# We should switch to dolutegravir in 1st line

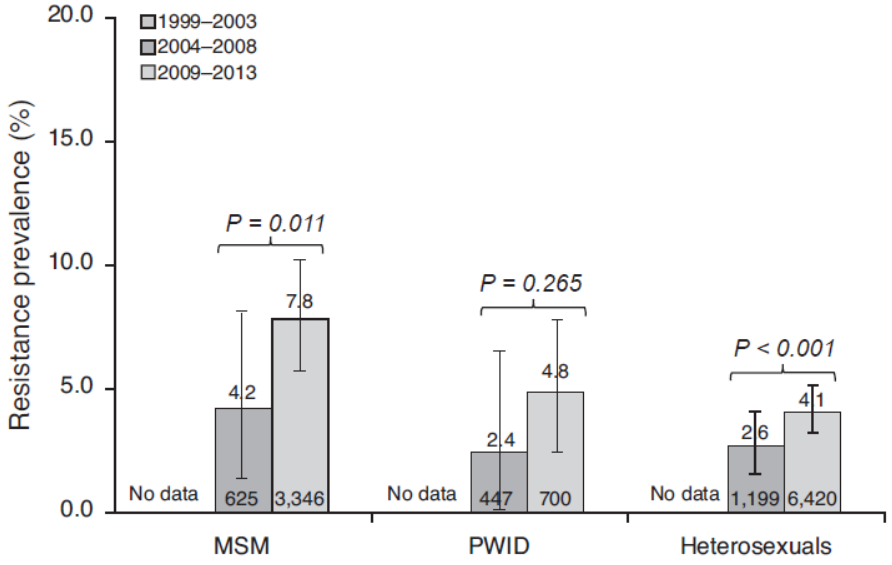
Gary Maartens

# EFV resistance

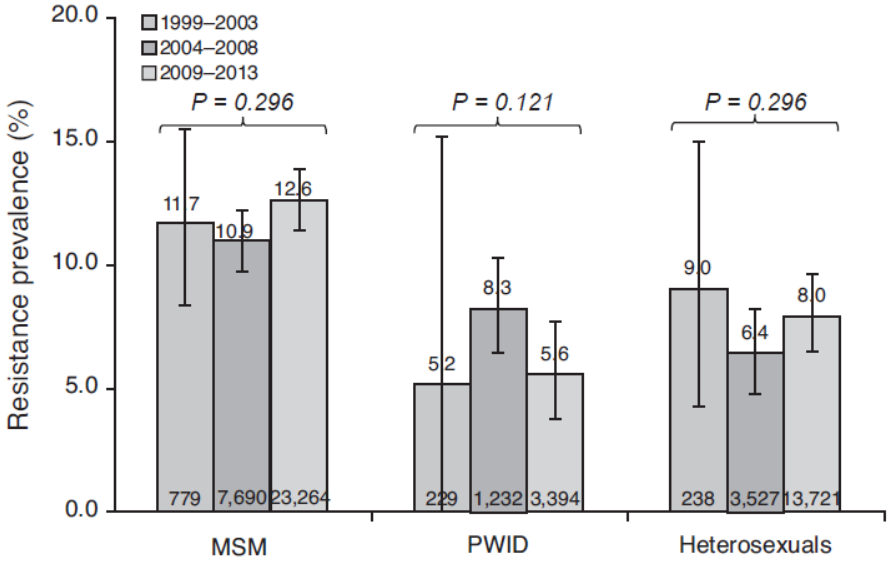
- Low genetic barrier to resistance
- Several single mutations confer high level resistance
- Variable cross-NNRTI resistance

