Exploring First-line ART Strategies: Dolutegravir

Michelle Moorhouse

Oct 2017

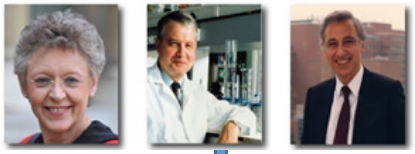
First-line ART Strategies Roadshow

University of the Witwatersrand

WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

The evolving HIV treatment paradigm



HIV-1 discovered

1983

ZDV monotherapy

1987

ZDV/3TC

1995

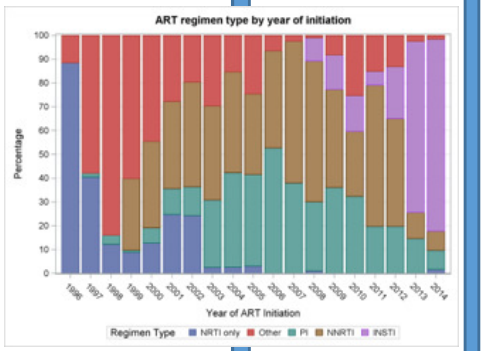
Triple-Drug Therapy

1996

Single-Tablet Regimens

2006

The Integrase Era



2012–2013

Long Acting Injectable?

2017

?????

2020

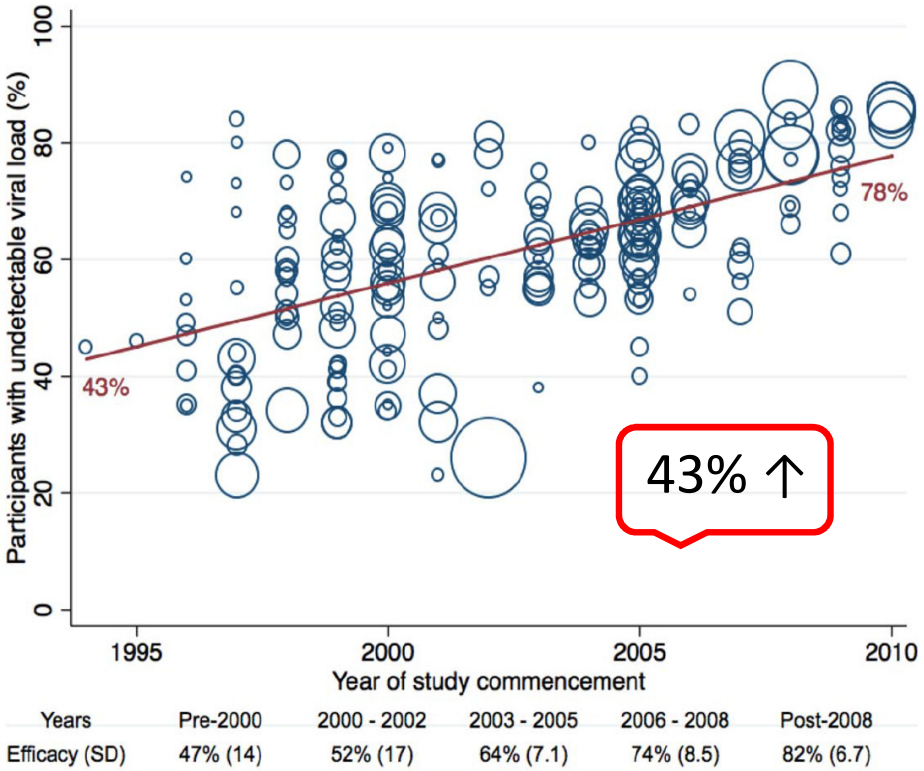
3TC=lamivudine; ZDV=zidovudine

Joe Eron

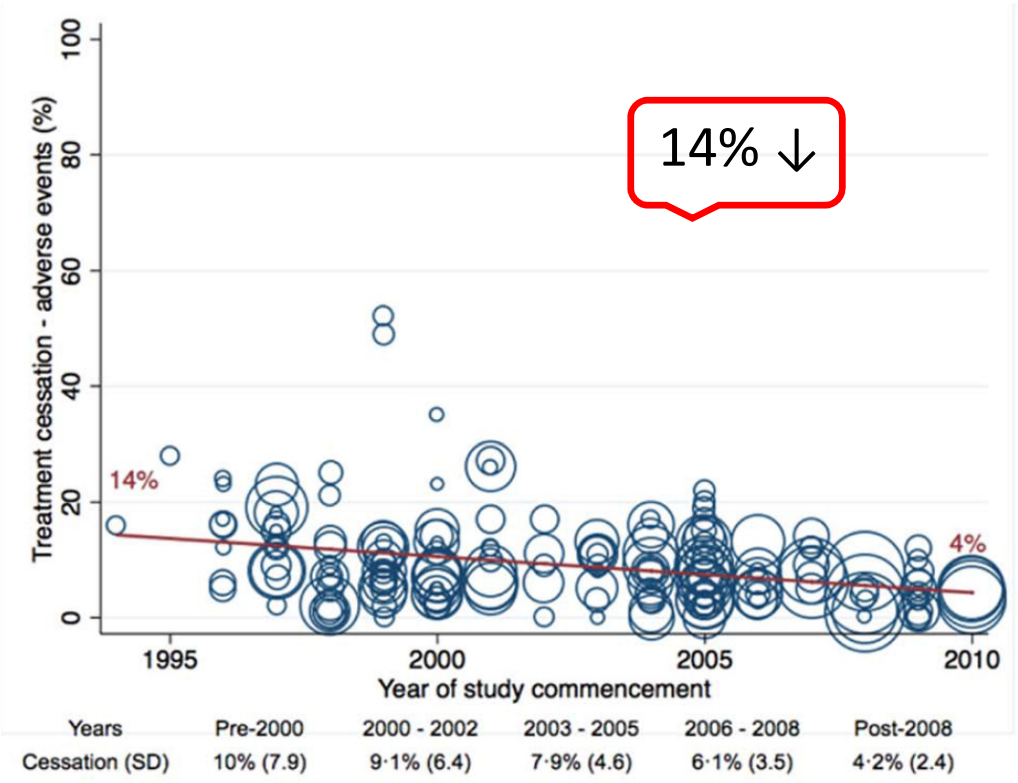
ART trials

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

Virologic responses

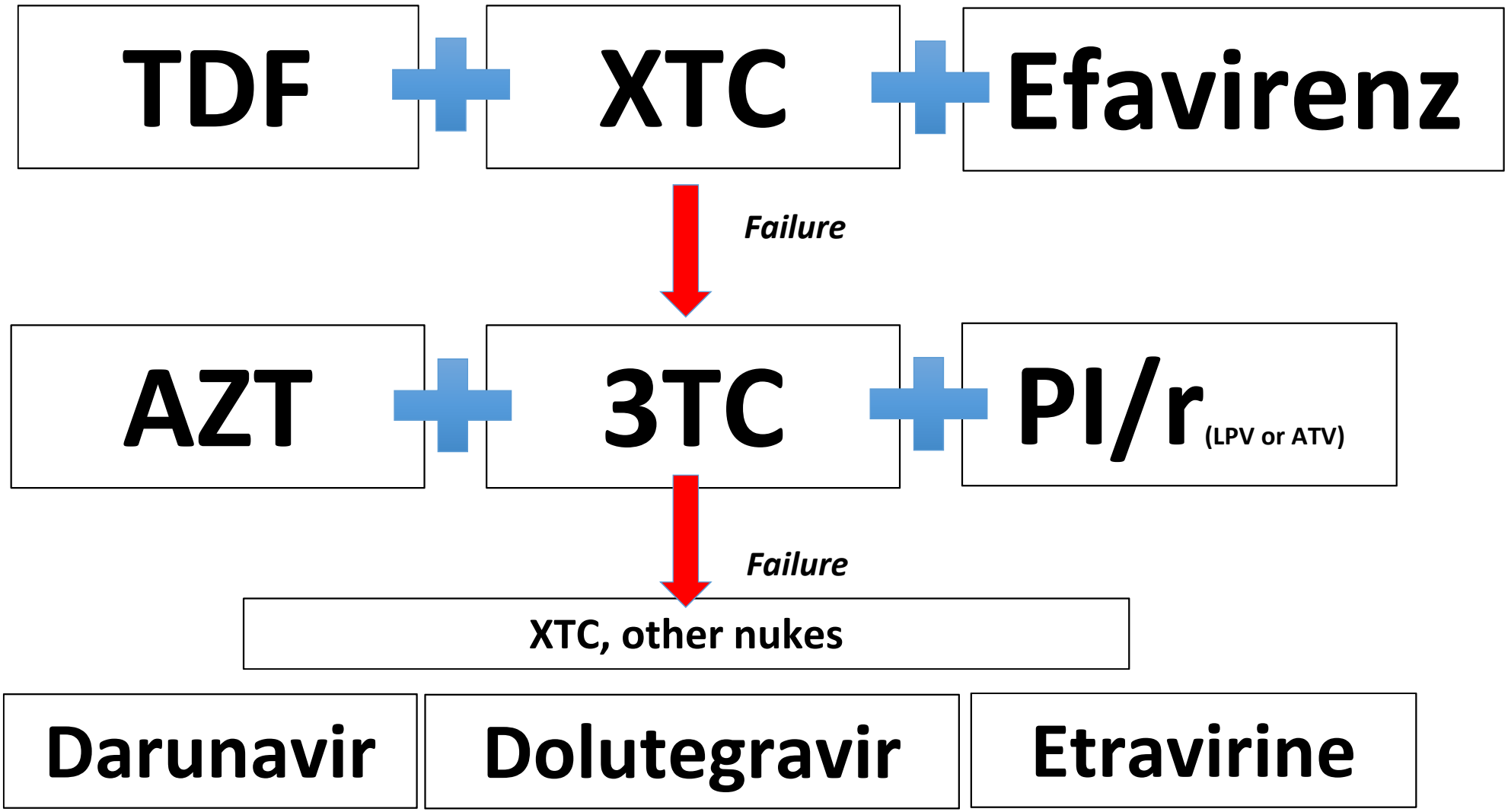


Safety and tolerability



Lee et al. PLoS One 2014

The drugs rock



But there’s room for improvement

First-line….

