Naïve

Experienced

Adolescent

TIVICAY®

(Dolutegravir)

DOLUTEGRAVİR BASED REGİMEN

Sibongile KUBHEKA

MBCHB, MPharmMED, DipHIVMan
Regional Medical Director,
Middle East & Africa
ViiV Healthcare

TK/DLG/0018/16

DISCLOSURE:

- Employee of ViiV Healthcare
- Non-Executive Director on the South Africa GlaxoSmithKline Consumer Healthcare Pty Ltd Subsidiary Board

ViiV HEALTHCARE

Shareholders

gsk Pfizer SHIONOGI Bristol-Myers Squibb

FDA

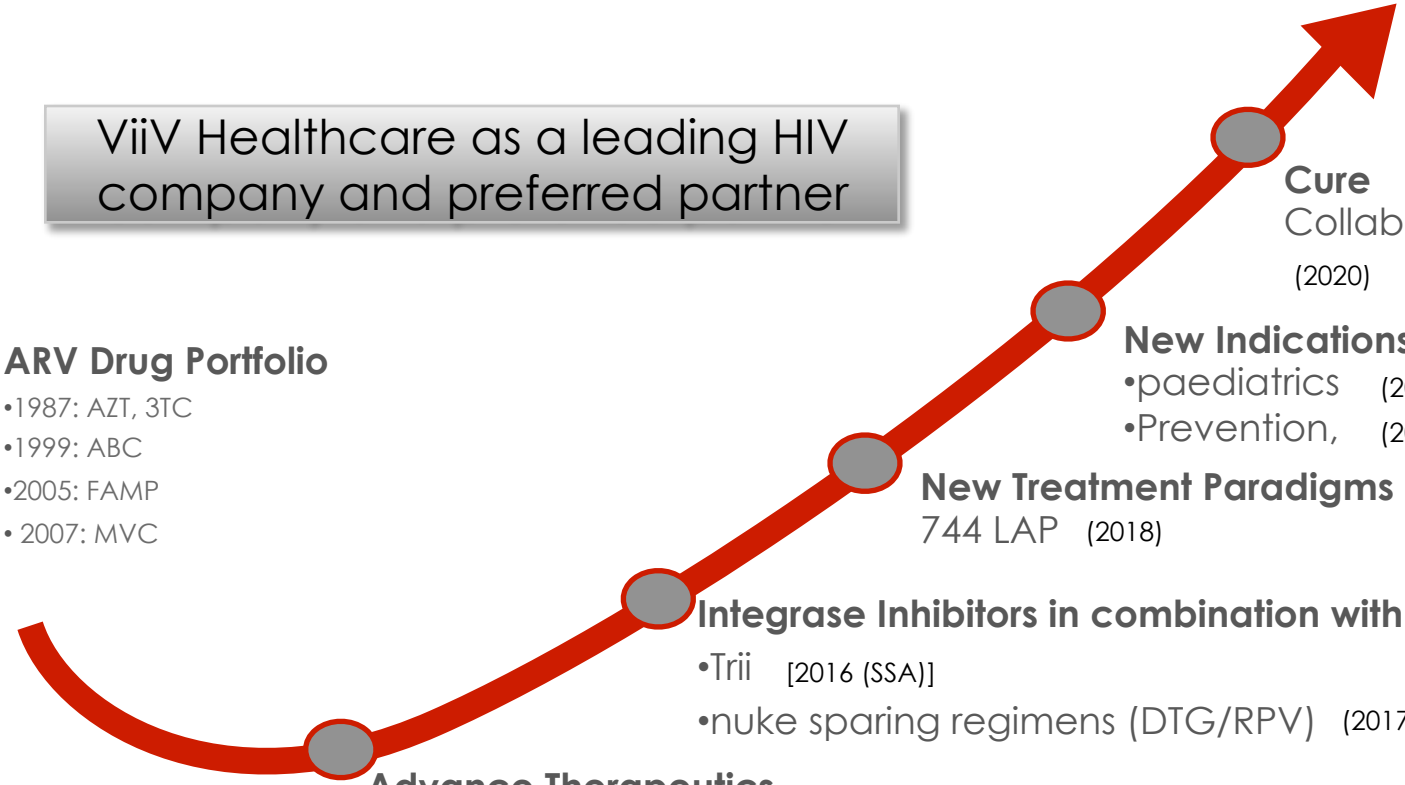
Pipeline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Developing a sustainable and successful business