# Transmitted ARV resistance trends

## Low-middle income




## High income

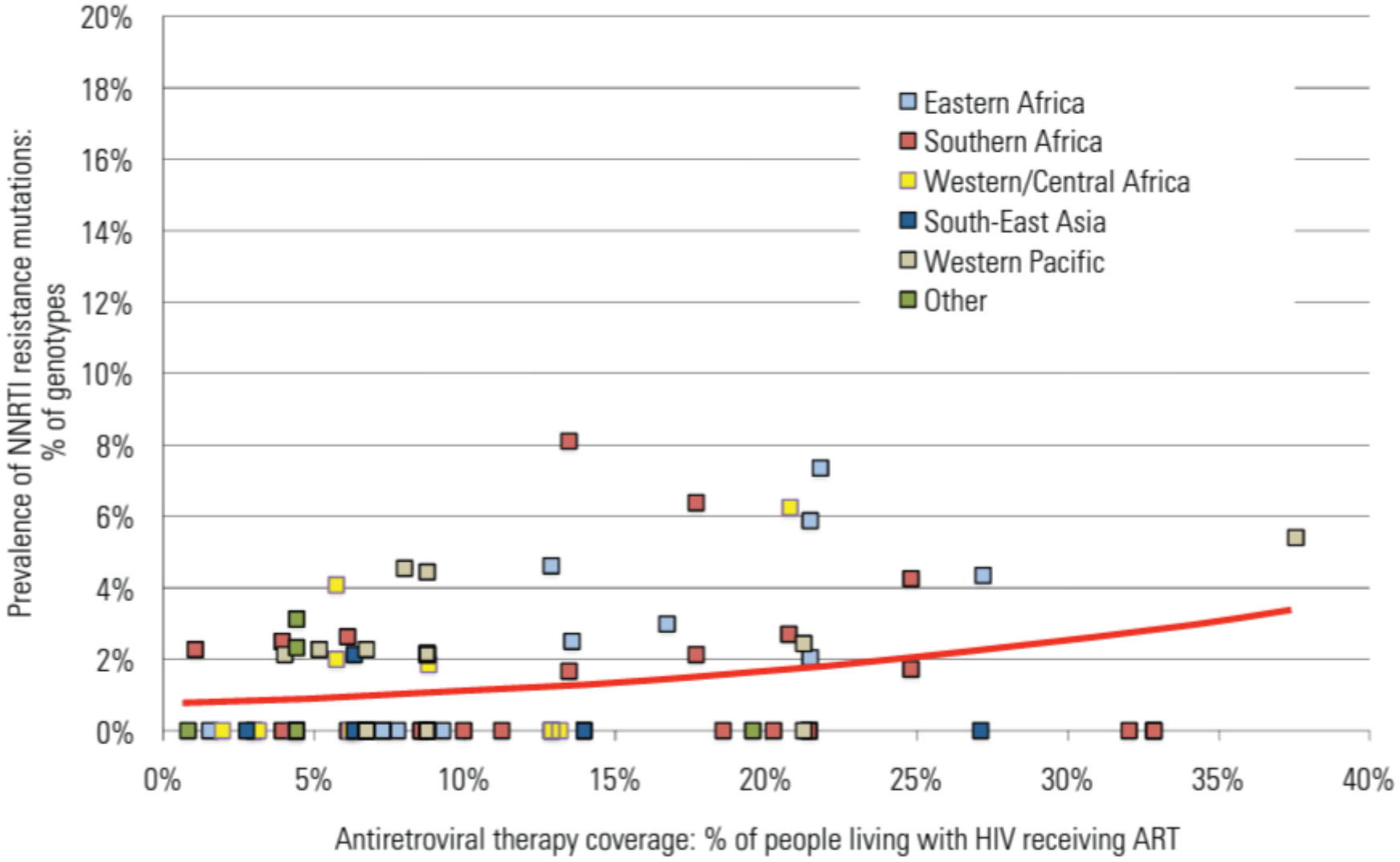



Prevalence of transmitted HIV drug resistance to NNRTI increased between 2004 and 2010.