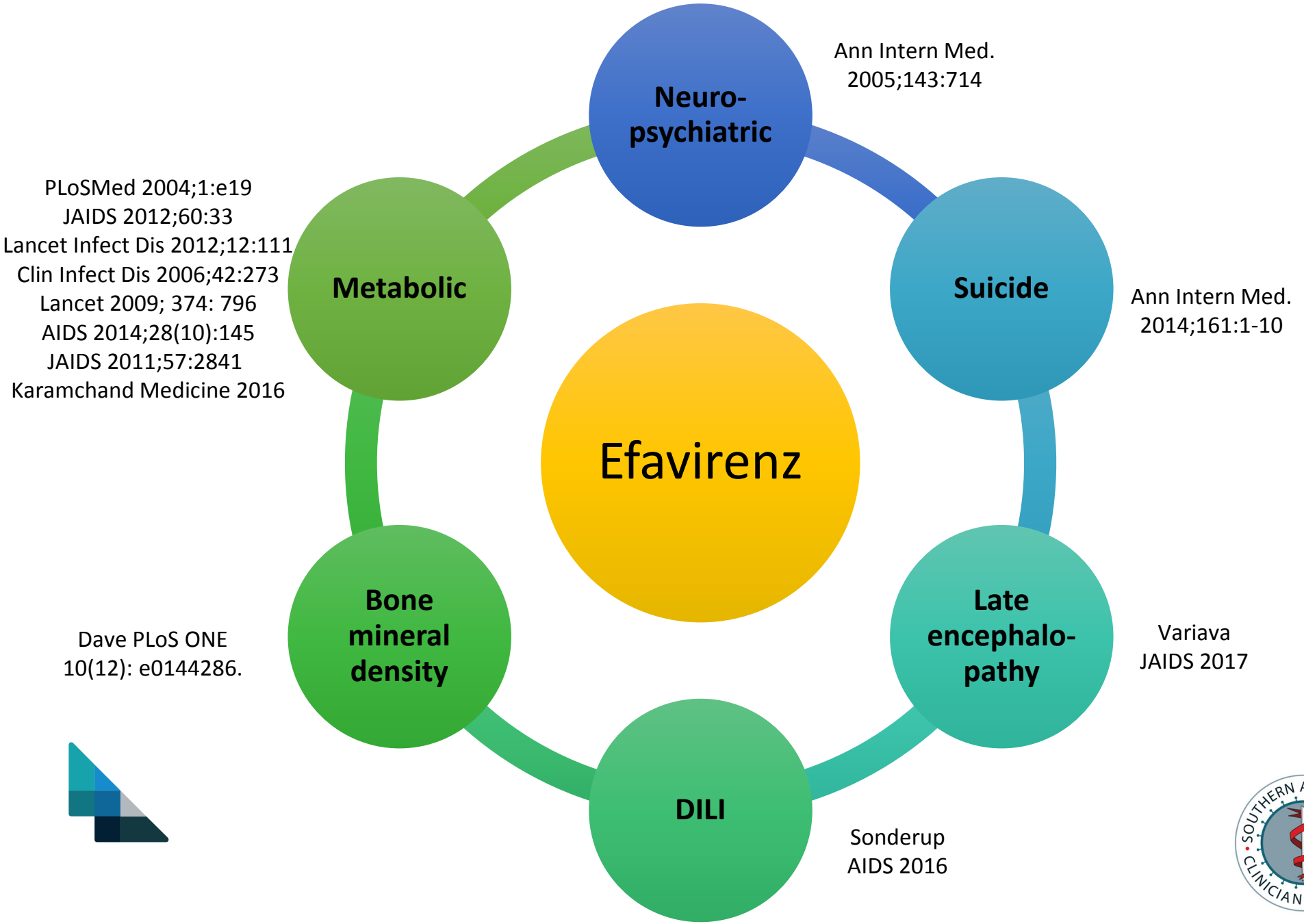
TDF + **XTC** + **EFV**

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 warts…



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.

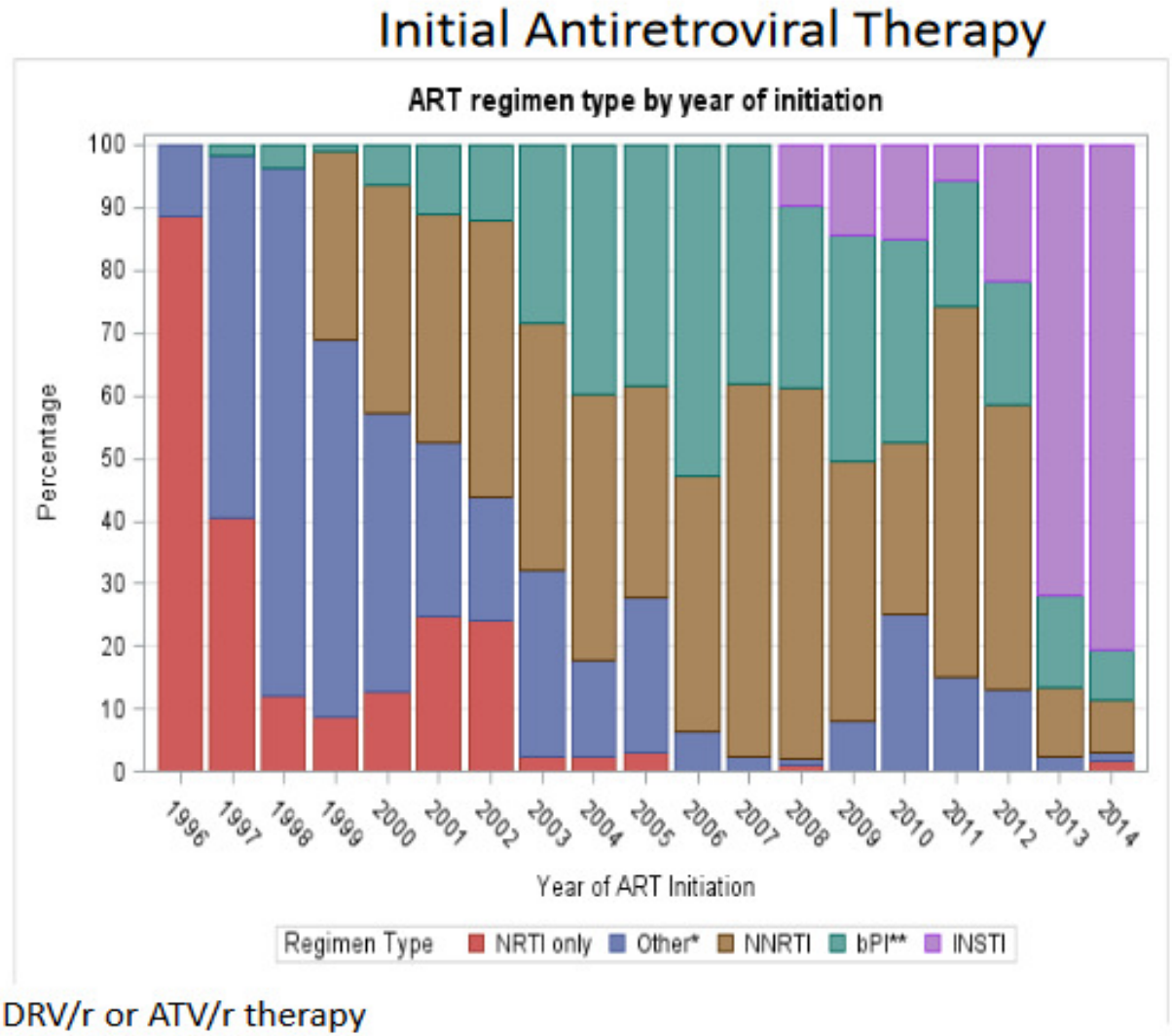
Recommended Alternative Not included

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

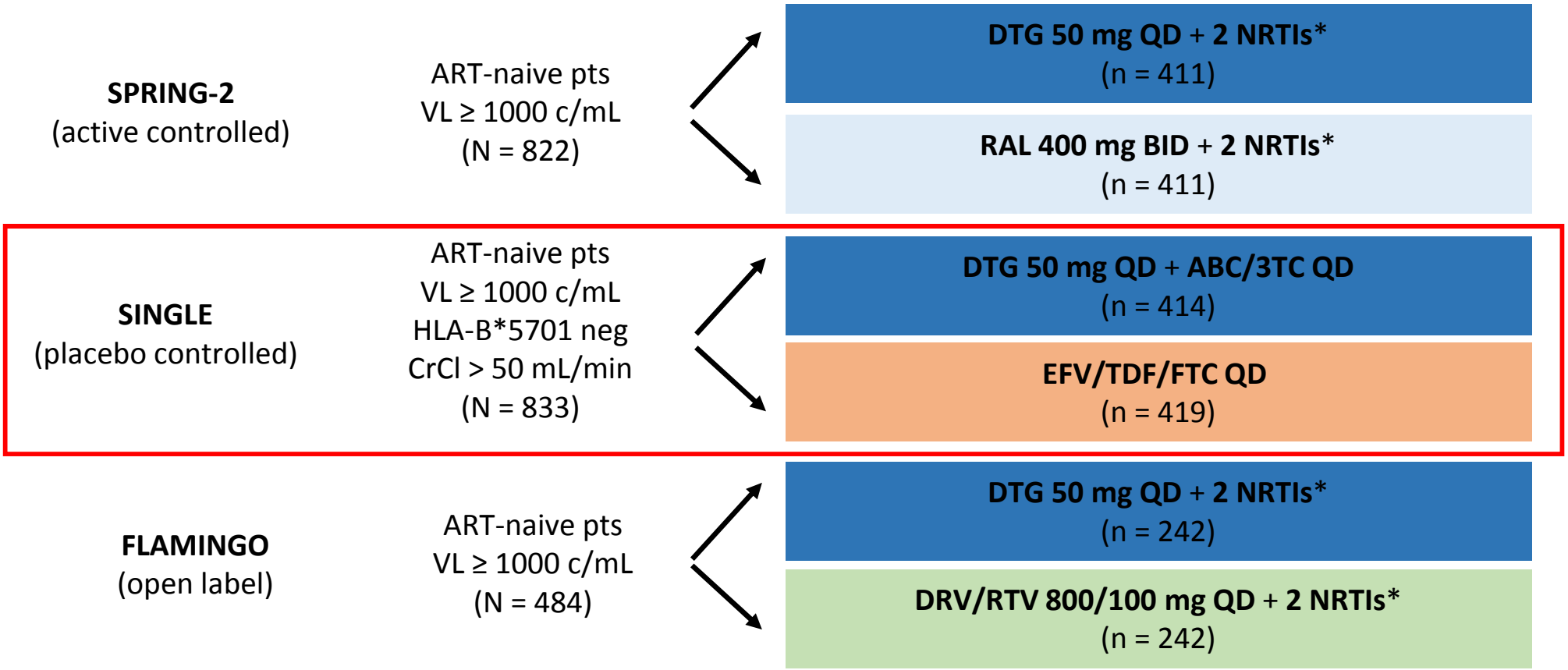
Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Thanks Joe Eron

