Efavirenz vs dolutegravir for 1st line ART: Is it time to change?

The argument AGAINST

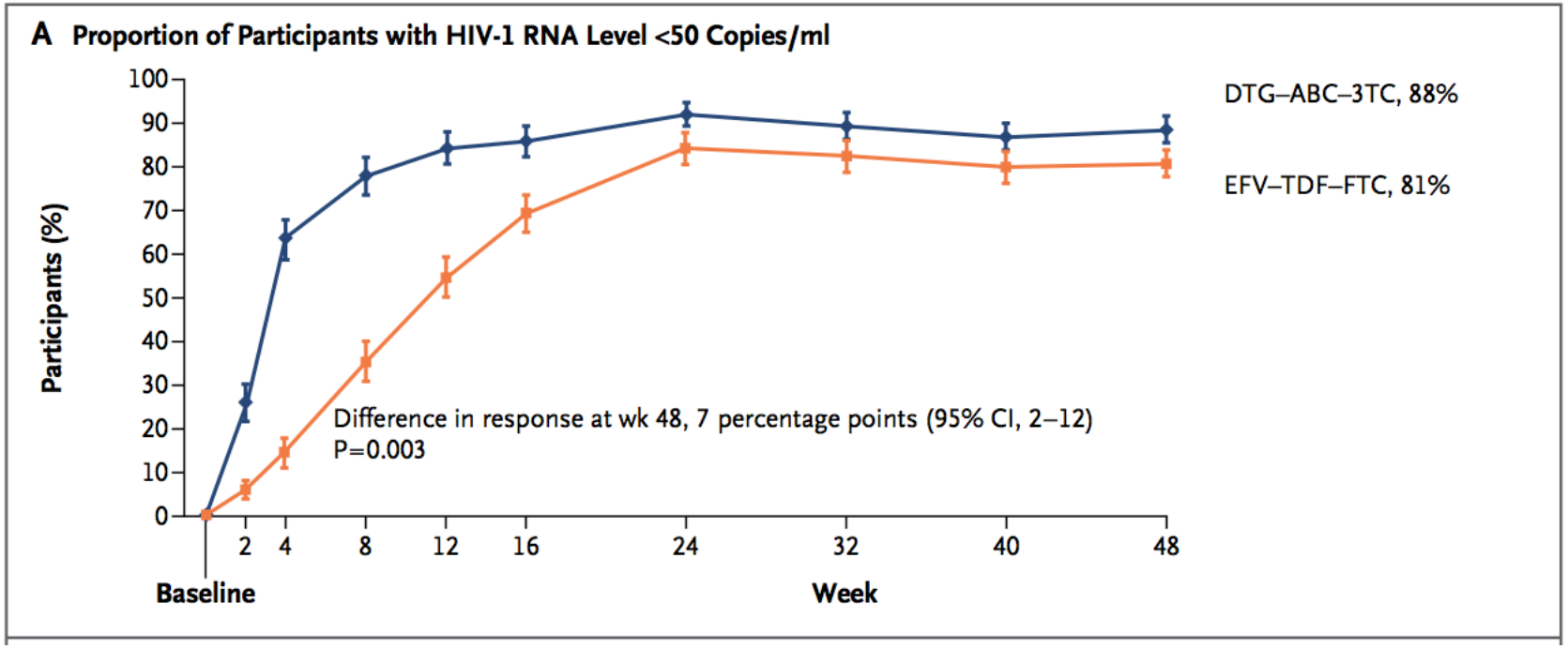
Graeme Meintjes

University of Cape Town

Benefits of dolutegravir

- Superior efficacy in SINGLE trial
- Side effect profile
- Resistance profile

Efficacy in SINGLE trial



Walmsley, NEJM 2013

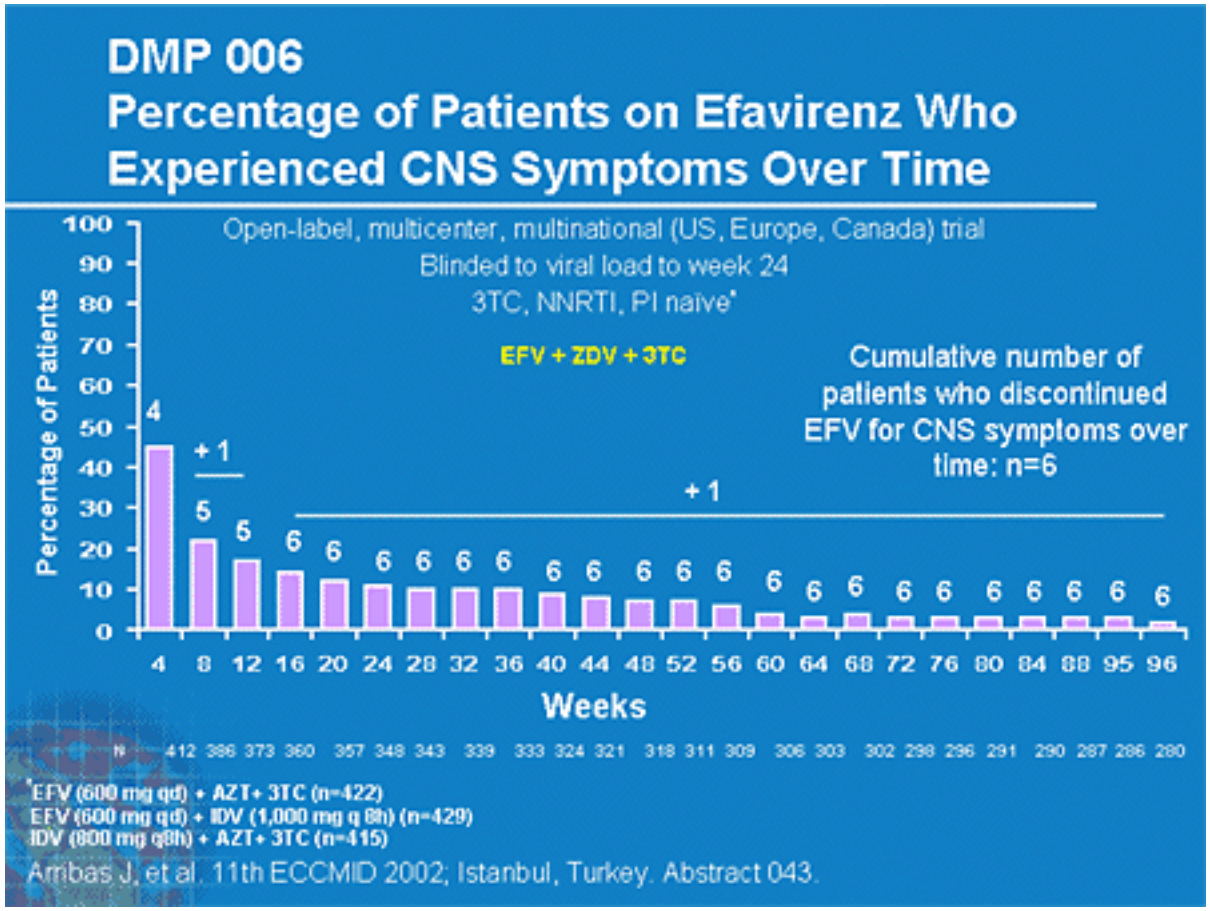
Virological efficacy

- SINGLE findings not driven by superior virological efficacy but by superior tolerability
- Protocol-defined virologic failure by week 48
  - Efavirenz arm: 4%
  - Dolutegravir arm: 4%
- Discontinuations due to adverse events were counted as failures & accounted for difference
  - Efavirenz arm: 10%
  - Dolutegravir arm: 2%