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

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

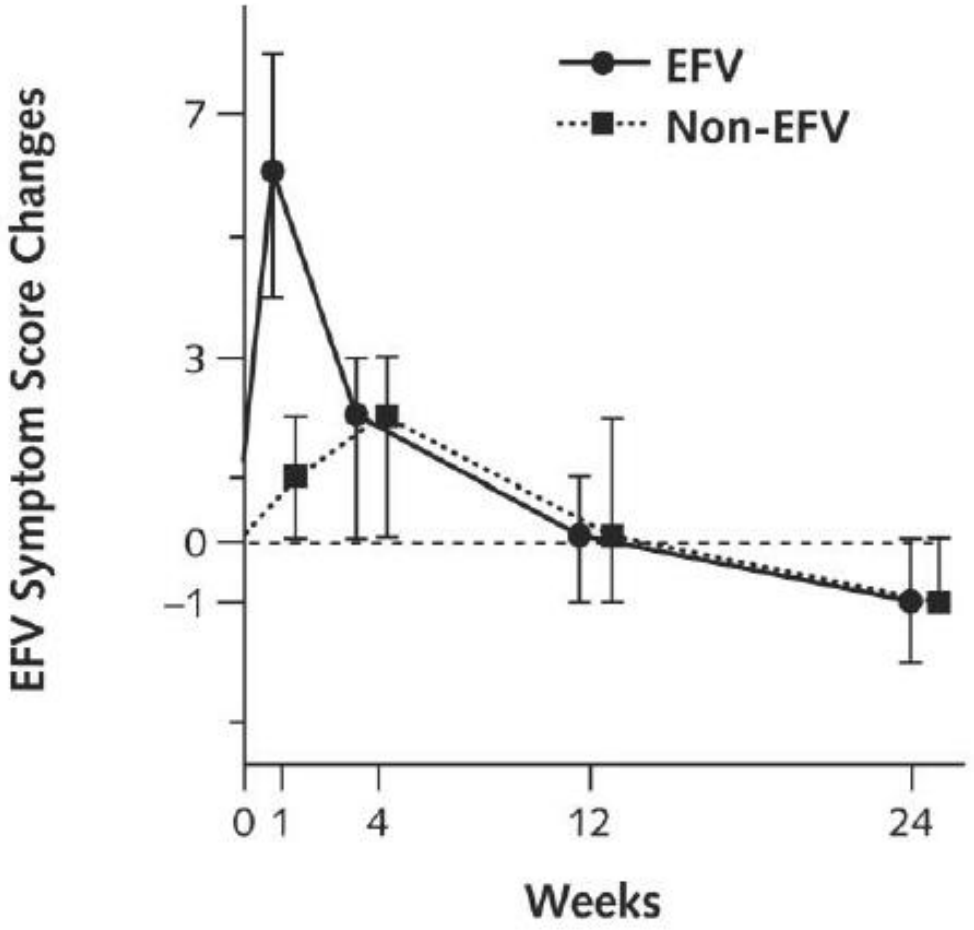
**Figure 2** Relationship between transmitted resistance to NNRTI drugs and antiretroviral therapy coverage




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

# Early EFV neuropsychiatric toxicity




Ann Intern Med. 2005;143:714

# EFV CNS symptoms over time

- ACTG study of EFV in ART naives
- Neurocognitive test improved
- “small increases from baseline in EFV-associated symptoms, bad dreams, and anxiety were detected.”