Driving Innovation in HIV R&D

ViiV Healthcare as a leading HIV company and preferred partner



ARV Drug Portfolio
- 1987: AZT, 3TC
- 1999: ABC
- 2005: FAMP
- 2007: MVC

Advance Therapeutics

Dolutegravir

[2015 (SSA)]

Integrase Inhibitors in combination with
- Trii [2016 (SSA)]
- nuke sparing regimens (DTG/RPV) (2017)

New Treatment Paradigms

744 LAP (2018)

New Indications
- paediatrics (2017)
- Prevention, (2019)

Cure

Collaborations

(2020)

Focus on people living with and affected by HIV

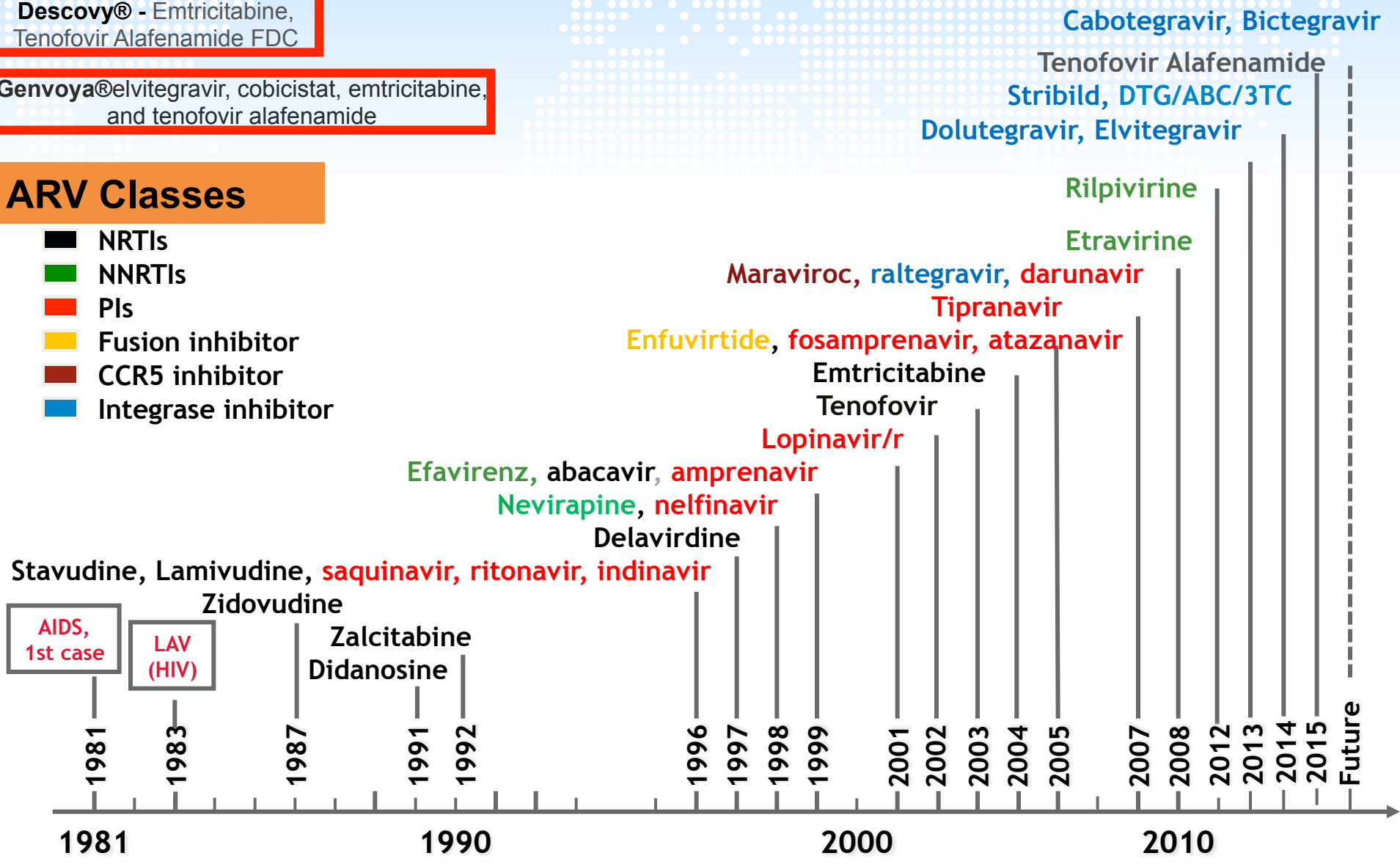
2016: ARV HISTORY

Descovy® - Emtricitabine, Tenofovir Alafenamide FDC

Genvoya®elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide

ARV Classes

- NRTIs
- NNRTIs
- PIs
- Fusion inhibitor
- CCR5 inhibitor
- Integrase inhibitor



PREFERRED INITIAL REGIMENS FOR ARV-NAÏVE PATIENTS

