The next generation of ART regimens

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Current state of ART in resource limited settings

- Current regimens are highly effective
- First line regimen EFV TDF XTC in a single tablet FDC
- Some countries have introduced a 3rd line regimen
- Can we do better?

First line regimen: EFV TDF XTC

Desirable Property	EFV TDF FTC
High resistance barrier	No
Well tolerated	Not initially
No lab tox monitoring	TDF creat
Safe in pregnancy	Yes (?TDF)
Low pill burden	Yes FDC
Once a day	Yes
Use with TB (rif)	Yes

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

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

Increasing primary resistance

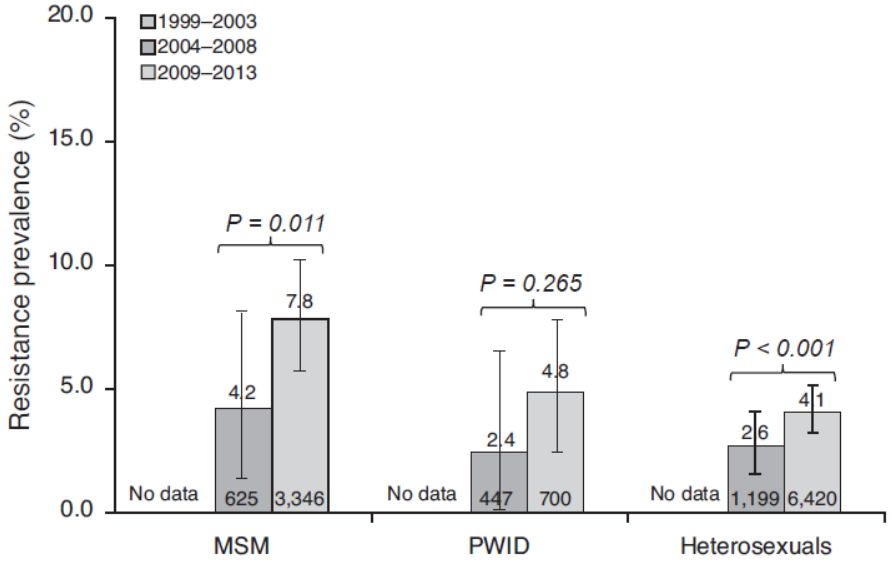
Toxicity issues

Newer regimens more effective

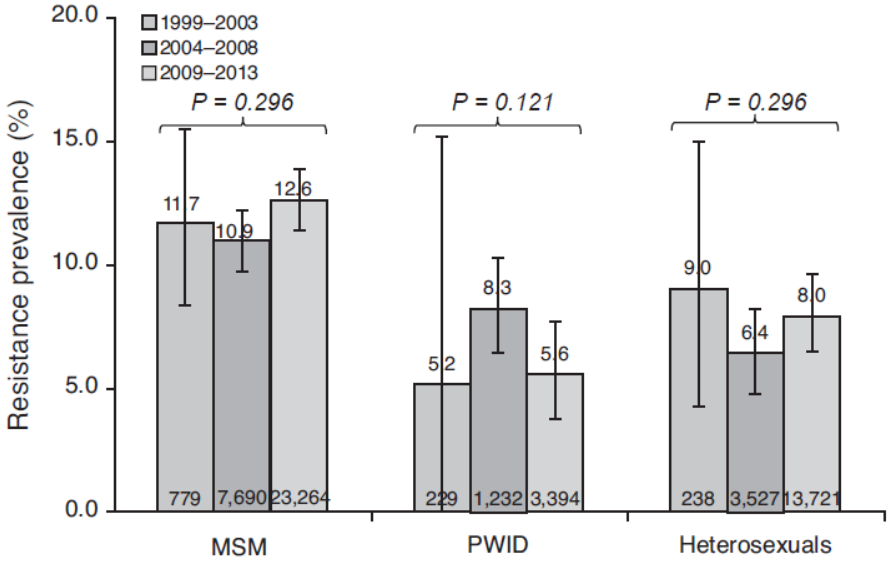
J Antimicrob Chemother 2014; 69: 1742

Transmitted ARV resistance trends

Low-middle income



High income

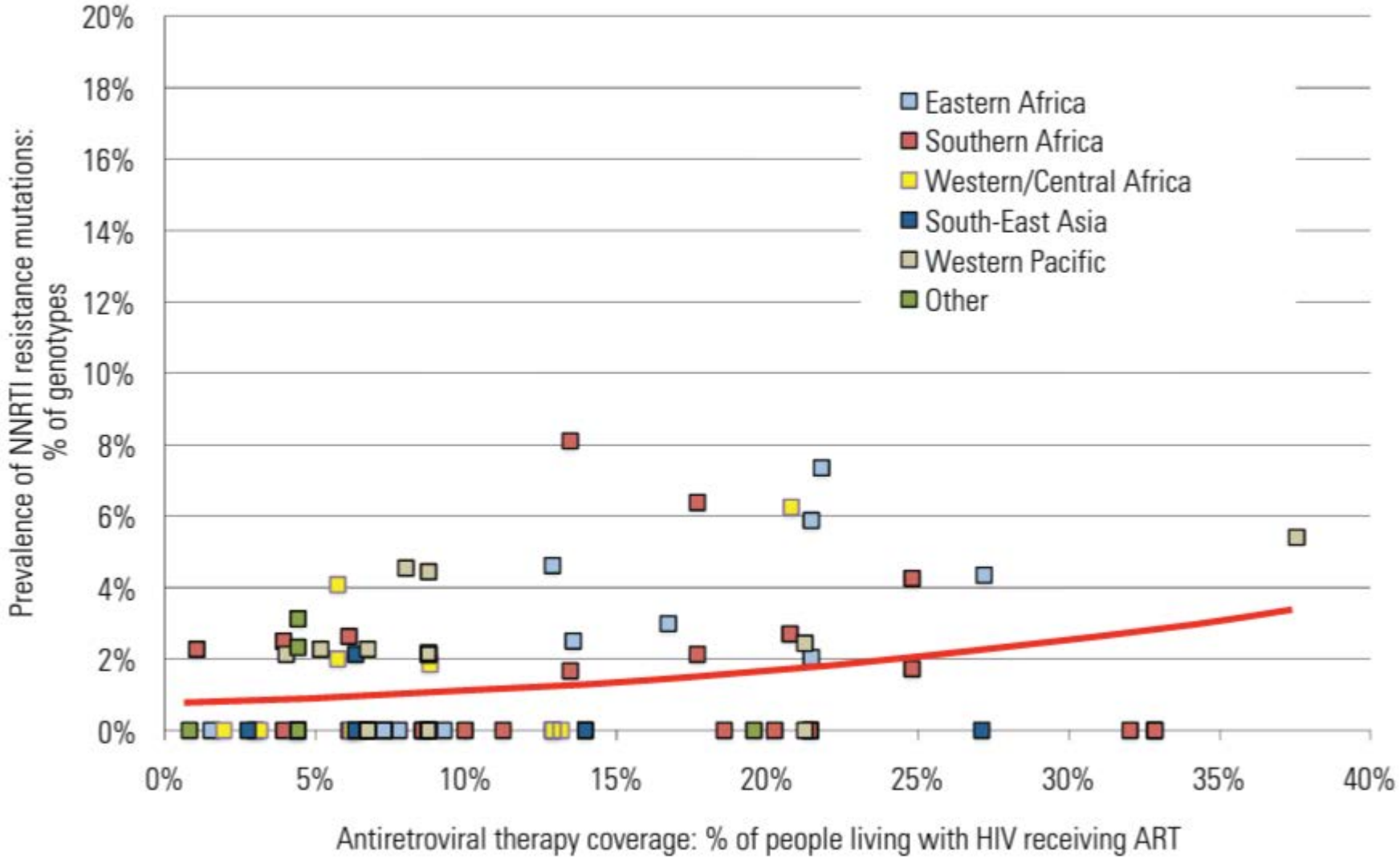


Prevalence of transmitted HIV drug resistance to NNRTI increased between 2004 and 2010.

