **CYP450** system
- **Metablolites** may be implicated in EFV-related CNS adverse events
- Documented incidence of neuropsychiatric symptoms 60-90%:
  -dizziness -difficulty concentrating -sleep disturbance -vertigo
  -hang-over sensation -headache -euphoria -irritability & nervousness
- Severe neurological effects- registered in few than 2% of patients:
  -severe depression -delirium -paranoia -depersonalization -anxiety
  -hallucinations -aggressive behaviour -abnormal thinking and mania
- EFV-related neuropsychiatric events lead to therapy interrupted in 2-24% of patients
- Majority of CNS symptoms diminish or disappear several weeks after initiation
  - rare cases these can persist over longer periods of time or
  - appear for the first time after several months of exposure to EFV

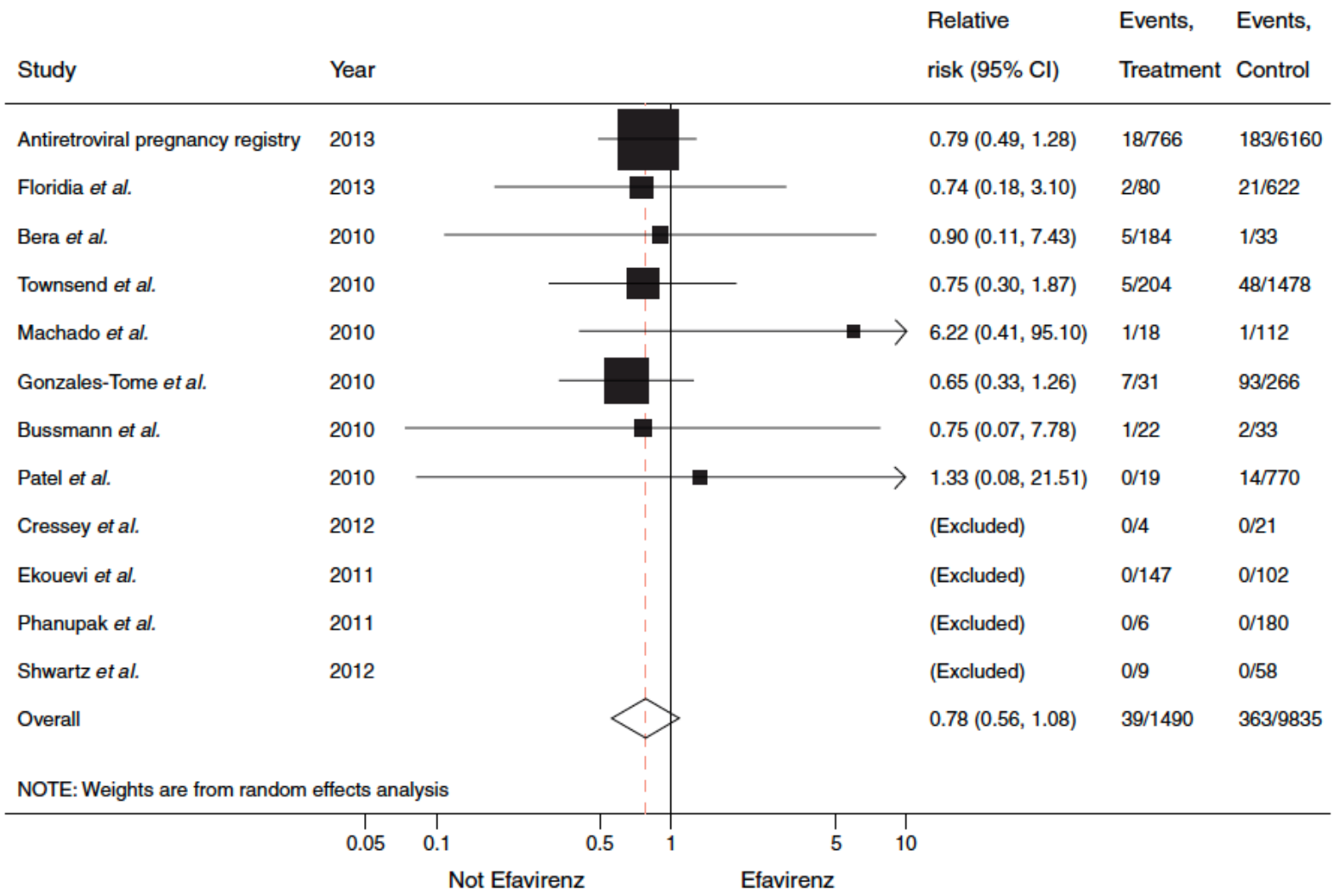
European Journal of Pharmacology. 2017.07.016