HIV Clin Trials 209;10:343

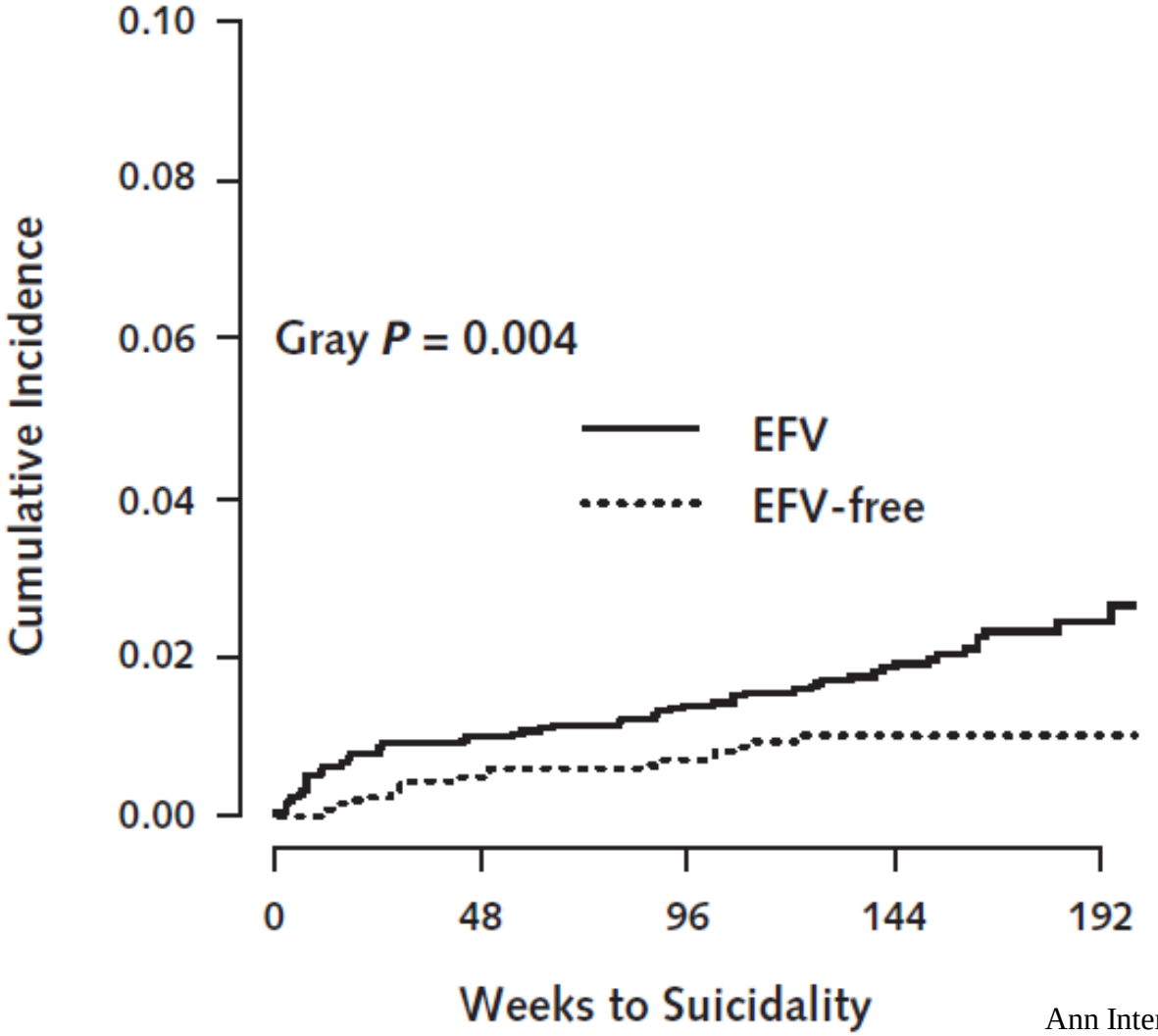
# ART & neurocognitive function

- ART improves HIV-associated neurocognitive dysfunction
- ACTG observational study of people stopping ART for median 4.5 years
- Neurocognitive tests IMPROVED after stopping ART, significantly more in those  on EFV
- Many ARVs, especially EFV (mostly its 8-OH metabolite) are toxic to neuronal cells in vitro

