



Dolutegravir in first-, second- and third-line regimens



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Ezintsha

INVESTIGATE INNOVATE ADVANCE

Disclosures...

- Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care



O P T I M I Z E

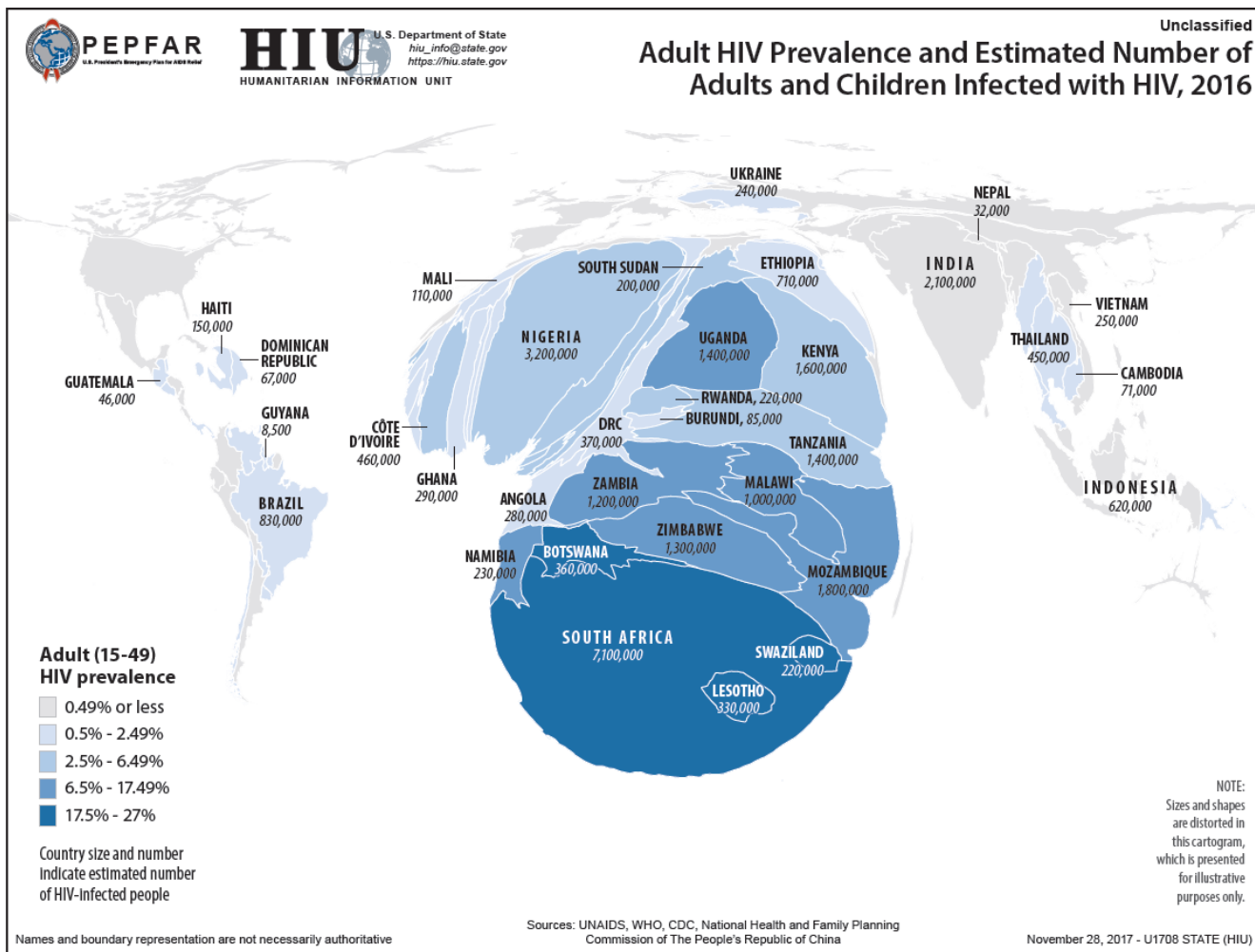


Challenges for SA

- **Increasing efavirenz resistance**
- **Re-entry to system – drive this resistance**
- **Stockout of singles**
- **Lots of pregnancies**
- **Patients getting older – increased co-morbidities**
- **(very small numbers of paeds)**



African HIV Burden



The Evolving HIV Treatment Paradigm

??????

- 3TC=lamivudine; ZDV=zidovudine



ZDV monotherapy



Triple-Drug Therapy

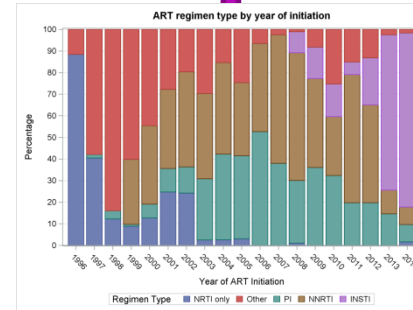


Single-Tablet Regimens

Long Acting Injectable?

The Integrase Era

HIV-1 discovered



1983
WITS RHI

1987

1995

1996

2006

2012–2013

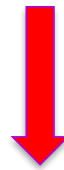
2017

2020



WHO/African regimens

Tenofovir + **XTC** + **Efavirenz**



Failure

AZT + **Lamivudine** + **PI** (lopinavir or atazanavir)

Failure

XTC, other nukes

Darunavir

Dolutegravir

Etravirine

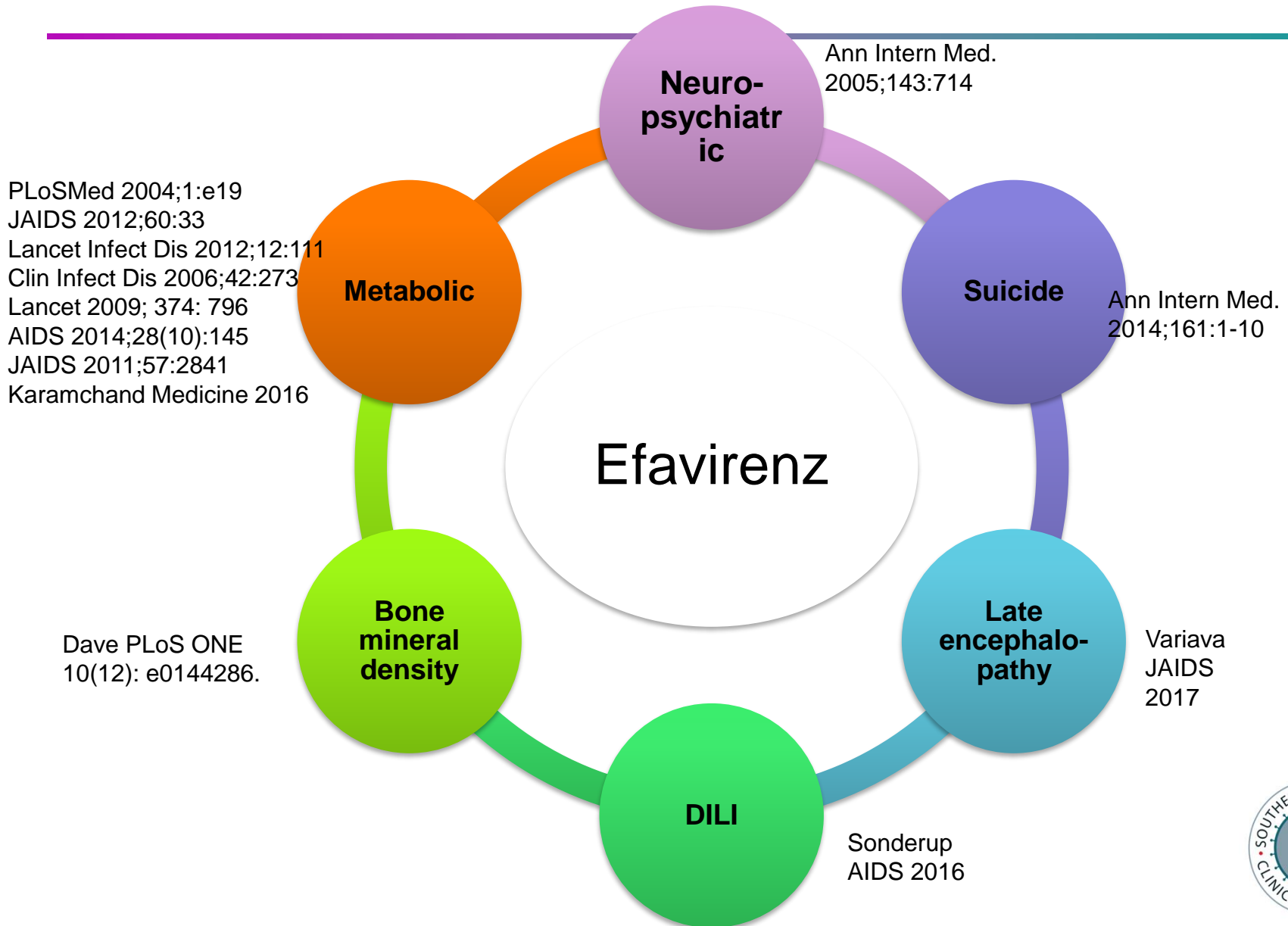
First-line...



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

Toxicity driver
Pill size
Low genetic barrier
Cost
Contraception
drug interactions

Efavirenz's warts...

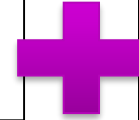


WHO/African regimens

AZT



Lamivudine



PI (lopinavir or atazanavir)

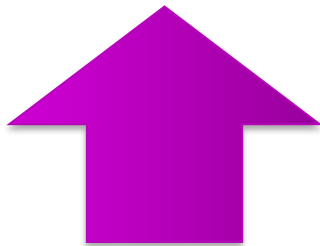
Failure

XTC, other nukes

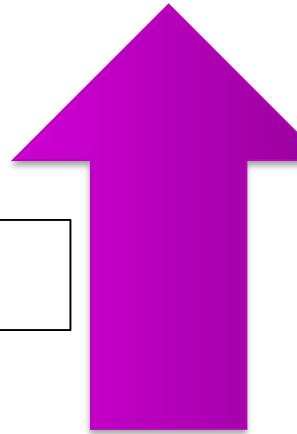
Darunavir

Dolutegravir

Etravirine



Toxicity driver
Pill size
Cost
Drug interactions
No FDCs



Safety issues with PIs

LPV/r

- GI upset
- Lipids
- Hepatitis
- Dysglycaemia



ATV/r

- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis



DRV/r

- Rash
- GI upset
- Hepatitis

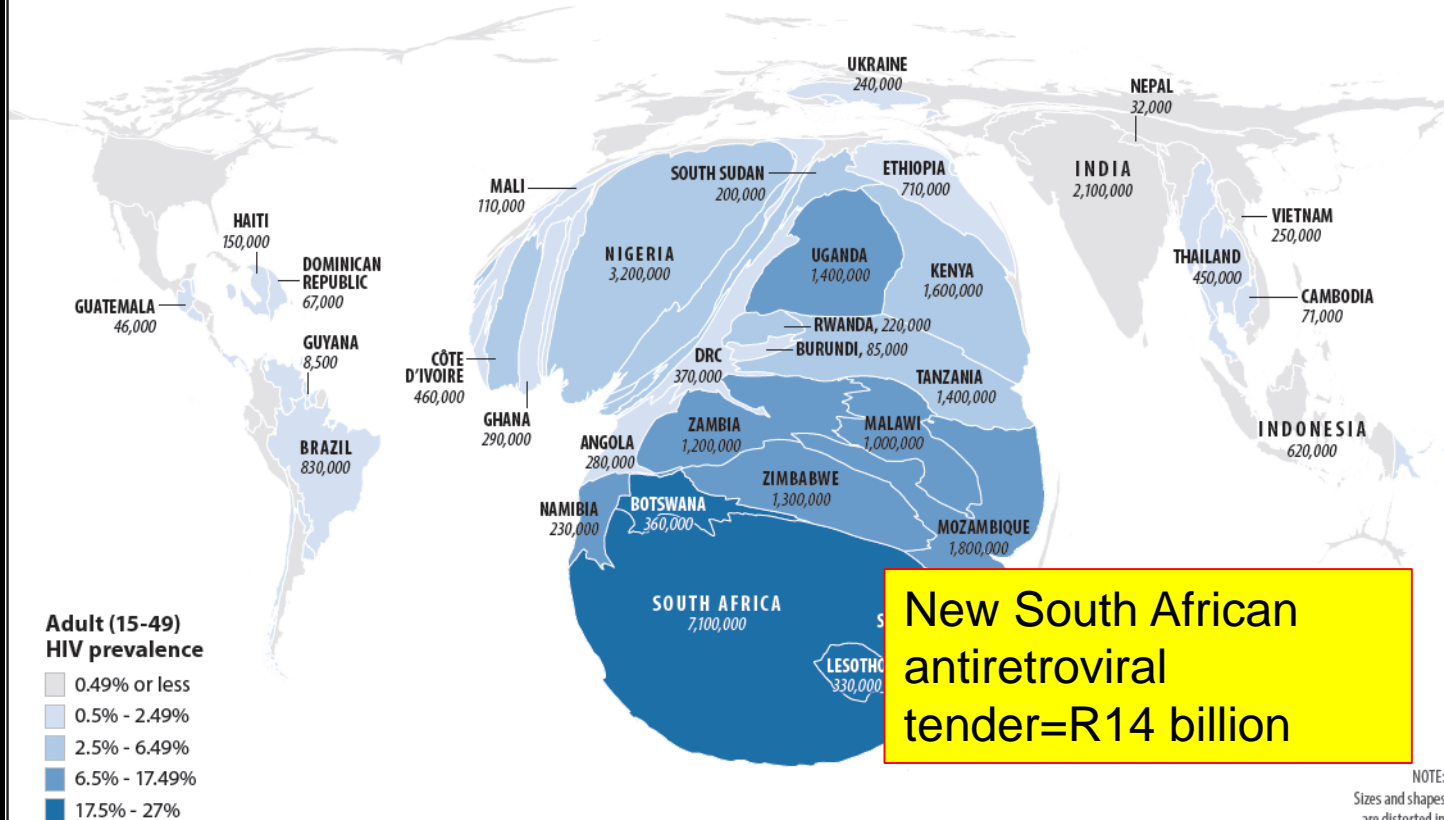


Treatment costs money!