We know DTG works in ARV-naives

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

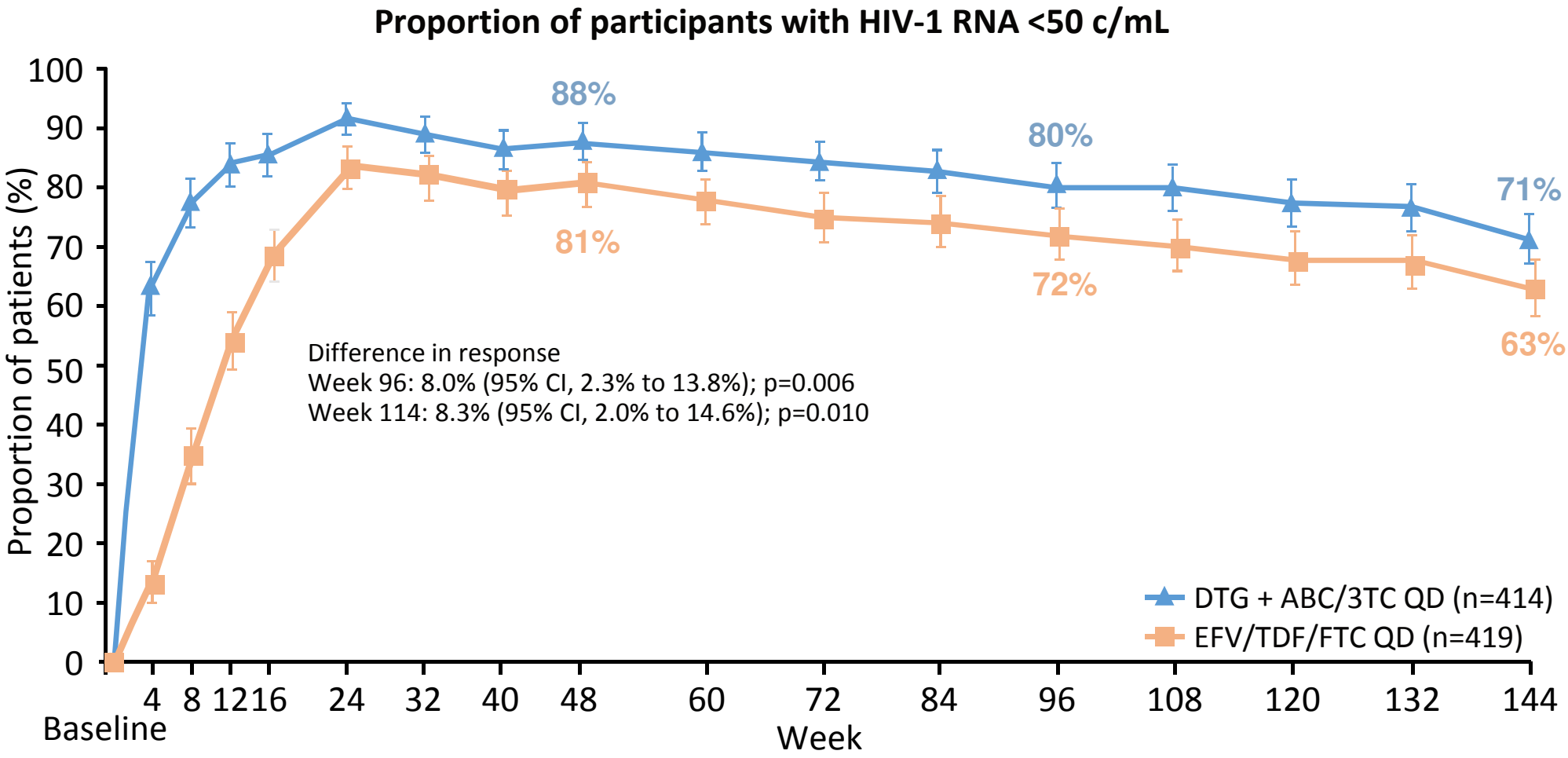


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

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

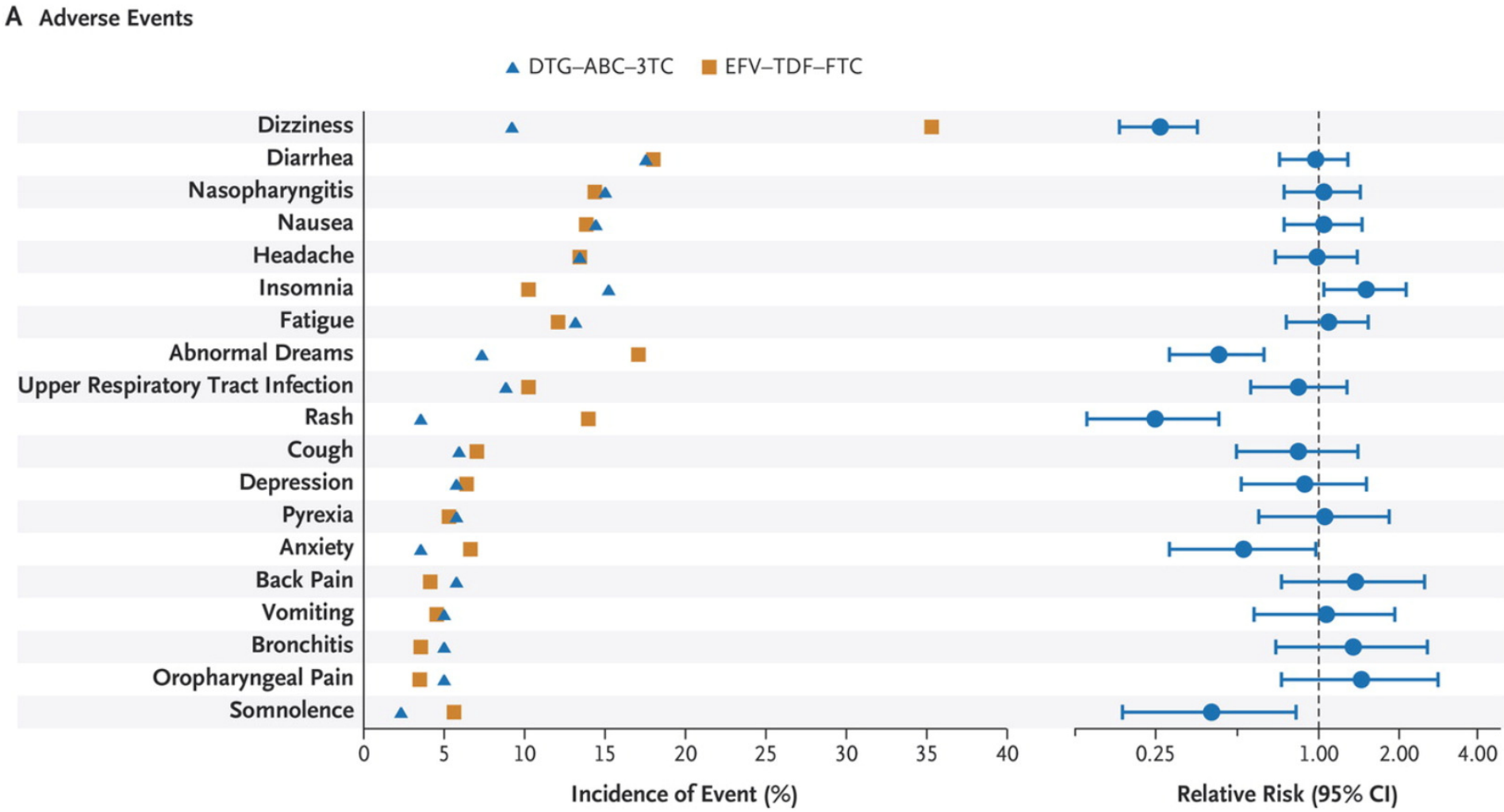
SINGLE study: DTG vs. EFV

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



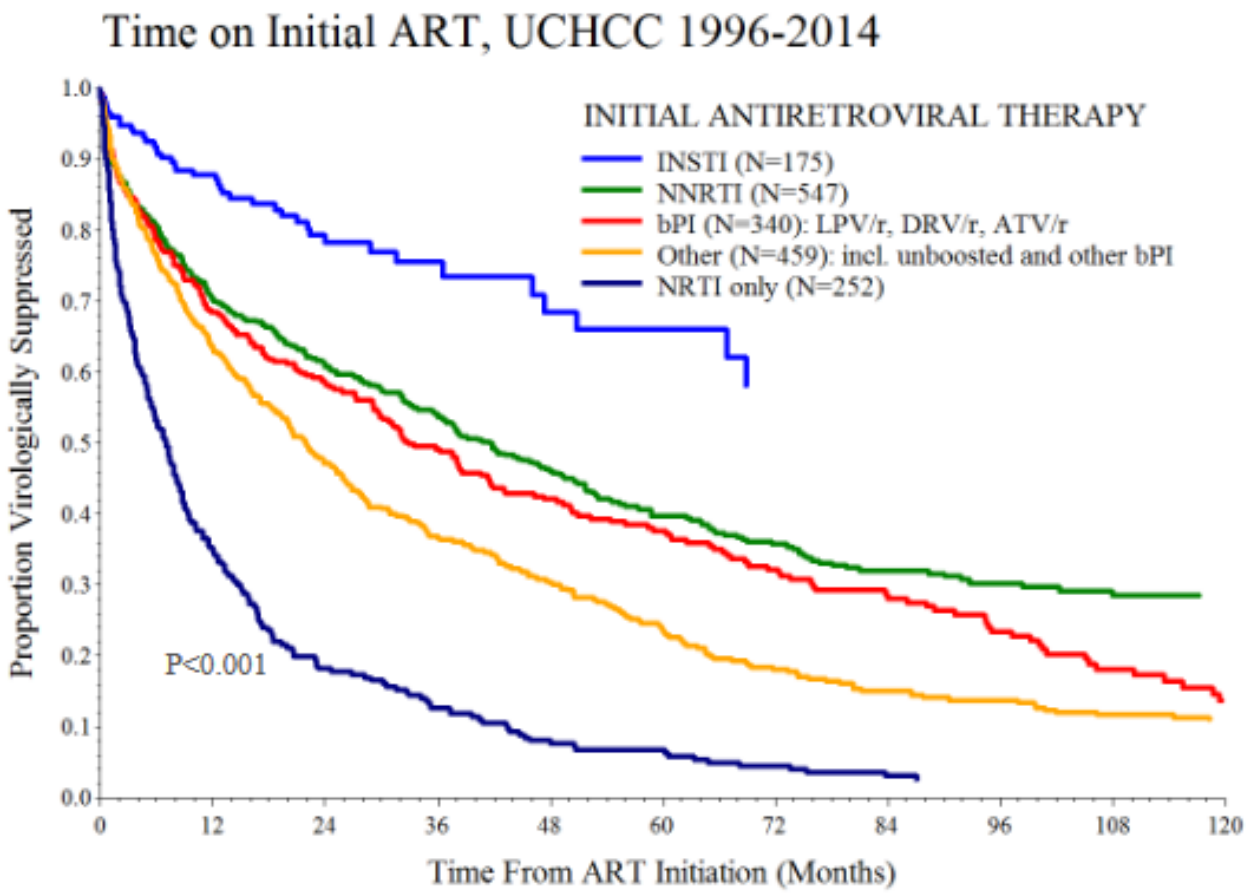
Discontinuations: DTG+ABC/3TC 2% vs. EFV/TDF/FTC 10%