- Long-term EFV-associated symptoms (months or years)
  - Less understood
  - More difficult to foresee and control
- Long-term EFV-produced effects include sustained neuropsychological symptoms (albeit mild)
  - Elevated risk of suicide
  - Depression
  - Neurocognitive decline

- phenomena that are currently the subject of controversy

European Journal of Pharmacology. 2017.07.016

Efavirenz in Pregnancy



AIDS 2014. 28 (Suppl 2):S123-S131

Medicine®

Plasma Efavirenz Concentrations Are Associated With Lipid and Glucose Concentrations

Phumla Zuleika Sinxadi, MBChB, MMed Clin Pharm, Helen Margaret McIlleron, MBChB, PhD, Joel Alex Dave, MBChB, FCP(SA), PhD, Peter John Smith, PhD, Naomi Sharlene Levitt, MBChB, MD, FCP(SA), David William Haas, MD, and Gary Maartens, MBChB, FCP (SA)

- EFV based ART associated with dysglycemia & dyslipidemia
  - increased
    - total cholesterol : HDL cholesterol ratio
    - LDL cholesterol
    - Triglycerides
- Pathogenesis of these metabolic effects unclear
  - ? Mitochondiral toxicity by EFV

Medicine 2016. 95(2):e2385

Prevalence and risk factors for efavirenz-based antiretroviral treatment–associated severe vitamin D deficiency

Hanna Nylén, PhD[a], Abiy Habtewold, PhD[b], Eyasu Makonnen, PhD[b], Getnet Yimer, PhD[b], Leif Bertilsson, PhD[c], Jürgen Burhenne, PhD[d], Ulf Diczfalusy, PhD[a], Eleni Aklillu, PhD[c,*]

A prospective cohort study

RESEARCH ARTICLE

Antiretroviral Therapy, Especially Efavirenz, Is Associated with Low Bone Mineral Density in HIV-Infected South Africans

Joel A. Dave[1]*, Karen Cohen[2], Lisa K. Micklesfield[3,4], Gary Maartens[2], Naomi S. Levitt[1]