This estimated increase was particularly apparent in the areas surveyed in the African region

AIDS 2014, 28:2751–2762
WHO HIV DR 2012

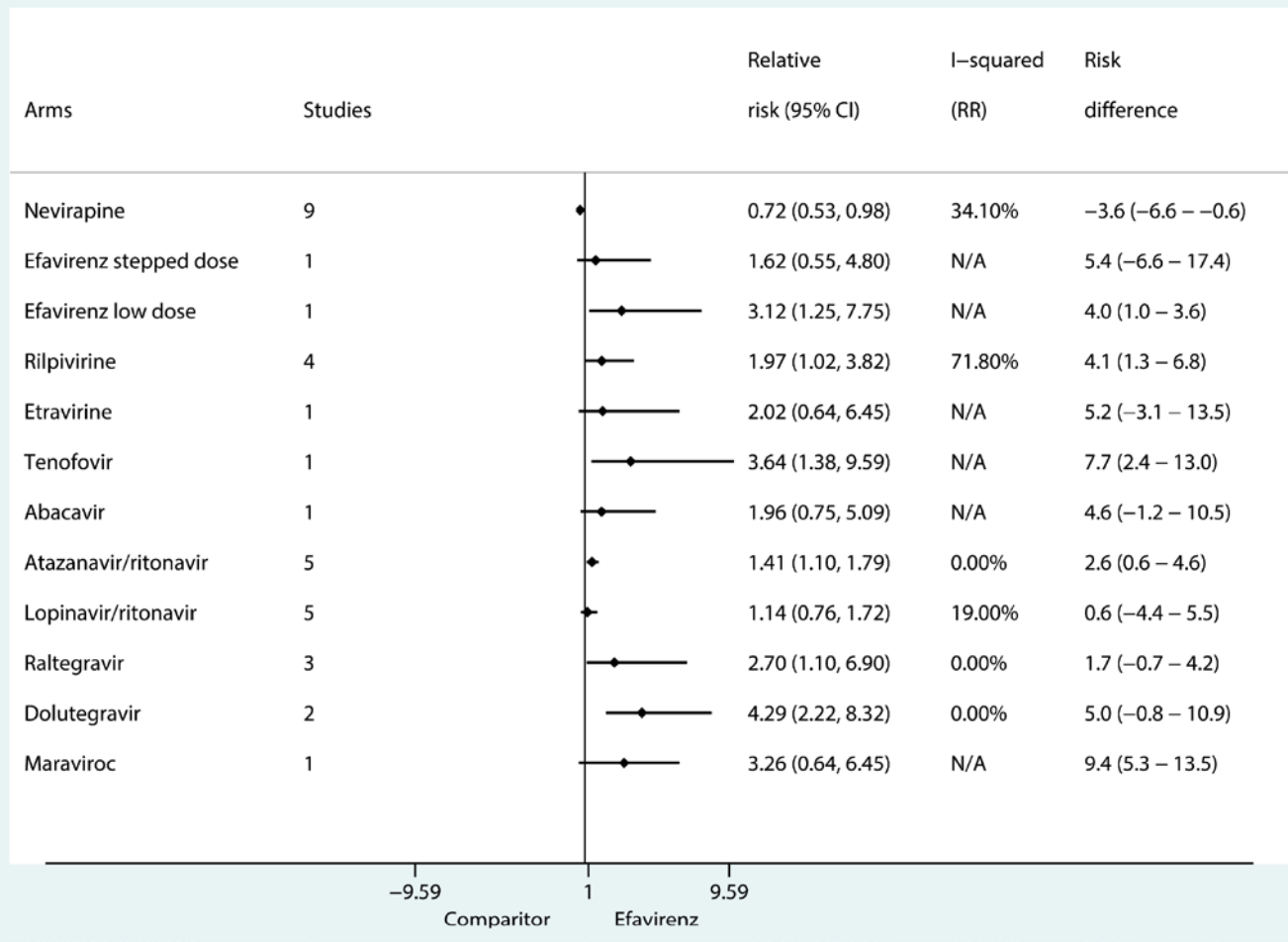
Figure 2 Relationship between transmitted resistance to NNRTI drugs and antiretroviral therapy coverage



P-value adjusted for region= 0.039; Odds-ratio per 10% increase in ART coverage= 1.49 (95% C.I: 1.07 – 2.08)

