Exploring First-line ART Strategies: Dolutegravir

Michelle Moorhouse

Mar 2018

First-line ART Strategies Roadshow

University of the Witwatersrand

WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

Disclosures

- Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan and Janssen, and has received conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan.
- Part of ART optimisation collaborations
- Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies

The evolving HIV treatment paradigm



HIV-1 discovered

1983

ZDV monotherapy

1987

ZDV/3TC

1995

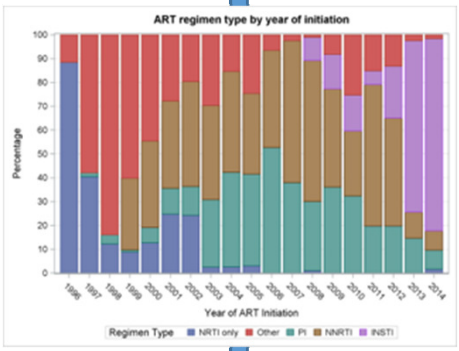
Triple-Drug Therapy

1996

Single-Tablet Regimens

2006

The Integrase Era



2012–2013

Long Acting Injectable?

2017

?????

2020

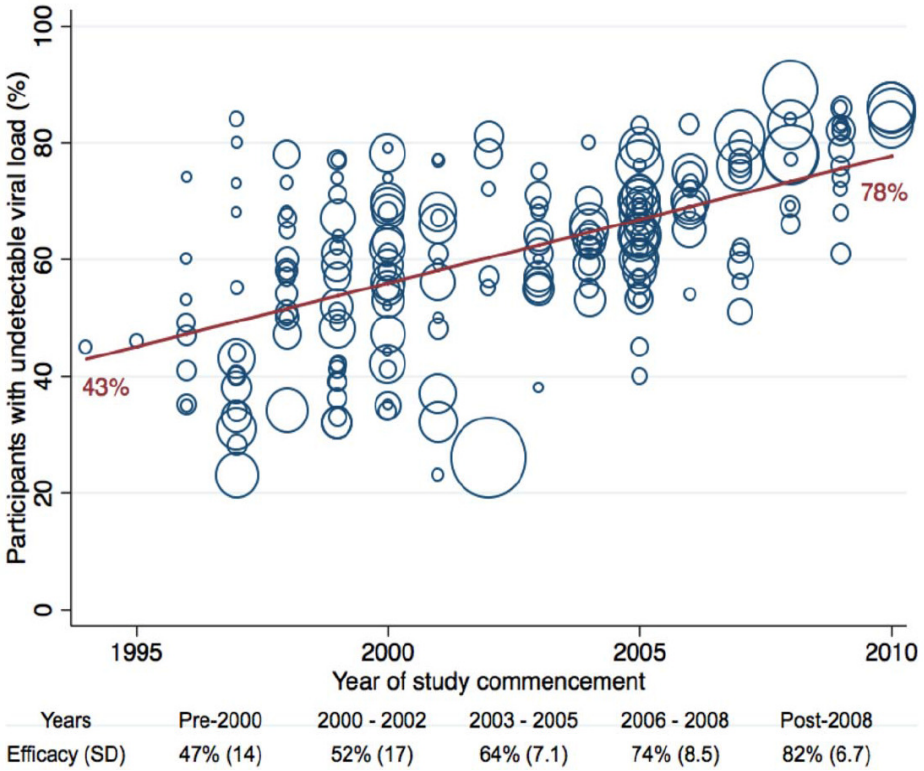
3TC=lamivudine; ZDV=zidovudine

Joe Eron

ART trials

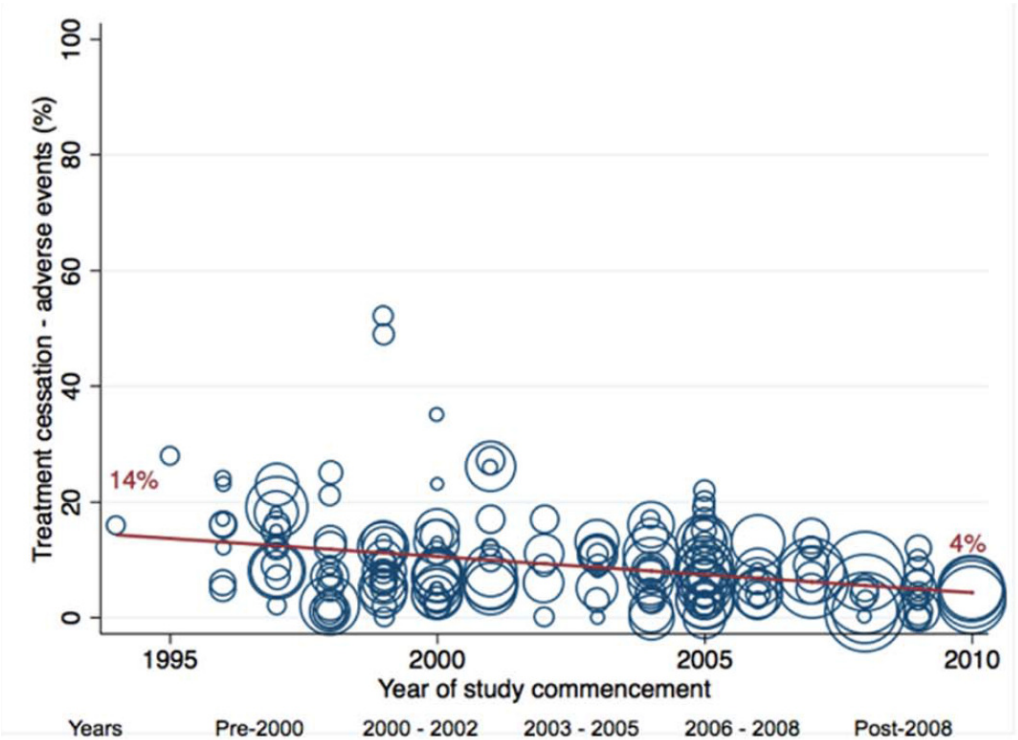
114 studies through 2010, up to 3 years of f/u: ITT analyses

Virologic responses



Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Efficacy (SD)	47% (14)	52% (17)	64% (7.1)	74% (8.5)	82% (6.7)

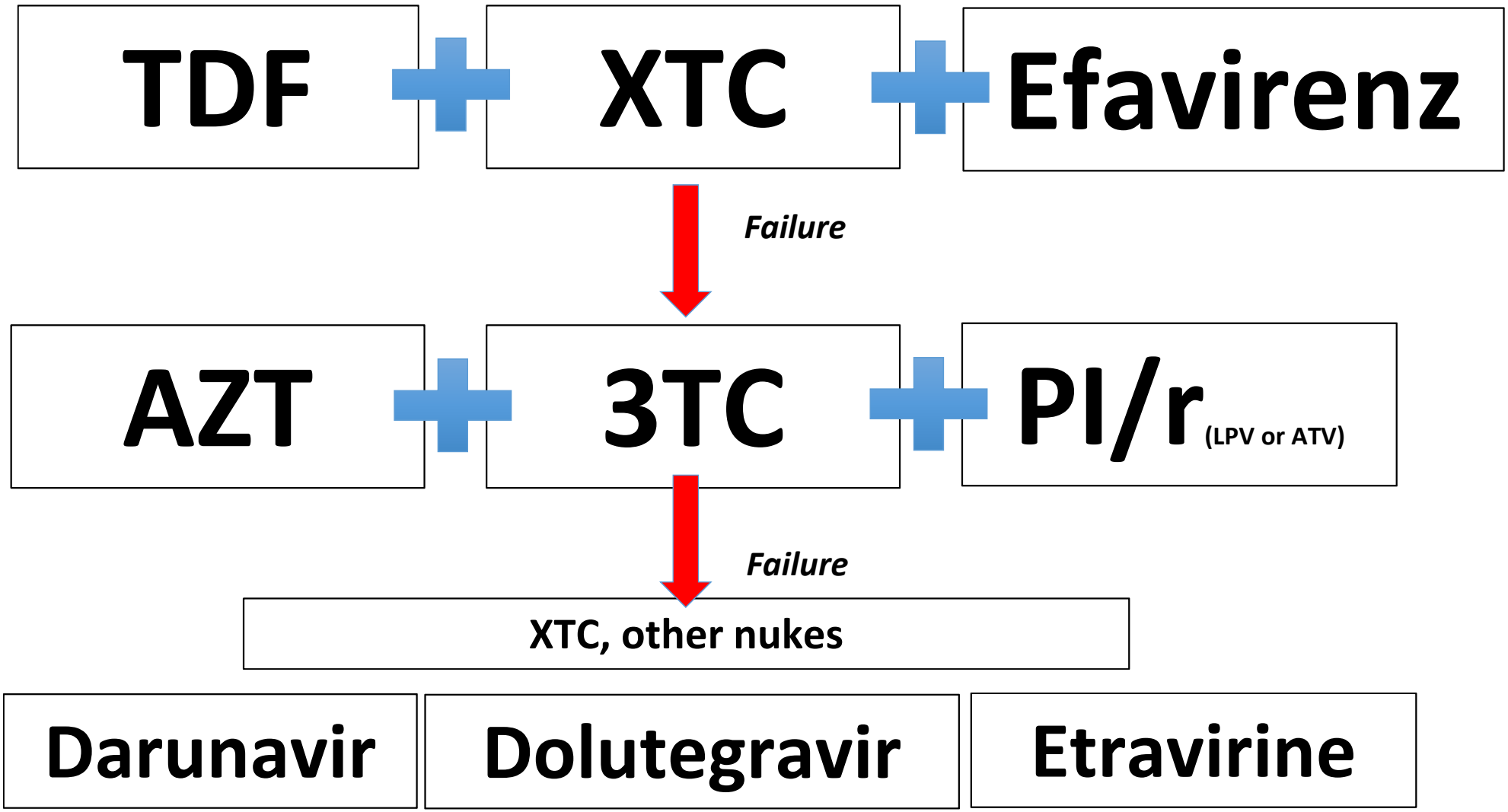
Safety and tolerability



Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Cessation (SD)	10% (7.9)	9·1% (6.4)	7·9% (4.6)	6·1% (3.5)	4·2% (2.4)

Lee et al. PLoS One 2014

The drugs rock



But there’s room for improvement

First-line….

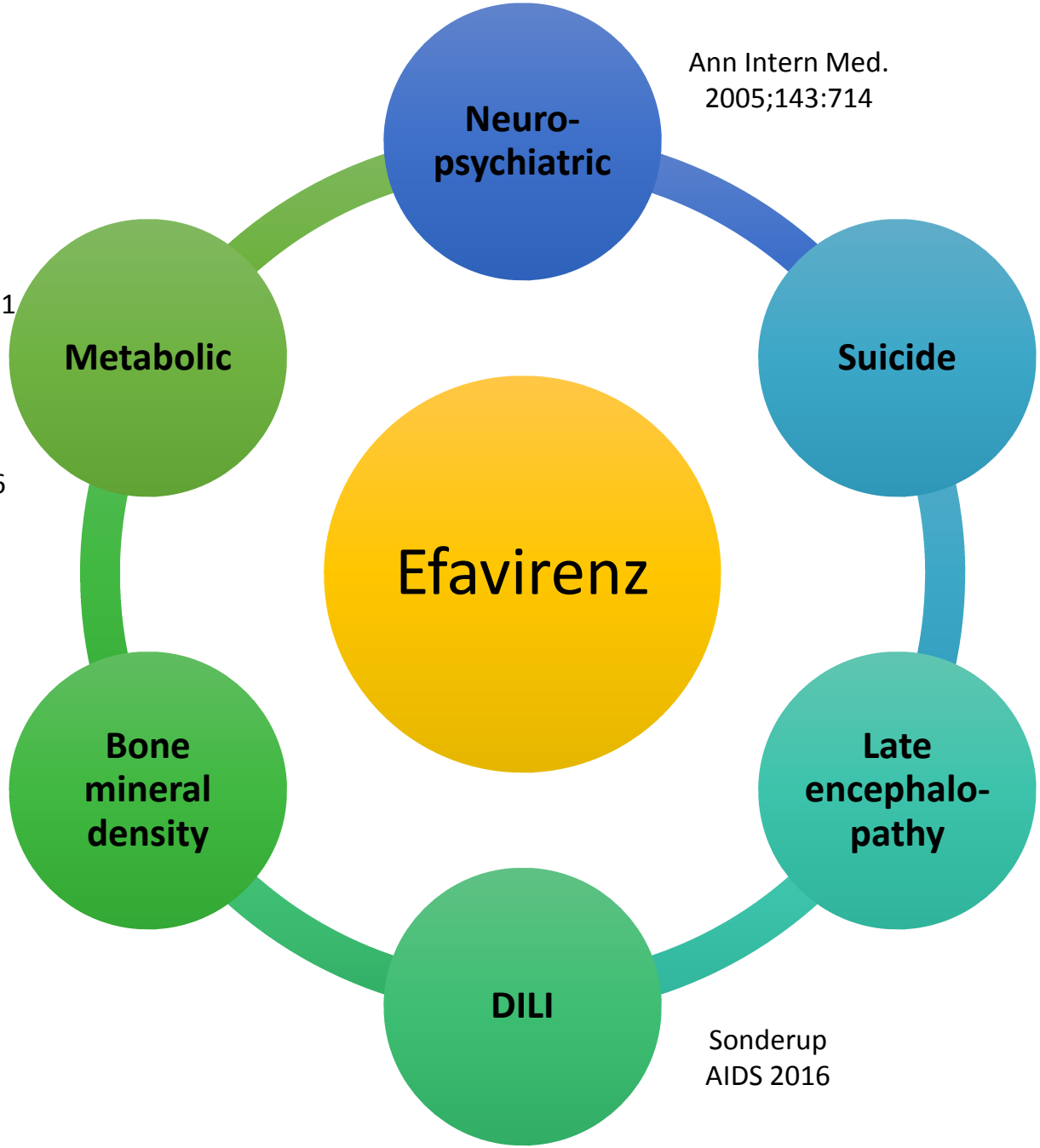
TDF + **XTC** + **EFV**

Cost driver
Toxicity

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 (rifampicin)	Yes

Toxicity driver
Pill size
Low genetic barrier
Cost

Efavirenz's side effects…



Ann Intern Med. 2005;143:714

Ann Intern Med. 2014;161:1-10

Variava JAIDS 2017

Sonderup AIDS 2016

Dave PLoS ONE 10(12): e0144286.