Unclassified

Adult HIV Prevalence and Estimated Number of Adults and Children Infected with HIV, 2016



Adult (15-49) HIV prevalence

- 0.49% or less
- 0.5% - 2.49%
- 2.5% - 6.49%
- 6.5% - 17.49%
- 17.5% - 27%

Country size and number
Indicate estimated number
of HIV-infected people

**New South African
antiretroviral
tender=R14 billion**

NOTE:
Sizes and shapes
are distorted in
this cartogram,
which is presented
for illustrative
purposes only.

Names and boundary representation are not necessarily authoritative

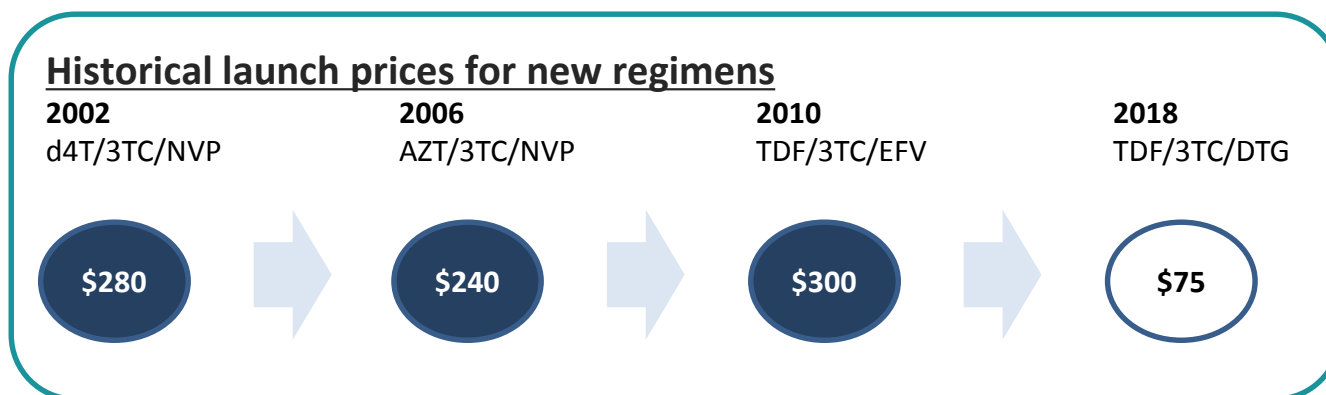
Sources: UNAIDS, WHO, CDC, National Health and Family Planning
Commission of The People's Republic of China

November 28, 2017 - U1708 STATE (HIU)



Ceiling price agreement announced

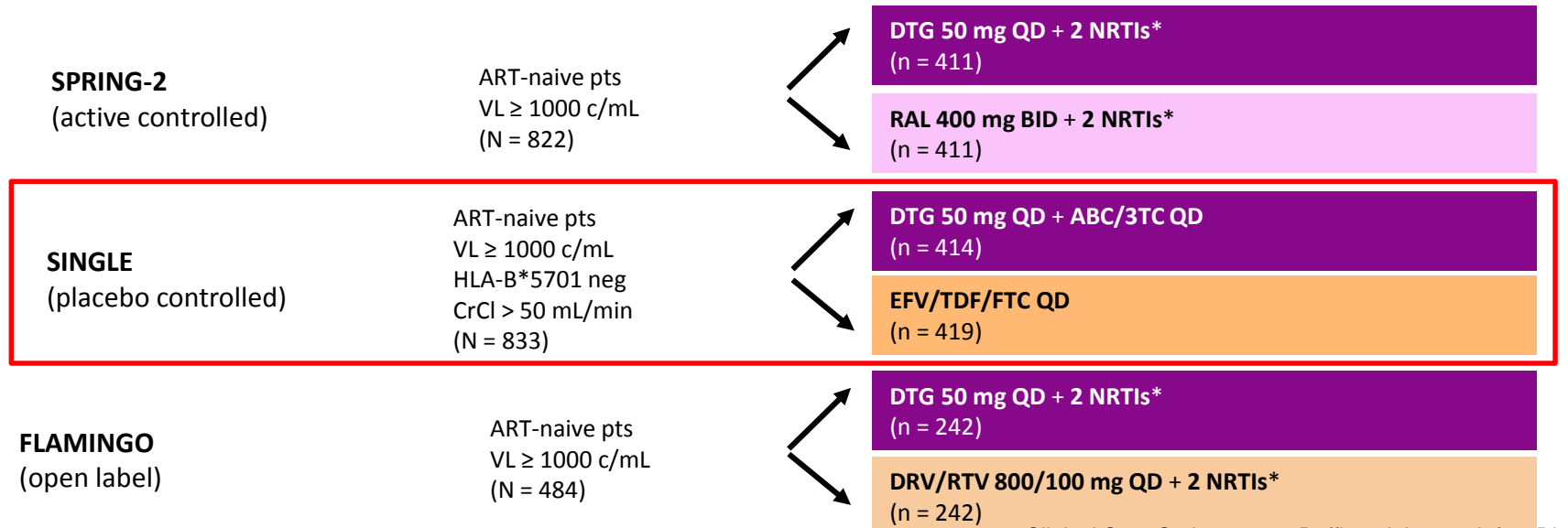
- This ceiling price agreement could yield billions of rand in savings through TLD rollout and enable widespread access to a clinically superior regimen



- The TLD agreement lasts four years: 01 April 2018 – 31 March 2022
- Applies to over 90 countries
- Results of collaboration from many partners: Governments of Kenya and South Africa, the Bill & Melinda Gates Foundation; Clinton Health Access Initiative; Global Fund to Fight AIDS, Tuberculosis and Malaria; President's Emergency Plan for AIDS Relief (PEPFAR); United Kingdom's Department for International Development; Unitaid; UNAIDS; and USAID, with Mylan Laboratories and Aurobindo Pharma.

We know DTG works in ARV-naïve patients

- Randomised, non-inferiority phase 3 studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at week 48

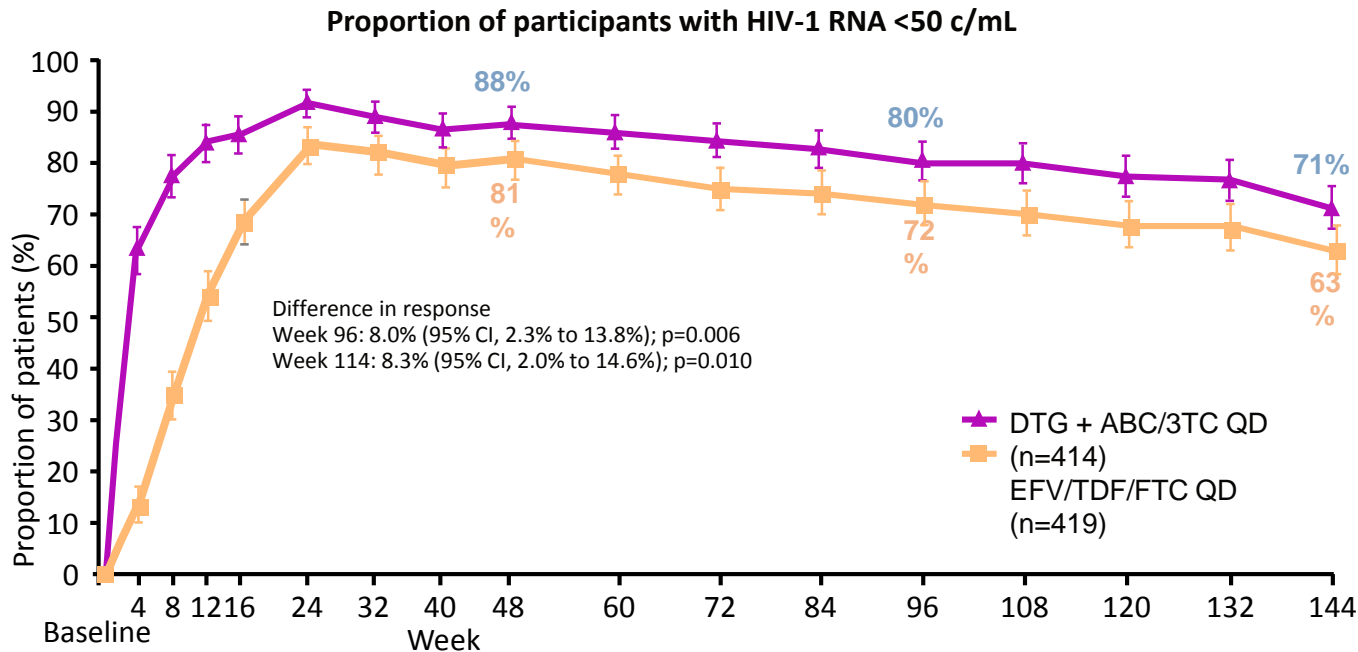


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

Clinical Care Options 2014; Raffi et al. Lancet Infect Dis 2013
Walmsley et al. N Engl J Med 2013; Clotet et al. Lancet 2014

SINGLE study: DTG vs. EFV

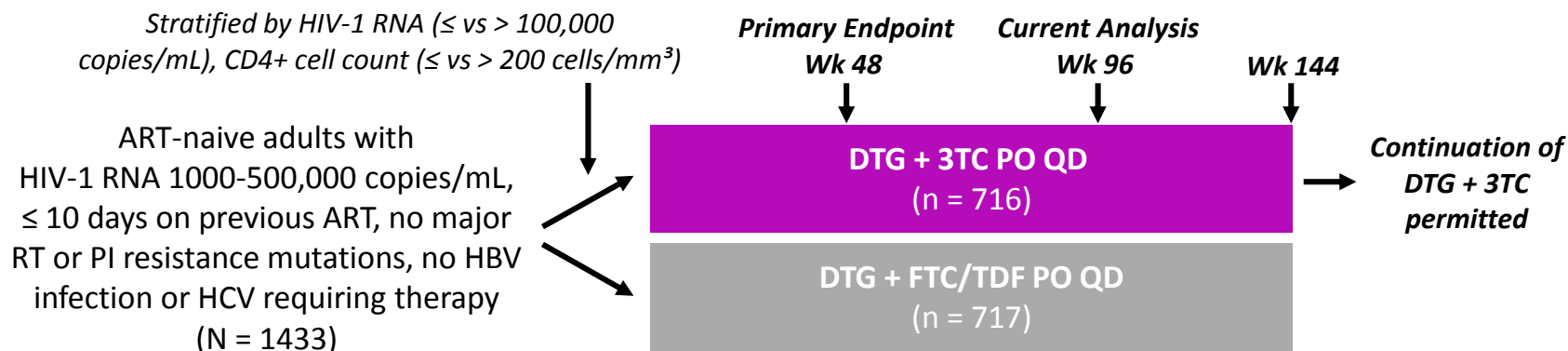
Better tolerated than EFV (but more insomnia)



Walmsley et al. N Engl J Med 2013; Walmsley et al. J Acquir Immune Defic Syndr 2015

GEMINI-1 and -2: DTG + 3TC in ART-Naive Adults

- Parallel, international, randomized, double-blind phase III noninferiority studies

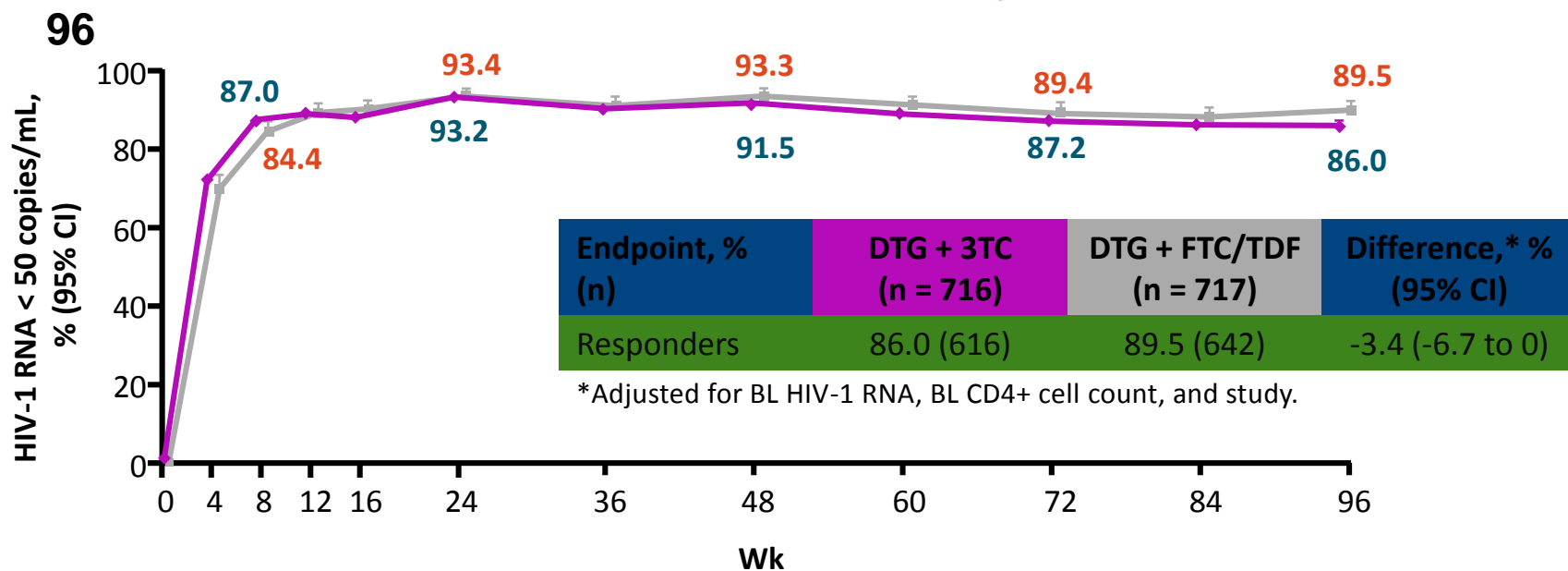


- Secondary endpoints at Wk 96: HIV-1 RNA $<$ 50 copies/mL (FDA Snapshot and TRDF analyses); AEs; resistance; changes from BL in bone, renal, and lipid parameters

Screening within 28 days of study start; studies double-blinded until Wk 96, open-label until Wk 144.