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

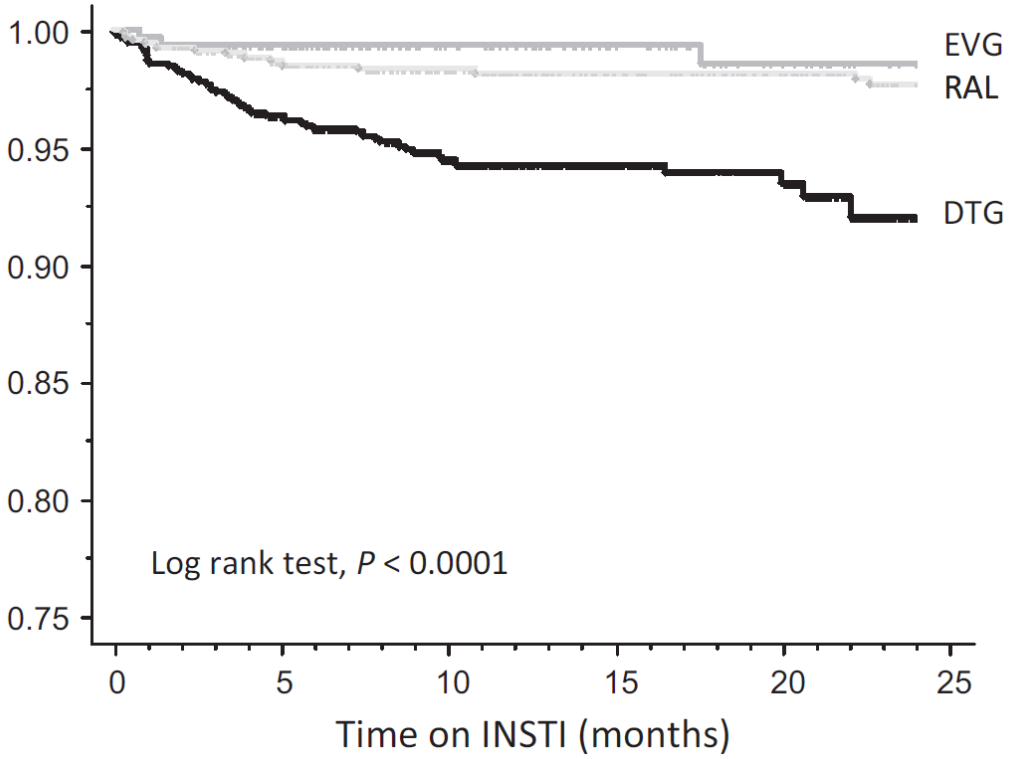
Thanks Joe Eron

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…

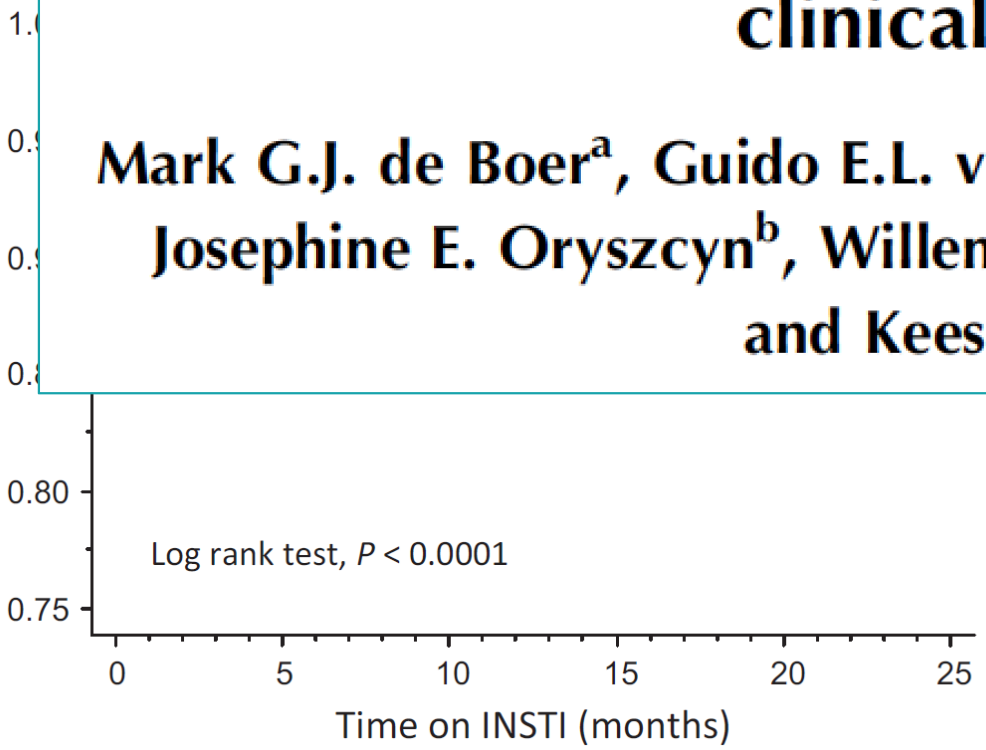
Dolutegravir: discontinuation due to AE

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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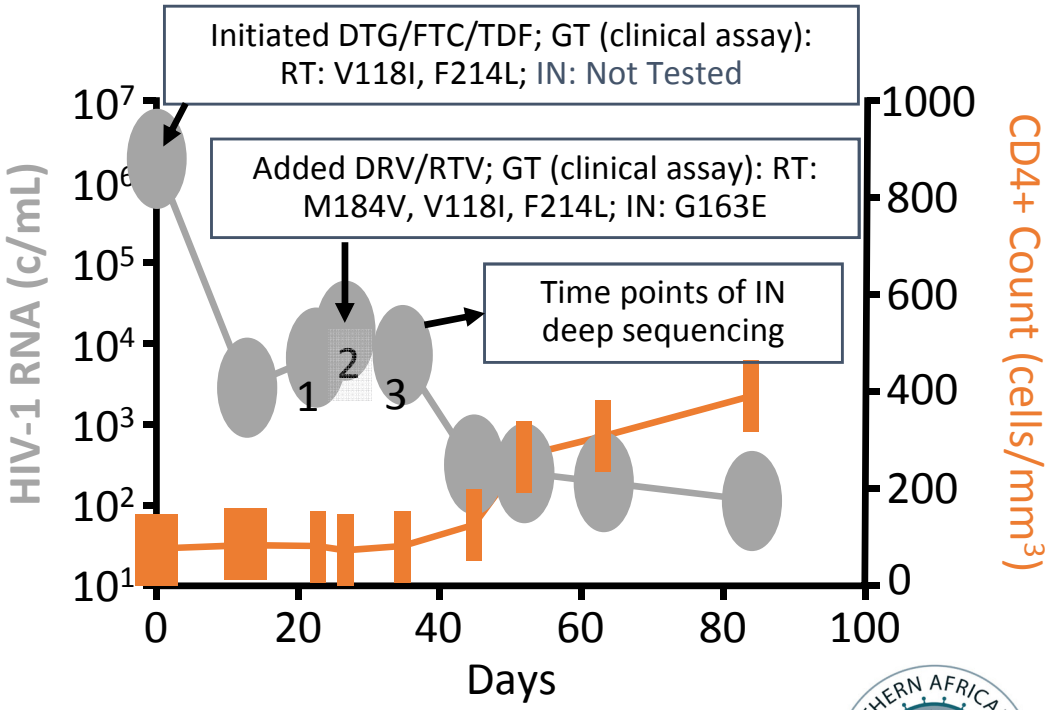
ABC, abacavir; CI, confidence interval.