DHHS[1] 2015 (Dept. of Health and Human Services)	IAS-USA[2] 2014 (International Antiviral Society USA Panel)	EACS[3] 2015 (European AIDS Clinical Society)	WHO[4] 2015 (World Health Organization)
NNRTI-based therapy			
~~EFV + TDF/FTC~~	EFV +TDF/FTC	~~EFV + TDF/FTC~~	TDF + 3TC (or FTC) + EFV
	EFV+ABC/3TC	RPV[y] + TDF/FTC or ABC/ 3TC	TDF + 3TC (or FTC) + EFV*$_{400}$
	RPV + TDF/FTC		
Ritonavir-boosted PI-based therapy			
	ATV/r + TDF/FTC	ATV/r + TDF/FTC or ABC/ 3TC	
DRV/r + TDF/FTC	ATV/r + ABC/3TC	DRV/r + TDF/FTC or ABC/ 3TC	
	DRV/r + TDF/FTC		
INI-based therapy			
RAL + TDF/FTC **ELV/c/TDF/FTC**	RAL +TDF/FTC **ELV/c/TDF/FTC**	RAL +TDF/FTC **ELV/c/TDF/FTC**	**DTG + TDF + 3TC or FTC***
DTG + TDF/FTC **DTG + ABC/3TC**	DTG + TDF/FTC **DTG + ABC/3TC**	DTG + TDF/FTC **DTG + ABC/3TC**	

* Alternative * Single Pill Regimen

1. http://aidsinfo.nih.gov/guidelines
2. https://www.iasusa.org
3. http://www.europeanaidsclinicalsociety.org