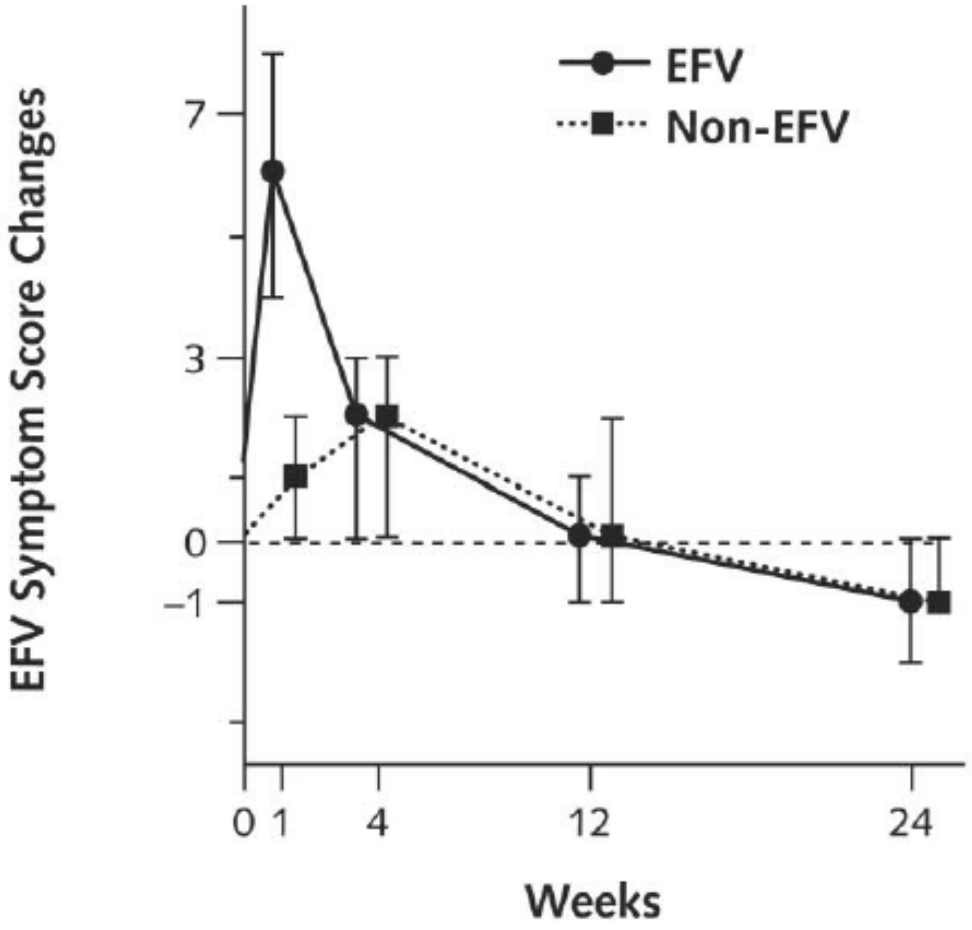
WHO HIV DR 2012

Meta-analysis: EFV discontinuations for toxicity



Ford JAIDS 2015

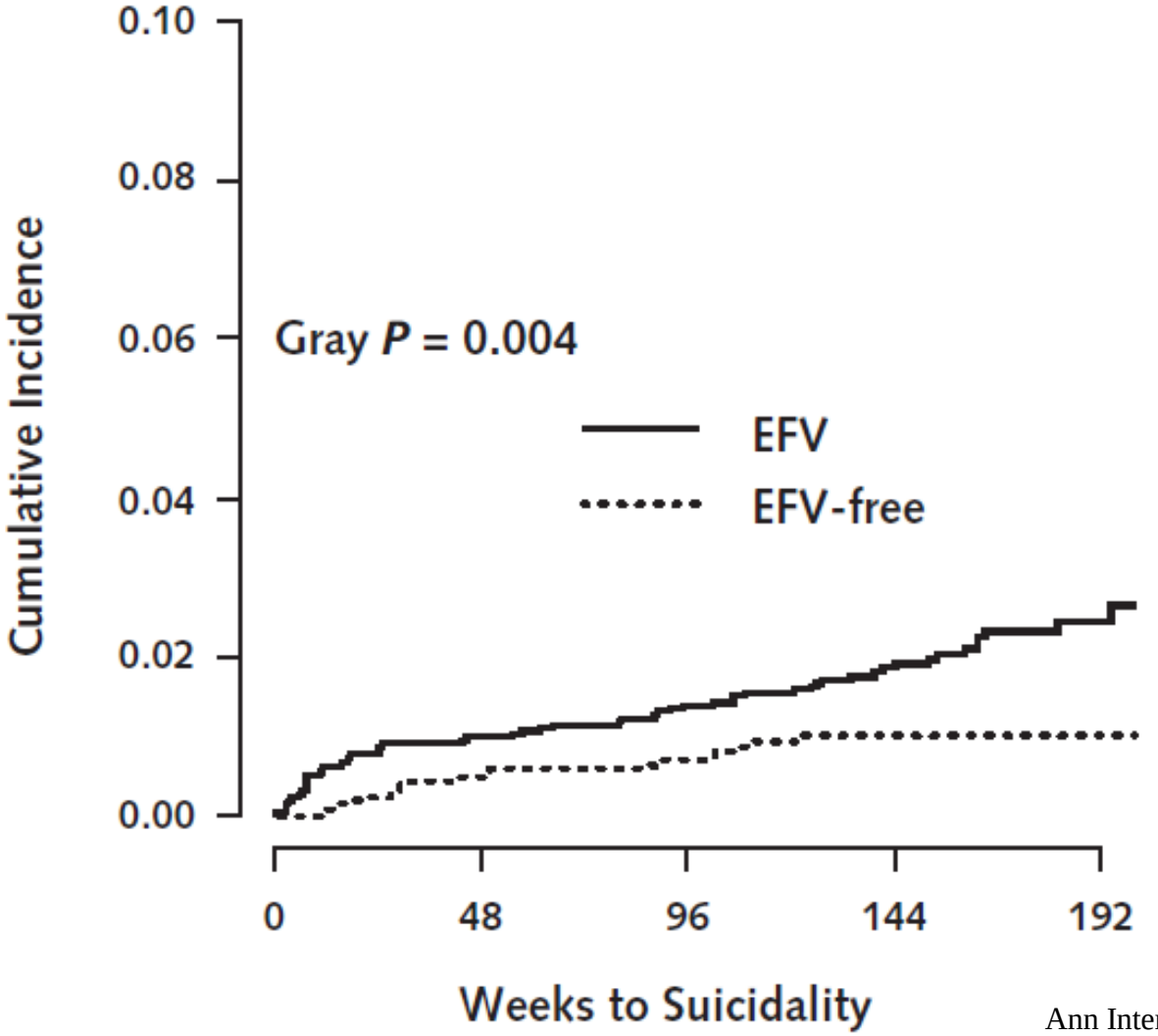
Early EFV neuropsychiatric toxicity



Ann Intern Med. 2005;143:714

EFV & suicidality

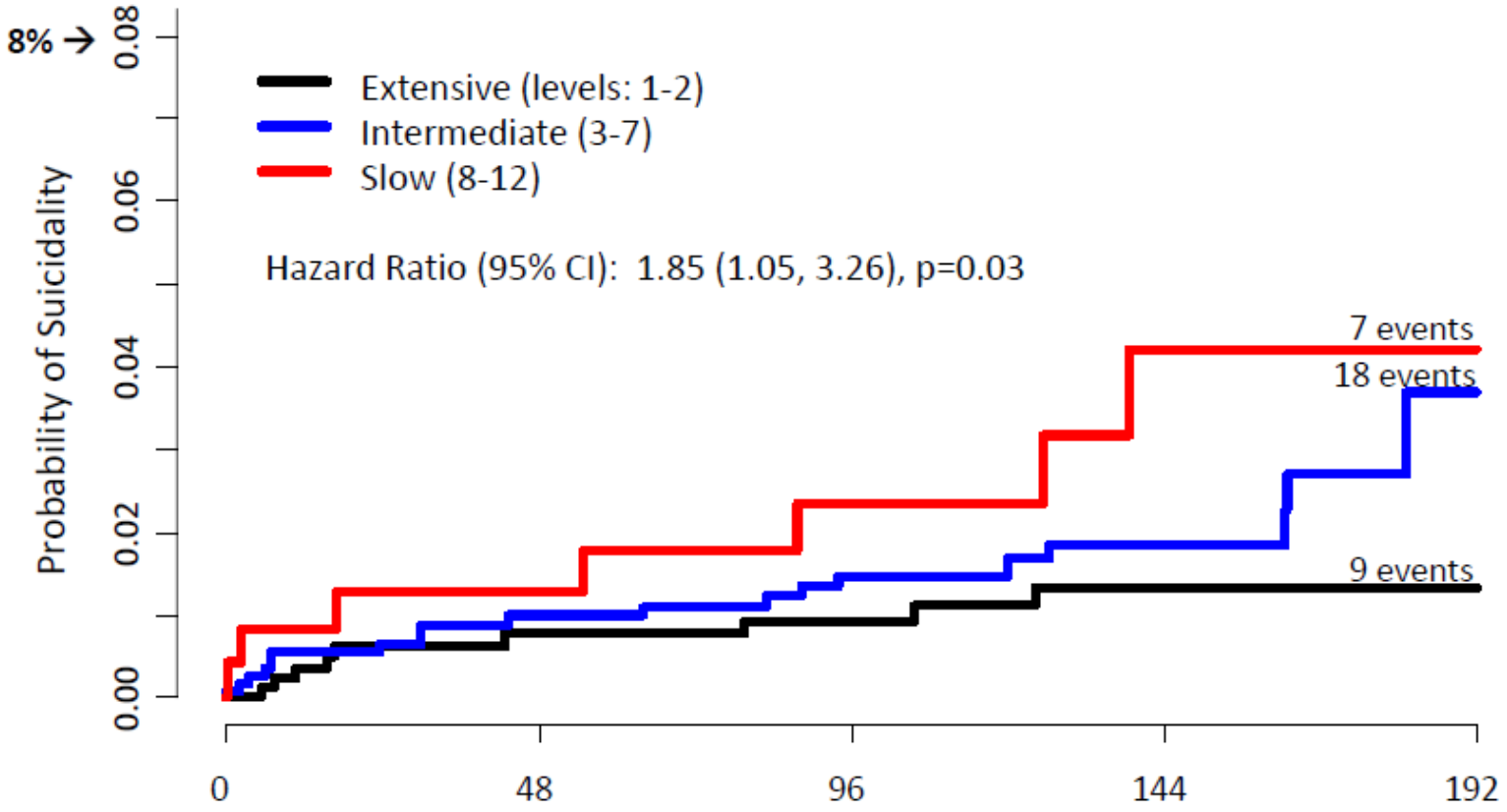
4 ACTG RCTs EFV n=3241; comparator n=2091