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

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

Guidelines	NRTI Backbone			NNRTI			INSTI			PI		
	TDF/XTC	ABC/3TC	AZT/3TC	EFV	NVP	RIL	DTG	EVG	RQL	ATV	DRV	LPV
IAS (2014)												
DHHS (2015)												
EACS (2015)												
WHO (2015)												

Preferred

Alternative

Not recommended/special situations

GUIDELINES	Preferred first-line options	Alternative first-line options
IAS (2014)	**11**	**16**
DHHS (2015)	**05**	**07**
EACS (2015)	**06**	**13**
WHO (2015)	**01**	**05**

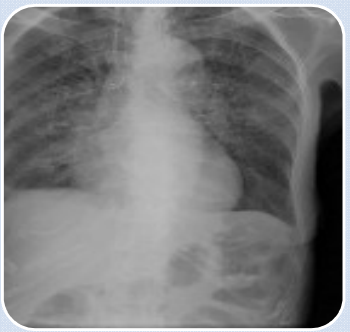
Courtesy of M. Vitoria

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

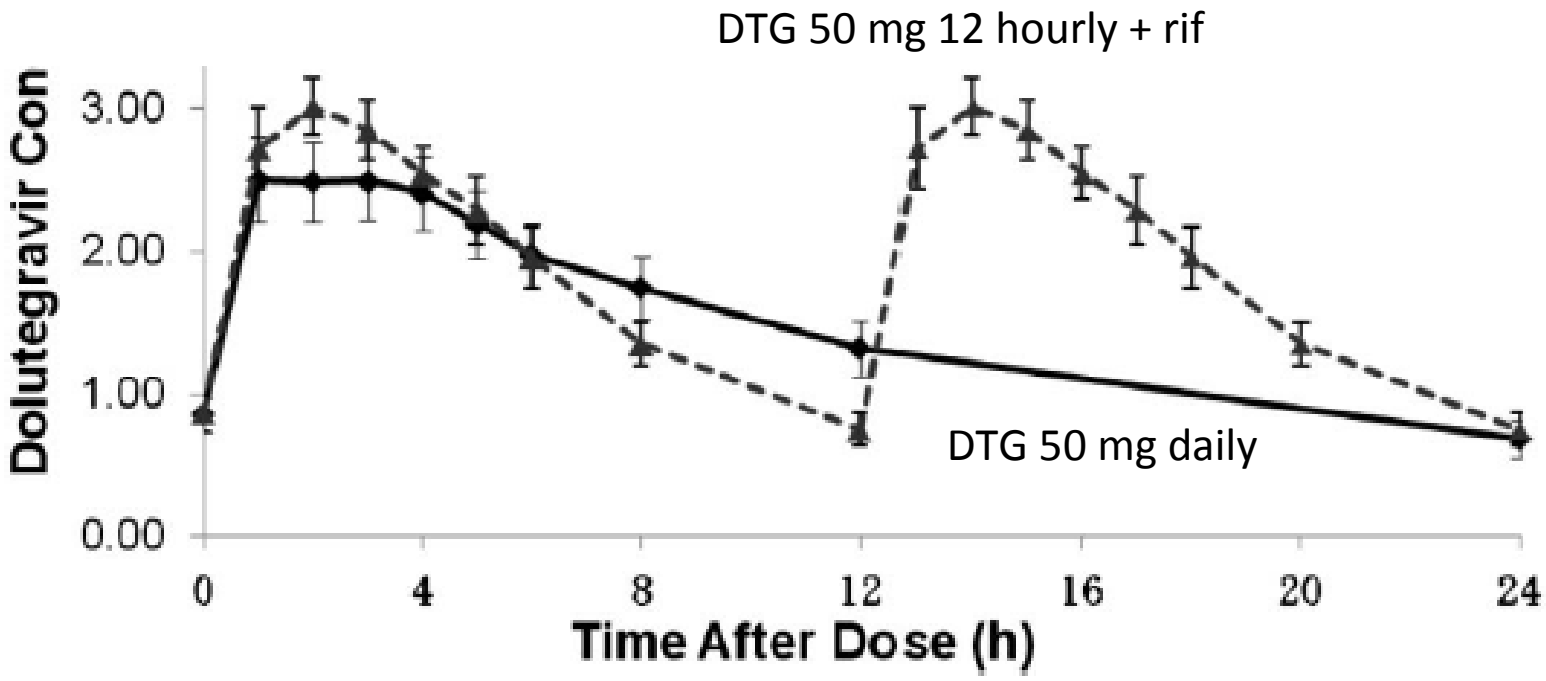


Limited data on use in TB (almost all new drugs)

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

Costs: abacavir, all integrase inhibitors – hope for dolutegravir

TB: DTG and rifampicin



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

DTG 50 mg 12 hly + rif 42.6

JAIDS 2013;62:21

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*

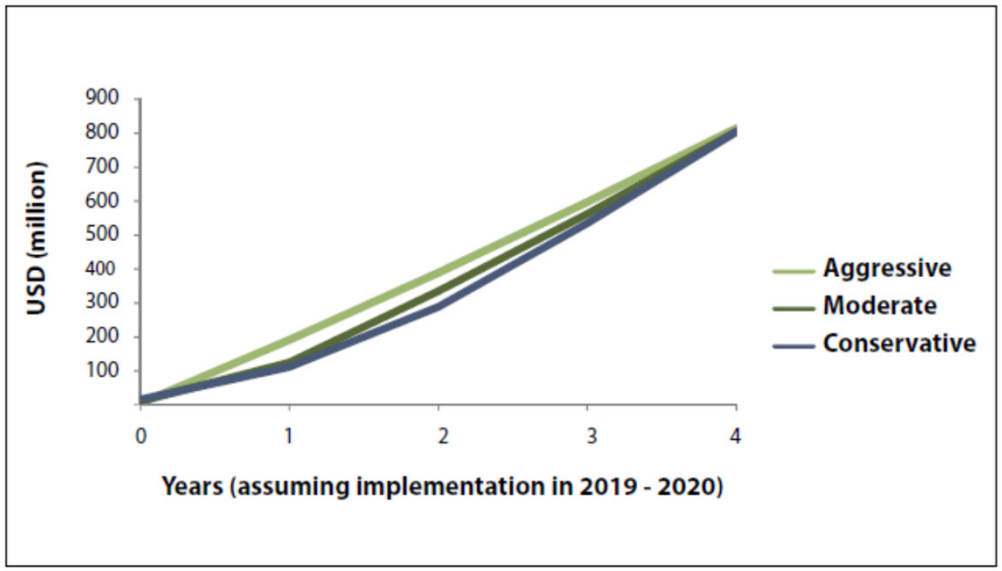
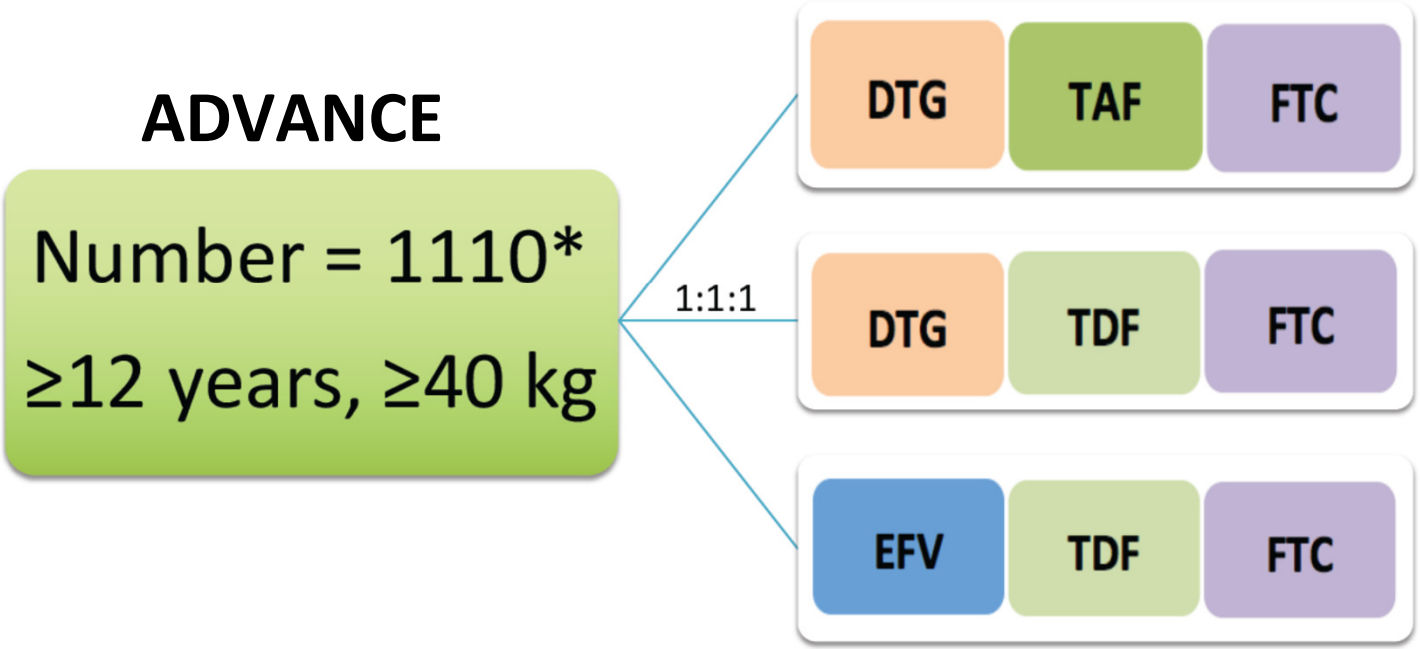


Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years;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

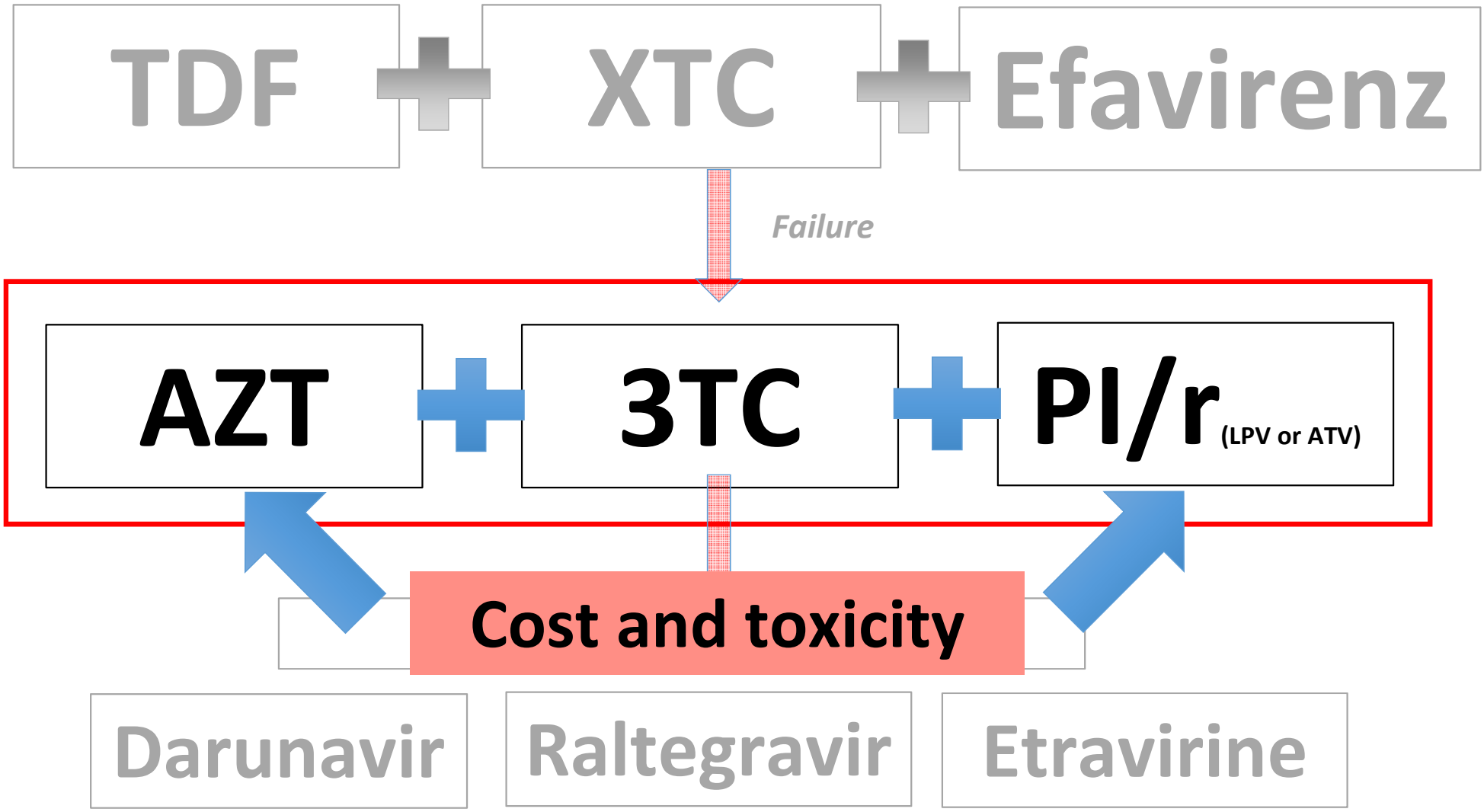
Real world patients are under-represented