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

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

High income countries no longer recommend EFV in first-line

J Antimicrob Chemother 2014; 69: 1742

Comparison of current international guidelines for ART-naive

Regimen	DHHS[1]	EACS[2]	BHIVA[3]	IAS-USA[4]	GeSIDA[5]
DTG/3TC/ABC*					
DTG + FTC/TDF					
EVG/COBI/FTC/TDF†					
EVG/COBI/FTC/TAF‡					
RAL + FTC/TDF					
ATV/RTV + FTC/TDF					
DRV/RTV + FTC/TDF					
EFV/FTC/TDF					
RPV/FTC/TDF§					

*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. § Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3.

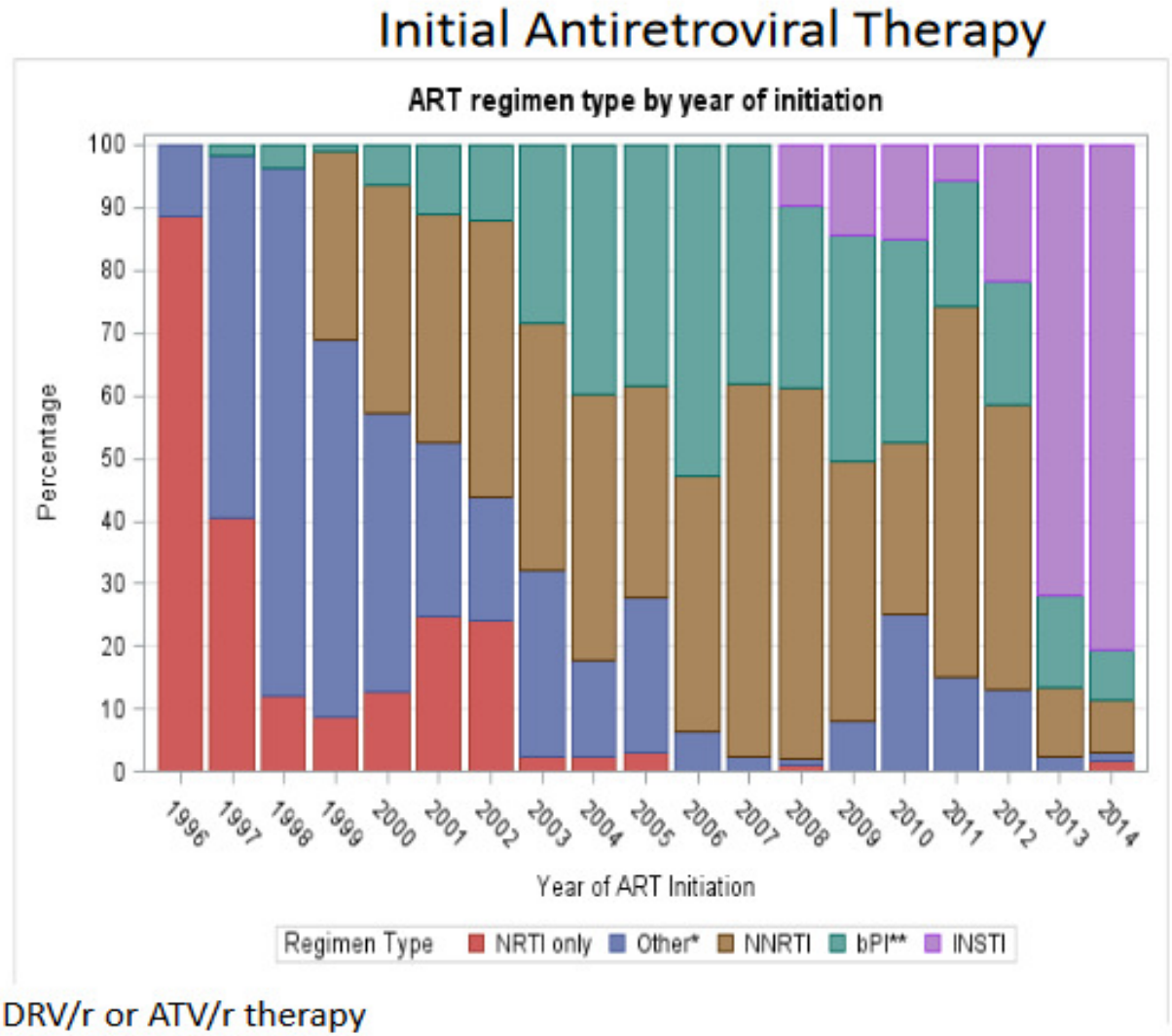
Recommended Alternative Not included

1. DHHS Guidelines. January 2016.
2. EACS HIV Guidelines. V 8.0. October 2015.
3. BHIVA Guidelines. 2015.
4. Günthard H, *et al.* JAMA. 2014;312:410-425.
5. GeSIDA. Enferm Infecc Microbiol Clin. 2013;31:602.e1-602.e98.

“The integrase inhibitor era”

UCHCC: UNC CFAR HIV Clinical Cohort

Shift To Integrase Inhibitor-based Therapy



1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

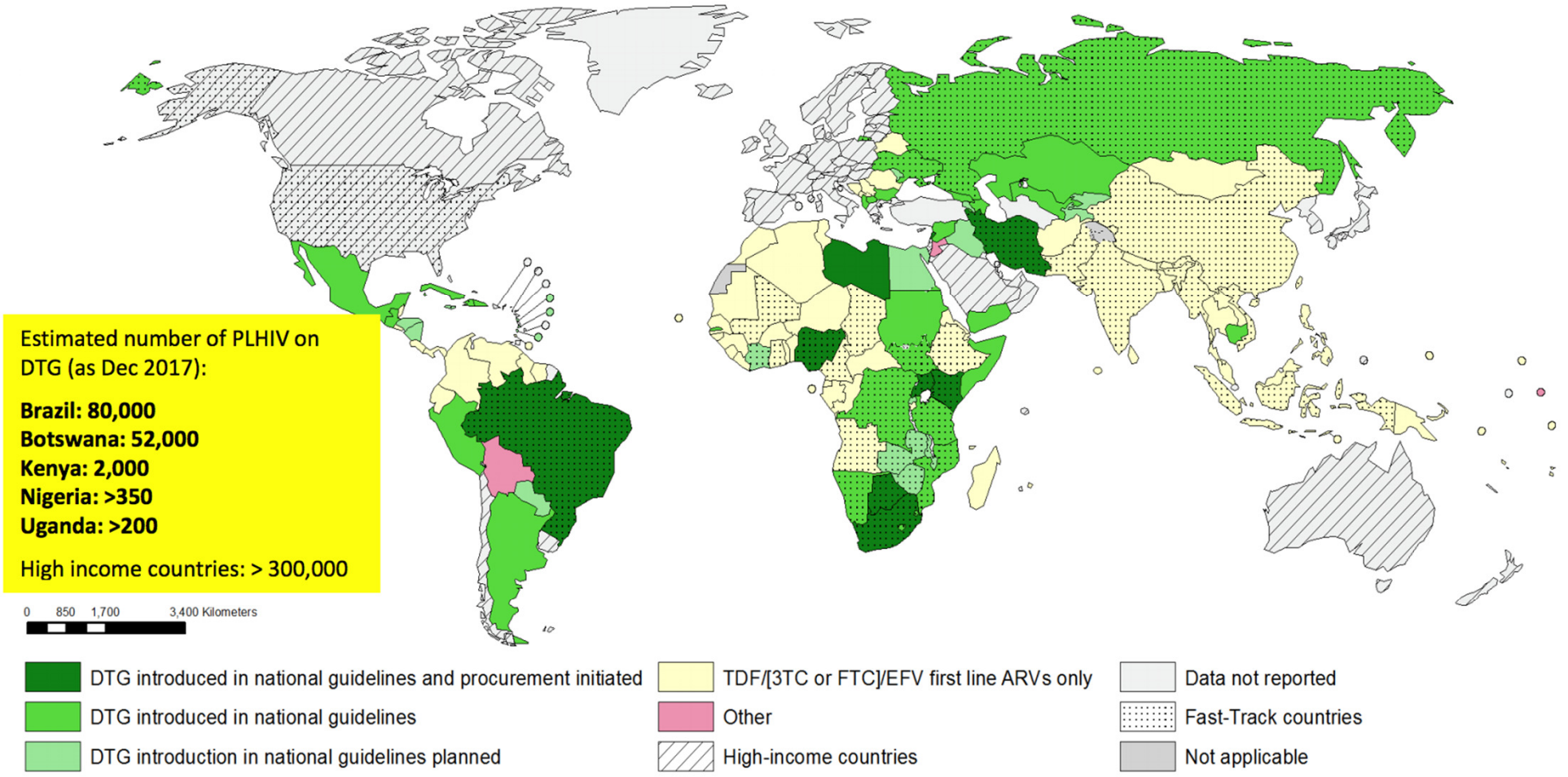
bPI = LPV/r, DRV/r or ATV/r therapy

Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Thanks Joe Eron

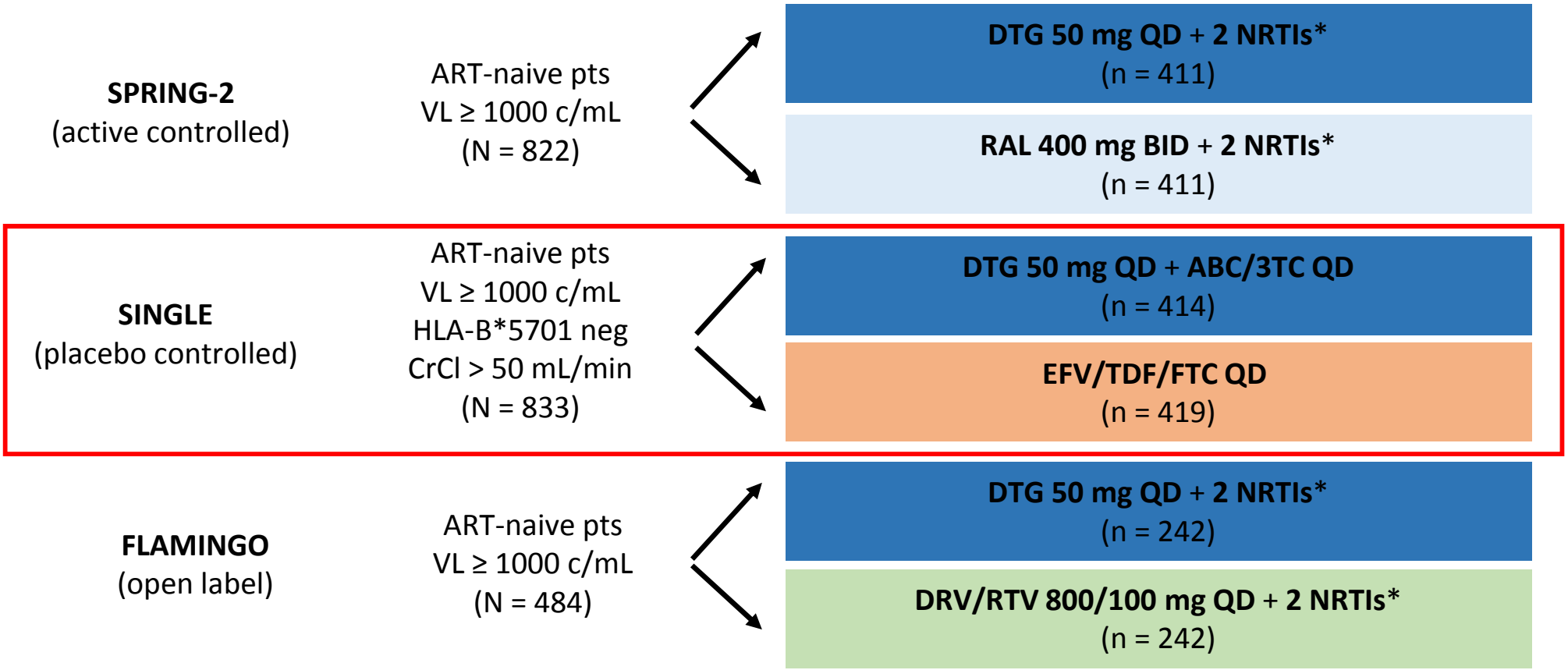
Even LMICs: 40% shifting to DTG (only 5% already completed)