SINGLE PILL REGIMEN

CURRENT

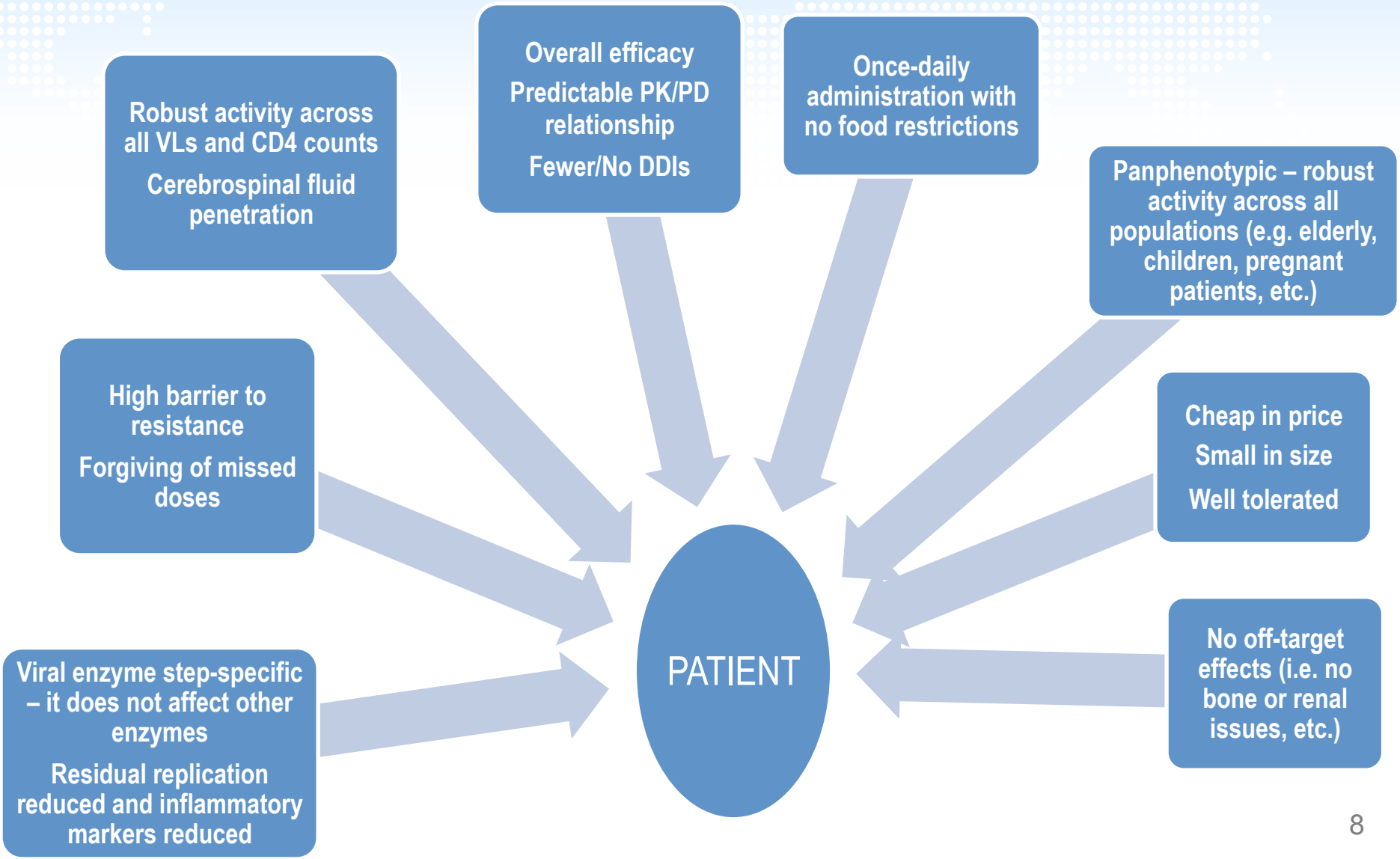
- **ATRIPLA®** (1550 mg): EFV 600 mg; FTC 200 mg; TDF 300 mg
- **EDURANT/COMPLERA®** (1150 mg): RPV 25 mg; FTC 200 mg; TDF 300 mg
- **STRIBILD®** (1350 mg): EVG 150 mg; COBI 150 mg; FTC 200 mg; TDF 300 mg
- **Tivicay+ABC/3TC** (950 mg): DTG 50 mg; ABC 600 mg; 3TC 300 mg

Future

- DRV-SPR (1550 mg)
- DRV/COBI/FTC/GS-7340
- STRIBILD 2.0 (1050 mg)
- EVG/COBI/FTC/GS-7340

1. Mathias AA, et al. J Acquir Immune Defic Syndr 2007;46:167–73
2. Mathias AA, et al. AIDS 2010. Abstract THLBPE17
3. German P, et al. J Acquir Immune Defic Syndr 2010;55:323–9

The COMBINATION REGIMEN



COMBINATION REGIMEN COMPARISON

Red, negative trait; **green**, positive trait; **orange**, may be positive or negative