- 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

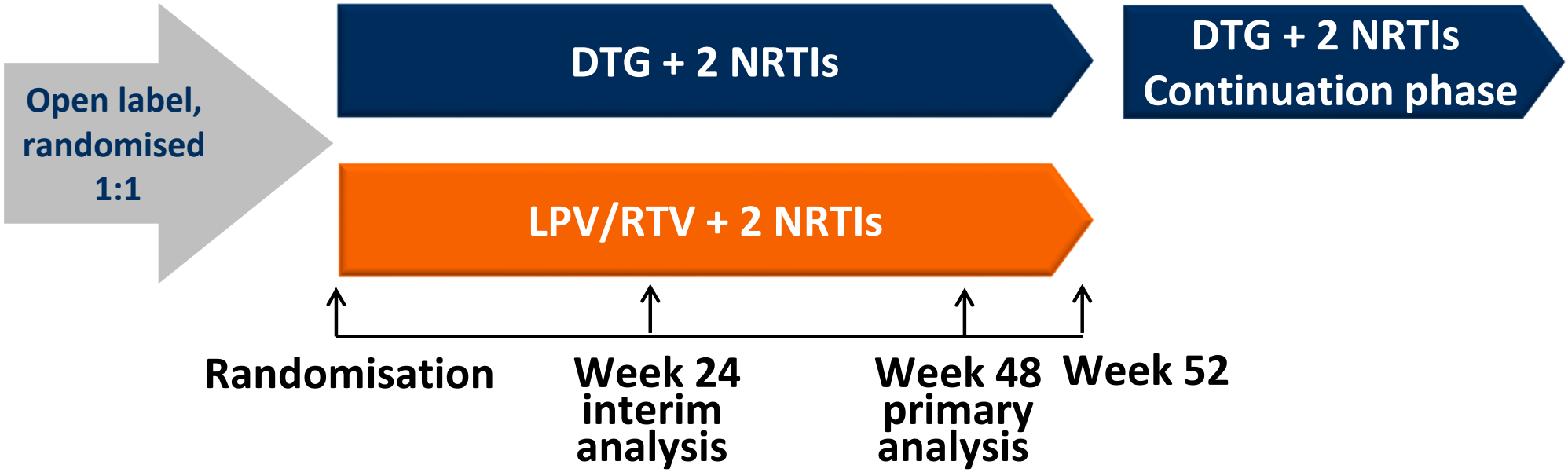
But what about second-line?

[and why am I talking about it in a talk on first-line?]



DAWNING: Study design

Open-label randomised noninferiority phase 3b study



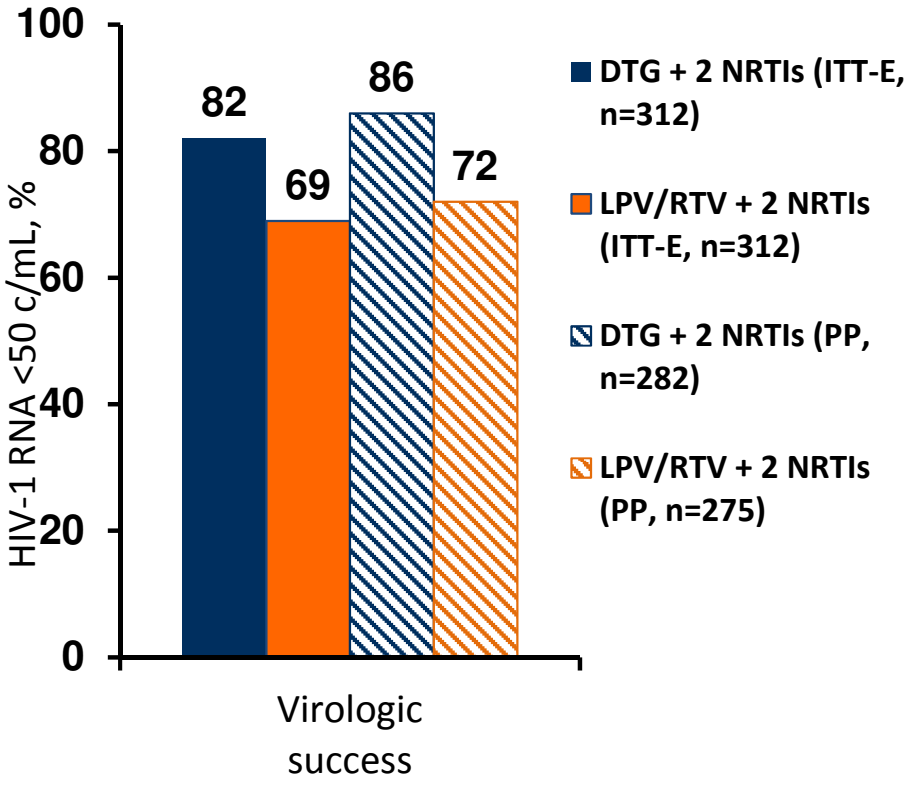
- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥ 400 copies/mL on 2 occasions); no primary viral resistance to PIs or INSTIs
- **Stratification:** by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or < 2)
- **Primary endpoint:** proportion with HIV-1 RNA <5 0 copies/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

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

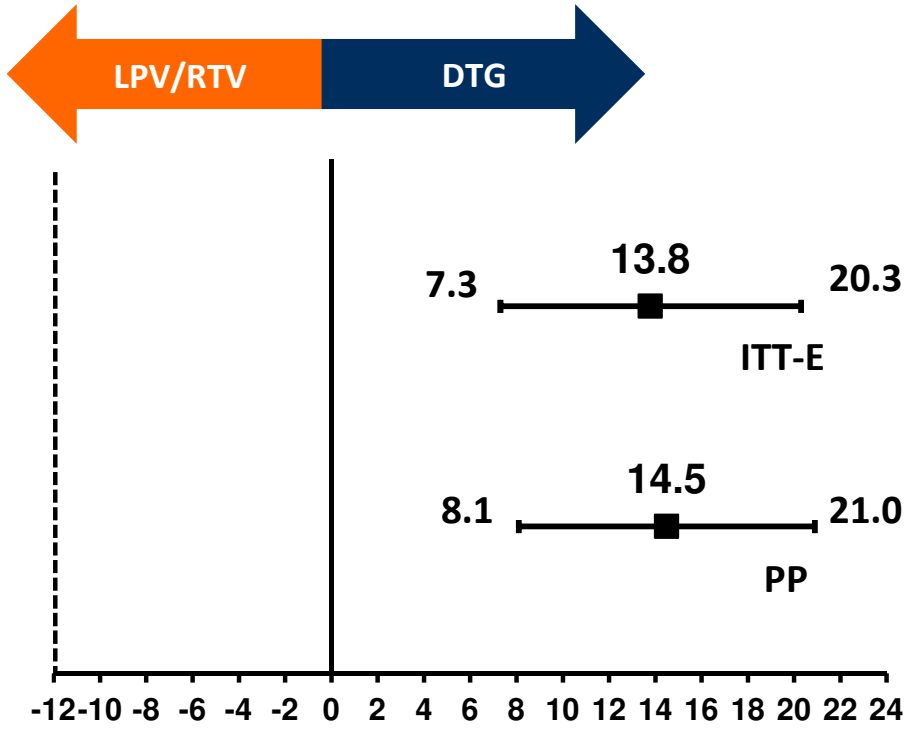
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

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

Virologic outcomes



Treatment differences (95% CI)



- DTG + 2 NRTIs is **superior** to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (<50 c/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.