Options to switch to in patients have persistent efavirenz CNS side effects

- Rilpivirine
- Lower dose efavirenz (400mg nocte)
- Protease inhibitor

Efavirenz CNS side effects resolve with time despite patients staying on drug



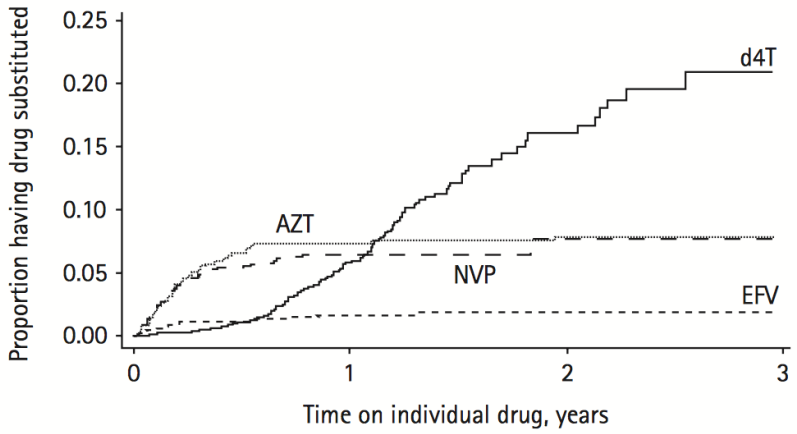
CNS symptoms of EFV
45% at week 4
< 5% in long term