	ATRIPLA[1] ((EFV/FTC/TDF)	EVIPLERA/ COMPLERA[2] (RPV/FTC/TDF)	STRIBILD[3]	Tivicay+ABC/3TC[4]	TAF-STRIBILD[5]	TAF+FTC +DRV/ COBI[6]	TAF+FTC+ RPV[7]	Generic SPRs?
Broad indication	Yes	No	No	Yes	?	?	?	?
Boosting requirement	No	No	Yes	No	Yes	Yes	No	?
DDIs	Few	Few	Many	Few	Many	Many	Few	?
Food restrictions	Yes	Yes	Yes	No	Yes?	No?	Yes	?
Efficacy in high VL	Yes	No	Yes	Yes	Yes?	Yes?	?	?
Resistance profile – barrier to resistance	Low	Low	Moderate	Probable high?	Moderate*	Probable high?	Low	?
Class cross resistance	Yes	Yes	Yes	No	Yes?	No?	Yes	?
Percentage of Grade 2–4 ADRs reported at 96 wks	Moderate (0–9%)	Low (1–2%)	Moderate (1–16%)	Low (0–3%)	Moderate?	Moderate?	Low	
Effect on lipids	Negative	Positive	Negative	Neutral	Neutral?	Negative?	Negative?	?
Link to CV, bone, renal toxicity	Renal/bone	Renal/bone	Renal/bone	CV	No?	No?	No?	?
Requires additional renal monitoring	No	No	Yes	No	No?	No?	No?	?
Requires screening genetic test	No	No	No	Yes	No	No	No	?
Contains tenofovir	Yes	Yes	Yes	No	No	No	No	?

Table not meant to imply that head-to-head safety and efficacy studies have been conducted. Note: efficacy takes in to account reduction in VL, CD4+ count, duration of response and speed of action (updated on 28 Aug 2014)

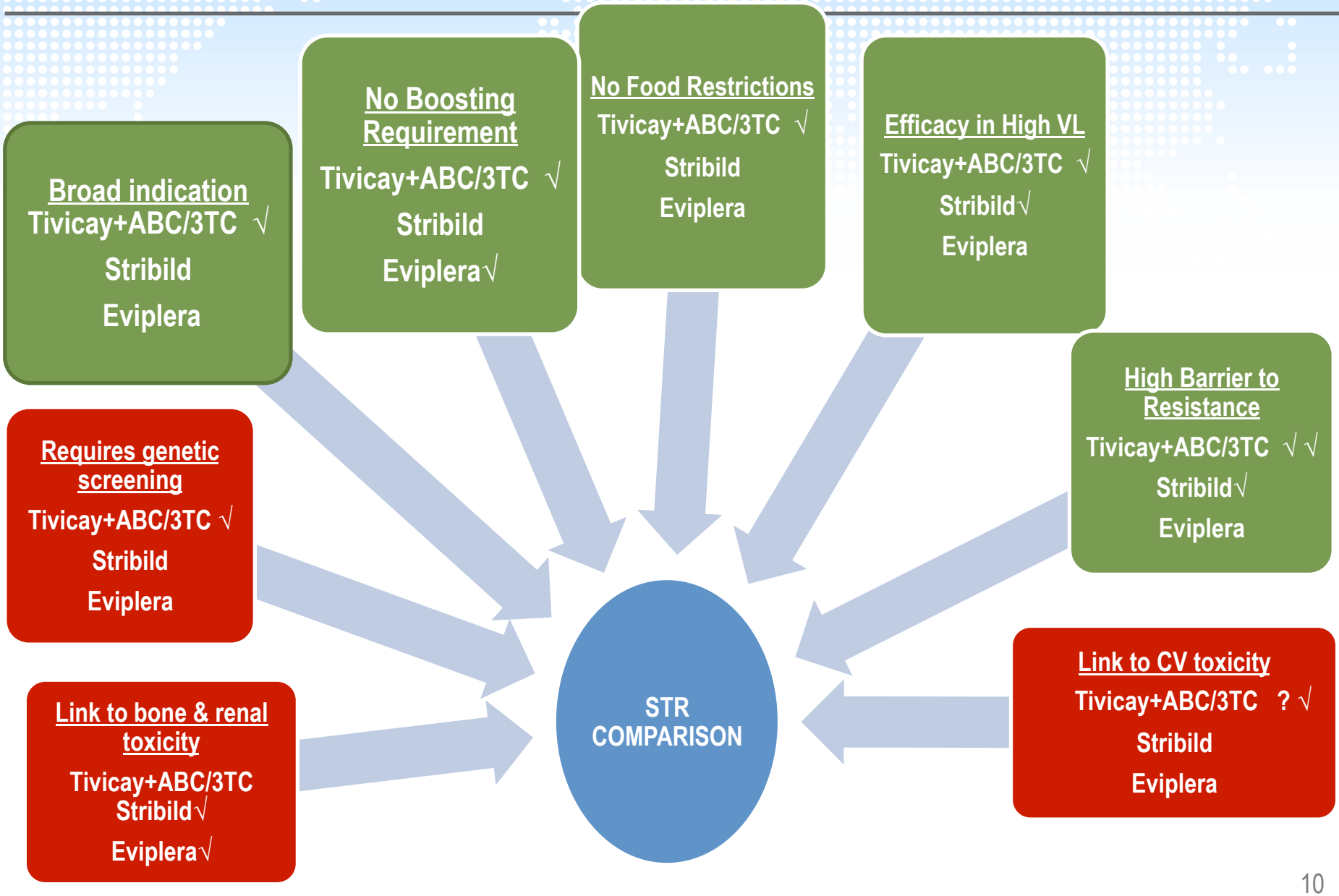
Slide based on feedback from advisory boards and internal communications