Ann Intern Med. 2014;161:1-10

CYP2B6 genotype & suicidality

Figure 4: Probability of suicidality by metabolizer group, on-treatment IPW analysis (per 1 level increase of 3 levels)



Mollan IAS 2015

EFV metabolic effects

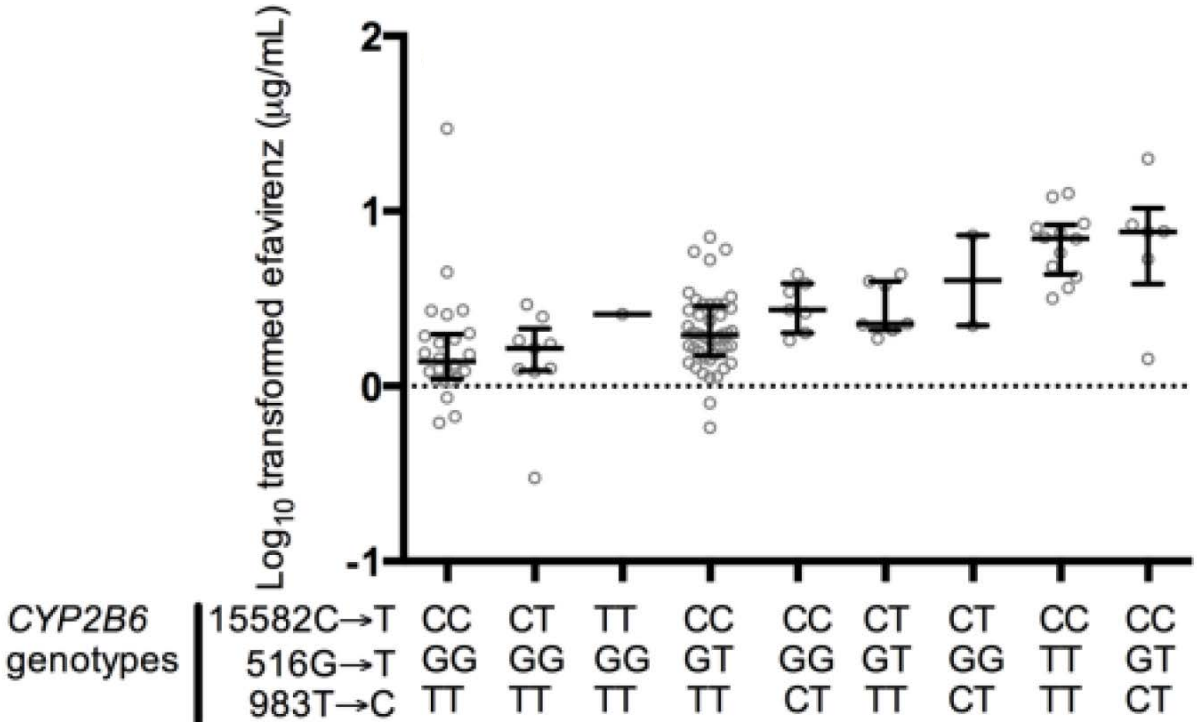
- Increased triglycerides, total & LDL-chol vs nevirapine, rilpivirine, atazanavir-r, dolutegravir, & raltegravir
- EFV fasting glucose higher than ATV
- Cross sectional study Cape Town dysglycaemia risk higher on EFV aOR 1.70 (95%CI 1.19-2.45)
- Higher risk of DM than NVP cohort study

PLoSMed 2004;1:e19
JAIDS 2012;60:33
Lancet Infect Dis 2012;12:111
Clin Infect Dis 2006;42:273
Lancet 2009; 374: 796
AIDS 2014;28(10):145
JAIDS 2011;57:2841
Karamchand Medicine 2016

EFV concentrations & metabolic effects

Metabolic measure	Beta coefficient (95% CI)	P
LDL cholesterol	0.62 (0.14 to 1.10)	0.012
Triglycerides	0.58 (0.09 to 1.08)	0.022
Glucose (fasting)	0.60 (0.11 to 1.10)	0.017
Glucose (2 hours)	1.14 (0.28 to 2.00)	0.010

Pharmacogenetics of EFV metabolism



17% in SA genetic slow metabolisers (vs 3% Caucasians)