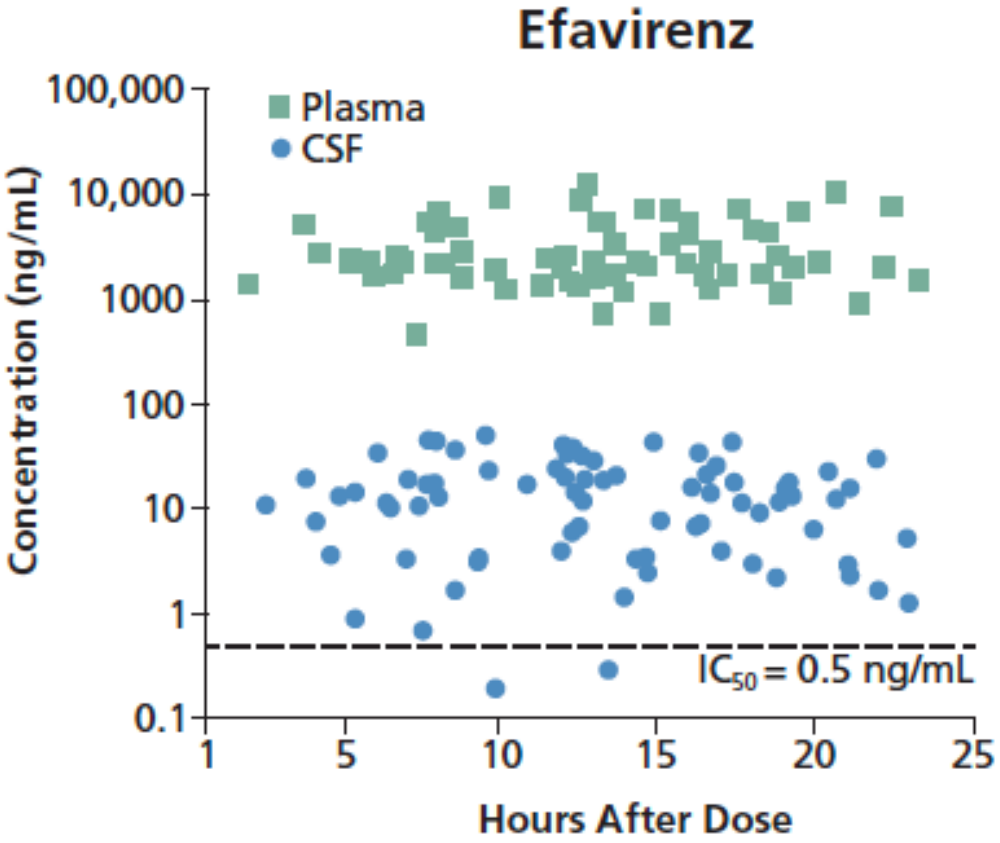
- EFV induces the metabolism of vitamin D
  - resulting in low Vit D
- Cross-sectional study in Cape Town showed
  - EFV independently associated with lower bone mineral density

Medicine (2016) 95:34(e4631)
PLoS ONE 2015. 10(12):e0144286

Neuro-Psychiatry

Psychiatric Illness	Consider avoiding EFV and RPV-based regimens	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality
HIV-associated dementia (HAD)	Avoid EFV-based regimens if possible Favor DRV-based or DTG-based regimens	EFV-related neuropsychiatric effects may confound assessment of ART's beneficial effects on HAD –related symptoms. Theorectical CNS penetration advantage

Antiretrovirals & the Blood-Brain Barrier



Top in Antivir Med. 2011;19:4:137-142

Table 1. Central Nervous System Penetration-Effectiveness Ranking

Drug Class	CPE Score 4	3	2	1
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Nonnucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine Rilpivirine	
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Strand Transfer Inhibitors	Dolutegravir	Raltegravir		

Top in Antivir Med. 2011;19:4:137-

Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series

Ebrahim Variava, MD, FCP(SA),†‡ Farai R. Sigauke, MD, MSc,* Jennifer Norman, BPharm,§ Modiehi Rakgokong, PN,‡ Petudzai Muchichwa, MD,* Andre Mochan, MD, FCPNeuro(SA),†‖ Gary Maartens, MD, FCP(SA),§ and Neil A. Martinson, MD, MPH‡¶*

- 20 women
- On EFV based therapy for a median 2 years
- Median weight 34kg
- Median $CD4^+$ count 299 cells/mm^3
- 17 of 20 were virally suppressed
- Elevated EFV levels

This case series most likely describes women who are genetic slow metabolizers of EFV
With SNPs in CYP2B6