Courtesy of M. Vitoria

We know DTG works in ARV-naives

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

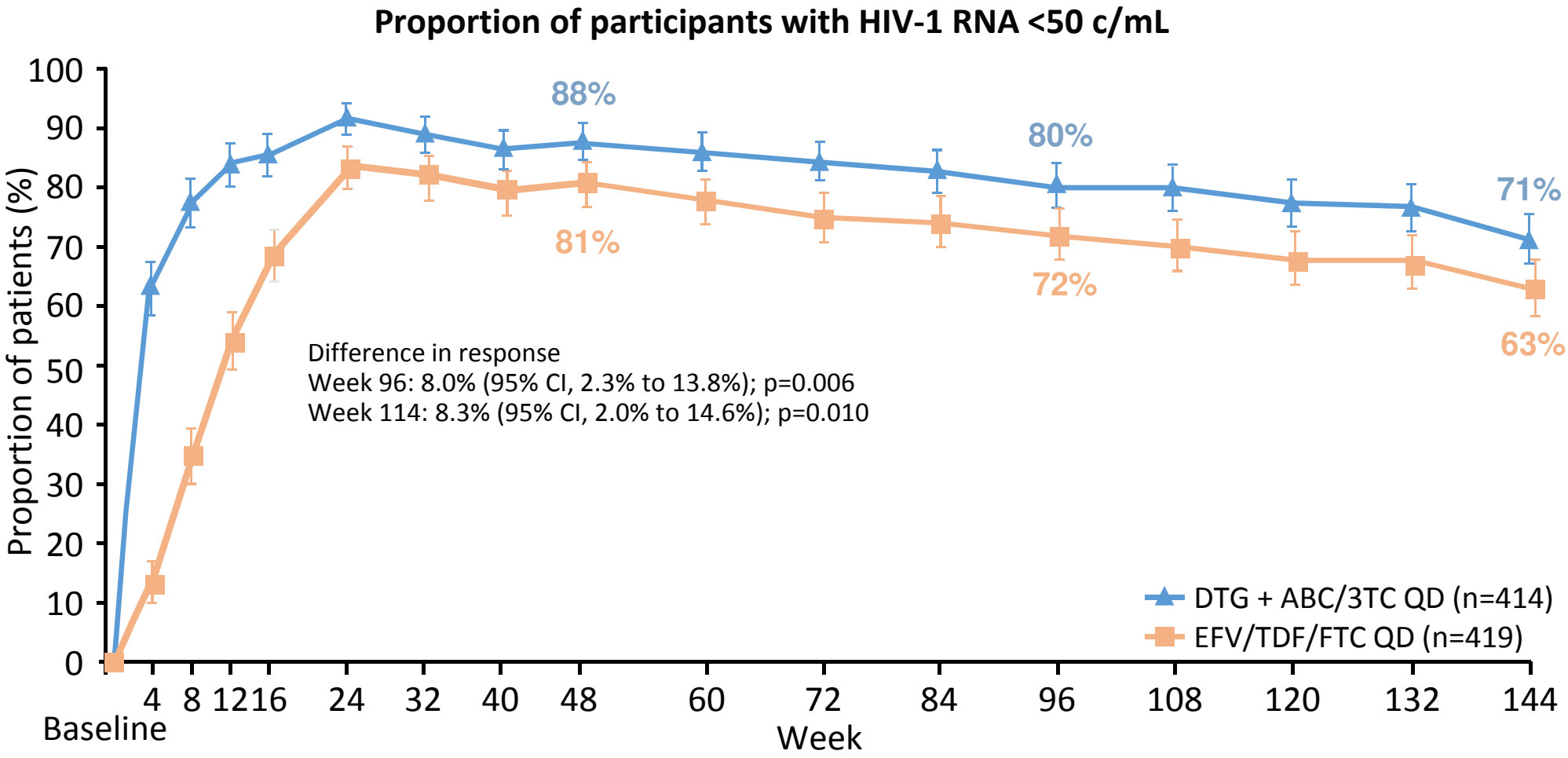


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

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

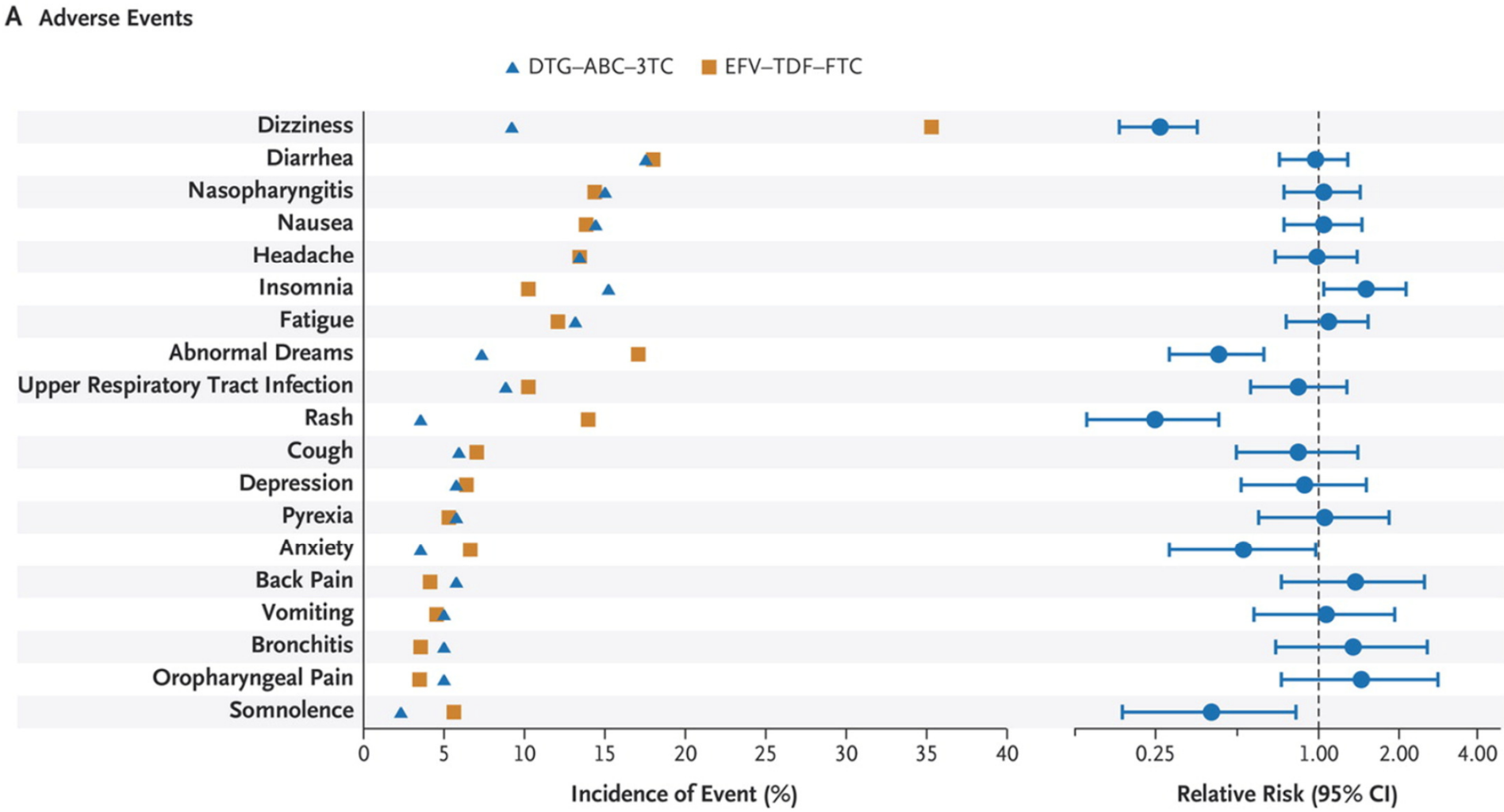
SINGLE study: DTG vs. EFV

Better tolerated than EFV (but more insomnia)



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

SINGLE study: safety



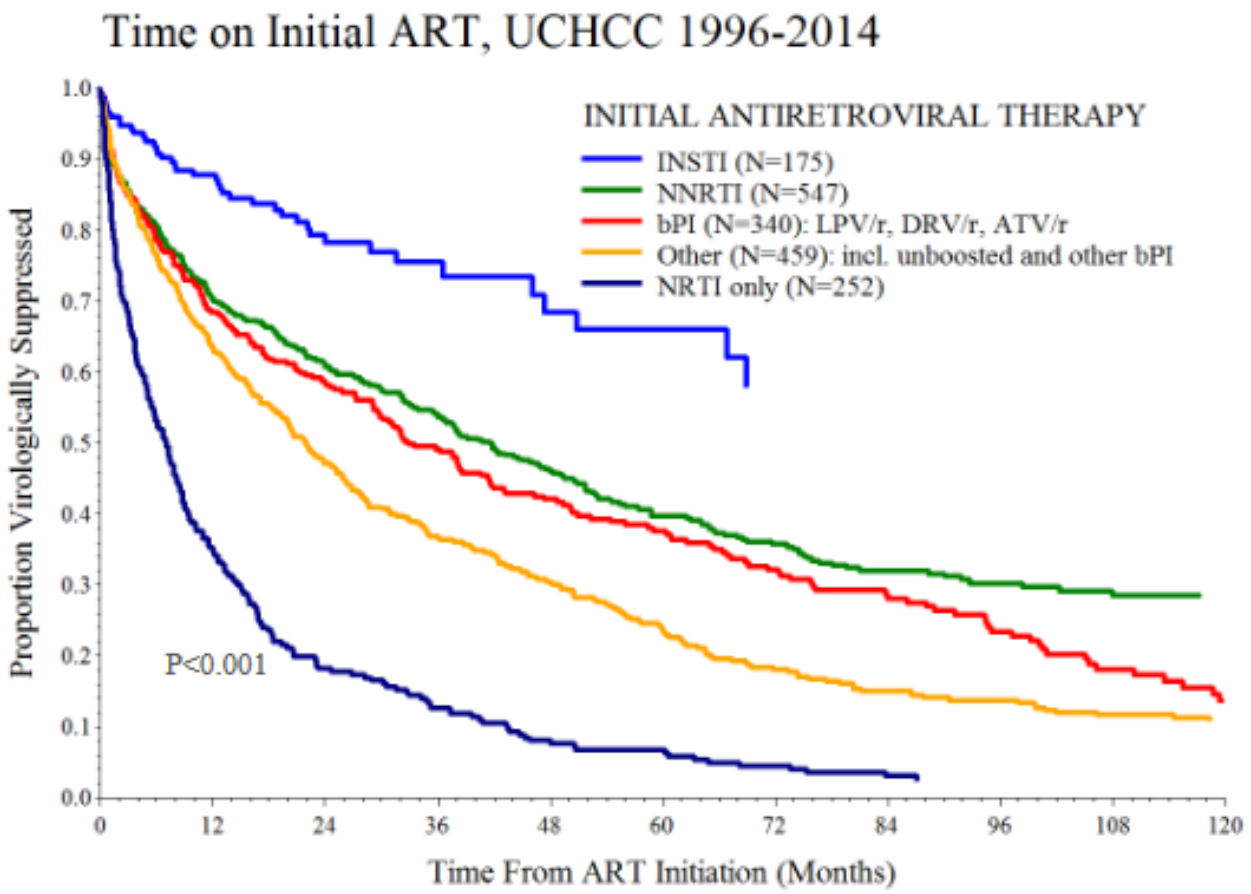
Discontinuations: DTG+ABC/3TC 2% vs. EFV/TDF/FTC 10%

Walmsley et al. N Engl J Med 2013

And they do well in the real (US) world!

UCHCC: UNC CFAR HIV Clinical Cohort

Persistence of Initial ART



In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression

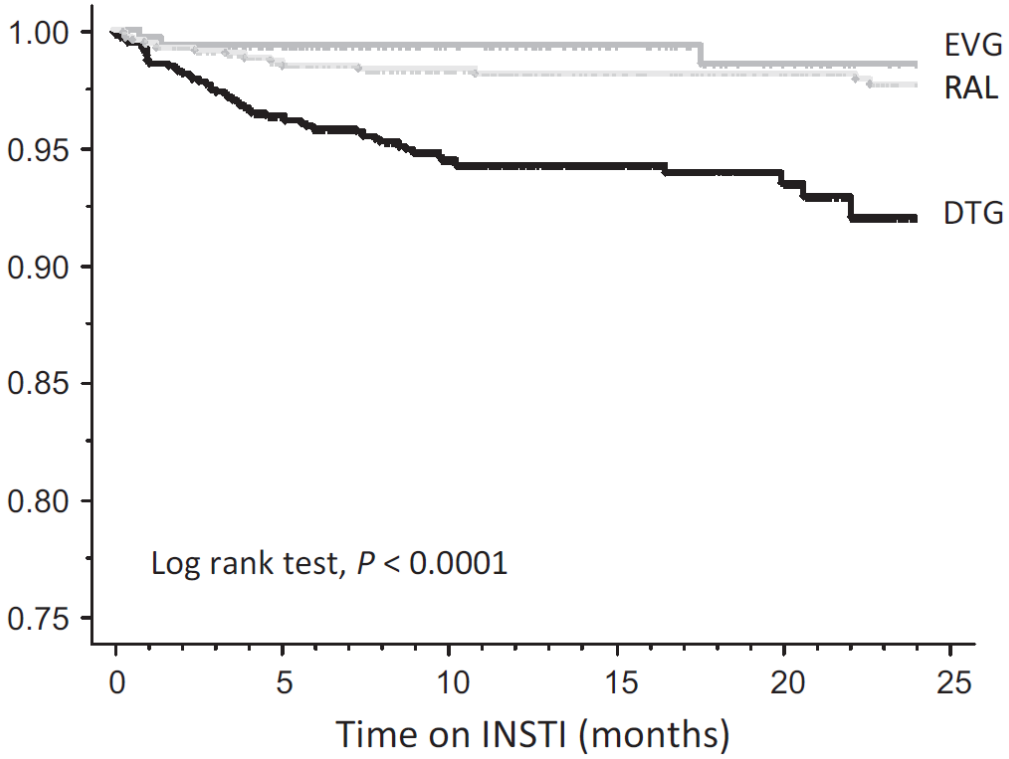
Thanks Joe Eron

DTG in the REAL real world…

Dolutegravir: discontinuation due to AE

Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE



Factors associated with DTG discontinuation

	RH	95% CI	P
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.