Arribas
ECCMID 2002

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

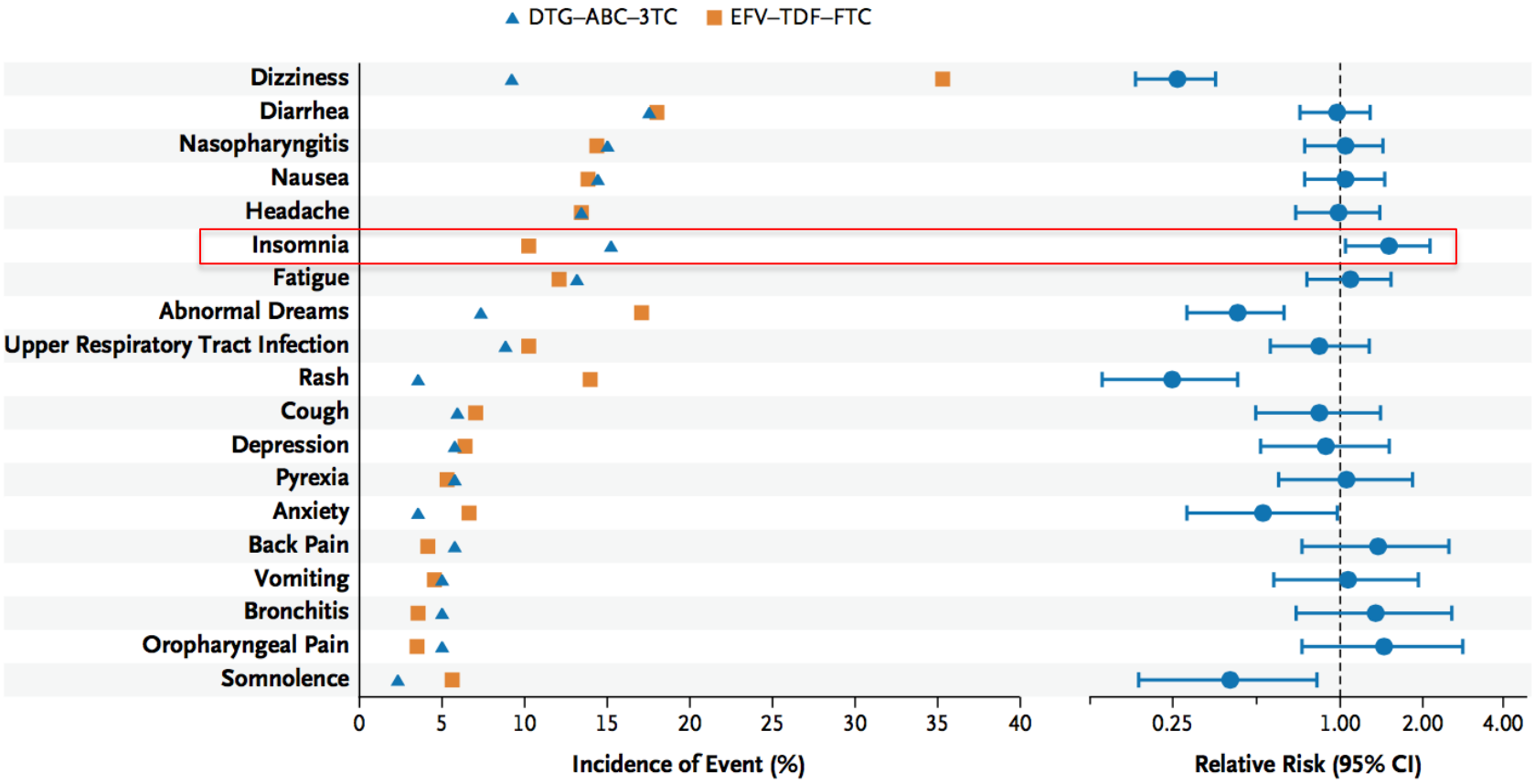


	n				Changed by 36 months, % (95% CI)
AZT	676	469	295	126	7.8 (5.9–10.3)
EFV	1,613	858	334	74	1.9 (1.3–2.8)
NVP	1,062	376	75	44	7.6 (5.3–10.9)
d4T	1,996	782	137	15	20.8 (16.2–26.5)

Over 3 years:
2% substituted efavirenz

Dolutegravir also has CNS side effects

Adverse events in SINGLE trial



Walmsley, NEJM 2013

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)

Van den Berk
Abstract 948, CROI 2016

Psychiatric disorders after starting dolutegravir: report of four cases

Dolutegravir is an integrase inhibitor with an excellent safety profile and antiviral activity. We report here four cases of patients who experienced psychiatric disorders. Symptoms resolved in three patients after stopping dolutegravir and in one patient who continued treatment. HIV healthcare professionals should pay attention to psychiatric disorders when beginning dolutegravir.