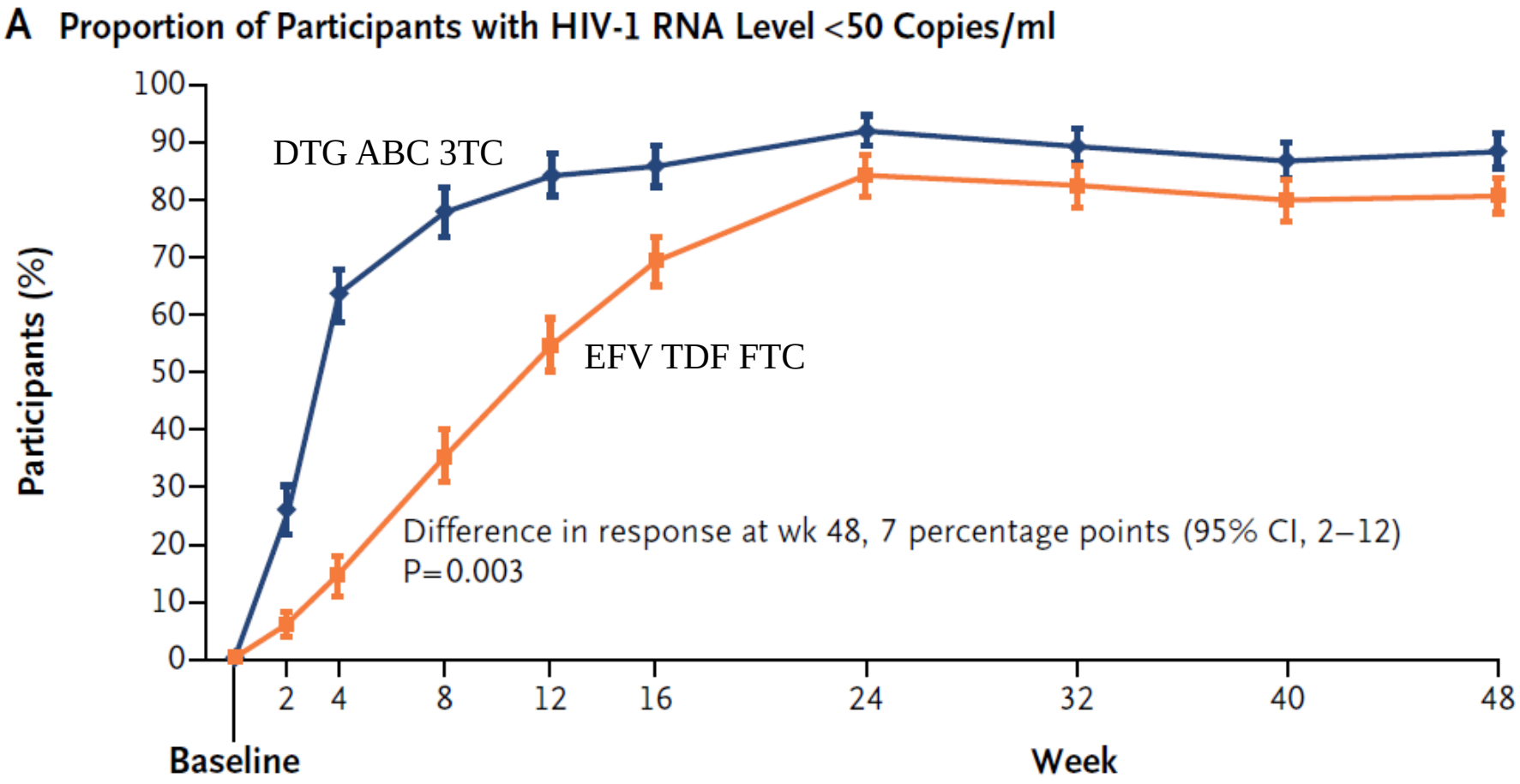
Sinxadi BJCP 2015

EFV metabolism

- Much higher prevalence of slow metabolizer genotypes in Africa & SE Asia
- Increased risk of dose-related toxicity:
  - Neuropsychiatric
  - Hepatitis
  - Lipids
  - Glucose

Antiviral therapy 2005; 10(4): 489 – 98
Sinxadi Medicine 2016
Haas AIDS 2004
Mollan IAS 2015

Dolutegravir vs EFV in ART naive



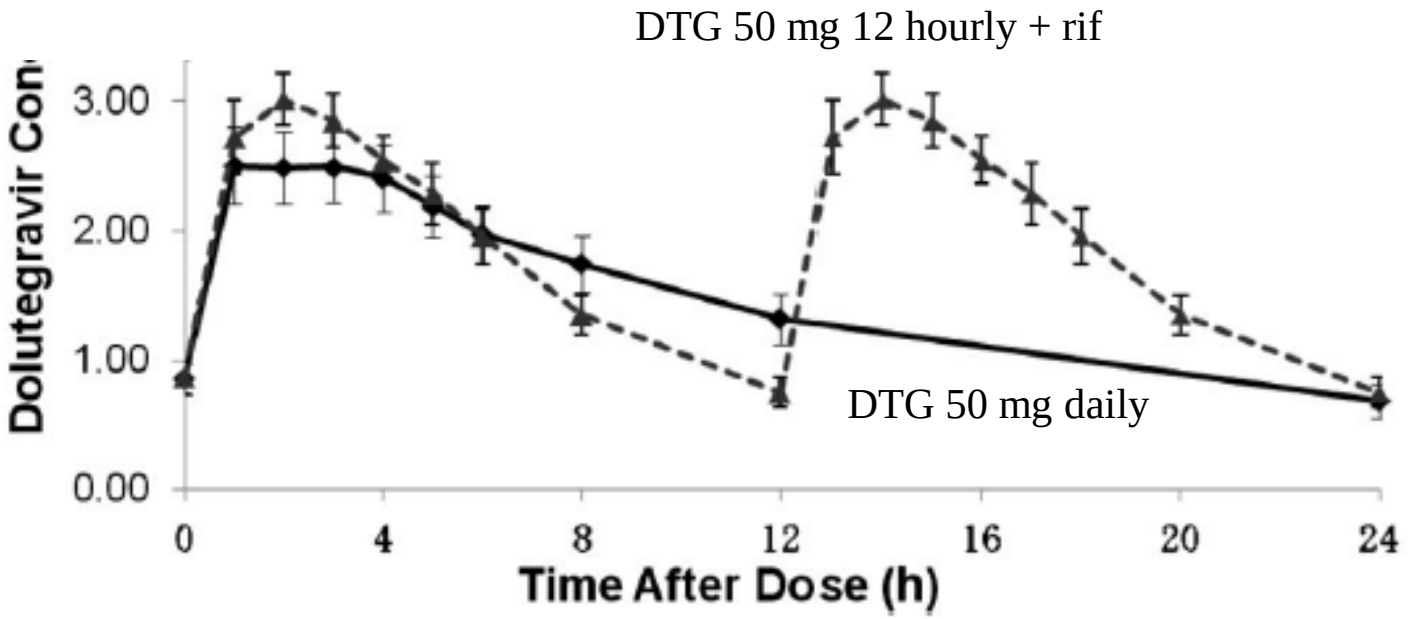
N Engl J Med 2013;369:1807

Dolutegravir resistance

- Single mutation results in moderate resistance, which impedes replicative capacity
- With other integrase inhibitors (raltegravir & elvitegravir), initial resistance mutation is rapidly followed by compensatory mutations that restore replicative capacity, which doesn't appear to occur with DTG
- Selection of DTG resistance without prior exposure to raltegravir or elvitegravir appears to be very uncommon

Wainberg Retrovirol 2014

Dolutegravir & rifampicin



$AUC_{0\text{-}24}$ DTG 50 mg/d 32.1
DTG 50 mg 12 hly + rif 42.6

JAIDS 2013;62:21

First line regimens compared

Desirable Property	EFV TDF FTC	DTG ABC 3TC
High resistance barrier	No	Yes
Well tolerated	Not initially	Yes
No lab tox monitoring	TDF creat	Yes
Safe in pregnancy	Yes (?TDF)	? (FDA cat B)
Low pill burden	FDC	FDC
Once a day	Yes	Yes
Use with TB (rif)	Yes	12 h dose (need RCT)

Second line regimen: LPV-r AZT 3TC

Desirable Property	LPV-r AZT 3TC
High resistance barrier	Yes++
Well tolerated	No
No lab tox monitoring	LPV lipids, AZT FBC
Safe in pregnancy	Yes
Low pill burden	No
Once a day	No (LPV-r could be)
Use with TB (rif)	Double dose