Neurology 2010;74(16):1260-6
Decloedt Exp Opin Drug Safety 2014

# EFV & suicidality

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



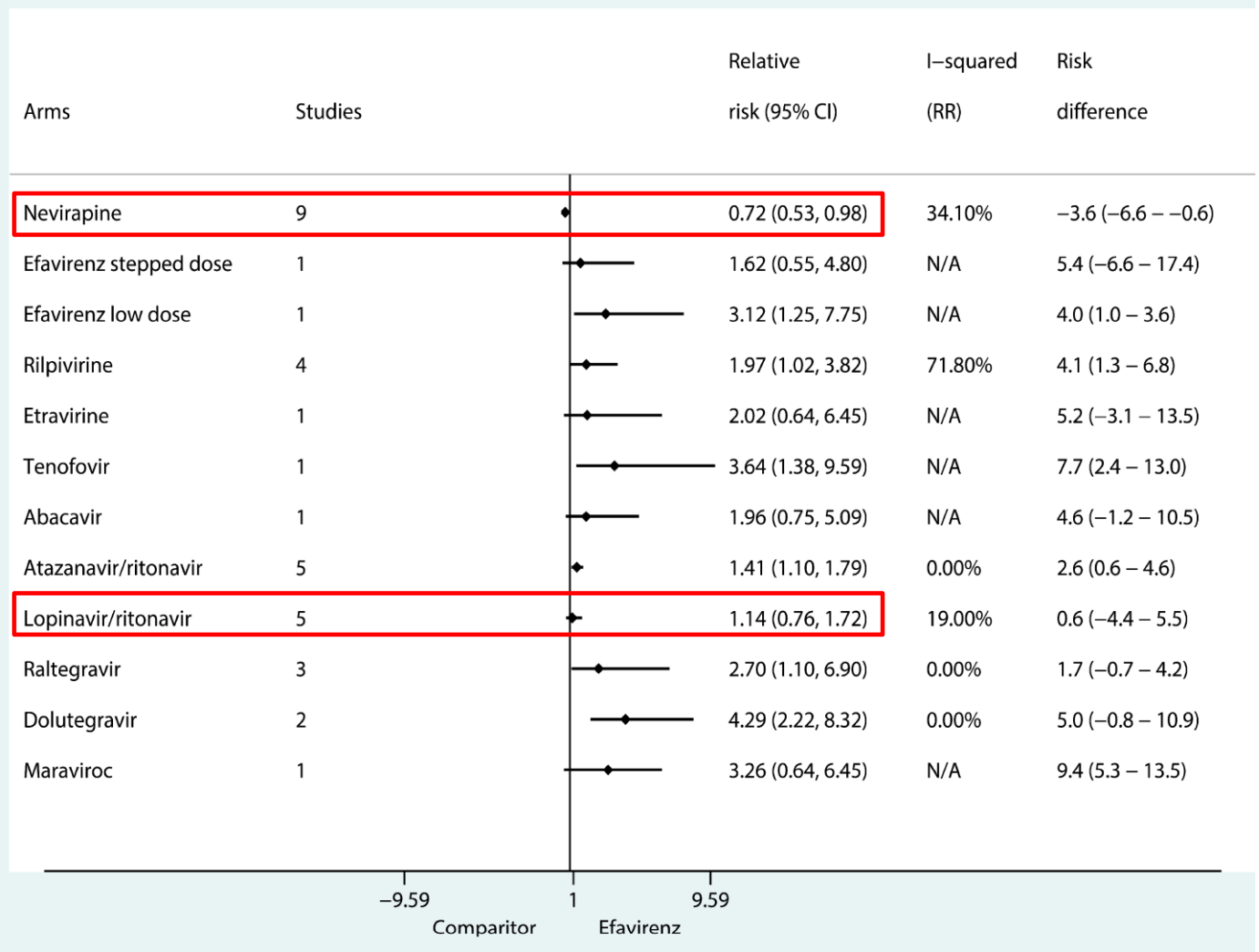

Ann Intern Med. 2014;161:1-10

# 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

# Meta-analysis: EFV