symptoms quickly disappeared. There was not any past history of psychiatric troubles.

Patient 2 is a 43-year-old woman treated with abacavir/lamivudine/atazanavir. Atazanavir was switched to dolutegravir because of metabolic adverse effects. After 1 month of treatment, she presented headaches, and felt

Kheloufi, AIDS 2015

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

Resistance

- Dolutegravir is more robust that efavirenz

But

- Current 1st & 2nd line regimens not doing badly
- And its still early days

IeDEA-Southern Africa Collaboration (8 ART cohorts)

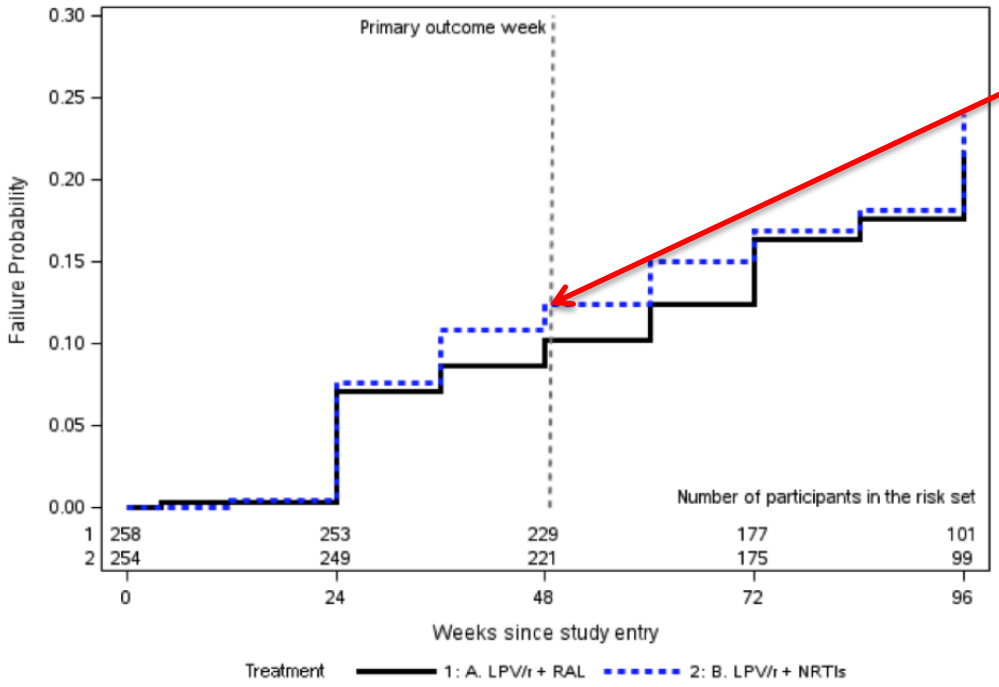
Measurement	12 mo		24 mo		36 mo	
	Female (n = 21,032)	Male (n = 10,702)	Female (n = 13,232)	Male (n = 6,826)	Female (n = 7,440)	Male (n = 3,950)
Viral load tests						
Total tested, n	13,529	6,600	8,280	3,798	4,225	1,958
Proportion suppressed[a]	0.87	0.86	0.86	0.86	0.93	0.95
Proportion missing data	0.36	0.38	0.37	0.44	0.43	0.50