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

DTG in the REAL real world…

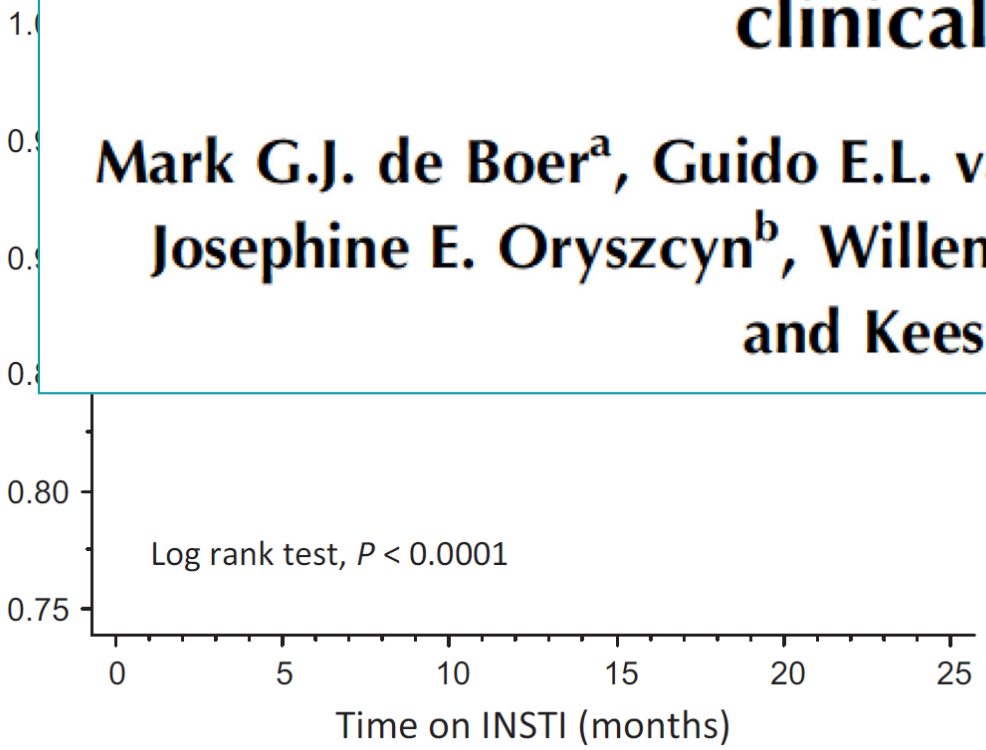
Dolutegravir: discontinuation due to AE

Germany (2 cohorts), 1950 INSTI-based therapies

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. Oryszcyn[b], Willemien Dorama[a], Daoud ait Moha[b] and Kees Brinkman[b]



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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.

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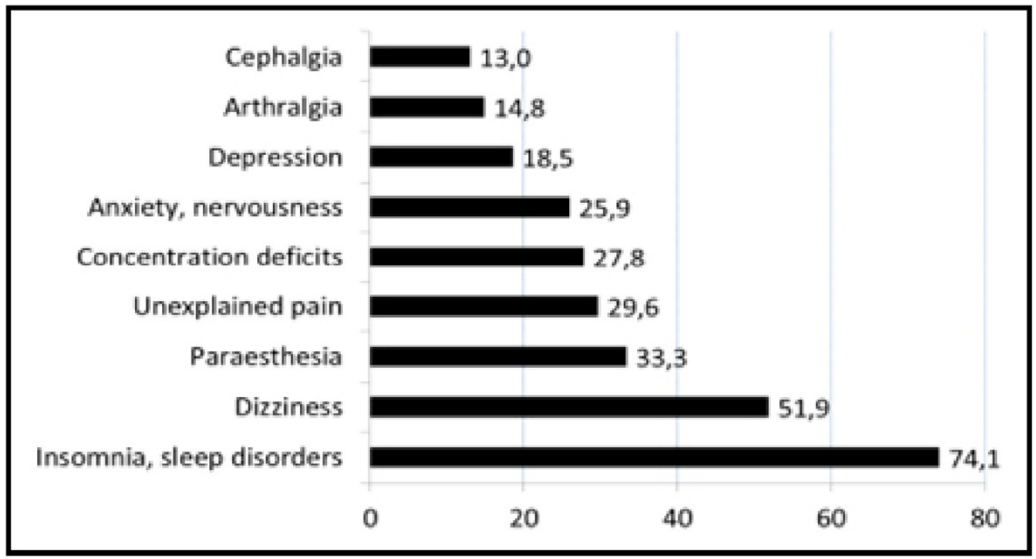
Hsu et al. CROI 2017 abstract #664

From CROI: Risk factors for neuropsychiatric events

Table 1: Adjusted Relative Hazards (RH) for the covariables of interest, using the Cox model.

Risk factors for NPAEs leading to DTG discontinuation	RH	95 % CI	p
Female, versus male gender	2.31	1.12-4.74	0.03
Older age (> 60 years), versus younger age	2.14	1.10-4.18	0.025
Depressive disorders, versus no	1.00	0.54-1.88	0.952
Other neuropsychiatric diagnoses, versus no	0.93	0.29-3.00	0.896

Figure 3. Reasons (%) for discontinuing DTG, n=54
(mean of 2.9 symptoms/NPAEs were reported)

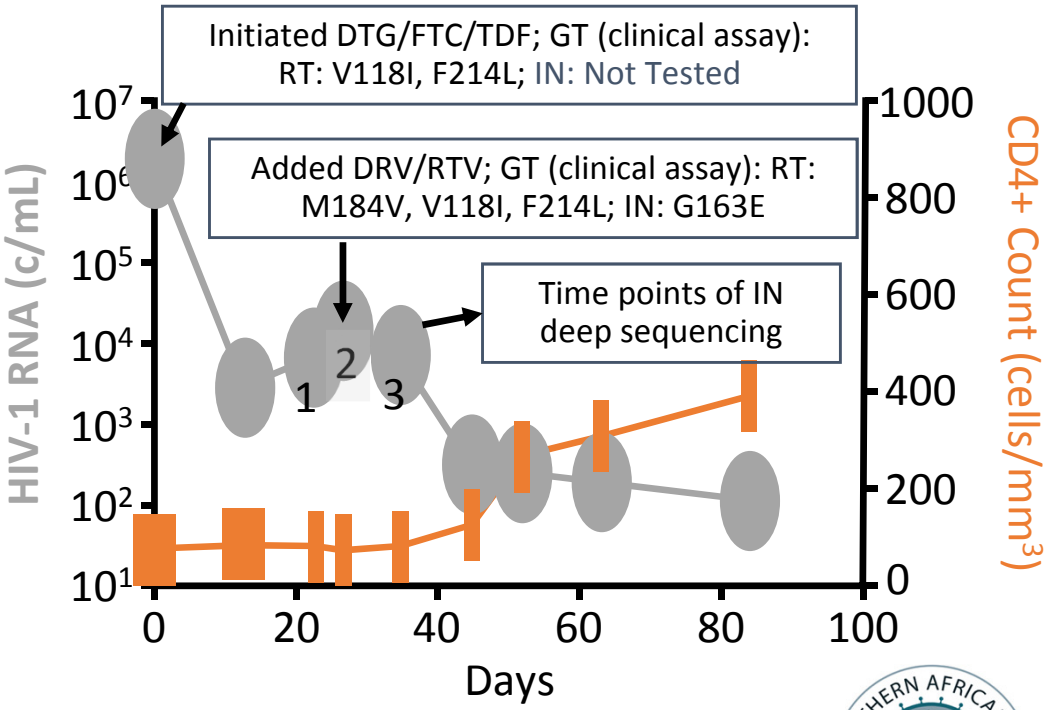


Hoffman et al. CROI 2018 abstract #424

Case report: INSTI resistance in acute HIV treated with DTG + FTC/TDF

- 45-yr-old man, no PMH, presented with *P jirovecii* and new acute HIV diagnosis
- Initiated DTG + FTC/TDF and discharged; readmitted to ICU several days later for worsened hypoxia
- HIV-1 RNA increased after readmission despite med adherence (including DOT in hospital) and no concurrent divalent cation use
  - DRV/r added, HIV-1 RNA decreased
  - Pneumonia improved and pt discharged
- HIV-1 RNA remains suppressed; DRV/r switched to RPV for diffuse erythroderma

- Rapid INSTI emergence by deep seq: eg, Q148K population increased from 0.0015% at time point 1 to 20.9% at time point 3



Slide credit: clinicaloptions.com

Fulcher JA, et al. CROI 2017. Abstract 500LB.

Preferred option in most guidelines, but not WHO (yet)

Guidelines	NRTI Backbone				NNRTI			InSTI			PI		
	TDF/XTC	TAF/XTC	ABC/3TC	AZT/3TC	EFV	NVP	RIL	DTG	EVG	RAL	ATV	DRV	LPV
IAS (2016)	Alternative	Preferred	Preferred		Alternative		Alternative	Preferred	Preferred	Preferred		Preferred	
DHHS (2017)	Preferred	Preferred	Preferred					Preferred	Preferred	Preferred			
EACS (2017)	Preferred	Preferred	Preferred		Alternative		Preferred	Preferred	Preferred	Preferred	Alternative	Preferred	
WHO (2016)	Preferred			Alternative	Preferred	Alternative		Alternative					

Preferred

Alternative

Not recommended/special situations

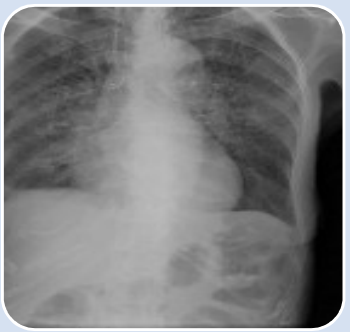
Courtesy of M. Vitoria; updated M. Moorhouse

Why aren’t these drugs used?

RCTs don’t address real world issues

Women, children and LMICs under-represented in pivotal studies

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

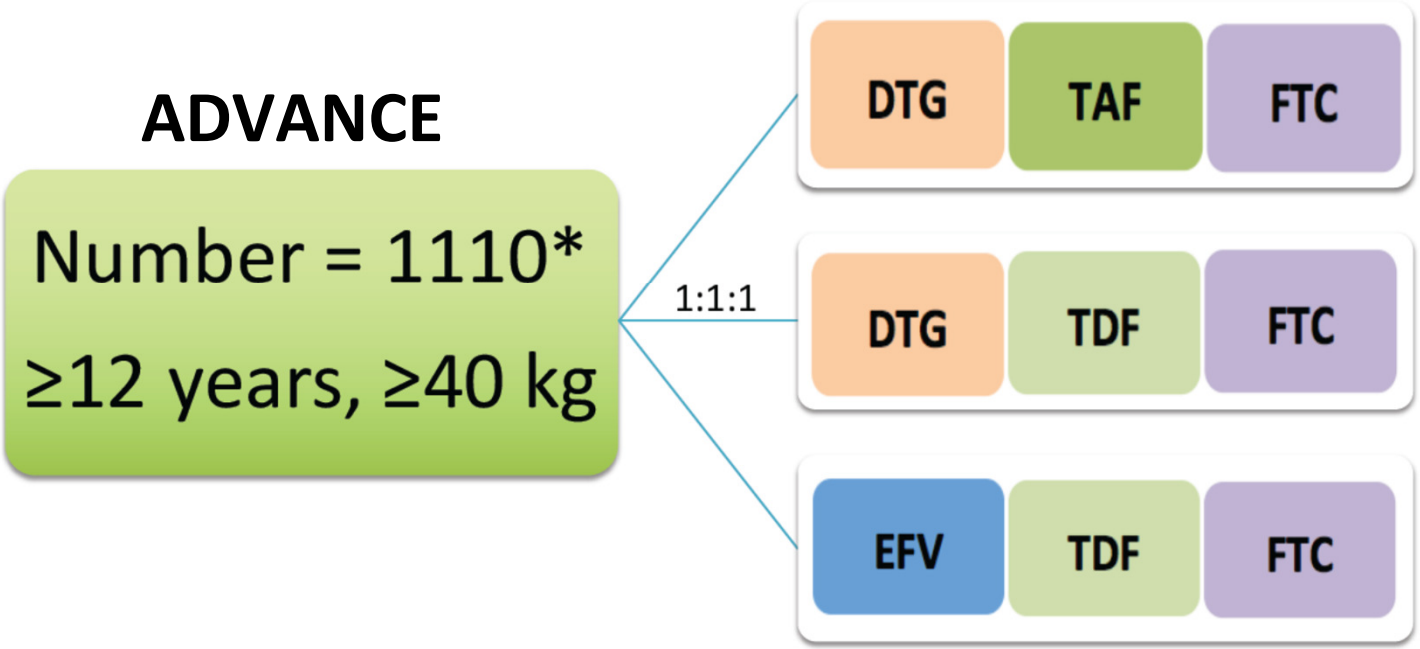


Limited data on use in TB (almost all new drugs)