CASTLE: ART naïve atazanavir-r vs lopinavir-r

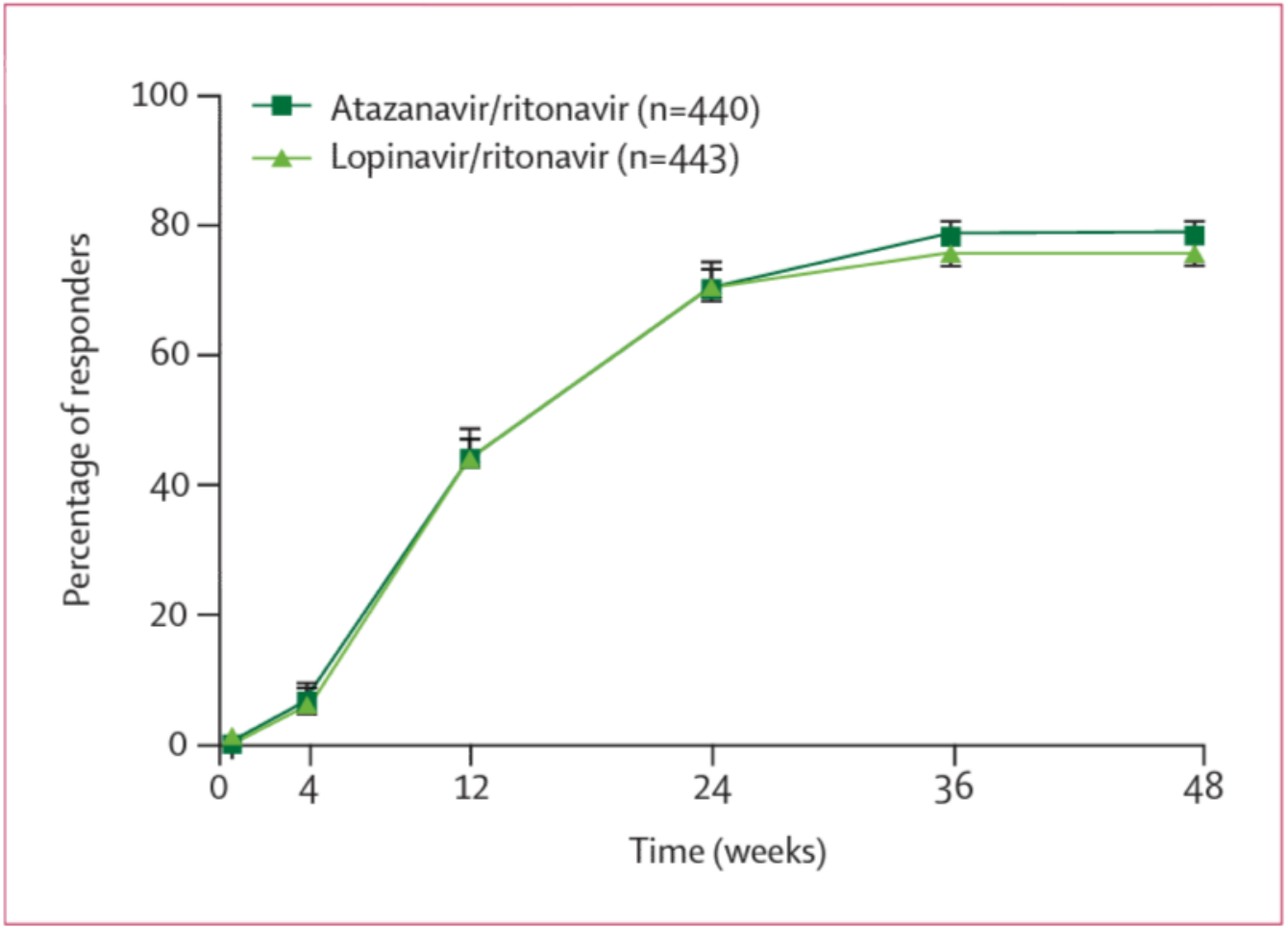


Figure 2: **Proportion of patients with HIV RNA below 50 copies per mL at week 48 (ITT; CVR, NC=F analysis)**

Lancet 2008; 372: 646–55

CASTLE - safety

Adverse event	ATV-r	LPV-r
CLINICAL grade 2-4		
Jaundice	4%	0%
Nausea	4%	8%
Diarrhoea	2%	11%
LAB grade 3-4		
Bilirubin	34%	<1%
Cholesterol	4%	18%
Triglycerides	<1%	4%

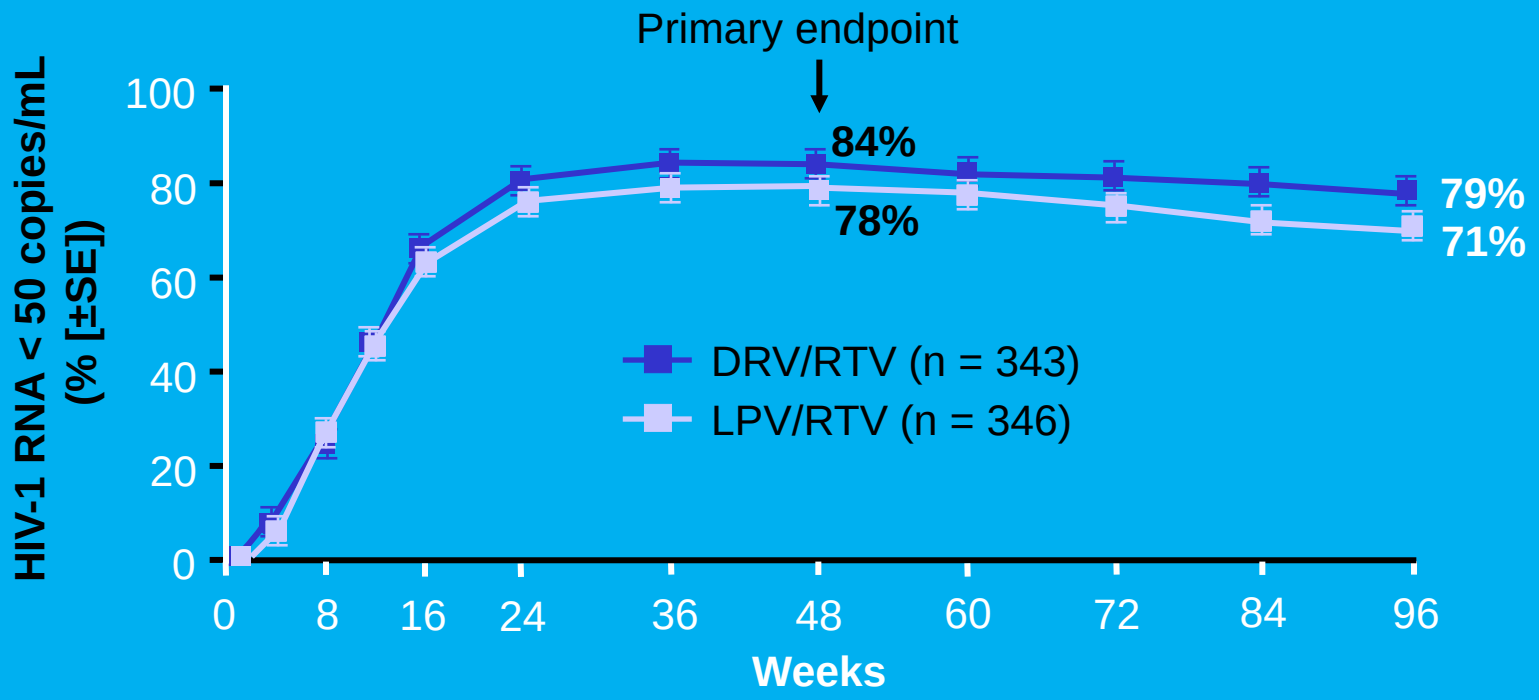
Lancet 2008; 372: 646–55

ATV-r vs LPV-r in experienced patients

- Median ART duration 5.1 years
- Median 2 PI resistance mutations
- 96 week follow up
- Similar virologic efficacy
- “Grade 3–4 elevations in bilirubin were more common in ATV-r patients (53%) than LPV-r patients (<1%) with no resulting discontinuations.”