93% of women and 95% of men had VL < 400 at 3 years on ART

Cornell, PLoS Medicine 2012

ACTG 5273: Second-line ART trial

Time to virological failure > 400 copies/ml



At week 48 on 2nd line
12% of patients had virological failure on LPV/r + 2NRTI despite >90% NRTI + NNRTI resistance at 1st line failure

Our current 2nd line performs well after 1st line failure

La Rosa, CROI 2016, Abstract 30

Drug's resistance profile always looks more robust when first used

Failure of lopinavir–ritonavir (Kaletra)-containing regimen in an antiretroviral-naive patient

The protease inhibitor (PI) lopinavir–ritonavir (Kaletra) combination is a potent antiretroviral drug, with a high resistance barrier [1]. Primary failure as a result of PI resistance has not previously been described in an antiretroviral-naive patient.

A 25-year-old black female South African patient was enrolled onto the Early Access Programme, 6 November 2000. The patient had no history of international travel.

Her baseline CD4 cell count was 282 cells/ml and her viral load was 325 000 copies/ml. (Roche Amplicor 1.5). She received 2 weeks of stavudine, didanosine and hydroxyurea in June 2000, but the treatment was

The initial sample, before starting therapy, showed M36I and L63P mutations. These are naturally occurring polymorphisms in subtype C viruses, in the protease gene.

On the sample taken on the failing regimen, the only reverse transcriptase mutation identified was M184V. The PI mutations identified were M36I, I54V, L63P and V82A. Lopinavir–ritonavir mutations are poorly characterized, but the first three are regarded as minor lopinavir–ritonavir mutations and the last is a multiple PI resistance mutation [2,3].

In addition, the PI sequences were sent to the Stanford database for drug resistance. The initial specimen before

Conradie et al, AIDS 2004

Why move away from NNRTI 1st line?

- The reason why dolutegravir was superior to efavirenz was because of **fewer switches**

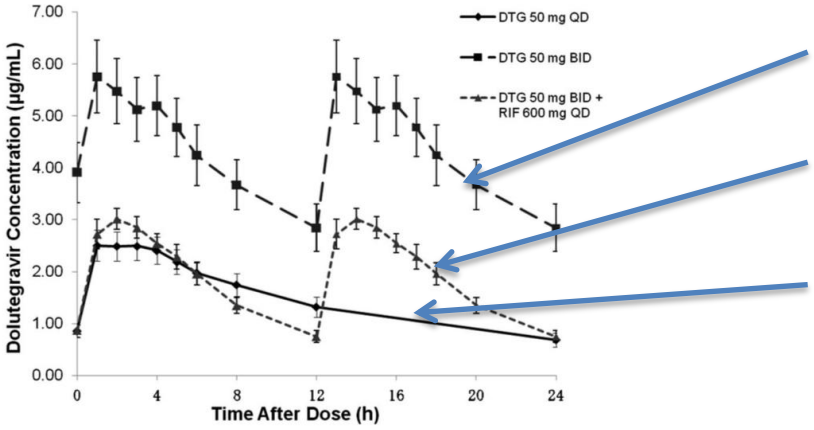
- If we stay with efavirenz but ensure those who develop severe or persistent CNS side effects are **switched from efavirenz to rilpivirine** this should result in similar virological outcomes to a dolutegravir regimen