GEMINI-1 and -2: Virologic Response

- DTG + 3TC met criteria for **noninferior efficacy** vs DTG + FTC/TDF at Wk 96

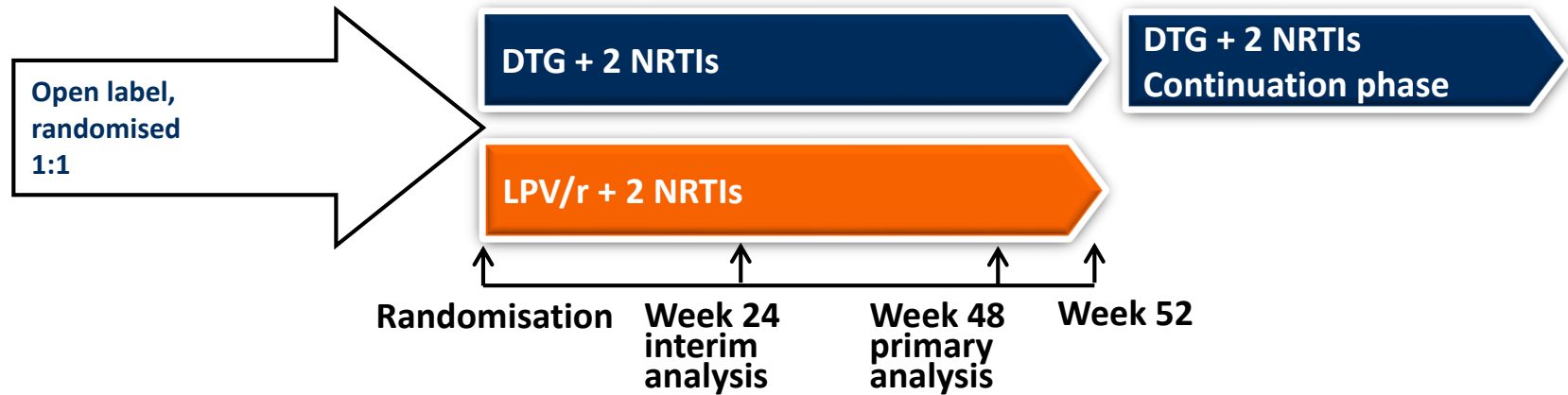


Rates of HIV-1 RNA \geq 50 copies/mL unchanged from Wk 48 to 96.

D/c for reasons other than AEs or death higher with DTG + 3TC at Wk 96 (8% vs 5% with 3-drug ART).

DAWNING: Study design

Open-label randomised noninferiority phase 3b study



- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥ 400 copies/mL on 2 occasions); no primary viral resistance to PIs or INSTIs
- **Stratification factors:** HIV-1 RNA (\leq or $>100,000$ copies/mL), number of fully active NRTIs in the investigational study background regimen (2 or < 2)
- **Primary endpoint:** proportion with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

DAWNING: Safety

Safety outcome, n (%)	DTG + 2 NRTIs (n = 314)*	LPV/r + 2 NRTIs (n = 310)
Any AE	223 (71)	244 (79)
AE in ≥ 5% in either arm		
• Diarrhoea	28 (9)	105 (34)
• Upper RTI	45 (14)	43 (14)
• Headache	25 (8)	17 (5)
• Nausea	10 (3)	30 (10)
• Lower RTI	13 (4)	14 (5)
• Anaemia	11 (4)	15 (5)
• Vomiting	5 (2)	21 (7)
Any neuropsychiatric AE	19 (6)	17 (5)

*Includes 2 subjects randomised to LPV/r but treated with DTG

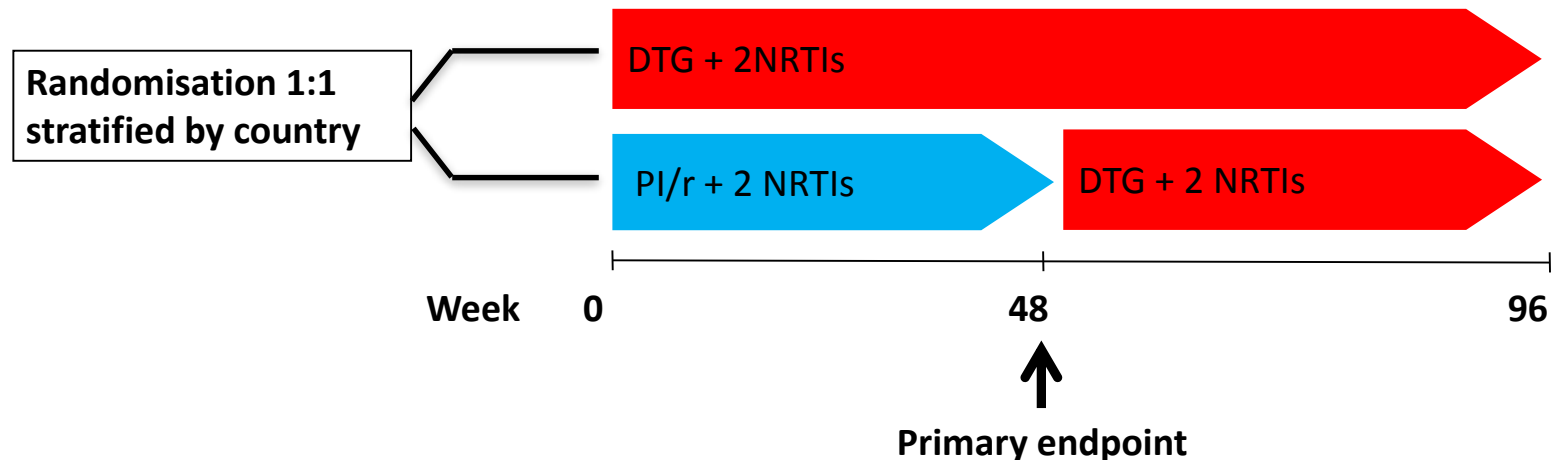
Safety outcome, n (%)	DTG + 2 NRTIs (n = 314)*	LPV/r + 2 NRTIs (n = 310)
Drug-related AEs	50 (16)	119 (38)
• Grade 2-4	11 (4)	44 (14)
○ Diarrhoea	1 (< 1)	23 (7)
○ Nausea	0	6 (2)
Serious AEs or deaths [†]	20 (6)	20 (6)
Drug-related serious AEs	3 (< 1)	2 (< 1)
AEs leading to withdrawal	8 (3)	18 (6)

[†]Fatal serious AEs: DTG, n = 2 (pneumonia, IRIS-associated TB); LPV/r, n = 3 (pneumonia, encephalitis/IRIS, cerebral toxoplasmosis/EBV infection/IRIS)

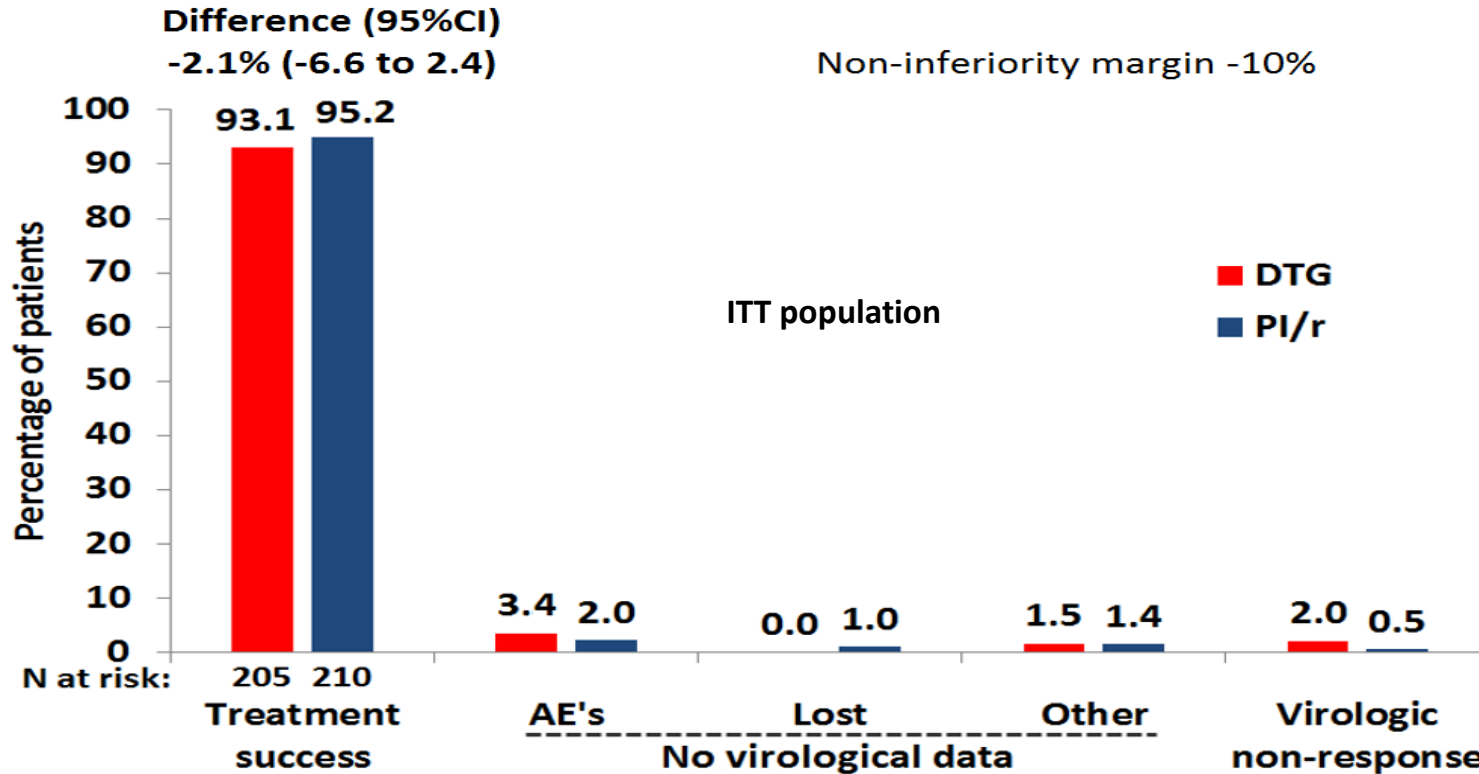
Aboud M, et al. AIDS 2018. Abstract THPEB040.

Switching from a boosted protease inhibitor (PI/r) based regimen to a dolutegravir (DTG) regimen in virologically suppressed patients with high cardiovascular risk (Framingham score > 10% or age > 50 years) is non-inferior and decreases lipids: The NEAT 022 study

J.M. Gatell¹, L. Assoumou², G. Moyle³, L. Waters⁴, E. Martinez⁵, H.-J. Stellbrink⁶, G. Guaraldi⁷, S. de Wit⁸, F. Raffi⁹, A. Pozniak¹⁰ on behalf of NEAT022 Study Group



Results: Co-primary efficacy endpoint



WHO Review

Safety and Efficacy of DTG and EFV600 in 1st line ART (summary 2018 WHO Sys Review & NMA)

major outcomes	DTG vs EFV ₆₀₀	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	DTG better	moderate
Treatment discontinuation	DTG better	high
CD4 recovery (96 weeks)	DTG better	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

WHO, 2018

WHO 2019 guidelines

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (incl. women of childbearing potential and pregnant women)	Two NRTIs + DTG	Two NRTIs + (ATV/r or LPV/r)	DRV/r + DTG + 1–2 NRTIs (if possible, consider optimisation using genotyping)
	Two NRTIs + EFV	Two NRTIs + DTG	
Children (0–10 years)	Two NRTIs + DTG	Two NRTIs + (ATV/r or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG	
	Two NRTIs + NNRTI	Two NRTIs + DTG	

- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR¹
 - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

1. [http://www.who.int/hiv/pub/arv/arv-2016/en/World Health Organization. HIV treatment interim guidance](http://www.who.int/hiv/pub/arv/arv-2016/en/World%20Health%20Organization.%20HIV%20treatment%20interim%20guidance). Accessed August 2018

Why INSTI?