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

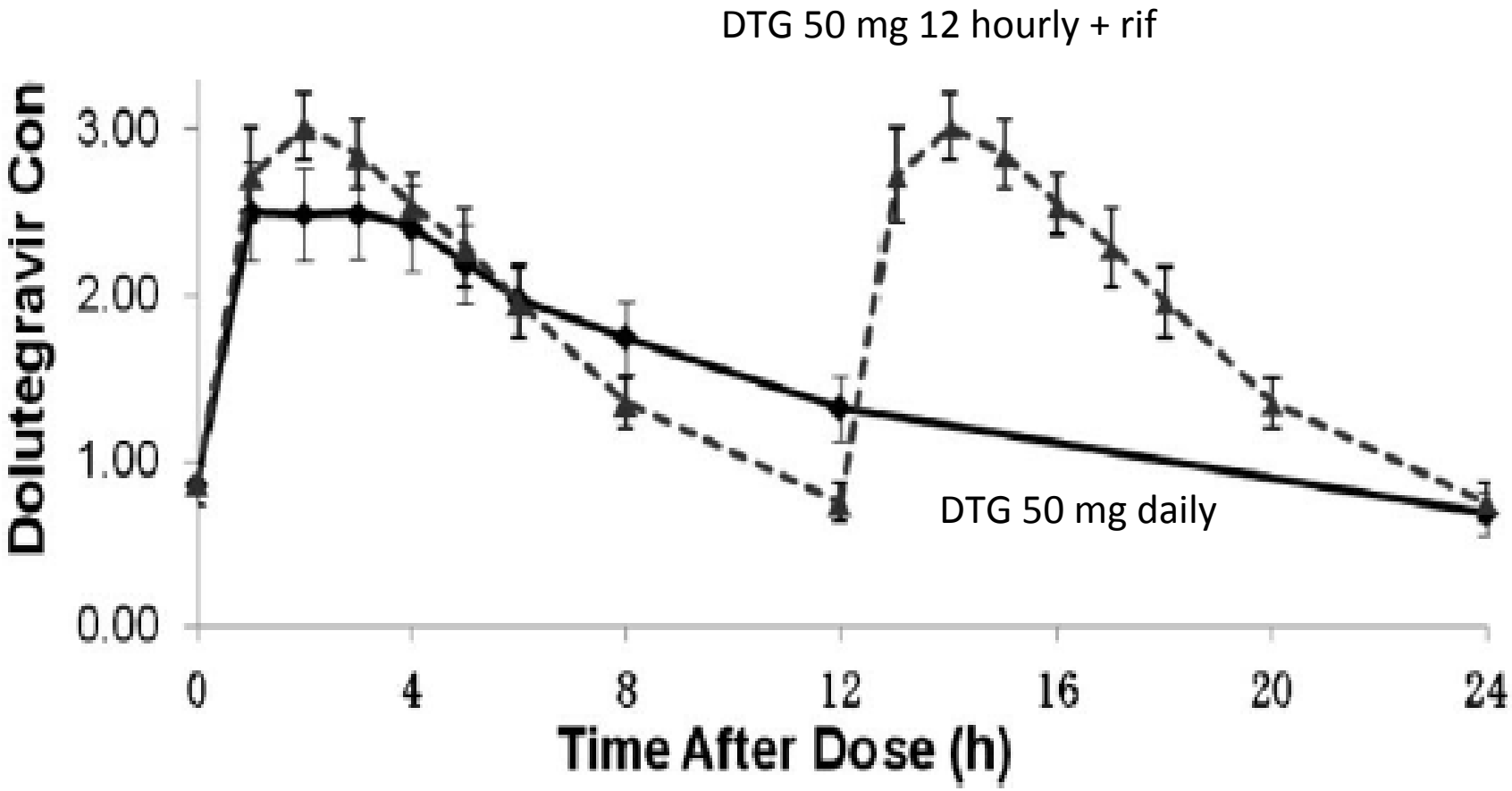
Costs: abacavir, all integrase inhibitors – hope for dolutegravir

Real world patients are under-represented



- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years

TB: DTG and rifampicin

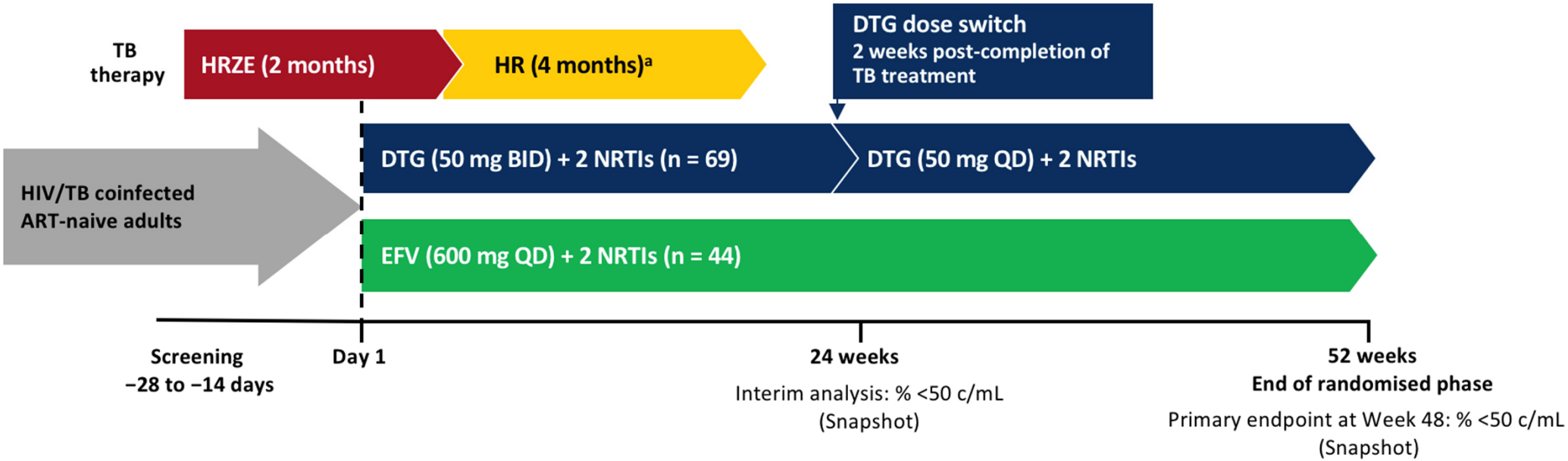


$AUC_{0\text{-}24}$ DTG 50 mg/d 32.1

DTG 50 mg 12 hourly + rifampicin 42.6

JAIDS 2013;62:21

INSPIRING: Phase 3b study design



Inclusion criteria

- HIV-1 RNA ≥ 1000 copies/mL and CD4+ ≥ 50 cells/mm^3
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomisation and no later than the screening date

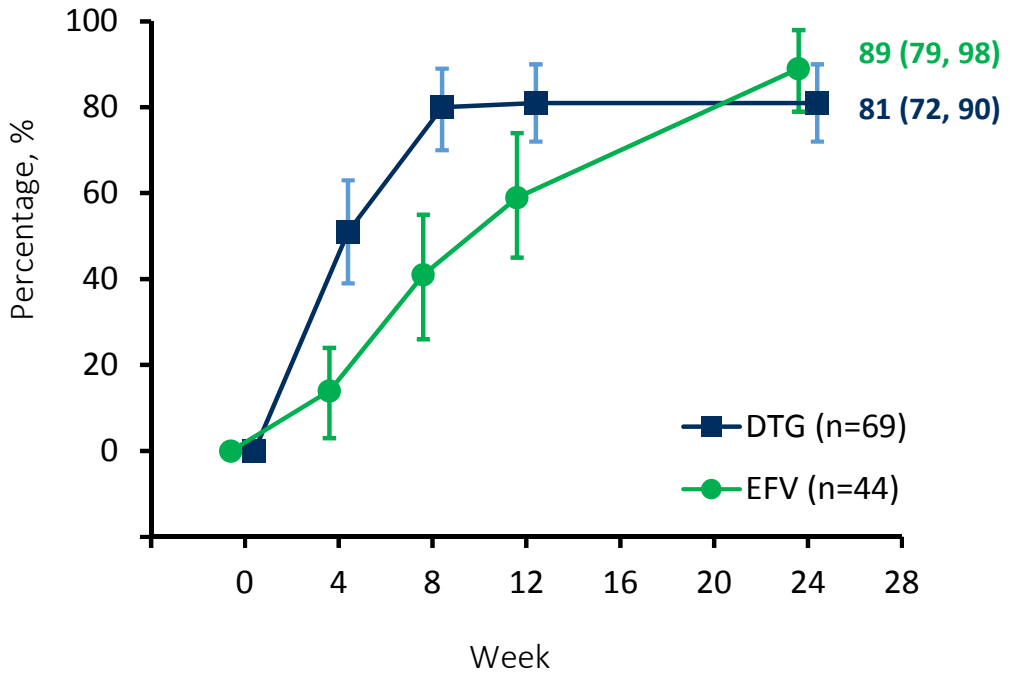
Primary endpoint

- Proportion of DTG subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 using the modified Snapshot algorithm in the ITT-E population

Dooley K, et al. CROI 2018. Abstract 33

Virologic and PK results through week 24

Proportion of participants with HIV-1 RNA <50 copies/mL, % (95% CI)



Pharmacokinetic data

Pre-dose concentration: DTG 50 mg BID with RIF		
Time	n	DTG Conc (ng/mL) Geomean (90%CI) %CV
Week 8	41	852 (208-2340) 118
Week 24	22	942 (19-3380) 276

Pre-dose concentration: DTG 50 mg QD without RIF (post-TB treatment phase)		
Time	n	DTG Conc (ng/mL) Geomean (90%CI) %CV
Week 36	16	1143 (80-4370) 151
Week 48	12	591 (19-3310) 359

INSPIRING DTG C_{tau} when administered twice daily with RIF were similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in Phase 2/3 HIV trials.

Dooley K, et al. CROI 2018. Abstract 33

Pregnancy: Birth outcomes of first-line DTG vs EFV (Tsepamo)

Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

Adverse Birth Outcomes, n (%)	DTG (n = 845)	EFV (n = 4593)	aRR* (95% CI)
Any	291 (34.4)	1606 (35.0)	1.0 (0.9-1.1)
▪ Severe	92 (10.9)	519 (11.3)	1.0 (0.8-1.2)
Stillbirth	18 (2.1)	105 (2.3)	0.9 (0.6-1.5)
Neonatal death (< 28 days)	11 (1.3)	60 (1.3)	1.0 (0.5-1.9)
Preterm birth (< 37 wks)	149 (17.8)	844 (18.5)	1.0 (0.8-1.1)
▪ Very preterm (< 32 wks)	35 (4.2)	160 (3.5)	1.2 (0.8-1.7)
SGA (< 10th percentile weight)	156 (18.7)	838 (18.5)	1.0 (0.9-1.2)
▪ Very SGA (< 3rd percentile weight)	51 (6.1)	302 (6.7)	0.9 (0.7-1.2)

*For DTG vs EFV; adjusted for maternal age, education, gravida.

Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396); most second/third trimester

Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)

ABO risks similar when initiating first-line DTG vs EFV in pregnancy

Zash R, et al. IAS 2017. Abstract MOAX0202LB.

Costs

SAMJ IN PRACTICE

CLINICAL UPDATE

Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter,[1] FCP (SA), MMed; **B Kaiser**,[2] MPH, PharmD, BCPS; **Y Pillay**,[3] PhD; **F Conradie**,[4] MB BCh; **G B Gomez**,[5] PhD; **P Clayden**;[6] **M Matsolo**;[7] **C Amole**,[8] BA; **L Rutter**,[7] BA; **F Abdullah**,[9] MB ChB, FCPHM, BSc Hons (Epi); **E J Abrams**,[10] MD; **C P Casas**,[11] MSc; **M Barnhart**,[12] MD, MPH; **A Pillay**,[13] PhD; **A Pozniak**,[14] M **M Moorhouse**,[1] MB BCh; **M Chersich**,[1] MB BCh, PhD; **C**

[1] *Wits Reproductive Health and HIV Institute, University of t*
[2] *Formerly UNITAID, Geneva, Switzerland*
[3] *HIV/AIDS, TB and Maternal, Child and Women's Health i*