'?' after a characteristic denotes that it is currently unknown, but has been assumed based on available data

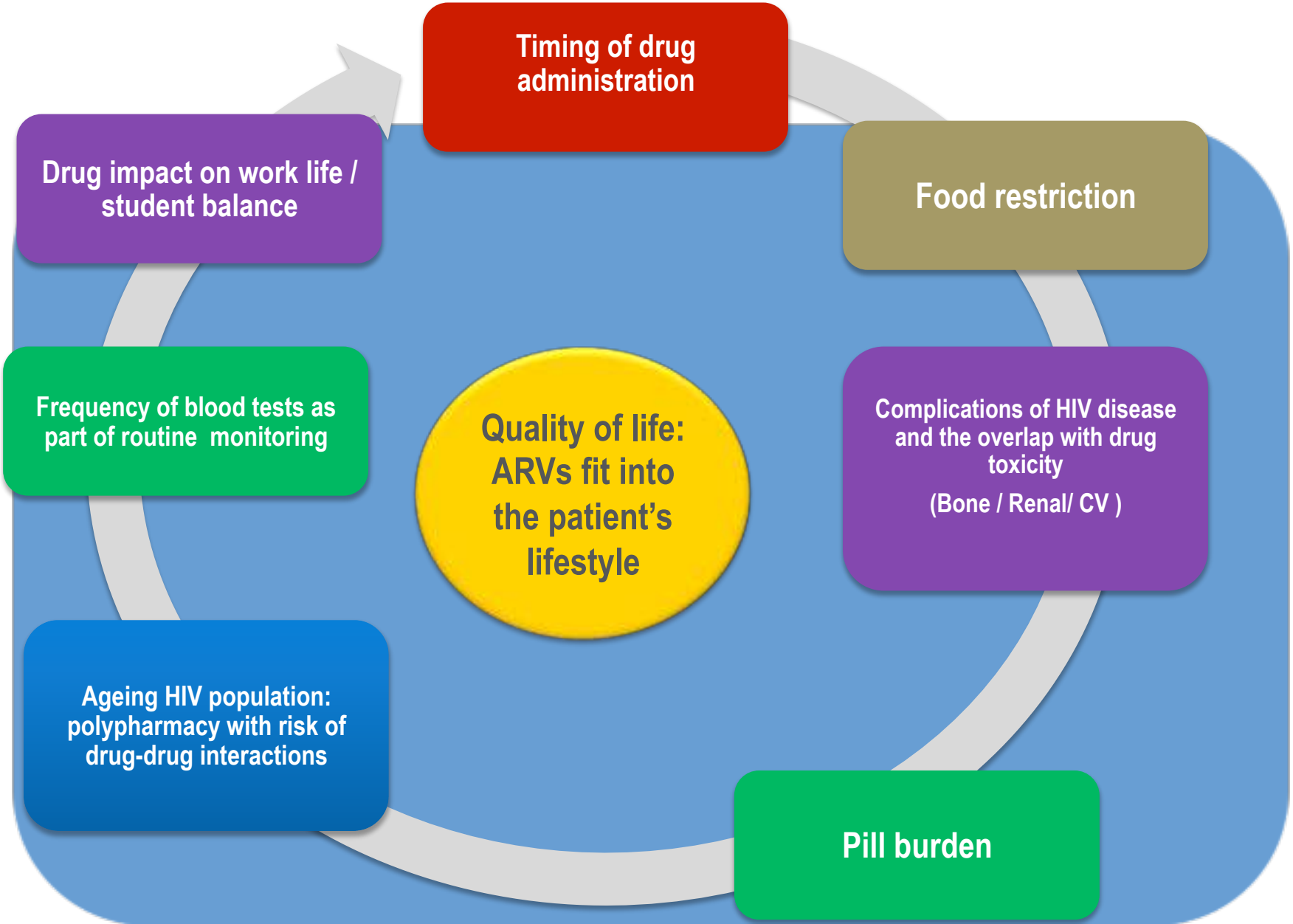
ADR, adverse drug reaction; CV, cardiovascular; DDI, drug–drug interaction; VL, viral load; TAF, tenofovir alafenamide