- All well tolerated
- Highly effective
- New reference for “third drug”



Which INSTI agents are we talking about?

▪ Raltegravir

- Well studied, relatively widely registered
- Can be used in paed (>4 weeks)
- Had a role in PEP, Rx
- Expensive, high mg, twice daily till recently, no FDC
- Use in lower income countries largely confined to third line
- Unlikely to change in next 5 years – cost, co-formulation, TB, resistance barrier
- Role in children
- ? Any role in adults

▪ Elvitegravir

- QUAD-Stribild
- First drug registered as FDC
- 'Boosted' – lots of drug interactions
- Limited registration, Gilead drug
- Expensive, but potential for price reduction
- Unlikely to change in next 5 years – cost, TB, pregnancy
- In fact, unlikely to be around!

▪ Bictegravir

- Very similar to dolutegravir
- Co-formulated with TAF
- Very limited data in Africa
- Almost no pregnancy data
- TB data – high drug interaction potential
- ?role in our setting

▪ Cabotegravir

- Phase 2-3 as prevention and treatment
- Injectable
- 4 or 8 weekly
- For treatment: switch strategy with injectable rilpivirine
- Remarkably well tolerated! May be a more popular than first blush

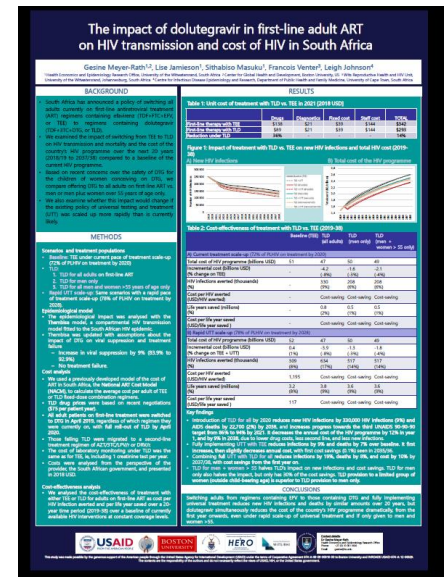
Why dolutegravir?



- **Very well tolerated**
- **Highly effective**
 - Low mg, co-formulation with TDF and TAF by generics (ABC co-formulation registered)
 - Resistance profile compelling
 - Creatinine clearance issue?
 - TB a problem, but ?double dosing
- **Neuropsychiatric**
- **Neural tube defects**
- **Weight gain - NEW**

“Dolutegravir in first line therapy has by far the highest impact in getting to the last 90 for South Africa”

Professor Gesine Meyer-Rath -Boston University/HE²RO



... reduces infections by 19%, deaths by 8%, and cost by 10% by 2037/38, with cost savings from the first year on.

The impact of dolutegravir in first-line adult ART on HIV transmission and cost of HIV in South Africa

Gesine Meyer-Rath^{1,2}, Lise Jamieson¹, Sithabiso Masuku¹, Francois Venter³, Leigh Johnson⁴

¹Health Economics and Epidemiology Research Office, University of the Witwatersrand, South Africa; ²Center for Global Health and Development, Boston University, US; ³With Reproductive Health and HIV Unit, University of the Witwatersrand, Johannesburg, South Africa; ⁴Centre for Infectious Disease Epidemiology and Research, Department of Public Health and Family Medicine, University of Cape Town, South Africa

BACKGROUND

- South Africa has announced a policy of switching all adults currently on first-line antiretroviral treatment (ART) regimens containing efavirenz (EFV)+ZIDV+FTC, or TEE, to regimens containing dolutegravir (DTG)+FTC+DTG, or TLD.
- We examined the impact of switching from TEE to TLD on HIV transmission and mortality and the cost of the country's HIV programme over the next 20 years (2018/19 to 2037/38) compared to a baseline of the current HIV programme.
- Based on recent concerns over the safety of DTG for the children of women conceiving on DTG, we compare offering DTG to all adults on first-line ART vs men or men plus women over 55 years of age only.
- We also examine whether this impact would change if the existing policy of universal testing and treatment (UTT) was scaled up more rapidly than is currently likely.

METHODS

- Scenarios and treatment populations**
- Baseline: TEE under current pace of treatment scale-up (72% of PLHIV on treatment by 2020)
 - TLD:
 - TLD for all adults on first-line ART
 - TLD for men only
 - TLD for all men and women >55 years of age only
 - Rapid UTT scale-up: Same scenarios with a rapid pace of treatment scale-up (78% of PLHIV on treatment by 2020)
- Epidemiological model**
- The epidemiological impact was analysed with the Themboisa model, a compartmental HIV transmission model fitted to the South African HIV epidemic.
 - Themboisa was updated with assumptions about the impact of DTG on viral suppression and treatment failure
 - Increase in viral suppression by 9% (83.9% to 92.9%)
 - No treatment failure.
- Cost analysis**
- We used a previously developed model of the cost of ART in South Africa, the National ART Cost Model (NACM), to calculate the average cost per adult of TEE or TLD fixed-dose combination regimens.
 - TLD drug prices were based on recent negotiations (\$75 per patient year).
 - All adult patients on first-line treatment were switched to DTG in April 2019, regardless of which regimen they were currently on, with full roll-out of TLD by April 2020.
 - Those failing TLD were migrated to a second-line treatment regimen of AZT/3TC/FTC or DRV/z.
 - The cost of laboratory monitoring under TLD was the same as for TEE, including 1 creatinine test per year.
 - Costs were analysed from the perspective of the provider, the South African government, and presented in 2018 USD.
- Cost-effectiveness analysis**
- We analysed the cost-effectiveness of treatment with either TEE or TLD for adults on first-line ART as cost per HIV infection averted and per life year saved over a 20-year time period (2019-38) over a baseline of currently available HIV interventions at constant coverage levels.

RESULTS

Table 1: Unit cost of treatment with TLD vs. TEE in 2021 (2018 USD)

	Drugs	Diagnostics	Fixed cost	Staff cost	TOTAL
First-line therapy with TEE	\$138	\$21	\$39	\$144	\$342
First-line therapy with TLD	\$89	\$21	\$39	\$144	\$293
Reduction under TLD	36%				14%

Figure 1: Impact of treatment with TLD vs. TEE on new HIV infections and total HIV cost (2019-38)



Table 2: Cost-effectiveness of treatment with TLD vs. TEE (2019-38)

	Baseline (TEE)	TLD (all adults)	TLD (men only)	TLD (men + women > 55 only)
A) Current treatment scale-up (72% of PLHIV on treatment by 2020)				
Total cost of HIV programme (billions USD)	51	47	50	49
Incremental cost (billions USD)	-	-4.2 (-8%)	-1.6 (-3%)	-2.1 (-4%)
HIV infections averted (thousands)	-	330 (9%)	208 (6%)	208 (6%)
Cost per HIV averted (USD/HIV averted)	-	Cost-saving	Cost-saving	Cost-saving
Life years saved (millions)	-	0.8 (2%)	0.5 (1%)	0.5 (1%)
Cost per life year saved (USD/life year saved)	-	Cost-saving	Cost-saving	Cost-saving
B) Rapid UTT scale-up (78% of PLHIV on treatment by 2020)				
Total cost of HIV programme (billions USD)	52	47	50	49
Incremental cost (billions USD)	0.4 (1%)	-3.9 (-8%)	-1.3 (-3%)	-1.8 (-4%)
HIV infections averted (thousands)	309 (6%)	634 (17%)	517 (14%)	517 (14%)
Cost per HIV averted (USD/HIV averted)	1,195	Cost-saving	Cost-saving	Cost-saving
Life years saved (millions)	3.2 (8%)	3.8 (9%)	3.6 (9%)	3.6 (9%)
Cost per life year saved (USD/life year saved)	117	Cost-saving	Cost-saving	Cost-saving

Key findings

- Introduction of TLD for all by 2020 reduces new HIV infections by 330,000 HIV infections (9%) and AIDS deaths by 22,700 (24%) by 2038, and increases progress towards the third UNAIDS 90-90-90 target from 85% to 94% by 2021. It decreases the annual cost of the HIV programme by 12% in year 1, and by 9% in 2038, due to lower drug costs, less second line, and less new infections.
- Fully implementing UTT with TEE reduces infections by 9% and deaths by 7% over baseline. It first increases, then slightly decreases annual cost, with first cost savings (0.1%) seen in 2035/36.
- Combining full UTT with TLD for all reduces infections by 19%, deaths by 9%, and cost by 10% by 2037/38, with cost savings from the first year on.
- TLD for men + women > 55 halves TLD's impact on new infections and cost savings. TLD for men only also halves the impact, but only has 30% of the cost savings. TLD provision to a limited group of women (outside child-bearing age) is superior to TLD provision to men only.

CONCLUSIONS

Switching adults from regimens containing EFV to those containing DTG and fully implementing universal treatment reduces new HIV infections and deaths by similar amounts over 20 years, but dolutegravir simultaneously reduces the cost of the country's HIV programme dramatically, from the first year onwards, even under rapid scale-up of universal treatment and if only given to men and women >55.



This study was made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of Cooperative Agreement AID-A-09-00219-00 to Boston University and P4100-15-0-0000. The contents are the responsibility of the authors and do not necessarily reflect the views of USAID, USAID, or the United States Government.

Thanks Gesine Meyer-Rath; IAS July 2018

First-line dream...



Cost driver
Toxicity

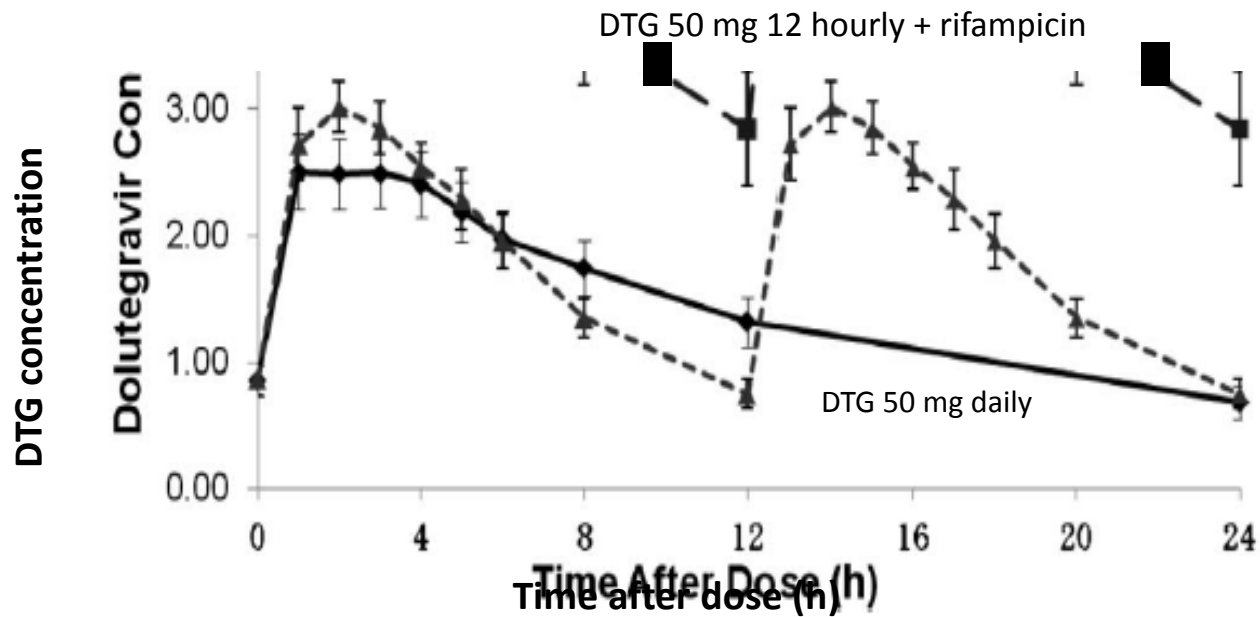
Desirable Property	EFV/TDF/FT C
High resistance barrier	No
Well tolerated	Not initially
No lab tox monitoring	TDF creat
Safe in pregnancy	Yes
Low pill burden	Yes FDC
Once a day	Yes
Use with TB (rif)	Yes

Toxicity driver
Pill size
Low genetic barrier
Cost
Contraception
drug interactions

What about drug interactions?

InSTI	Backbone	Key drug interactions
All regimens		Polyvalent cation–containing supplements/medication (including antacids), rifampicin
BIC	FTC/TAF	Metformin
DTG	ABC/3TC FTC/TAF FTC/TDF	Metformin
	RPV	Metformin, PPIs
EVG/ COBI	FTC/TAF FTC/TDF	Statins, inhaled/injected/systemic steroids
RAL	FTC/TAF FTC/TDF	

TB: DTG and rifampicin



AUC₀₋₂₄ DTG 50 mg/d 32.1
DTG 50 mg 12 hourly + rifampicin 42.6

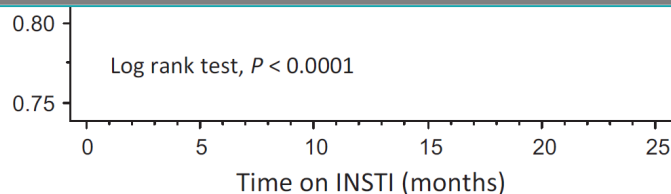
Dooley KE et al, JAIDS 2013;62:21-7

New drugs in the REAL real world...

Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice

AIDS 2016

Mark G.J. de Boer^a, Guido E.L. van den Berk^b, Natasja van Holten^a, Josephine E. Oryszczyn^b, Willemien Dorama^a, Daoud ait Moha^b and Kees Brinkman^b



Older age (> 60 years), vs. younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, vs. no ABC	2.42	1.38–4.24	0.002
DTG start in 2016, vs. in 2014/2015	11.36	4.31–29.41	< 0.0001

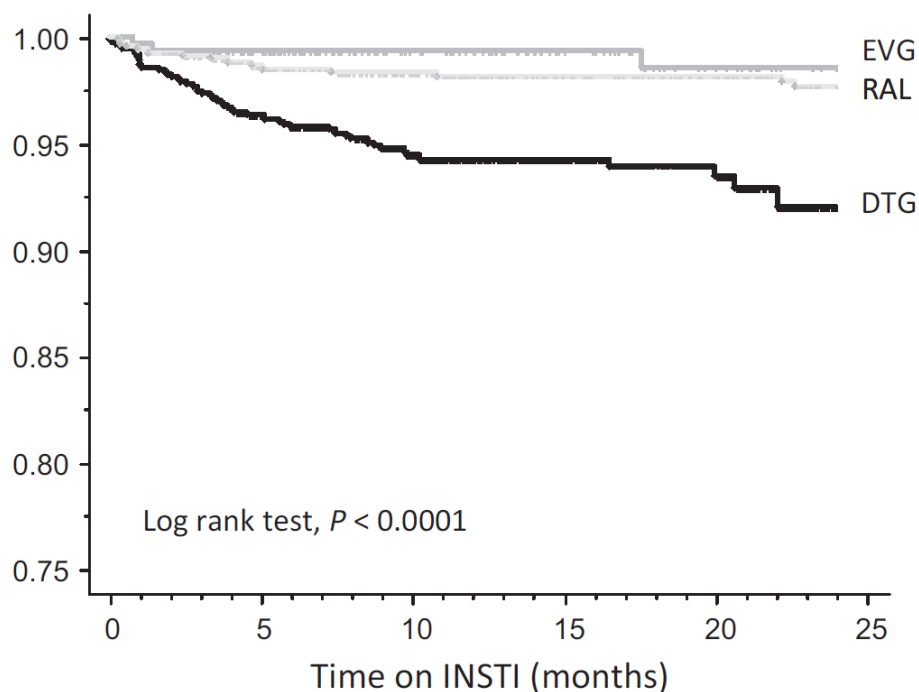
ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615; Hsu et al. CROI 2017 abstract #664



DTG in the real world...

Discontinuation due to neuropsychiatric AE



Factors associated with DTG discontinuation

	RH	95% CI	<i>P</i>
Any AE			
Female, vs. male gender	2.81	1.46–5.41	0.002
Older age (> 60 years), vs. younger age	2.88	1.56–5.34	< 0.001
ABC with DTG initiated, vs. no ABC	2.63	1.61–4.29	0.0001
DTG start in 2016, vs. in 2014/2015	8.93	3.76–21.28	< 0.0001
Neuropsychiatric AEs			
Female, vs. male gender	2.64	1.23–5.65	0.01
Older age (> 60 years), vs. younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, vs. no ABC	2.42	1.38–4.24	0.002
DTG start in 2016, vs. in 2014/2015	11.36	4.31–29.41	< 0.0001

ABC, abacavir; CI, confidence interval.

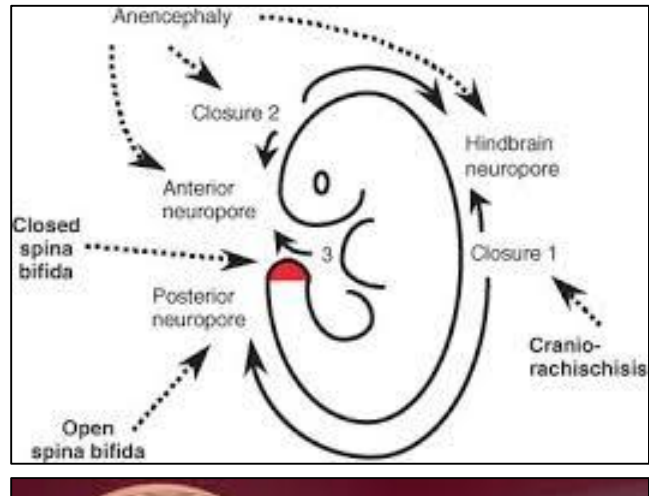
Psychiatric disorders after starting dolutegravir: report of four cases

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 quickly disappeared
history of psychiatric troubles

The recent signal

- 4 cases of severe NTDs among 426 women in women on DTG periconception
- Approx 45% of all births
 - ± 600 more expc
- 0.9% ver
- No clear obvious



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana

Rebecca Zash, M.D., Lewis Holmes, M.D., Modiegi Diseko, B.P.H.,

NTDs: neural tube defects
Zash R, et al. AIDS 2018

Efavirenz controversy: conflicting evidence

Preclinical data

- NTDs in primate studies



Clinical data: T1 EFV exposure

- 4 retrospective
- 1 prospective

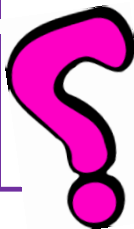
case report of NTD in humans



Meta analysis (2011):

1 NTD

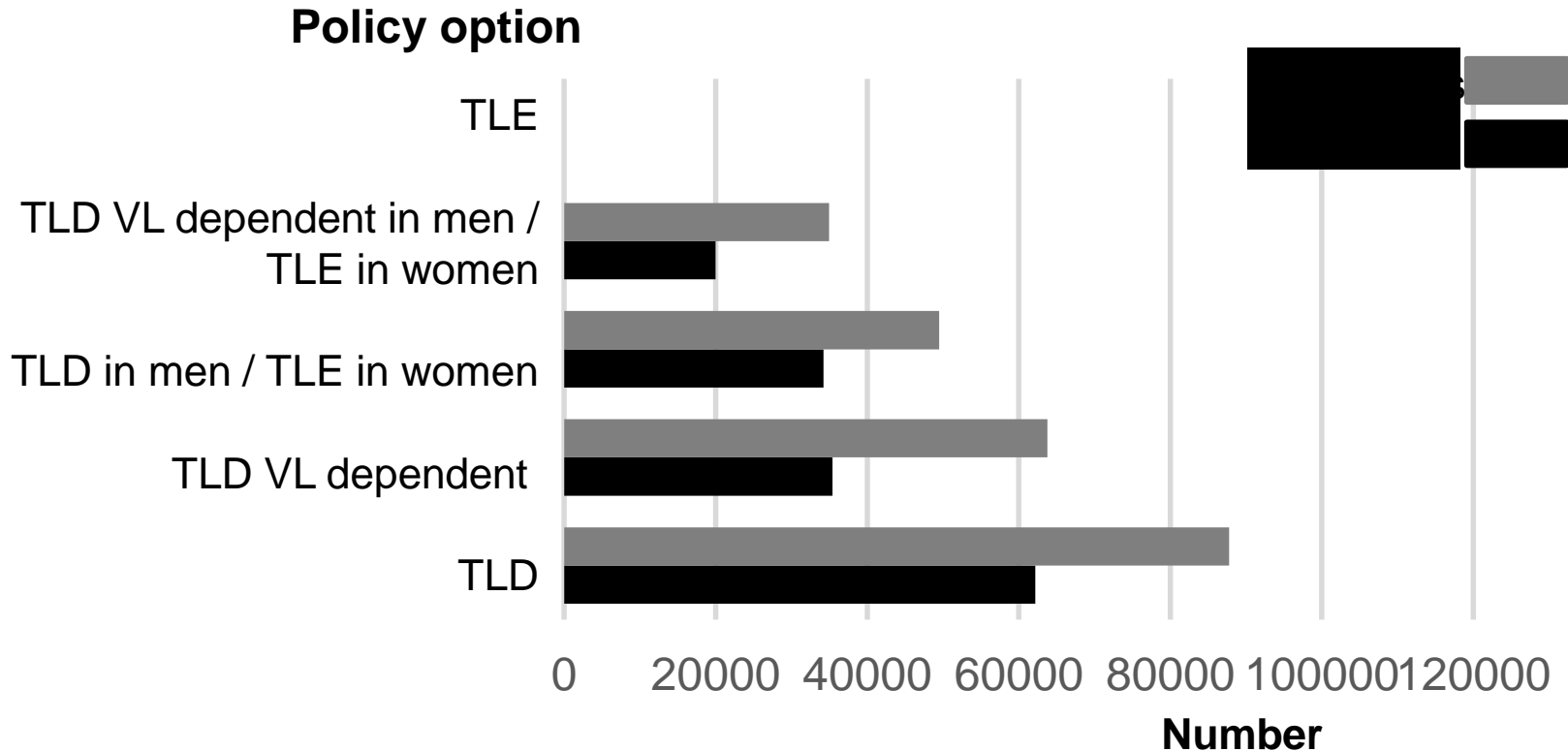
Incidence: 0.7 (95% CI 0.002 – 0.39%)
= NO association



Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study

Prof Andrew N Phillips, PhD • Prof Francois Venter, FCP[SA] • Prof Diane Havlir, PhD • Prof Anton Pozniak, PhD
Prof Daniel Kuritzkes, MD • Prof Annemarie Wensing, PhD • et al. [Show all authors](#)

Overall health benefit DALYs and cost-adjusted (net) DALYs averted per year compared with TLE



mean over 3 month periods from 2018-2038; cost adjustment based on cost effectiveness threshold \$500 / DALY averted

Are new antiretroviral treatments increasing the risks of clinical obesity?

Andrew Hill^{1*}, Laura Waters² and Anton Pozniak³

¹Department of Translational Medicine, University of Liverpool, UK

²Central and North West London NHS Trust, Mortimer Market Centre, London, UK

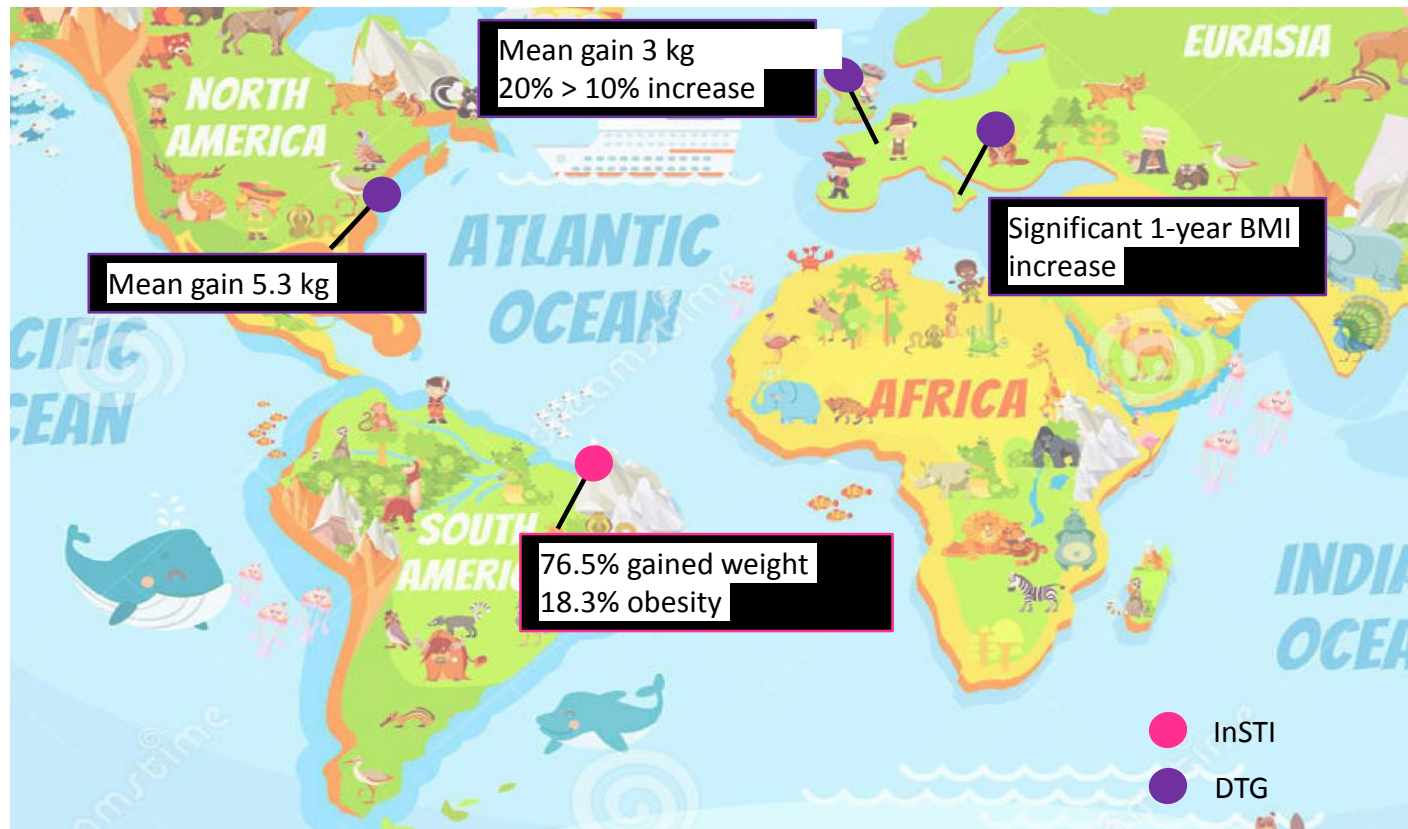
³Chelsea and Westminster Hospital, London, UK; London School of Hygiene and Tropical Medicine, UK