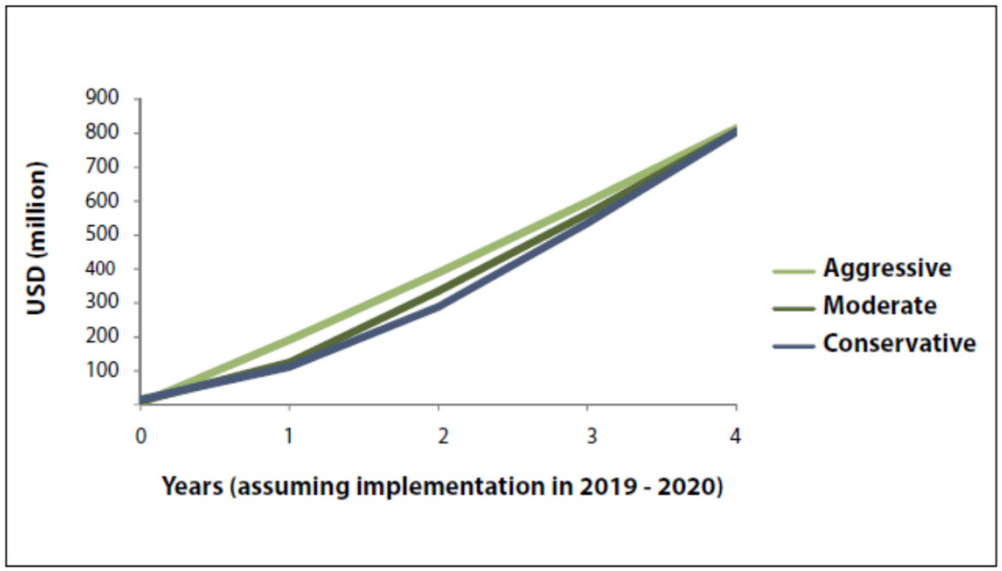
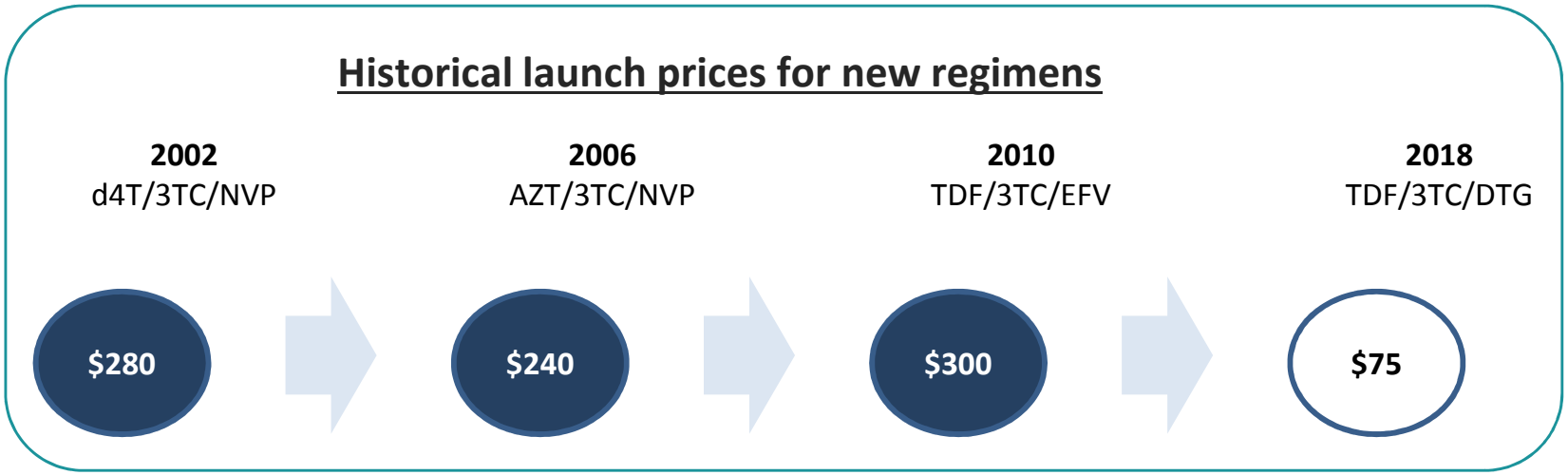


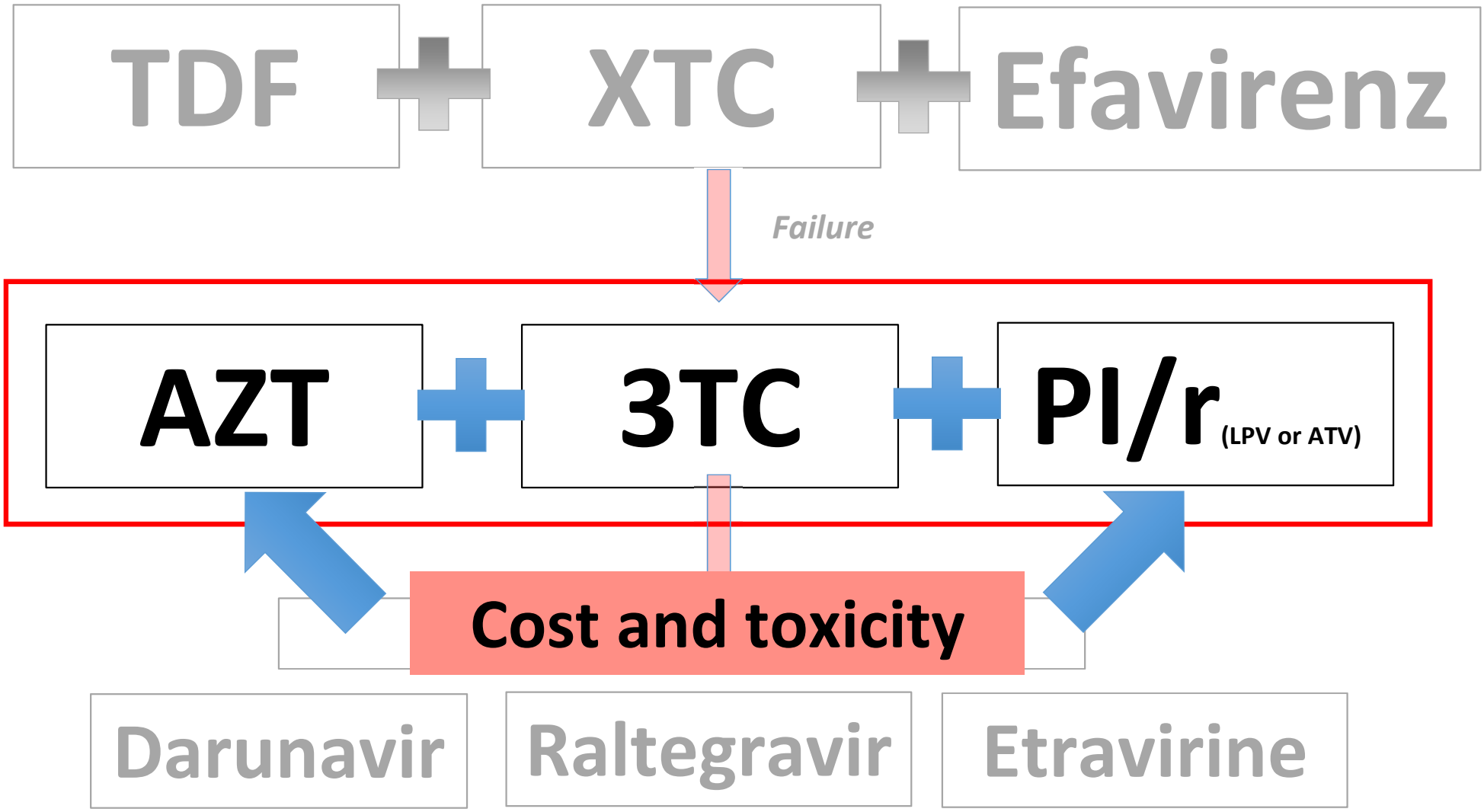
Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).

Ceiling price agreement was recently announced



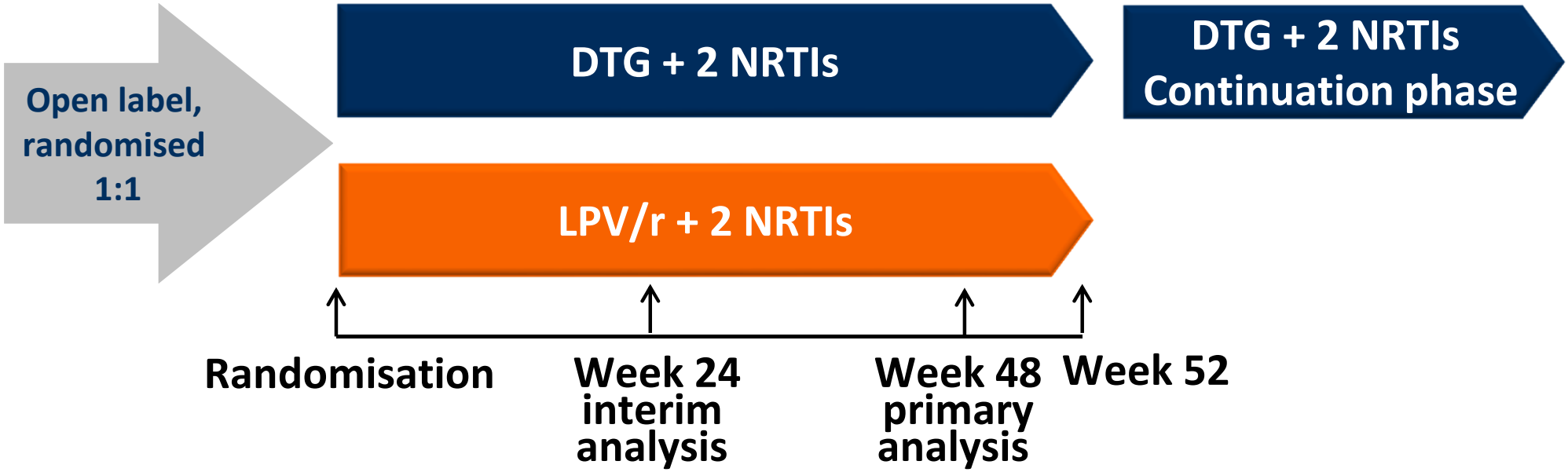
- This ceiling price agreement could yield billions of rand in savings through TLD rollout and enable widespread access to a clinically superior regimen
- The TLD agreement lasts four years: 01 April 2018 – 31 March 2022

But what about second-line?



DAWNING: Study design

Open-label randomised noninferiority phase 3b study



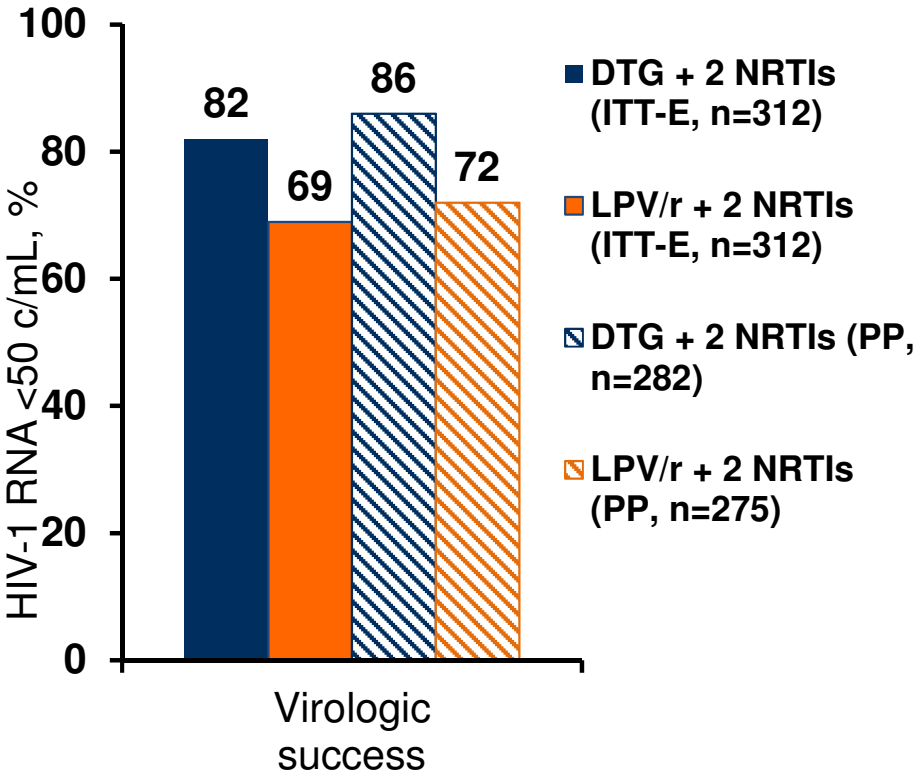
- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥ 400 copies/mL on 2 occasions); no primary viral resistance to PIs or InSTIs
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected 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)

FDA, US Food and Drug Administration; INSTI, integrase strand transfer inhibitor.