1. ATRIPLA Prescribing Information, October 2013; 2. COMPLERA Prescribing Information, June 2014; 3. STRIBILD Prescribing Information, August 2012; 4. TRIUMEQ Prescribing Information, August 2014; 5. Sax PE, et al. ICAAC 2013. Abstract H-146d; 6. Mills A et al. ICAAC 2014. Abstract H-647c; 7. Personal communication, ViiV Healthcare

Tivicay+ABC/3TC vs STRIBILD vs EVIPLERA



Putting the patient first when choosing a treatment regimen



PATIENTS ARE LIVING LONGER BECAUSE OF ADVANCEMENTS IN ART

The proportion of older HIV-infected individuals is increasing

Proportion of patients **≥50 years** of age in the French Hospital Database on HIV (FHDH ANRS CO4) by year of follow-up[1]

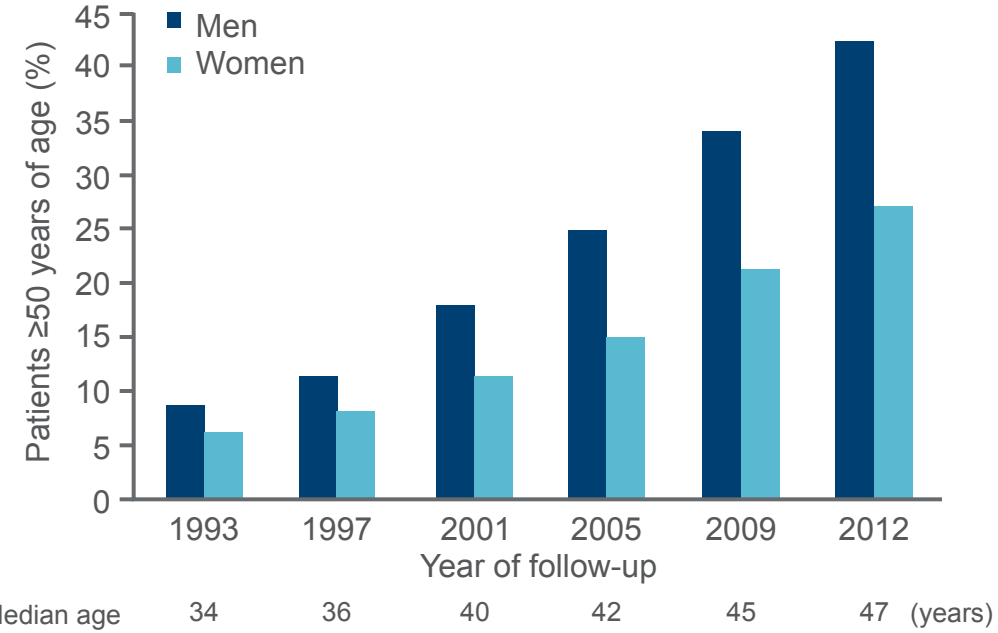


Figure adapted from Costagliola D. *Curr Opin HIV AIDS* 2014;9:294–301

The percentage of HIV-infected men ≥50 years of age increased from **8.5%** in 1993 to **42.0%** in 2012[1]