Table 1. Effects of raltegravir, dolutegravir and bicitegravir on body weight in randomised trials

Study [ref]	Design	Results
Raltegravir		
NEAT 001 [12] (naïve, n=126)	DRV/r+RAL DRV/r + TDF/FTC	DEXA sub-study: trunk fat 7.3% higher DRV/r/RAL vs TDF/FTC/RAL at week 96 (P=0.021)
ACTG 5260s [10,11] (naïve, n=126)	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	Higher risk of severe weight gain for RAL vs ATV/r
Dolutegravir		
NEAT 022 [13] (switch, n=415)	NRTIs + DTG NRTIs + PI/r	+1 kg increase in body weight to week 48 (P=0.002)
SPRING-1 [13] (naïve, n=204)	TDF/FTC/EFV TDF/FTC/DTG	Increases in body weight higher in DTG arms
Gilead 1490 [15] (naïve, n=645)	TAF/FTC/DTG TAF/FTC/BIC	+3.9 kg increase in body weight to week 96 +3.5 kg increase in body weight to week 96
MONODO [9] (naïve, n=8)	DTG monotherapy	+4.1 kg increase in body weight to week 24

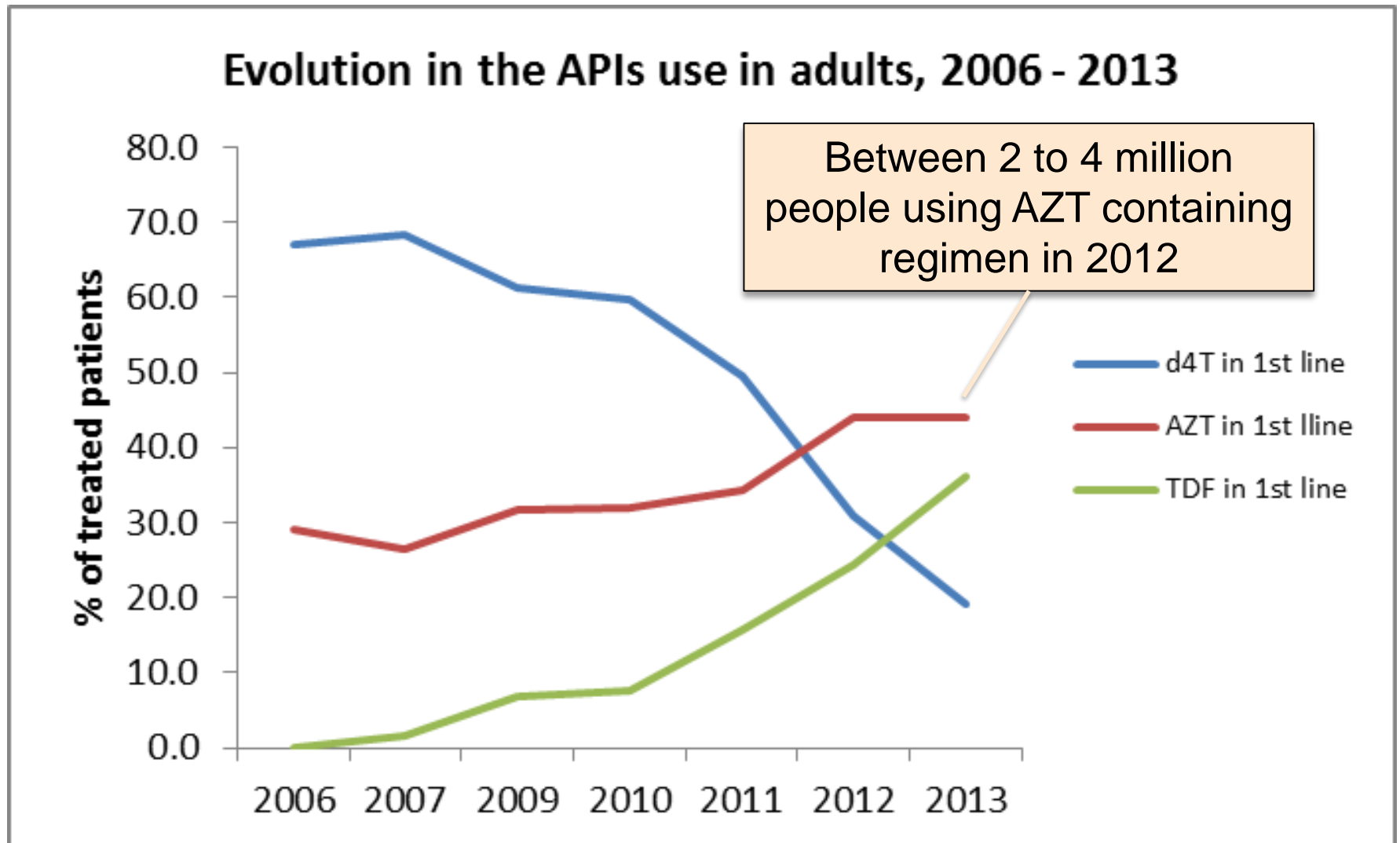
ATV/r; atazanavir/ritonavir; BIC: bicitegravir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitors; PI/r: ritonavir-boosted protease inhibitor; RAL: raltegravir; TAF: tenofovir AF; TDF: tenofovir DF.

Weight gain?

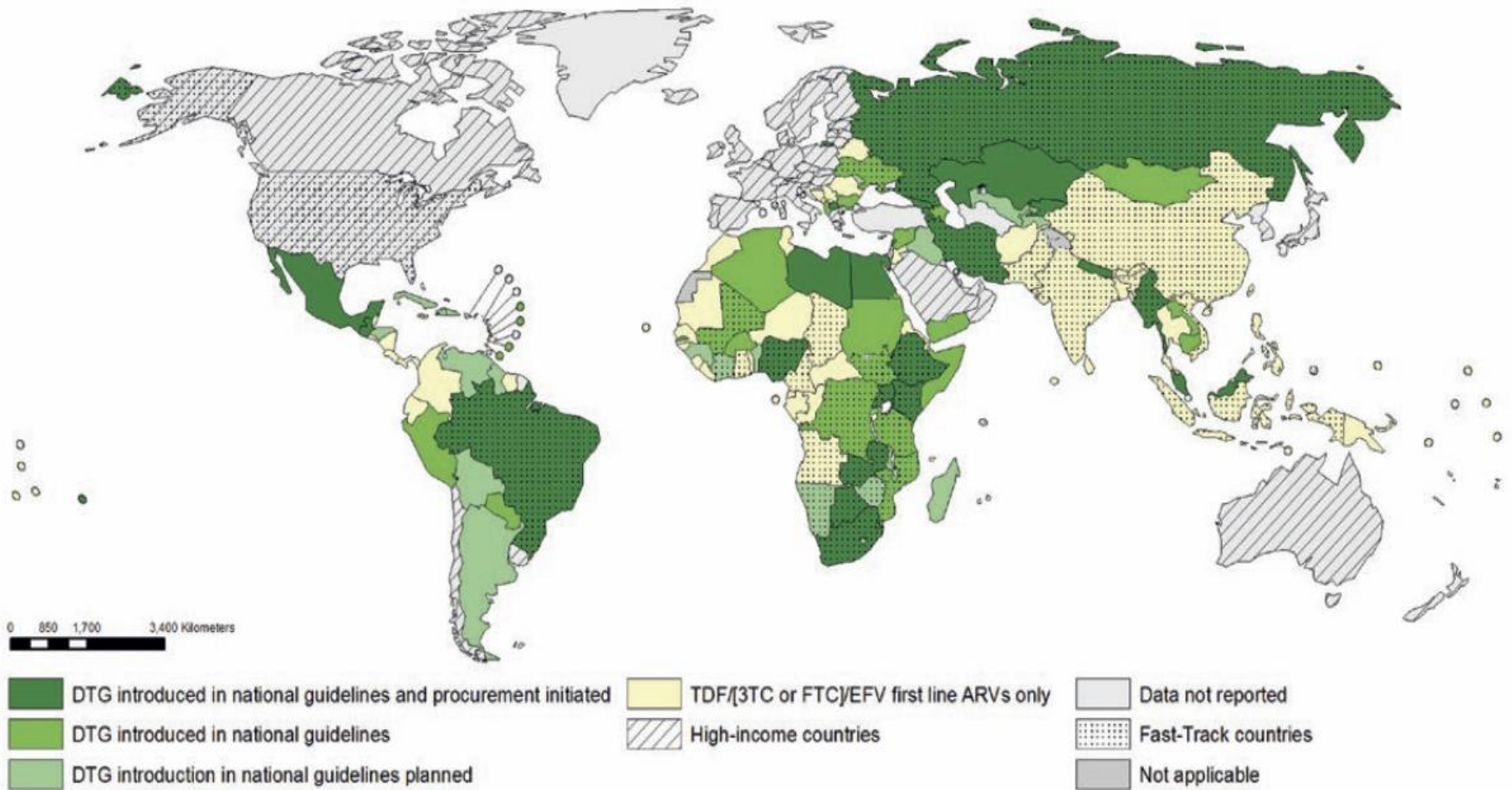


Menard A et al. AIDS, June 2017; Norwood et al, JAIDS, Aug 2017;
Bakal D et al. ID Week 2017; Taramasso et al. Open Forum Infectious Diseases, Nov 2017

Changes in D4T, AZT & TDF use – often FAST

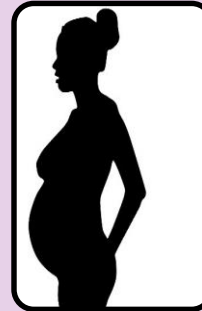


Preferred first line regimen among adults and adolescents in low- and middle-income countries (situation as of mid-2018)



Why aren't these drugs more widely available in LMICs?

>80% of HIV positive people black, most female;
registration usually >80% white, largely male



Not preferred options in WHO guideline

Many drugs are not registered and no co-formulations are available

Limited data on use in TB (almost all new drugs)

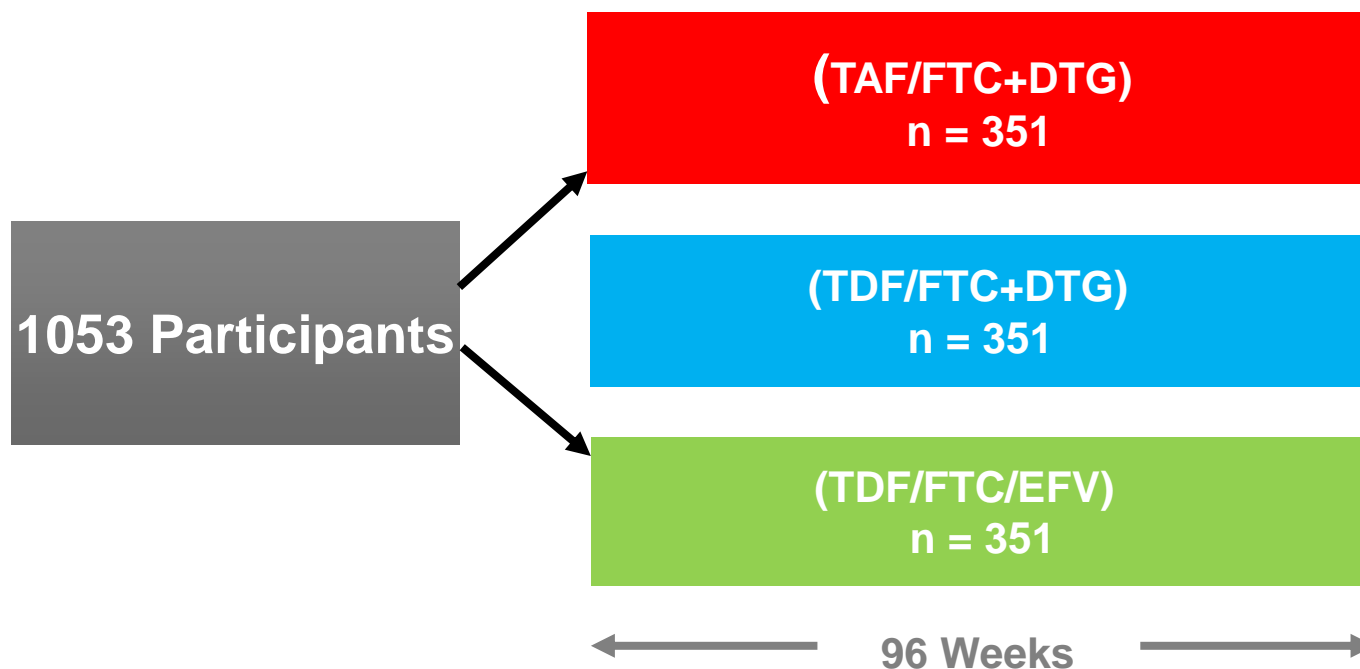
Limited data on use in pregnancy (almost all new drugs)

Costs: abacavir, all integrase inhibitors – hope for dolutegravir

ADVANCE: Study design

Inclusion criteria:

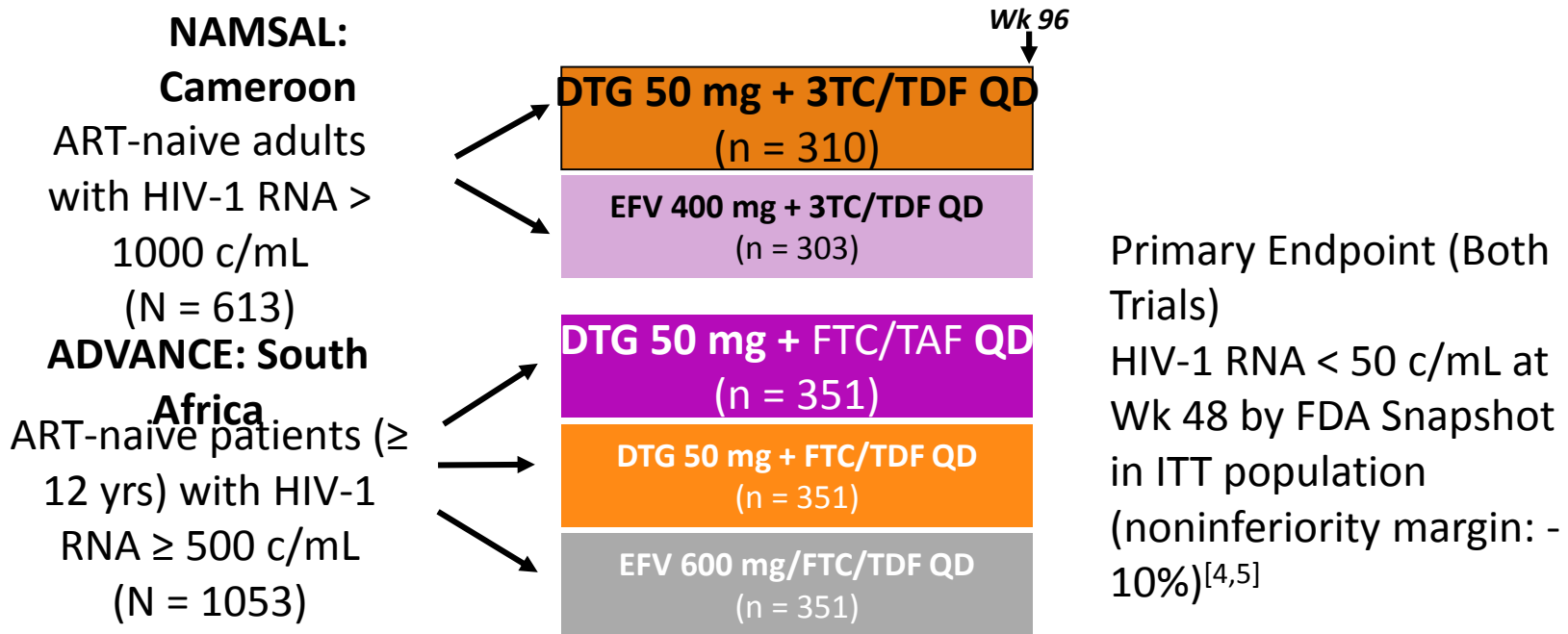
- Treatment-naïve, HIV-1 RNA level > 500 copies/mL



Open-label, 96-week study in Johannesburg, South Africa
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84 and 96

NAMSAL and ADVANCE: Study Design

- Multicenter, randomized, open-label phase III trials^[1-3]



1. Hill. IAS 2019. Abstr MOAX0102LB. 2. NCT02777229. 3. NCT03122267
4. NAMSAL ANRS 12313 Study Group. NEJM. 2019:[Epub]

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Dolutegravir-Based or Low-Dose Efavirenz-Based Regimen for the Treatment of HIV-1

The NAMSAL ANRS 12313 Study Group*



Slide credit: clinicaloptions.com



IAS 2019

10TH IAS CONFERENCE ON HIV SCIENCE
Mexico City, Mexico 21-24 July 2019

Progressive rises in weight and clinical obesity for TAF/FTC+DTG and TDF/FTC+DTG versus TDF/FTC/EFV: ADVANCE and NAMSAL trials

Andrew Hill, Francois Venter, Eric Delaporte, Simiso Sokhela, Charles Kouanfack, Michelle Moorhouse, Kaitlyn McCann, Bryony Simmons, Alexandra Calmy



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Find this presentation on www.ias2019.org

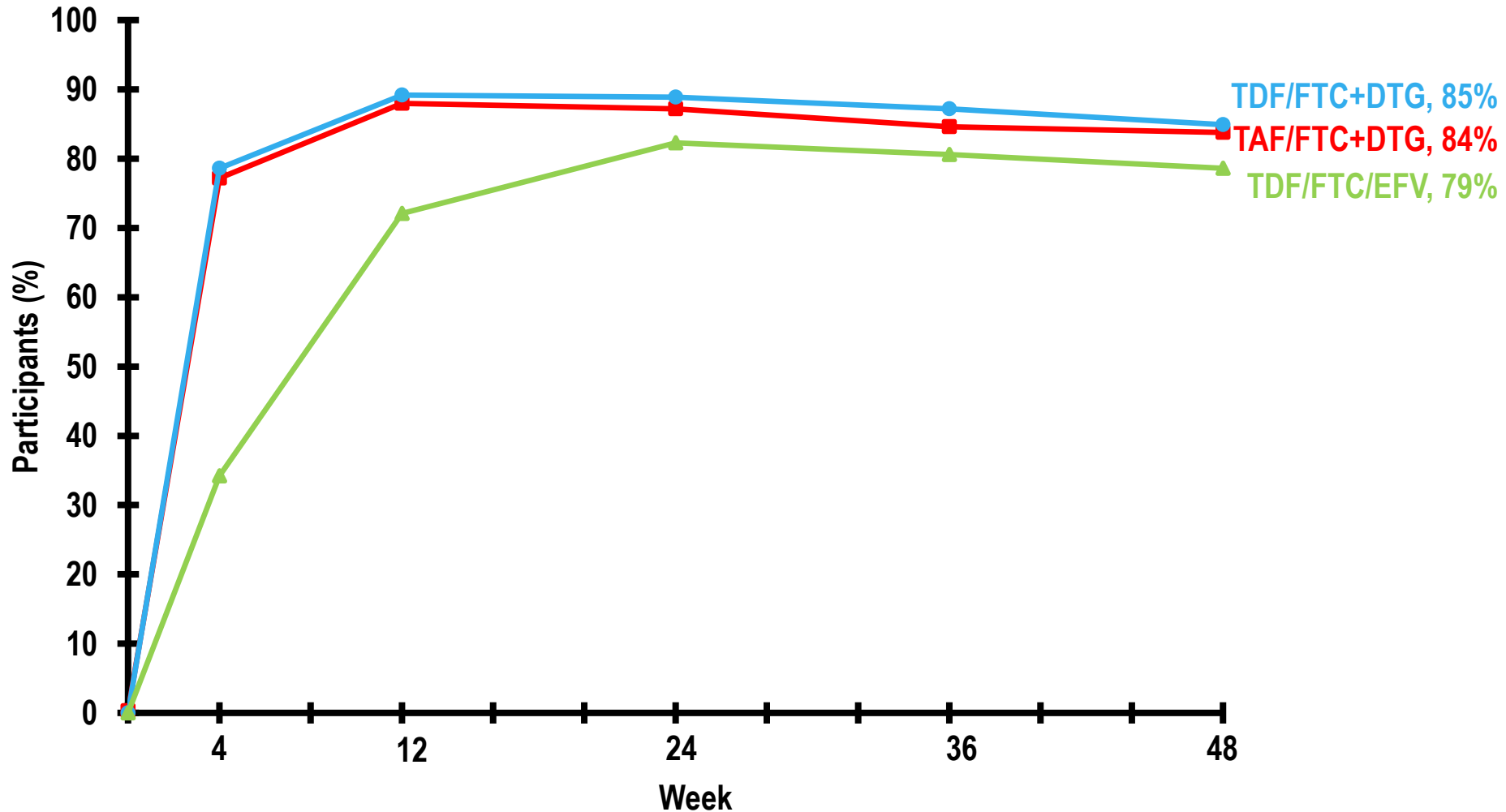


ORIGINAL ARTICLE

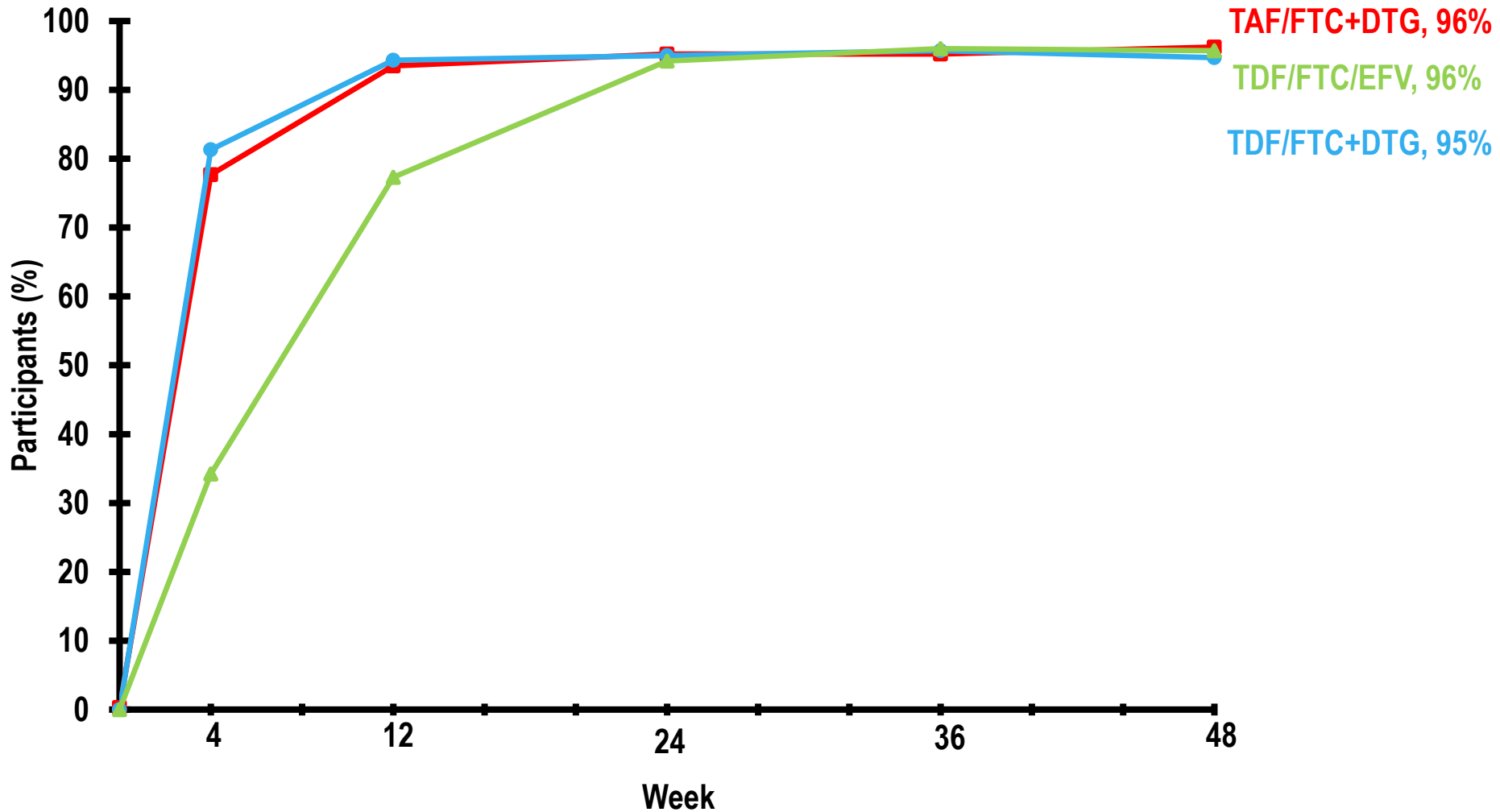
Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV

Willem D.F. Venter, F.C.P. (SA), Ph.D.,
Michelle Moorhouse, M.B., B.Ch., D.A. (SA),
Simiso Sokhela, M.B., Ch.B., Dip. HIV Man. (SA),
Lee Fairlie, M.B., Ch.B., M.Med., Nkuli Mashabane, M.B.L., B.Pharm.,
Masebole Masenya, M.B., Ch.B., Celia Serenata, M.B.A.,
Godspower Akpomiemie, M.P.H., Ambar Qavi, M.P.H.,
Nomathemba Chandiwana, M.B., B.Ch., M.P.H., Shane Norris, Ph.D.,
Mathew Chersich, M.B., B.Ch., Ph.D., Polly Clayden, , Elaine Abrams, M.D.,
Natasha Arulappan, N.D.: I.T., Alinda Vos, Ph.D., Kaitlyn McCann, M.P.H.,
Bryony Simmons, M.P.H., and Andrew Hill, Ph.D.

Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (ITT)



Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (per-protocol)



Outcomes after HIV RNA >50 at Week 48

TAF/FTC + DTG arm

PATIENT	Baseline RNA	Week-48 RNA	Follow-up
34	229982	56	<50 re-test
101	148806	269	<50 in window
187	7551	249	<50 in window
549	71810	26524	<50 in window
635	173999	12540	<50 in window
24	5179	462	<50 long term
134	17913	137	<50 long term
253	50052	160	<50 long term
266	161061	50	<50 long term
537	265330	73	<50 long term
630	9318	434	<50 long term
675	168531	391	<50 long term
747	38030	2893	<50 long term
768	62359	202	<50 long term
864	7250	107481	<50 long term
97	21875	48304	Early termination
167	42879	202	3795 at week-96
435	247385	149413	103 at week-96

Outcomes after HIV RNA >50 at Week 48

TDF/FTC + DTG arm

PATIENT	Baseline RNA	Week-48 RNA	Follow-up
484	33276	30949	<50 in window
60	21423	7201	<50 long term
137	20048	3067	<50 long term
142	39130	332	<50 long term
211	41774	66	<50 long term
451	4130	448	<50 long term
497	12317	6358	<50 long term
502	252	219	<50 long term
538	111443	2203	<50 long term
567	39449	91	<50 long term
734	93742	72	<50 long term
936	11599	41588	<50 long term
949	10612	3926	<50 long term
1010	13474	50	<50 long term
283	2542	1127	No follow-up
310	4090	1528	No-follow up
65	107696	42606	16545 at week-96
160	206058	1110	4822 at week-96
808	185339	397926	42295 at week-72

Outcomes after HIV RNA >50 at Week 48

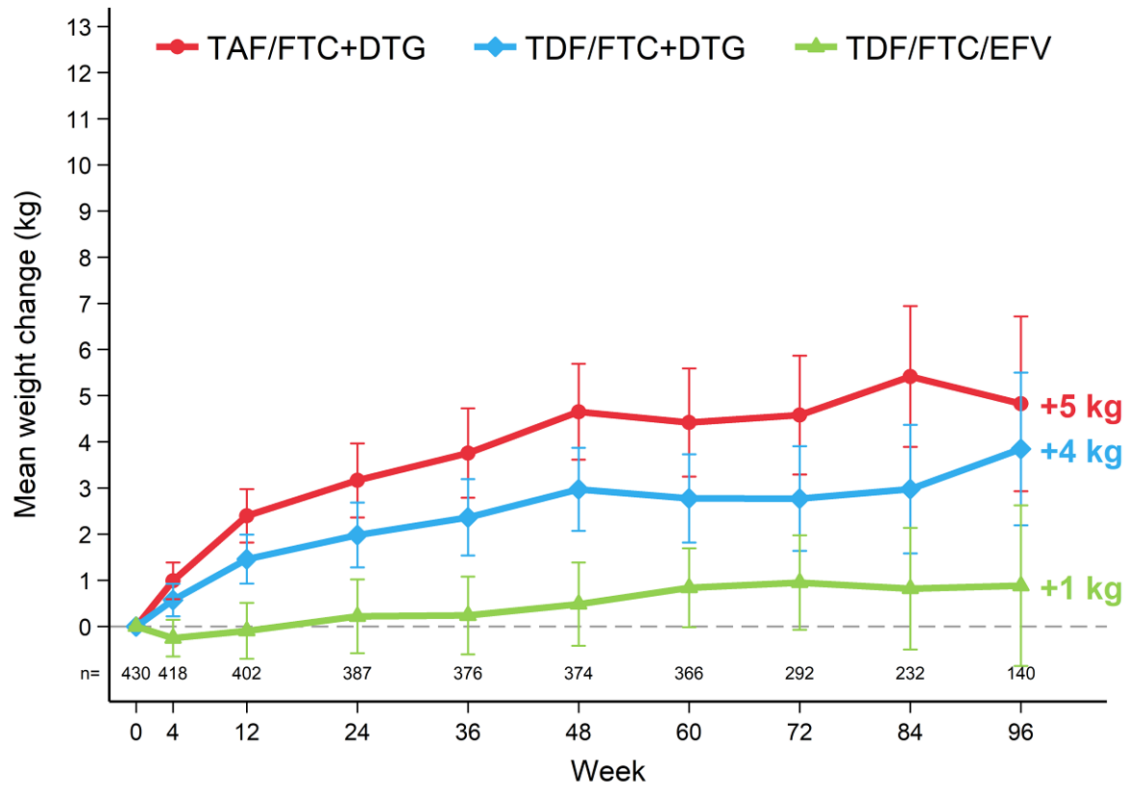
TDF/FTC/EFV arm

PATIENT	Baseline RNA	Week-48 RNA	Follow-up
531	35620	71	<50 re-test
736	1328	93	<50 in window
907	158933	2298	<50 in window
642	24663	23184	<50 long term
922	2375	814	<50 long term
913	219040	65	<50 long term
966	17517	161	<50 long term
730	29501	67282	Early termination
1011	3796	30237	No follow-up
79	2476	1645	383 at week-96
197	2199	164	848 at week-96
619	61792	34361	2672 at week-84
738	447781	234506	58910 at week-72
746	2626	842	1797 at week-72
813	116872	646	2245 at week-60
856	52764	482	6355 at week-60

Drug resistance

	(TAF/FTC+DTG) (n=351)	(TDF/FTC+DTG) (n=351)	(TDF/FTC/EFV) (n=351)
Number w/VF, tested for resistance with paired baseline genotype	1 (0.3%)	1 (0.3%)	6 (2%)
Emergent NRTI mutation	0 (0%)	1 (0.3%)	4 (1%)
Emergent NNRTI mutation	0 (0%)	0 (0%)	3 (1%)
Emergent InSTI mutation	0 (0%)	0 (0%)	0 (0%)

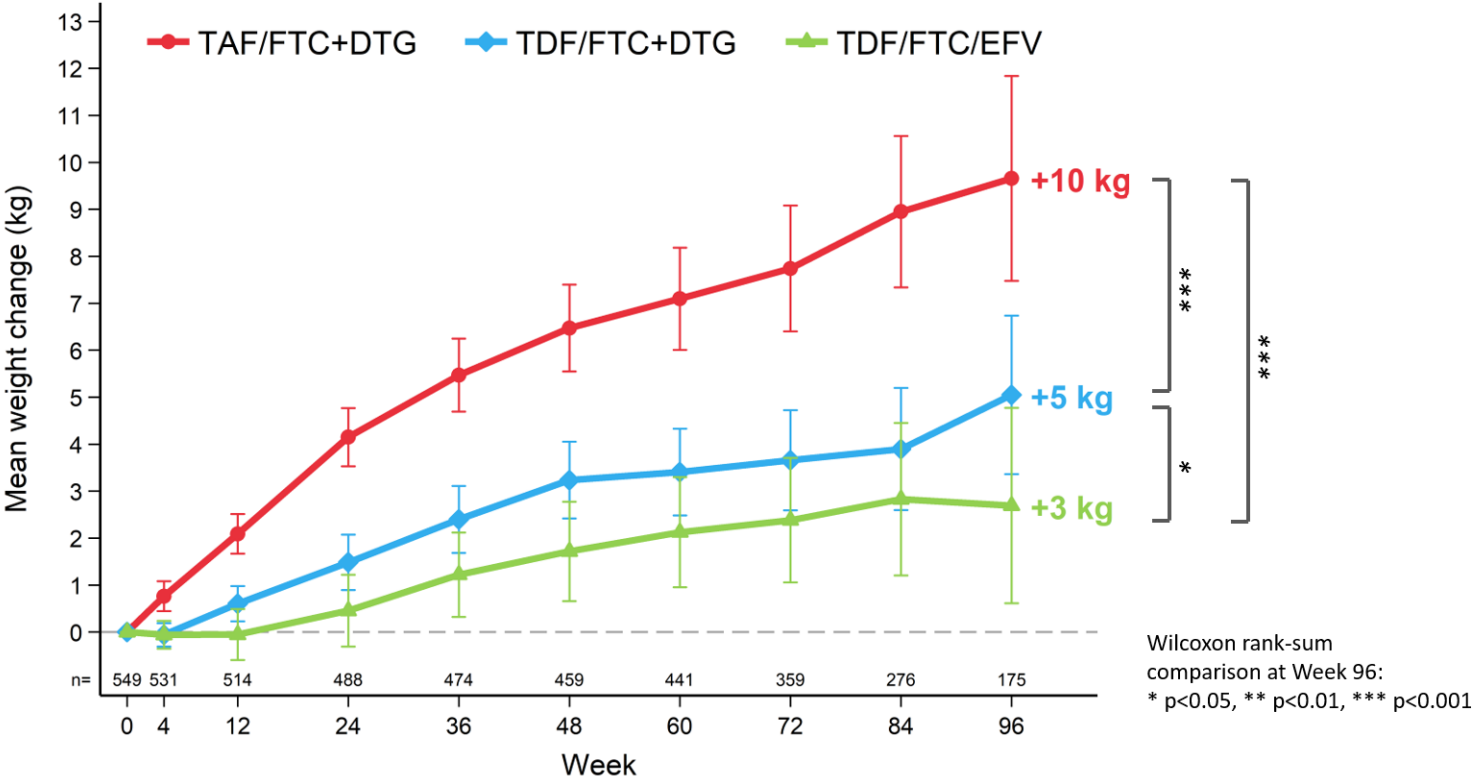
ADVANCE: Mean change in weight (kg) to Week 96: men



n.s.
**
**

Wilcoxon rank-sum comparison at Week 96:
n.s. not significant
* p<0.05, ** p<0.01, *** p<0.001

ADVANCE: Mean change in weight (kg) to Week 96: women



Notably:

- No notable changes in average blood pressure, lipids, glucose across arms or timelines
- No difference in week 48 HbA1C (not pre-specified, so no baseline)
- Fits other local data – cardiovascular risk still low in this community
- Weight gain NOT correlated with:
 - ❖ Nausea.
 - ❖ Sleep.
 - ❖ Mental illness .
 - ❖ Adherence.
 - ❖ Hormonal contraception.

* Not return to health of DTG>EFV. (VL very similar decay and the weight gain persists throughout)

NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

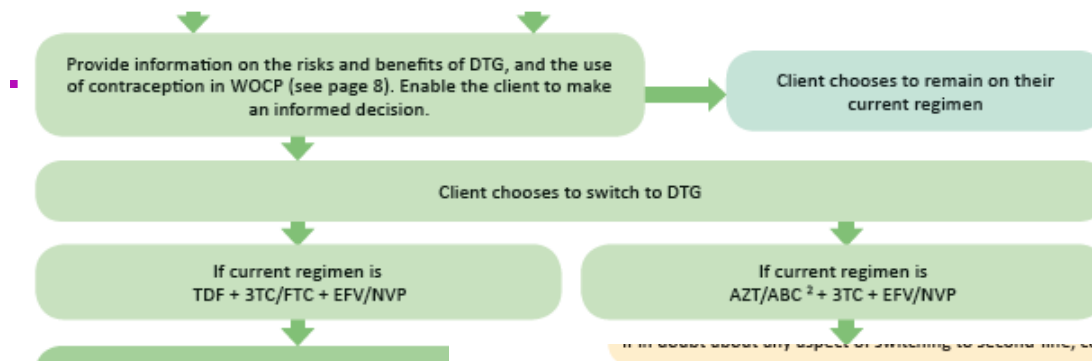
Outcome	NAMSAL			ADVANCE			
	DTG + 3TC/TDF (n = 293)	EFV + 3TC/TDF (n = 278)	P Value	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF	P Value
Mean Δ in weight, kg							
▪ Wk 48	+5	+3	< .001	+6	+3	+1	< .001
▪ Wk 96	NA	NA		+8	+5	+2	
Mean Δ in BMI at Wk 48	+1.7	+1.2	< .001	NR	NR	NR	
Treatment-emergent overweight (BMI 25-29.9), %							
▪ Wk 48	16	17	NS	23	14	9	NS
▪ Wk 96	NA	NA		25	13	11	
Treatment-emergent obesity (BMI \geq 30), %							
▪ Wk 48	12	5	< .01	14	7	6	< .01
▪ Wk 96	NA	NA		19	8	4	



2019 ART Clinical Guidelines

**for the Management of HIV in Adults, Pregnancy,
Adolescents, Children, Infants and Neonates**

Published: May 2019
Republic of South Africa National Department of Health



Only switch a stable pregnant longer in the first 6 weeks of pregnancy. Provide necessary information on DTG.

Second-line ART Regimens for Adults with Confirmed Virological Failure

	First-Line Regimens				Second-Line Regimens	
	NNRTI-based Regimen		INSTI-based Regimen for > 2 years		PI-based Regimen for > 2 years	
Regimen	TDF + 3TC/FTC + EFV/NVP		TDF + 3TC/FTC + DTG		AZT/TDF + 3TC/FTC + LPV/r or ATV/r	
Resistance Testing	Resistance test <u>not</u> required		Resistance testing may be required under expert consultation ⁴		Resistance test required	
Resistance Test results	Not applicable		Not applicable		No PI resistance	PI resistance
HBV Co-infection Status ¹	HBV-negative	HBV-positive	HBV-negative	HBV-positive	HBV-positive or -negative	
New Regimen	AZT + 3TC/FTC + DTG ²	TDF ¹ + AZT + 3TC/FTC + DTG ²	AZT + 3TC/FTC + LPV/r	TDF + 3TC/FTC + LPV/r ⁴	Continue current regimen and address adherence. If intolerance to LPV/r is affecting adherence, discuss possible substitutions with an expert	Refer to Third-Line Committee. Regimen will be determined by results of resistance test
	If DTG not suitable ² , AZT + 3TC/FTC + LPV/r	If DTG not suitable ² , TDF + 3TC + LPV/r ⁴				

Second and Third-line ART Regimens for Children and Adolescents with Confirmed Virological Failure



All children and adolescents with confirmed virological failure should be discussed with an expert.

	NNRTI-based Regimen	PI-based Regimen for > 2 years	INSTI-based Regimen for > 2 years
Regimen	ABC/AZT/TDF + 3TC/FTC + EFV/NVP	ABC/AZT/TDF + 3TC/FTC + LPV/r or ATV/r	ABC/AZT/TDF + 3TC/FTC + DTG

Conclusion re DTG



- DTG likely 1st line (and 2nd line, already 3rd line) everywhere in Africa
- Resistance - amazing
- TB and NTDs a headache
- Weight - ?????
- DTG introduction delayed (again!)

Thank you!

University of the Witwatersrand
WITS RHI