AIDS2006,20:711

ARTEMIS: ART naive patients TDF FTC plus DRV/r (800/100 od) vs LPV/r (400/100 bd or 800/200 od)



Non-inferior at 48 weeks, superior at 96 weeks

VF DRV 12% LPV 17% (P=0.04) – no PI mutations

Mills A, et al. ICAAC/IDSA 2008. Abstract 1250c. (Clinical Care Options) AIDS 2009;23:1679

ARTEMIS week 48 safety

	DRV-r	LPV-r	P
Grade 2-4 adverse events:			
GIT	7%	14%	<0.01
Triglycerides	3%	11%	<0.001
Cholesterol	13%	23%	<0.01
Rash	3%	1%	NS
Permanently stop for AE	3%	7%	<0.05

AIDS 2008;22:1389

With DRV in 2nd line, what's in 3rd line?

- Should we plan for failure or for success?
- Would need to wait for a new drug to construct an effective regimen, but there would be a long time before it was necessary

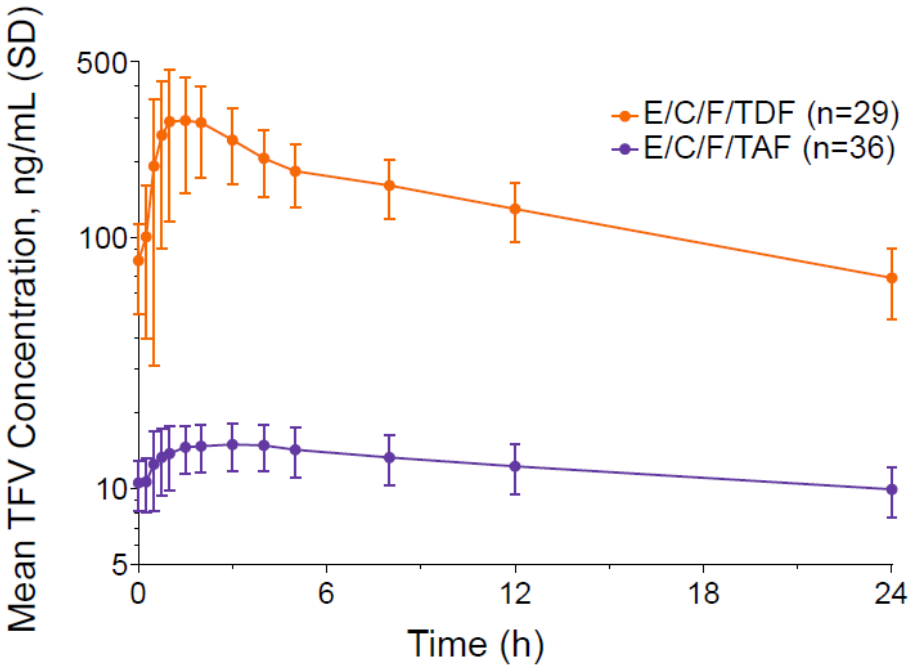
Second line regimens compared

Desirable Property	LPV-r AZT 3TC	ATV-r AZT 3TC	DRV-r AZT 3TC
High resistance barrier	Yes++	Yes	Yes+++
Well tolerated	No	Yes (jaundice)	Yes
No lab tox monitoring	LPV lipids, AZT FBC	AZT FBC	DRV lipids, AZT FBC
Safe in pregnancy	Yes	Yes	±Yes
Pill burden	6	5*	5*
Once a day	No (LPV-r could be)	Yes	Yes
Use with TB (rif)	Double dose	No data	No data

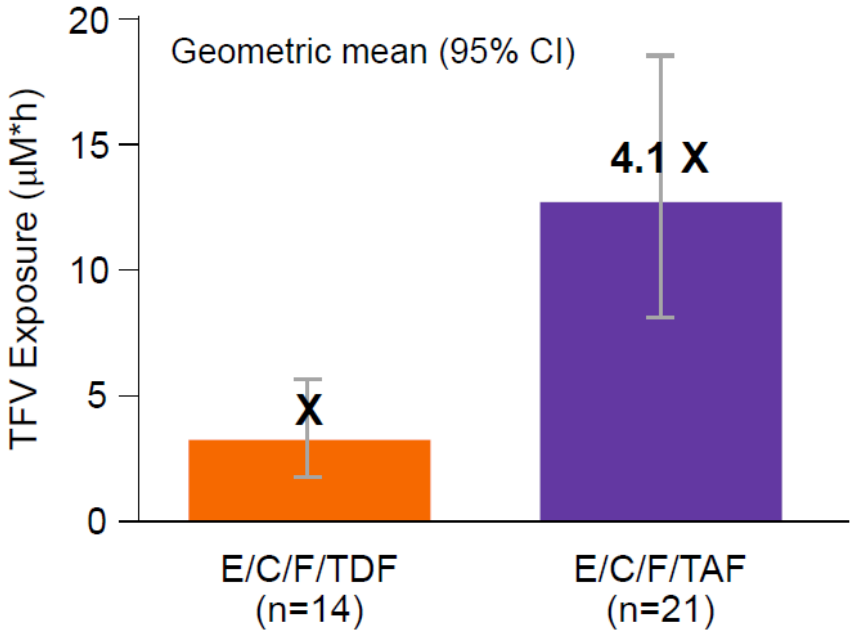
*FDC of ATV-r & DRV-cobicistat available