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

- DTG + 2 NR
  (<50 c/mL) at Week 24, *I*

- CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

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

The Doodle study

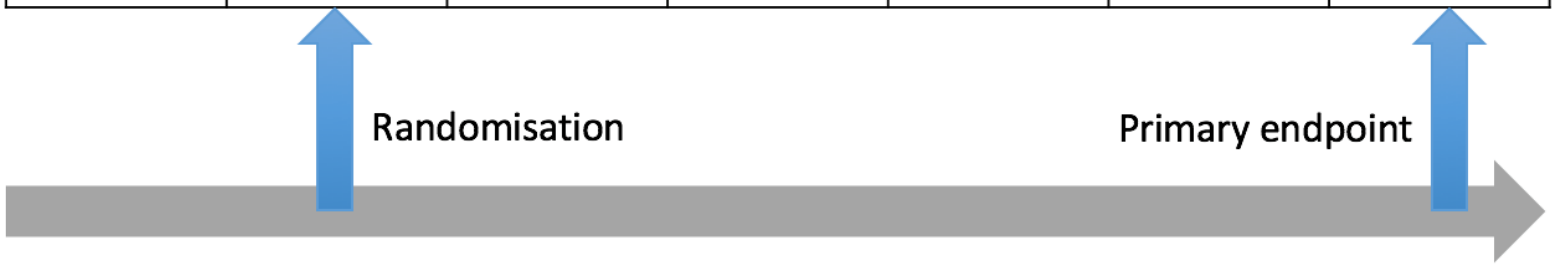
Number = 470
VL < 50 copies/mL
On PI/r-based ART
≥ 12 years, ≥ 40 kg

1:1

DTG 50 mg + TDF 300 mg + FTC 200 mg

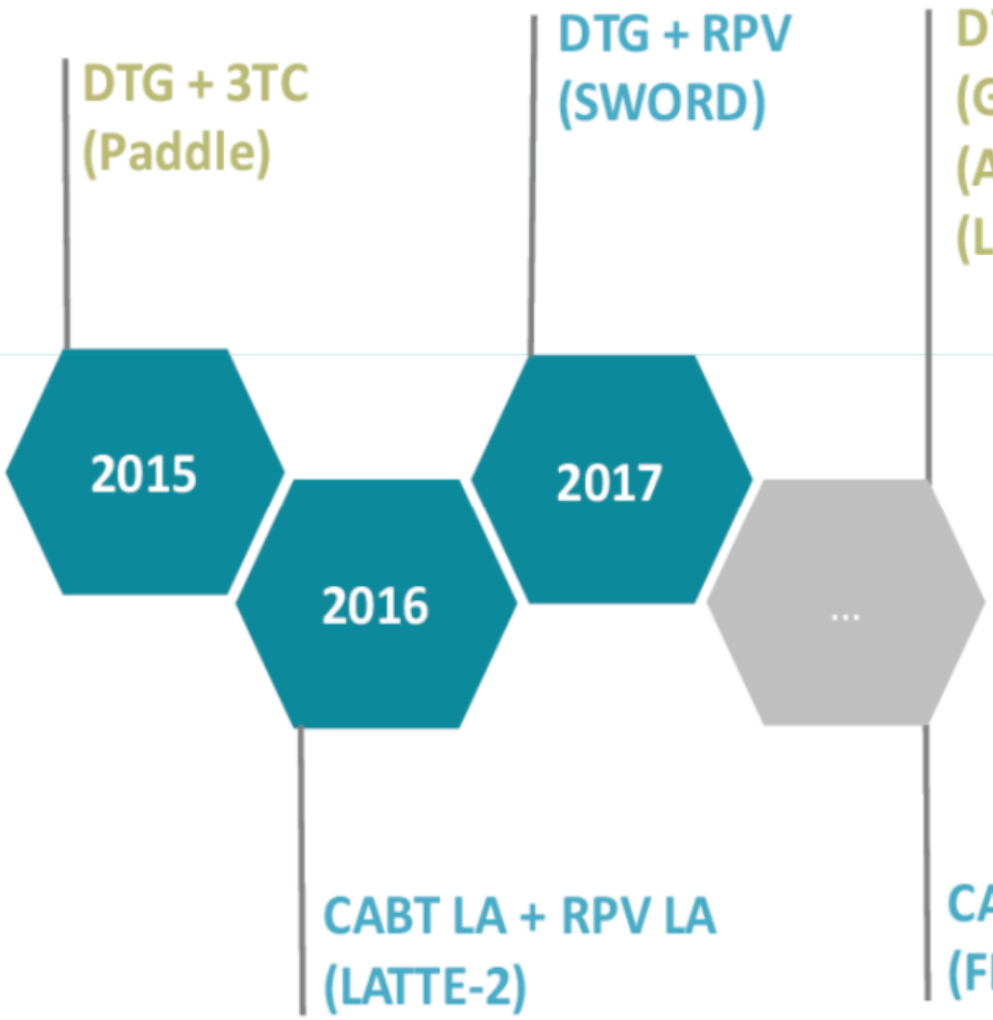
PI/r + TDF 300 mg + FTC 200 mg

Screen	Enrolment	Visit 1/2	Visit 3	Visit 4	Visit 5	EOS
Day -60 to -1	Week 0	Week 4/8	Week 12	Week 24	Week 36	Week 48



NEAT 022 study?

Reduced drug regimens in ARV-naïve patients?



Courtesy J Arribas

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

Study	N	Regimen	Results
PI-Based Dual Therapy			
NEAT001[1]	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts
GARDEL[2]	426	LPV/RTV + 3TC	Similar efficacy as LPV/RTV + 2 NRTIs
DTG-Based Dual Therapy			
PADDLE[3]	20	DTG + 3TC	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

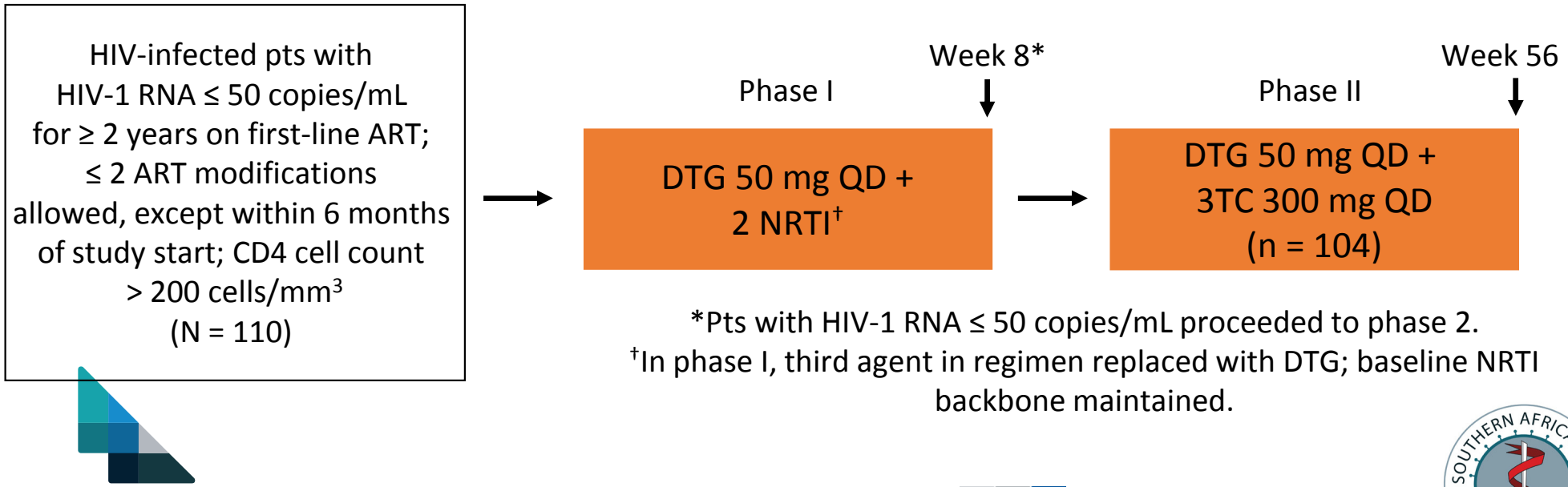
ANDES and ACTG A5353 studies presented at IAS 2017

1. Raffi F, et al. Lancet. 2014;384:1942-1951. 2. Cahn P, et al. EACS 2015. Abstract 961.
3. Cahn P, et al. IAC 2016. Abstract FRAB0104LB.

ANRS 167 LAMIDOL: Switch to DTG + 3TC from suppressive triple ART

Noncomparative, open-label, single-arm multicentre trial

- Primary endpoint: therapeutic success at Week 56 (ie, after 48 weeks of dual therapy)
  - Therapeutic failure: HIV-1 RNA > 50 copies/mL, interruption, LTFU, death



*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase 2.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

Slide credit: clinicaloptions.com

Joly V, et al. CROI 2017. Abstract 458.

LAMIDOL interim analysis: Switch to DTG + 3TC maintains suppression

- 97% (101/104) pts maintained therapeutic success through 40 weeks of dual therapy (study Week 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy
- DTG + 3TC dual therapy currently under phase 3 evaluation as both initial ART[2,3] and as a switch strategy for virologically suppressed pts[4]

Therapeutic Success, n/N* (%)	DTG + 3TC
Week 0 (entry; on BL triple therapy)	110/110 (100)
Week 8 (end of phase I, start of phase II)	104/104 (100)
Week 12	104/104 (100)
Wk 16	103/104 (99)
Week 24	103/104 (99)
Wk 32	103/104 (99)
Week 40	102/104 (98)
Wk 48	101/104 (97)

*Pts enrolled in phase 1, N = 110; pts enrolled in phase 2, N = 104.

1. Joly V, et al. CROI 2017. Abstract 458. 2. ClinicalTrials.gov. NCT02831673. 3. ClinicalTrials.gov. NCT02831764 4. ClinicalTrials.gov. NCT02263326.

ACTG A5353: DTG + 3TC for ARV-naïves

- Single-arm phase 2 study[1]

ART-naive pts with
HIV-1 RNA ≥ 1000 and < 500 000 copies/mL;
no RT, INSTI, major PI resistance mutations
(N = 120)

→ DTG 50 mg + 3TC 300 mg

Primary Endpoint
Week 24

- Baseline: 31% HIV-1 RNA > 100 000 copies/mL

Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

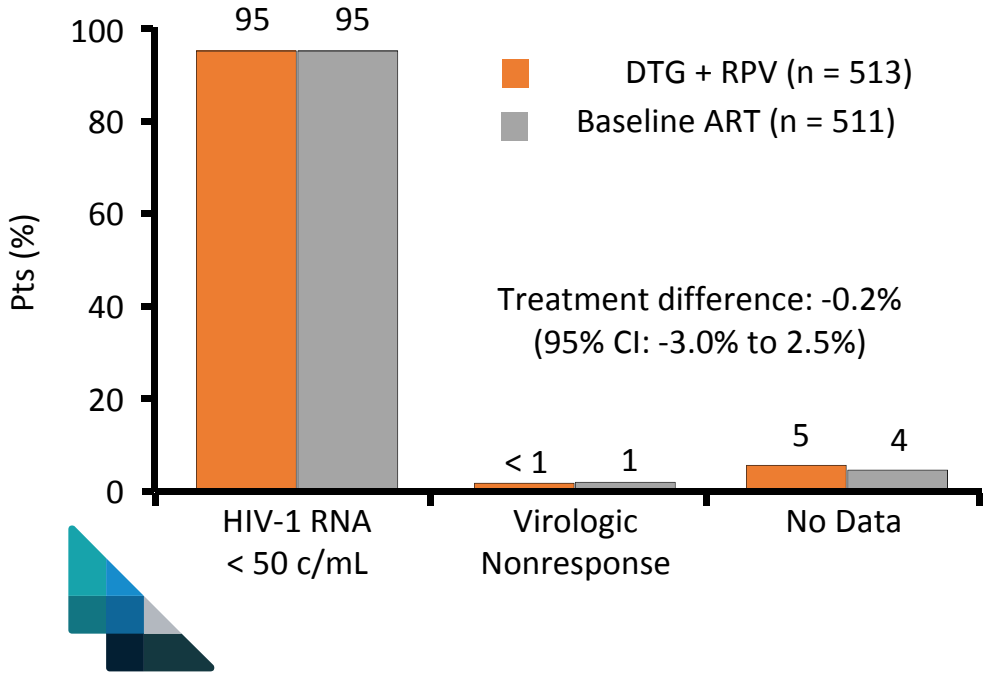
*HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
  - All 3 pts had DTG levels reflective of suboptimal adherence
- GEMINI 1/2 randomised phase 3 trials of DTG + 3TC ongoing[2,3]

1. Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB.
2. ClinicalTrials.gov. NCT02831673. 3. ClinicalTrials.gov. NCT02831764.