discontinuations for toxicity



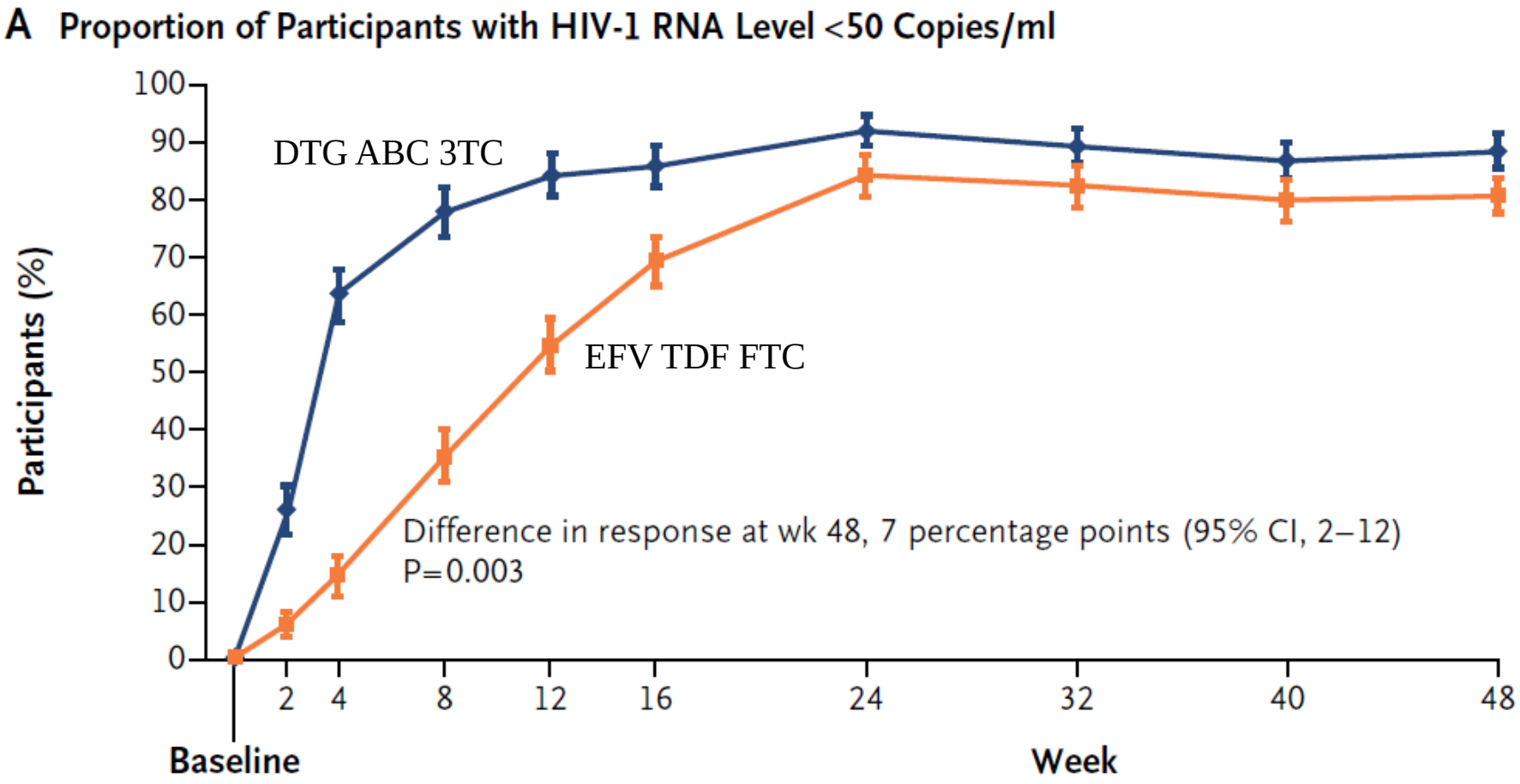

Ford JAIDS 2015

# EFV toxicity in SA

- High prevalence of slow metabolizer genotypes in SA (17% vs 3% Caucasians)
- Increased risk of dose-related toxicity:
  - Neuropsychiatric
  - Hepatitis
  - Lipids
  - Glucose