Tenofovir Alafenamide vs TDF: Pharmacokinetics

Plasma TFV

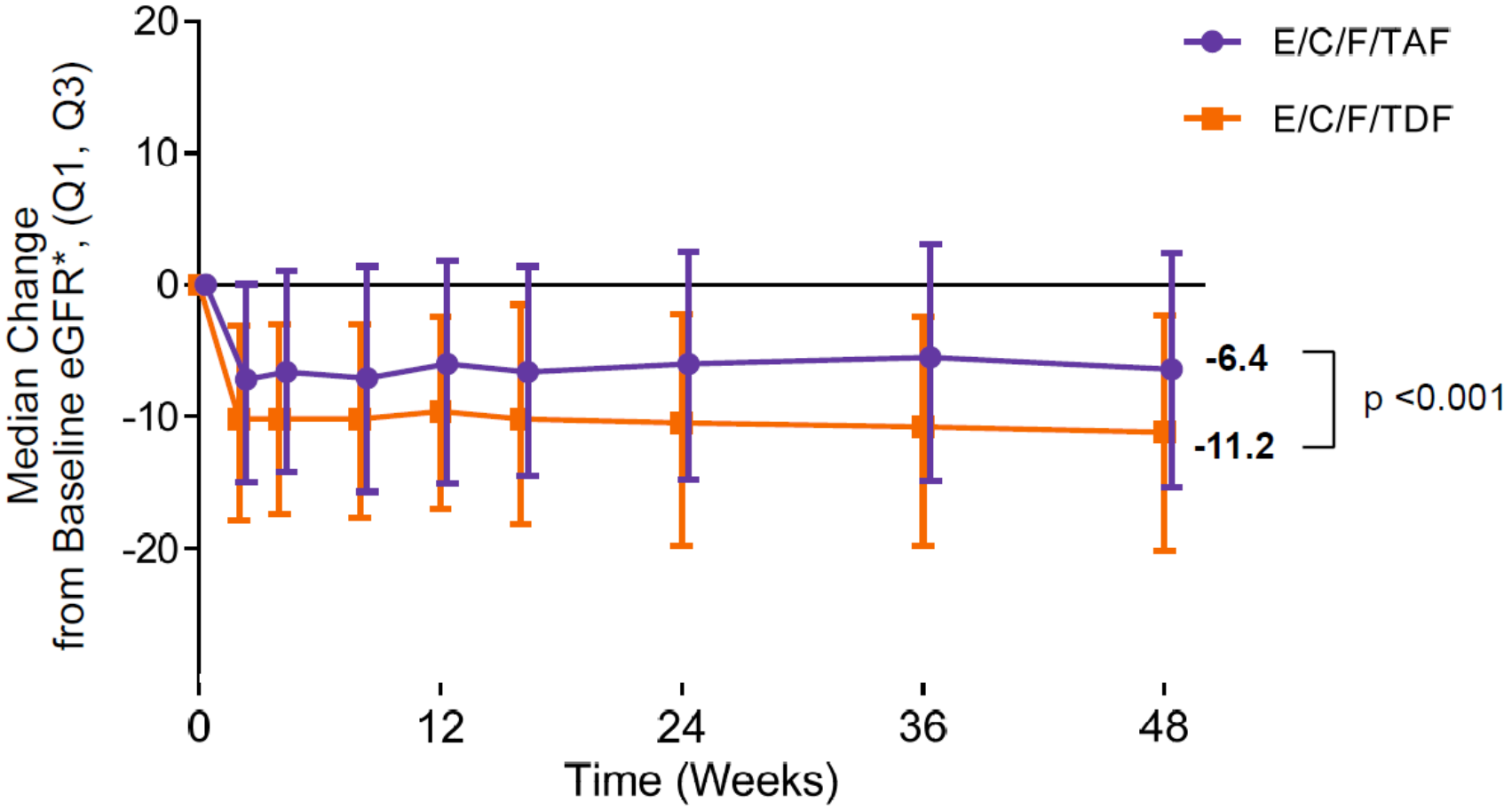


Intracellular TFV-DP



Wohl DA, et al. CROI 2015. Abstract 113LB. CCO

Change in eGFR: TAF vs TDF



Bone mineral density: TAF vs TDF

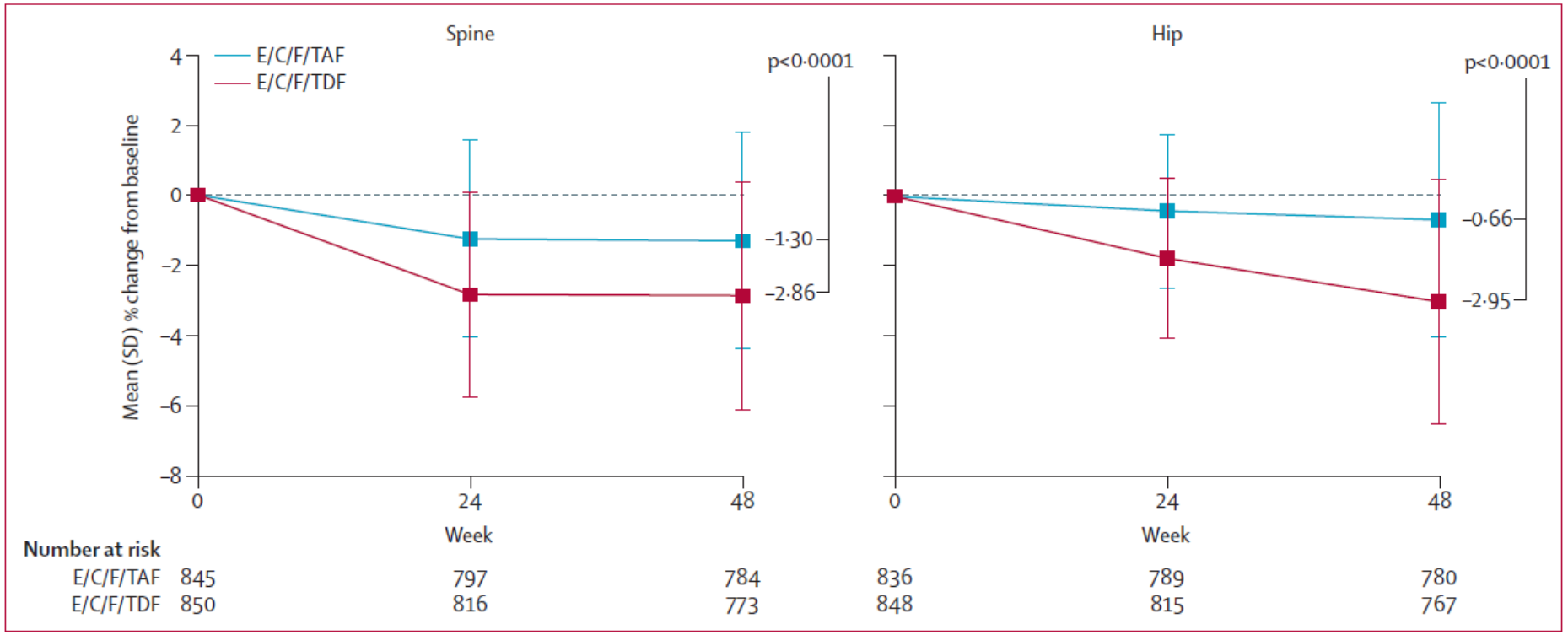


Figure 4: Changes in spine and hip bone mineral density through week 48

TAF summary

- Less toxic & similar efficacy to TDF
- More drug-drug interactions than TDF, including rifampicin (need data)
- Lower dose (25 mg vs 300 mg) will be much cheaper

Conclusions

- EFV low barrier to resistance major drawback
- EFV toxicity has been under-estimated. High prevalence of slow metabolisers in SA increases risk of dose-related toxicity
- DTG attractive 1st line alternative to EFV – high resistance barrier means fewer switches to 2nd line. FDC with TAF & FTC being tested in RCT in South Africa with TB sub-studies.
- We should reconsider LPV-r as first choice for 2nd line – ATV-r or DRV-r (daily) are better tolerated, but need PK studies of adjusted doses with rifampicin