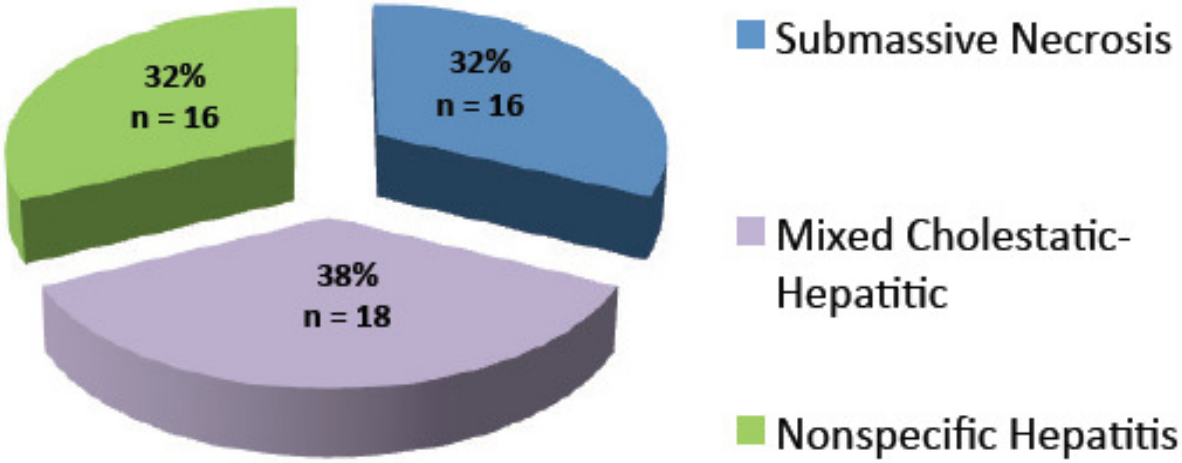
J Acquir Immune Defc Syndr 2017;75:577-579

Characteristics of Efavirenz drug induced liver injury: a cohort analysis

Mark W. Sonderup[1], Helen Wainwright[2], Debbie Maughan[1], Mashiko Setshedi[1], CWN Spearman[1]

1. Department of Medicine and Division of Hepatology, Groote Schuur Hospital and University of Cape Town 2. Department of Anatomical Pathology, University of Cape Town and National Health Laboratory System, Cape Town, South Africa

Histological patterns



- 3 distinct histological patterns of injury identified
- Submassive necrosis is the most severe of the histological spectrum & presents with jaundice + coagulopathy
- Clinical predictors of risk for severe EFV DILI
  - Younger age
  - CD4+ > 200
  - Female gender

AIDS 2016, 30:1483-1485

Porphyria

- Porphyria is group of metabolic disorders
  - relatively uncommon and underdiagnosed
- Acute porphyria precipitated by ART
  - Number of case reports world wide
  - ART drugs implicated include
    - Neverapine
    - Efavirenz
    - Boosted protease inhibitors i.e. Azatanavir/ritonavir
- Antiretrovirals least likely to be porphyrinogenic
  - Tenofovir
  - Lamivudine
  - Abacavir
  - Raltegravir
  - Unboosted protease inhibitors

AIDS. 2010; 24(16): 2597-2599

Compatibility of next-generation first-line antiretrovirals with rifampicin-based antituberculosis therapy in resource limited settings

Gary Maartens[a], *Marta Boffito*[b], *and Charles W. Flexner*[c]

Summary

Further research on drug–drug interactions between rifampicin and the next generation of first-line antiretrovirals will be needed before they can be recommended in patients with HIV-associated tuberculosis.

Dolutegravir (DTG)
Tenofovir alafenamide (TAF)

Curr Opin HIV AIDS. 2017; 12:355-358

Efavirenz reduced dose 400mg

- Reduced dose EFV-
  - Non-inferior efficacy & less toxicity than standard dose (600mg)
- Primarily metabolized by cytochrome P450 enzyme CYP2B6
- 3 loss-of-function SNPs in CYP2B6 gene
  - associated with impaired metabolism resulting higher plasma EFV levels
- Rif induces CYP2B6 but EFV also auto-induces CYP2B6
  - EFV auto-induction counteracts the induction of its metabolism by Rif
- Reduced dose EFV may result in sub-therapeutic EFV levels (wild-type CYP2B6)
- Pharmacokinetic study is underway to evaluate reduced dose EFV with Rif

Curr Opin HIV AIDS. 2017; 12:355-358

Advantages/ points in favour of EFV

- Greater efficacy
- Moderate toxicity
- Broad clinical experience accumulated over several decades of use
- Existence of generic forms of EFV
- EFV remains ARV of choice in treatment of TB co-infection

Conclusion

- Future place of EFV
  - maybe minimal role as 1st line ART
  - ART of choice in patients in TB co-infection
- EFV low barrier to resistance major drawback
- EFV toxicity has been under-estimated
  - Increased risk of dose-related toxicity
    - Neuropsychiatric
    - Glucose
    - Lipids
    - Hepatitis