- We then keep dolutegravir as a robust drug to use in **3rd line**, a select group of patients with adherence problems and few other options

Use in TB patients is complicated

- 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

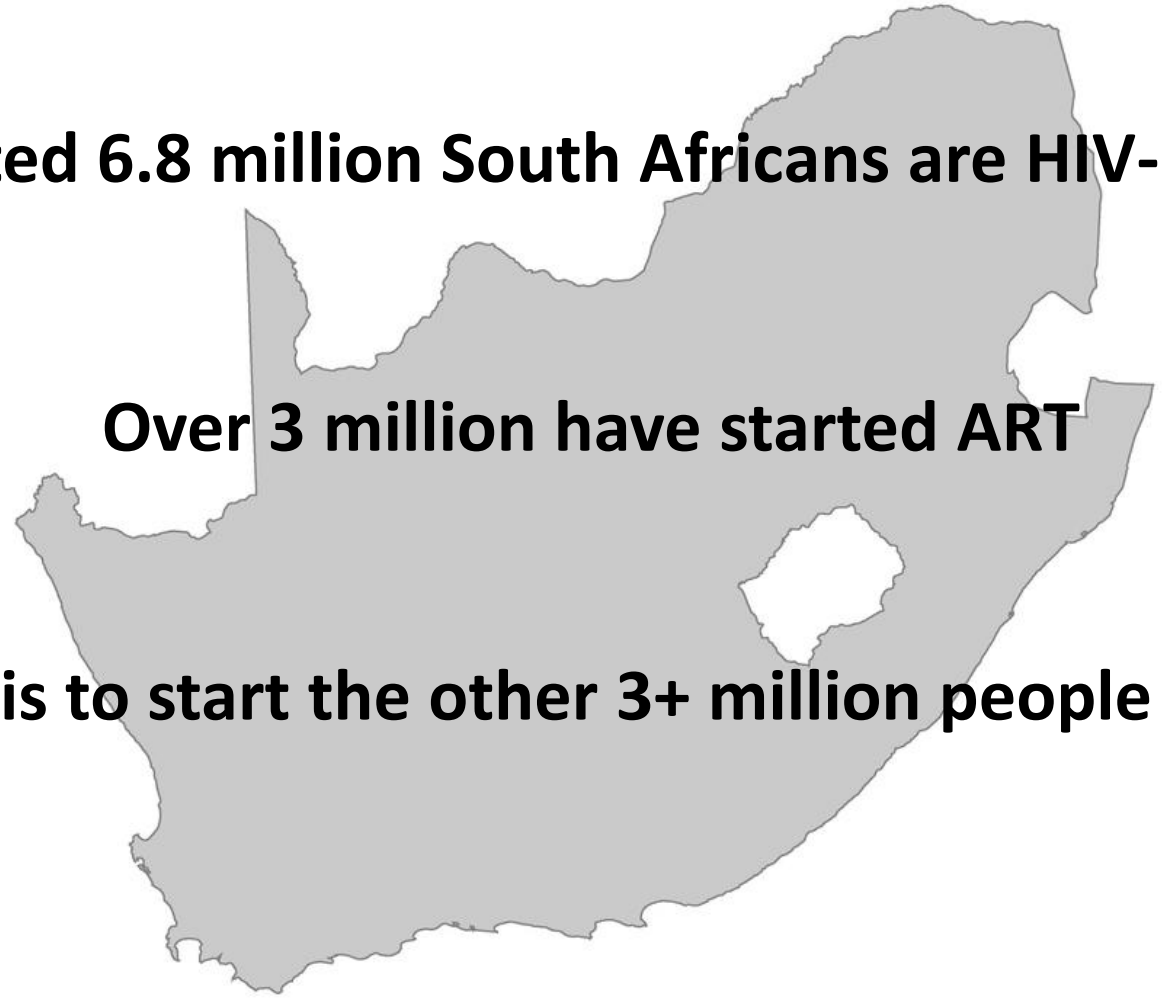
Dooley, JAIDS 2013

Use in TB patients is complicated

- However 12 hourly dosing
  - May compromise adherence
  - Needs clinicians to prescribe & counsel about additional dose
  - If FDC is used then will need to supply dolutegravir separately
- Dolutegravir results in faster VL drop and CD4 count rise
  - Could potentially increase risk of TB-IRIS
- These issues first need to be studied in a sufficiently powered RCT enrolling TB patients
  - Clinical trials to date have excluded TB patients

Programmatic issues

Estimated 6.8 million South Africans are HIV-infected



Over 3 million have started ART

Target is to start the other 3+ million people on ART

If we change to 1st line dolutegravir

(1) Efavirenz Cohort

1st line	2nd line	3rd line
2NRTI + EFV	2NRTI + LPV/r	2NRTI + DRV/r + Integrase inhibitor

If we change to 1st line dolutegravir

(1) Efavirenz Cohort

(2) Dolutegravir Cohort

If we change to 1st line dolutegravir

(1) Efavirenz Cohort

1st line	2nd line	3rd line
2NRTI + EFV	2NRTI + LPV/r	2NRTI + DRV/r + Integrase inhibitor

(3) Switch cohort

(2) Dolutegravir Cohort

1st line	2nd line	3rd line
2NRTI + DTG	2NRTI + LPV/r	2NRTI + DRV/r + NNRTI

Complexities that arise

- Three cohorts (each of several million people)
  - Requiring different 3rd line therapy
  - Will need health information systems that ensure 1st line history is reliably accessed to prescribe appropriate 3rd line
- Criteria for switch will need to be developed and adhered to
  - Failure to do this could compromise 1st & 3rd lines

Complexities that arise

- Currently no FDC containing dolutegravir
- Will need to ensure reliable forecasting and supply of ART to cover all 3 cohorts at each ART facility in South Africa
  - Efavirenz
  - Dolutegravir
  - Dolutegravir FDC when available
  - Dolutegravir individual tablets for TB patients even when have FDC

Summary of argument

- Dolutegravir does have attractive features
- However:
  - Current regimens are not doing badly
  - Other options if persistent CNS symptoms on efavirenz
  - Complexities in patients with TB and no trials data
  - With time *de novo* dolutegravir resistance is likely to emerge
- Switching to dolutegravir will introduce programmatic complexity that is not justified by the modest clinical benefits
- Better to keep dolutegravir for 3rd line

Primary ART resistance

	0–2 years after ART rollout	3–4 years after ART rollout	5–7 years after ART rollout	8–9 years after ART rollout	p value
East Africa	0·9 (0·5–1·6)	3·5 (2·1–5·7)	5·1 (2·6–9·9)	7·4 (4·2–12·9)	0·0006
Southern Africa	2·1 (1·6–2·6)	2·3 (1·6–3·3)	3·7 (2·5–5·4)	..	0·0006
West and central Africa	1·8 (1·1–3·1)	5·7 (4·0–8·0)	3·5 (2·5–5·0)	..	0·43
Latin America and the Caribbean	5·9 (4·1–8·4)	6·5 (4·7–9·0)	3·9 (2·7–5·8)	7·6 (4·8–12·2)	0·50

Data are % of population with with one more mutation as defined by the WHO surveillance drug resistance mutations list (95% CI). ..=no studies done 8–9 years after rollout.

Table 2: **Sensitivity analysis showing proportion of individuals with one or more drug-resistance mutation, by region and years after rollout of antiretroviral treatment (ART)**

Gupta, Lancet 2012

SINGLE trial: Serious adverse events

- DTG arm: 9%
- EFV arm: 8%

SINGLE trial:
Walmsley, NEJM 2013

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.