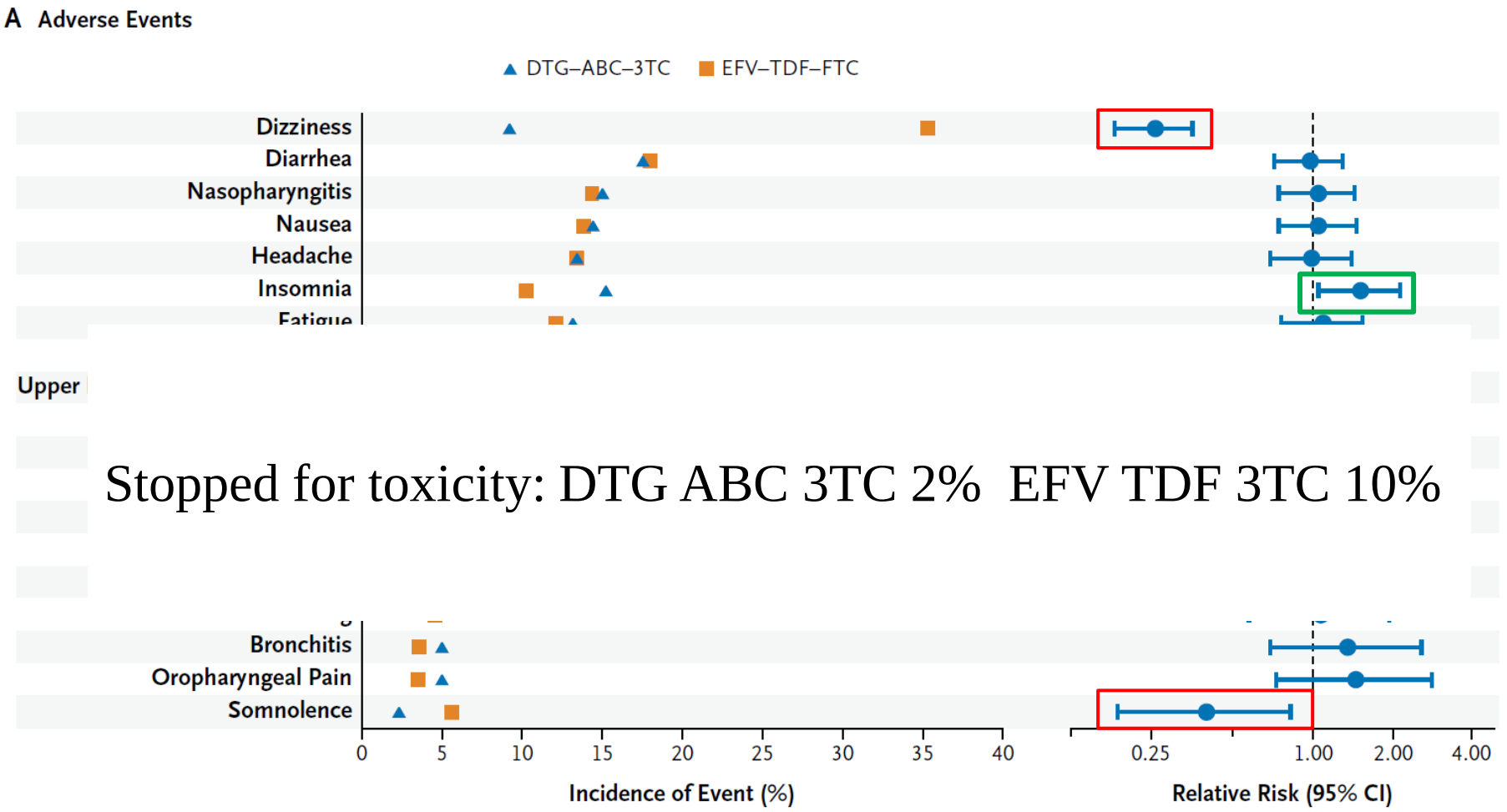
Sinxadi BJCP 2015
Antiviral therapy 2005; 10(4): 489 – 98
Sinxadi Medicine 2016
Haas AIDS 2004
Mollan IAS 2015