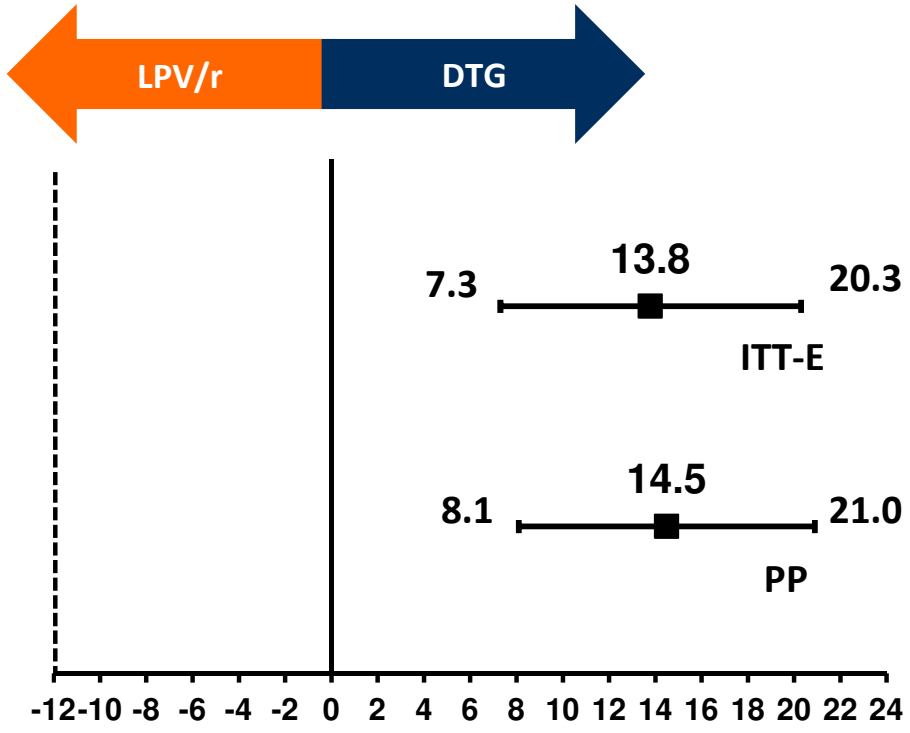
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

Snapshot outcomes at Week 24: ITT-E and PP Populations

Virologic outcomes



Treatment differences (95% CI)



- DTG + 2 NRTIs is **superior** to LPV/r + 2 NRTIs with respect to snapshot in the ITT-E (< 50 copies/mL) at Week 24, ***P* < 0.001**
  - CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

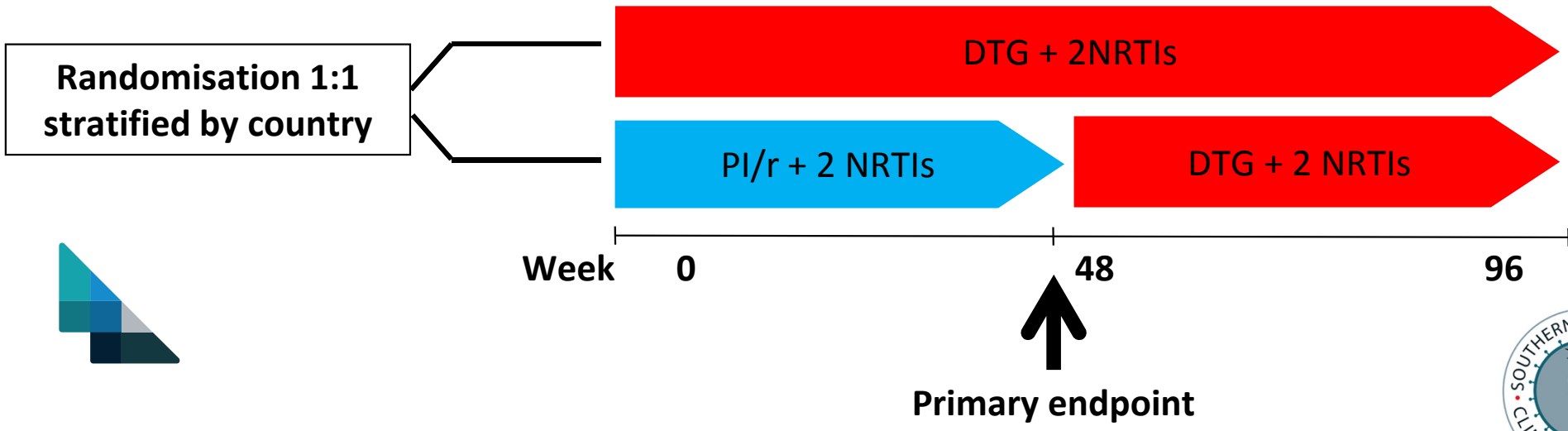
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

neatid The European treatment network for HIV, hepatitis and global infectious diseases

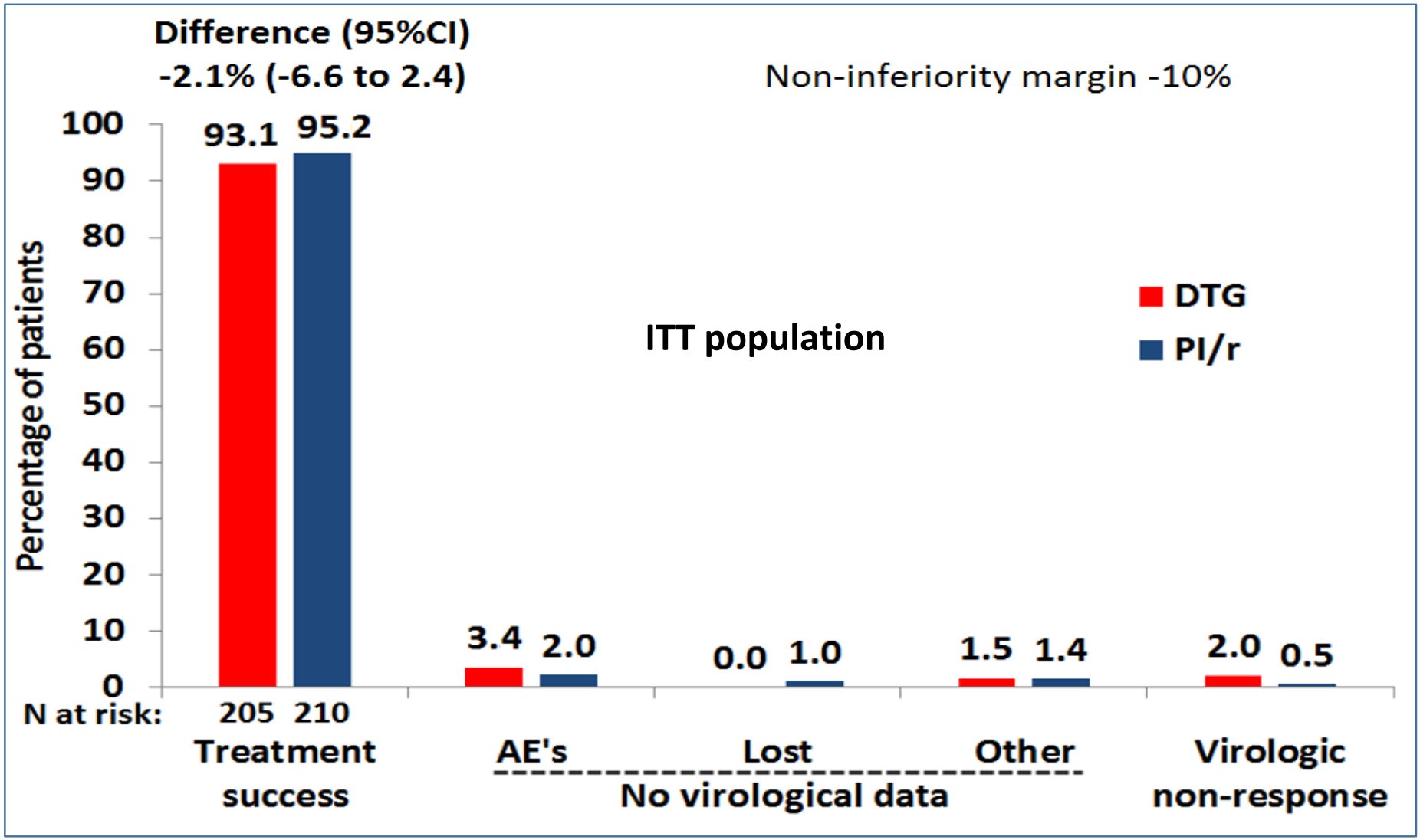
SSAT ST STEPHEN'S AIDS TRUST

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. Gatell[1], L. Assoumou[2], G. Moyle[3], L. Waters[4], E. Martinez[5], H.-J. Stellbrink[6], G. Guaraldi[7], S. de Wit[8], F. Raffi[9], A. Pozniak[10] on behalf of NEAT022 Study Group

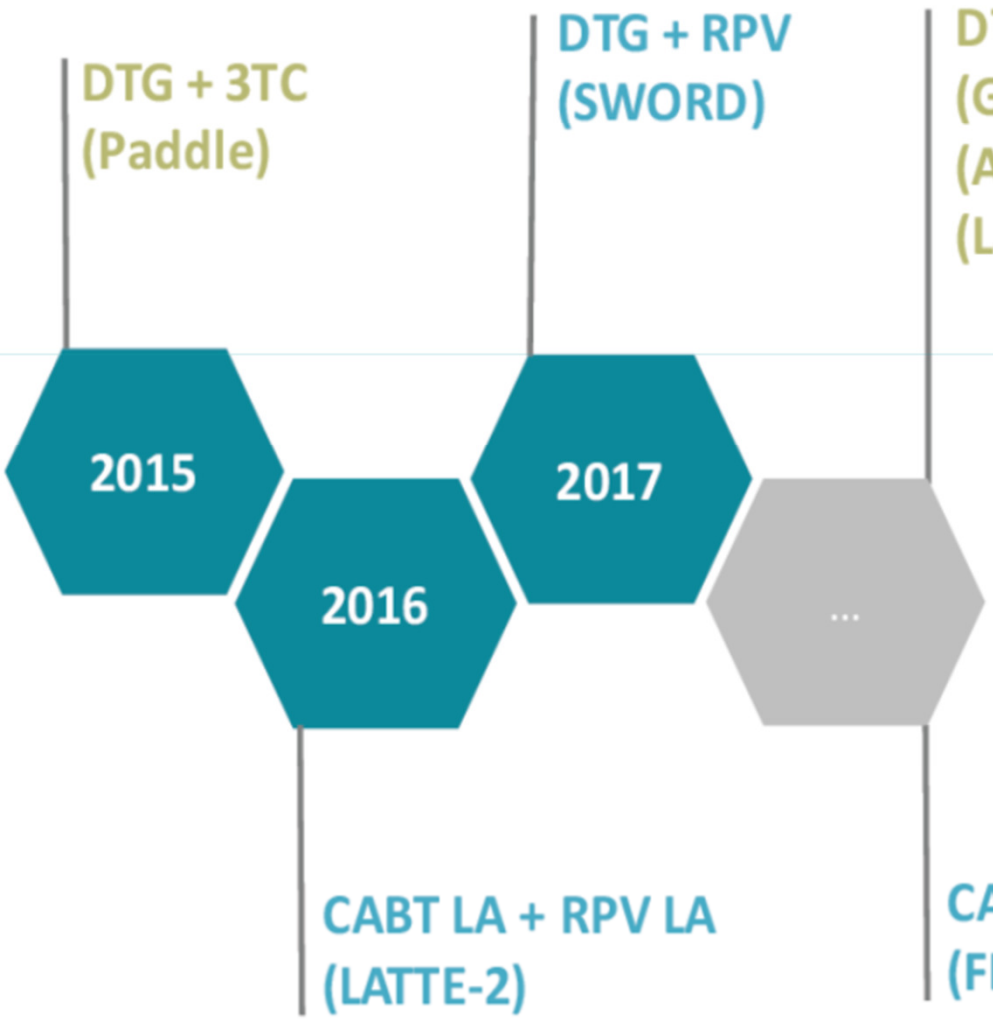


Results: Co-primary efficacy endpoint




MIND THE GAP

Reduced drug regimens in ARV-naïve patients?



Courtesy J Arribas

Previous studies of first-line dual-therapy ART: Selected data

Study	N	Regimen	Results
DTG-based dual therapy			
PADDLE[1]	20	DTG + 3TC ARV-naives	18/20 pts achieved virologic suppression; n = 1 experienced PDVF (BL HIV-1 RNA > 100 000 copies/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit
ACTG 5353[2]	120	DTG + 3TC ARV-naives	108/120 patients achieved virologic suppression at week 24; n = 3 experienced PDVF (all 3 had sub-therapeutic DTG levels)
ANRS 167 LAMIDOL[3]	110	DTG + 3TC (Switch study)	97% (101/104) pts maintained virologic suppression through 40 weeks of dual therapy (study Week 48)
SWORD 1,2[4]	1024	DTG + RPV versus continuing (Switch)	95% of pts in both arms maintained virologic suppression through 48 weeks of therapy (study Week 52)

1. Cahn P, et al. IAC 2016. Abstract FRAB0104LB. 2. Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB 3. Joly V, et al. CROI 2017. Abstract 458 4. Llibre JM, et al. CROI 2017. Abstract 44LB

Dolutegravir monotherapy in ART-naive

- N = 9 pts who refused NRTIs and initiated DTG monotherapy
  - All pts had baseline HIV-1 RNA < 100,000 copies/mL
  - No baseline NRTI, NNRTI, PI, or INSTI resistance

Pt	HIV-1 RNA, copies/mL			CD4+ Cell Count, cells/mm^3		Mos on DTG
	Baseline	After 4 Wks' DTG	At Last Visit	Baseline	At Last Visit	
1	20,400	Undetectable	Undetectable	248	600	10
2	18,400	Undetectable	< 20	335	471	9
3	90,500	31	Undetectable	356	527	7
4	39,000	35	Undetectable	350	623	7
5	43,300	< 20	Undetectable	329	613	7
6	17,500	45	< 20	229	404	6
7	18,200	< 20	Undetectable	785	879	6
8	16,900	Undetectable	Undetectable	214	309	8
9	52,000	< 20	Undetectable	345	484	6

Lanzafame M, *et al*. J Acquir Immune Defic Syndr. 2016

DOMONO: Switch to DTG monotherapy in suppressed patients not sufficient

Comparison of randomised switch to DTG 50 mg QD monotherapy vs continued baseline ART in suppressed patients with no previous VF[1]

- At Week 24, DTG monotherapy noninferior to continued baseline ART for maintained HIV-1 RNA < 200 copies/mL
- **Study discontinued early due to high rate of InSTI resistance mutations after 48 weeks of DTG monotherapy[2]**
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group (*P* = 0.03)
  - Of 8 monotherapy pts with VF, genotyping successful in 6; 3/6 with InSTI resistance (N155H, R263K, S230R, n = 1 each)