SWORD 1, 2: Switch from suppressive ART to DTG + RPV (no previous VF)

- Randomised, open-label phase 3 trials in which virologically suppressed pts with **no previous virologic failure** continued with baseline ART or switched to DTG + RPV (N = 1024)[1]
  - 70% to 73% of pts receiving TDF at baseline



- 1 pt receiving DTG + RPV with confirmed criteria for virologic withdrawal at Week 36 had K101K/E
  - Documented nonadherence at virologic failure; resuppressed with continued DTG + RPV
  - No INSTI resistance
- AE rates generally similar between treatment arms through Week 52; numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%
- For pts on TDF-containing regimens at BL (n = 102), improvements in BMD with switch[2]

1. Llibre JM, et al. CROI 2017. Abstract 44LB. 2. McComsey G, et al. IAS 2017. Abstract TUPDB0205LB.

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* = .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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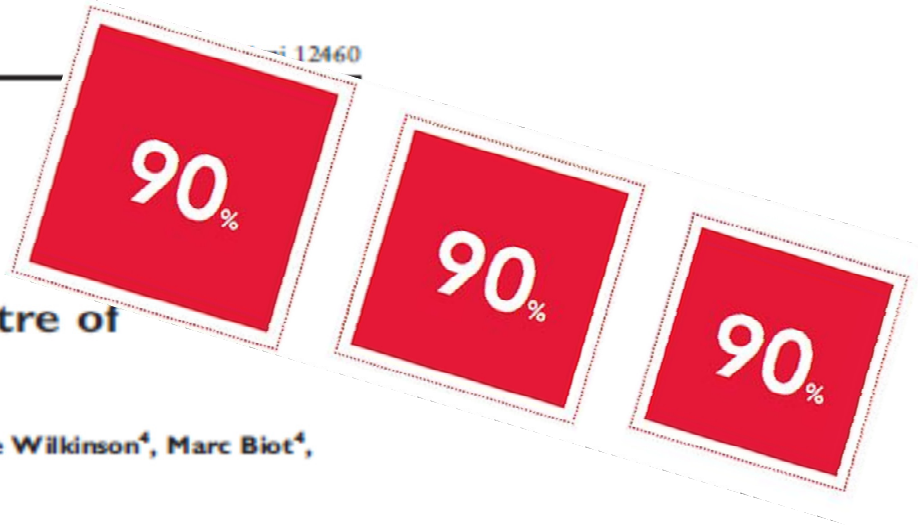


Review

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

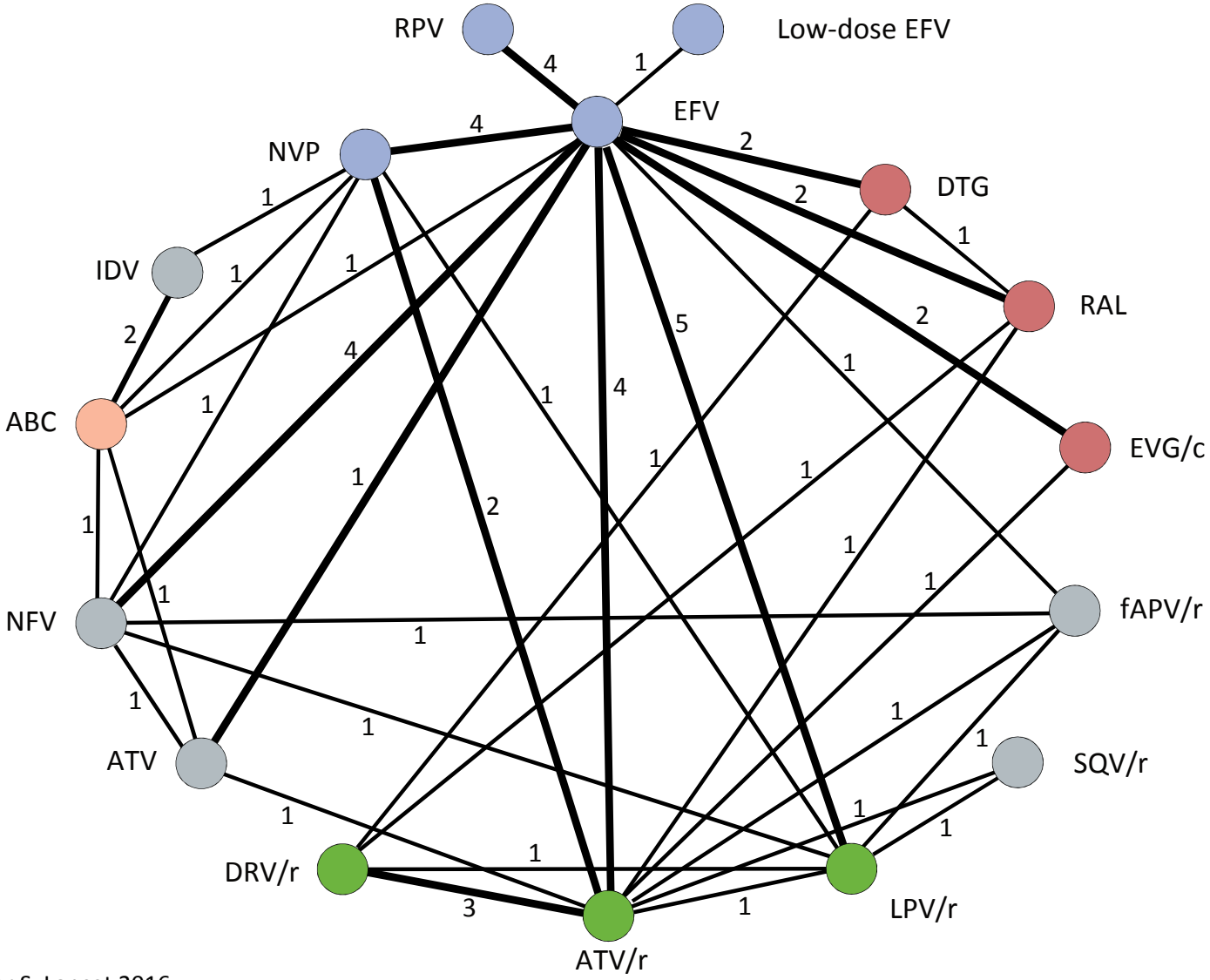
Figure 1 Four levers to tailor or adapt care to people's needs (service frequency, location, intensity and cadre).

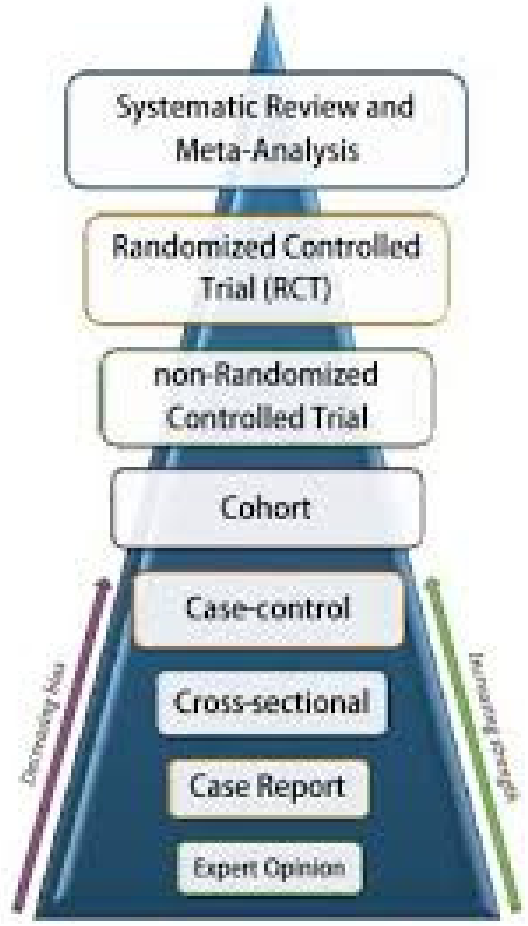
Comparing third drugs

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	Limited 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

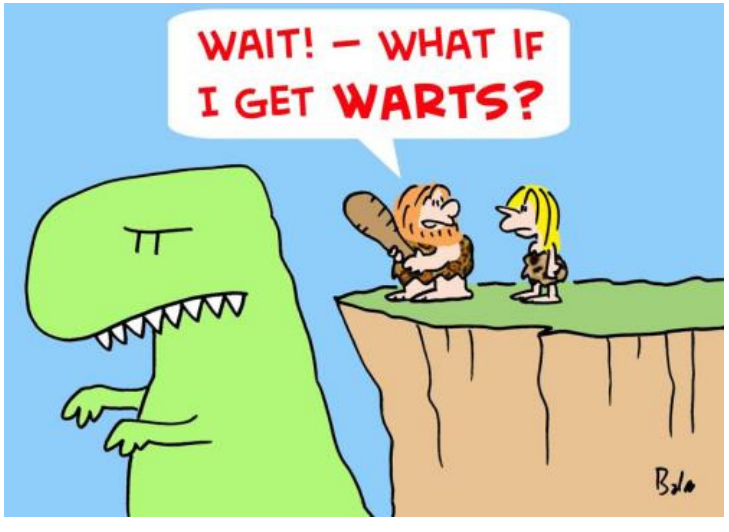
Robust with a formidable resistance barrier

Well-tolerated in RCTS

Real-world tolerability is emerging

Dual therapy?

ART alone is not enough



Acknowledgements