# Dolutegravir vs EFV in ART naive




N Engl J Med 2013;369:1807

# DTG vs EFV: Safety




Stopped for toxicity: DTG ABC 3TC 2%  EFV TDF 3TC 10%

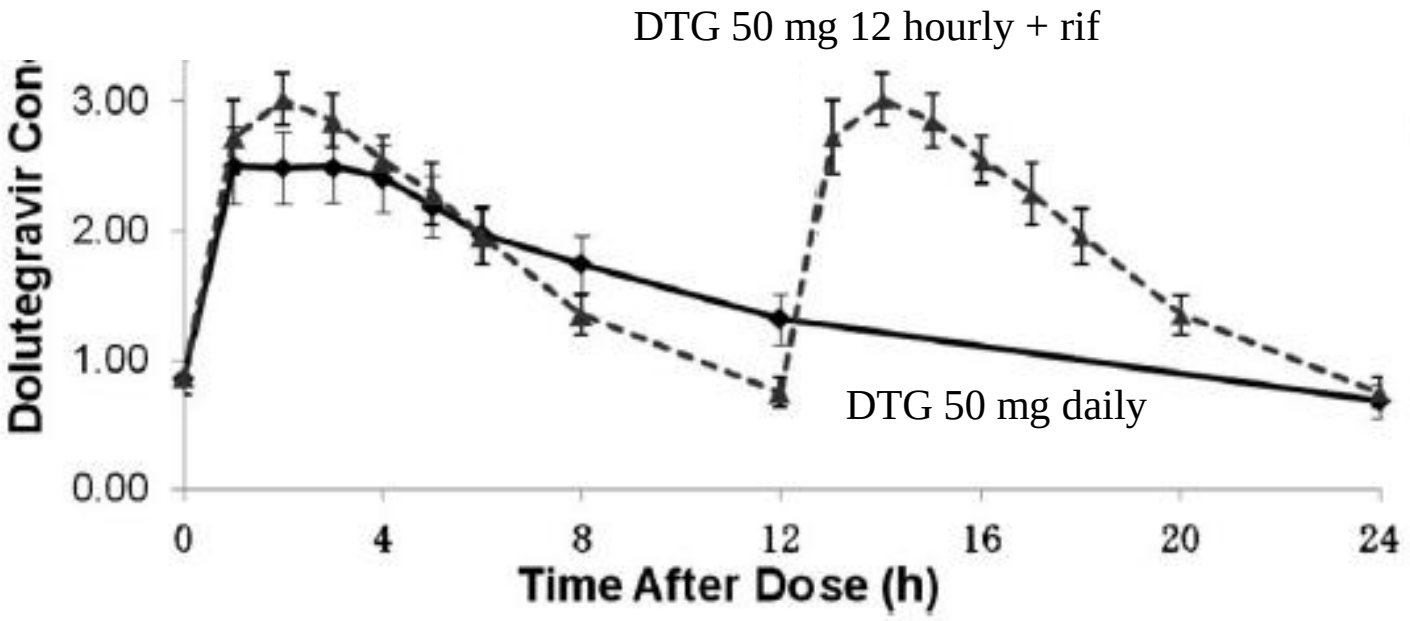
N Engl J Med 2013;369:1807

# 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 resistance hasn't been seen when used in initial therapy
- R263K mutation only confers low level resistance

Wainberg Front Pharmacol 2015

# Dolutegravir & rifampicin




$AUC_{0\text{-}24}$ DTG 50 mg/d 32.1

DTG 50 mg 12 hourly + rif 42.6

JAIDS 2013;62:21

# Conclusions

- EFV low barrier to resistance major drawback
- EFV toxicity has been under-estimated – no longer recommended 1st line in high-income countries
- The high prevalence of EFV slow metabolizer genotypes in SA increases risk of dose-related toxicity
- DTG is more effective, less toxic, much more robust – will virtually abolish need for 2nd line
- DTG will be cheaper to manufacture
- We should follow Botswana's lead & switch to the better drug