1. Wijting I, et al. HIV Glasgow 2016. Abstract O333.
2. Wijting I, et al. CROI 2017. Abstract 451LB.

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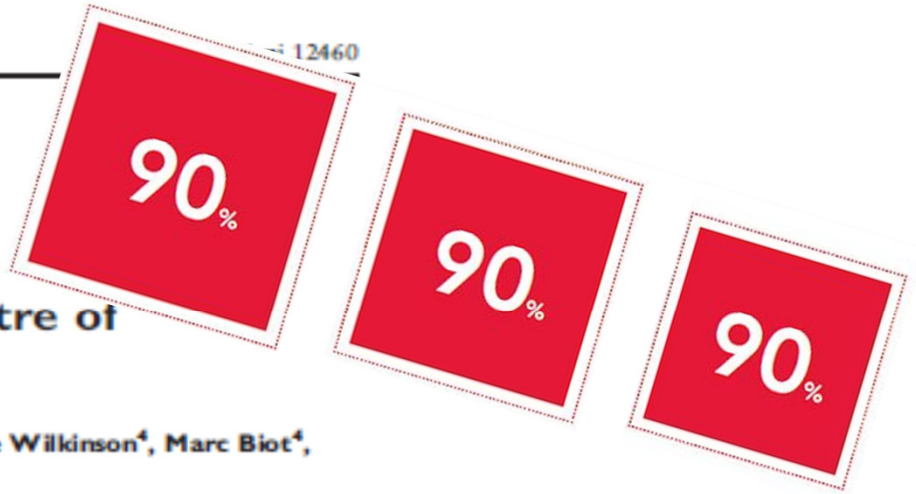


Review

Reframing HIV care: putting people at the centre of antiretroviral delivery

Chris Duncombe[1], Scott Rosenblum[1], Nicholas Hellmann[2], Charles Holmes[3], Lynne Wilkinson[4], Marc Biot[4], Helen Bygrave[4], David Hoos[5] and Geoff Garnett[1]

1 *The Bill an*
2 *Elizabeth G*
3 *Centre for I*
4 *Medecins S*
5 *Mailman Sc*

Summary

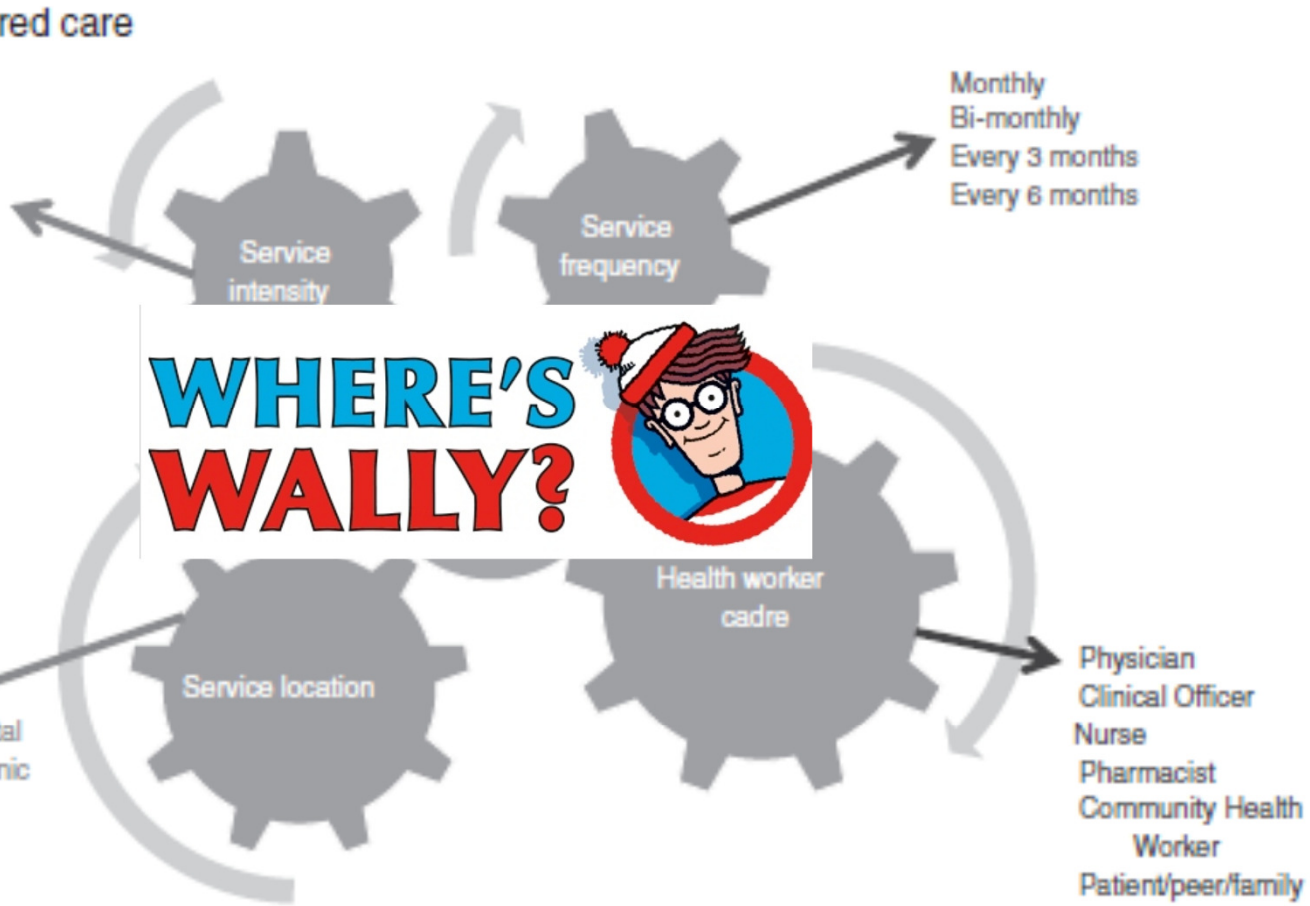


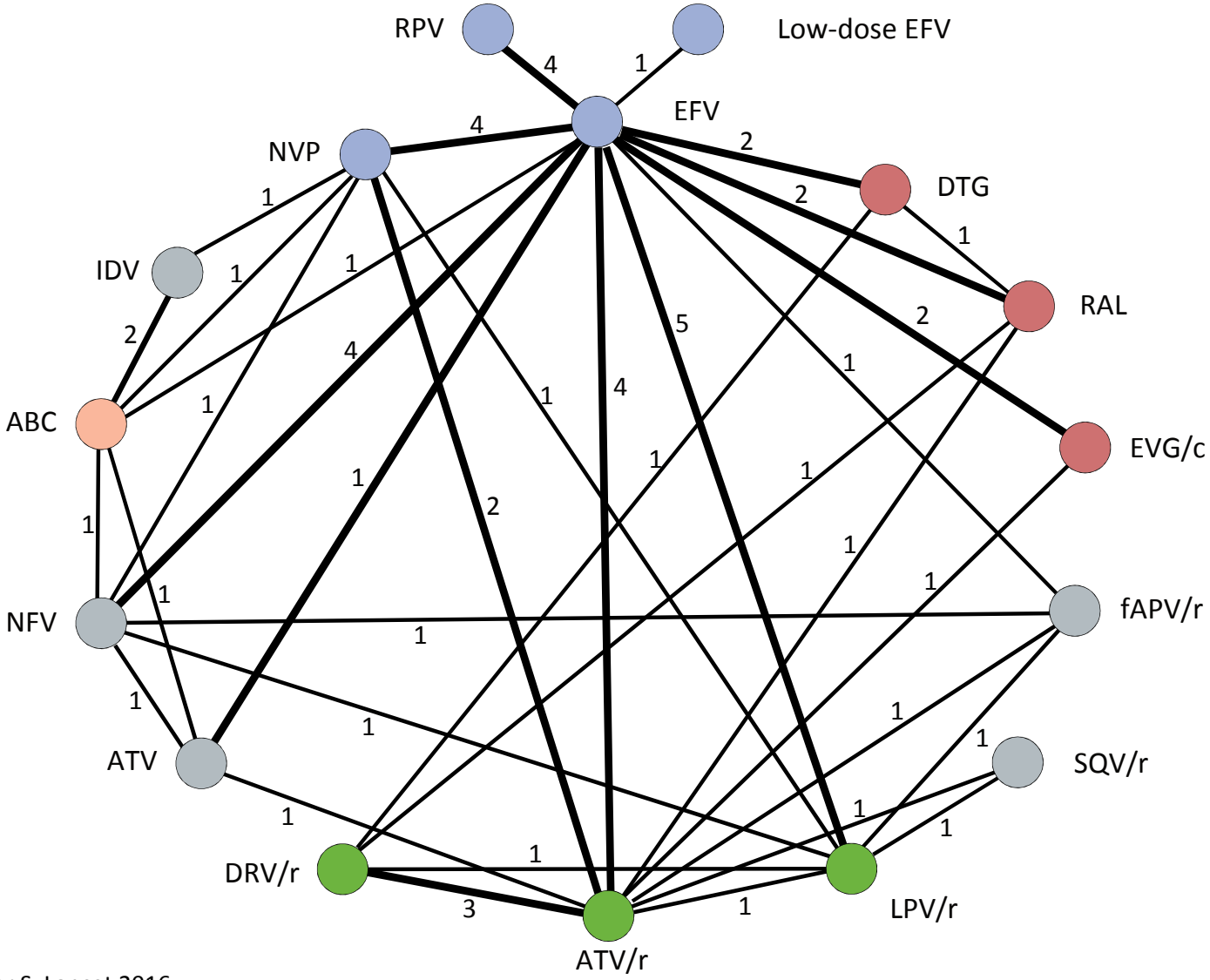
Figure 1 Four levers to tailor or adapt care to people's needs (service frequency, location, intensity and cadre).

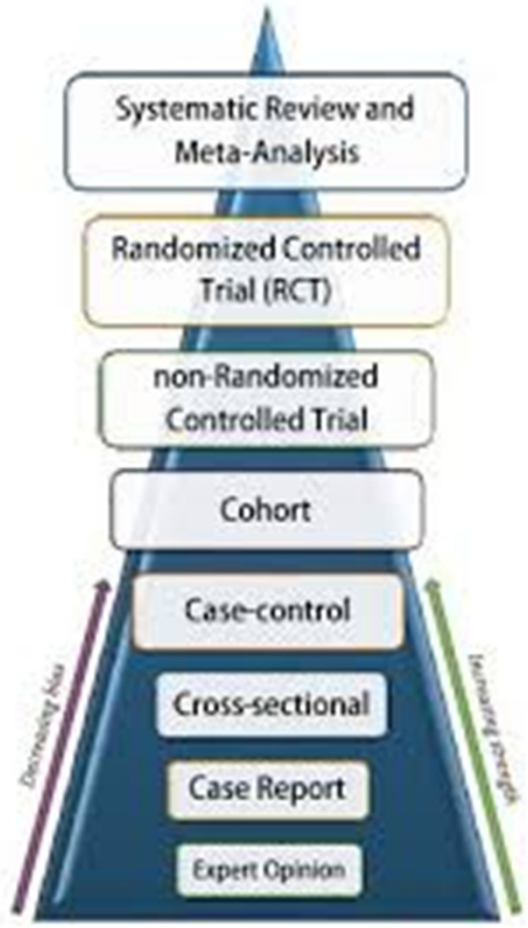
Comparing third drugs

Desirable Property	EFV	RPV	DTG
High resistance barrier	No	No	Yes
Well tolerated	Not initially	Yes	Yes
No lab tox monitoring	No	No	No
Safe in pregnancy	Yes	Limited data	Increasing data
Low pill burden	FDC	No FDC in SA	No FDC yet
Once a day	Yes	Yes	Yes
Use with TB (rifampicin)	Yes	No	Dose bid

Comparative efficacy and safety of first-line ART: A systematic review and network meta-analysis

Network of eligible comparisons between treatments





Kanter S, Lancet 2016

DTG is here

Superiority to currently used ARVs

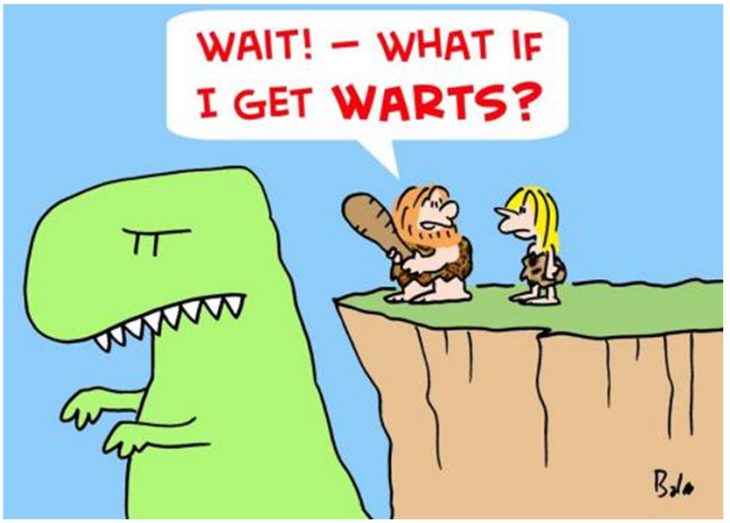
Robust with a formidable resistance barrier

Well-tolerated in RCTS

Real-world tolerability is emerging

Dual therapy?

ART alone is not enough



Acknowledgements