The corresponding figures for women were **6.0%** in 1993 and **26.9%** in 2012[1]

There is a need for a well-tolerated, effective, lifelong therapy with few DDIs

1. Costagliola D. *Curr Opin HIV AIDS* 2014;9:294–301

Naïve

Experienced

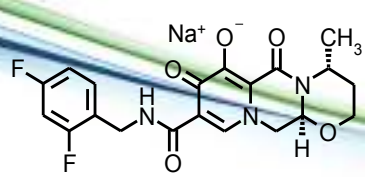
Adolescent

TIVICAY®

(Dolutegravir)

Tivicay is indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age or 40 kg.

gsk | ViiV Healthcare



ATTRIBUTES OF DOLUTEGRAVIR

Attributes of DTG

- Highly potent antiviral activity[1]
- Generally well tolerated[1,2]
- Distinct in-vitro resistance profile, with an apparent high barrier to resistance[3]
- Low potential for drug interactions[2] (favourable drug interaction profile)
- Diffusion & Control of VL in CSF and Genital track
- Low PK variability and predictable exposure-response relationship[1,2]
- Can be taken without regard to meals, no significant food effect[4]
- Once daily administration without a PK enhancer[2]
- Size: Very small pill

Long half-life (~14 hours) with steady-state achieved after ~5 days[1]

- Efficacy
- Tolerability
- Resistance
- PK Profile
- Convenience
- Specific population

Metabolised primarily by UGT1A1 pathway; it does not impact on other drugs and has few DDIs

PK, pharmacokinetics

1. Min, S. et al. AIDS 2011;25:1737–45
2. Min, S. et al. Antimicrob Agents Chemother. 2010;54:254–8
3. Kobayashi, M. et al. Antimicrob Agents Chemother 2011;55:813–21
4. Song, I. et al. Antimicrob Agents Chemother 2012;56:1627–9

EXTENSIVE CLINICAL PROGRAM WITH MORE THAN 3,500 PATIENTS INCLUDED ACROSS TRIALS

Done

Strong Methodology

FLAMINGO
DTG vs. DRV/r both+2NRTI

SINGLE
DTG+ABC/3TC vs. Atripla

SPRING 2
DTG vs. RAL both+2NRTI

STRIIVING
Switch from PI/r or NNRTI or INI regimen to Trii

Paediatrics
P1093 IMPAACT

SAILING
DTG v RAL +optimised regimen

VIKING-4
DTG bid vs. placebo for 7 days then DTG+OBT

VIKING-3
DTG bid +optimised regimen

Treatment Naive	Early Treatment	Later Treatment	Resistance INI

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
5. Cahn P, et al. *Lancet* 2013;382(9893):700-708
6. Nichols G, et al. IAS 2013. Poster TULBPE19

EXTENSIVE CLINICAL PROGRAM WITH MORE THAN 3,500 PATIENTS INCLUDED ACROSS TRIALS

Done

Ongoing

Strong Methodology

INSPIRING
TB co-infection

ARIA
DTG/ABC/3TC vs. Atazanavir/r

FLAMINGO
DTG vs. DRV/r both+2NRTI

SINGLE
DTG+ABC/3TC vs. Atripla

SPRING 2
DTG vs. RAL both+2NRTI

DAWNING
Second line study

STRIIVING
Switch from PI/r or NNRTI or INI regimen to Trii

Paediatrics
P1093 IMPAACT

SAILING
DTG v RAL
+optimised regimen

VIKING-4
DTG bid vs. placebo for 7 days then DTG+OBT

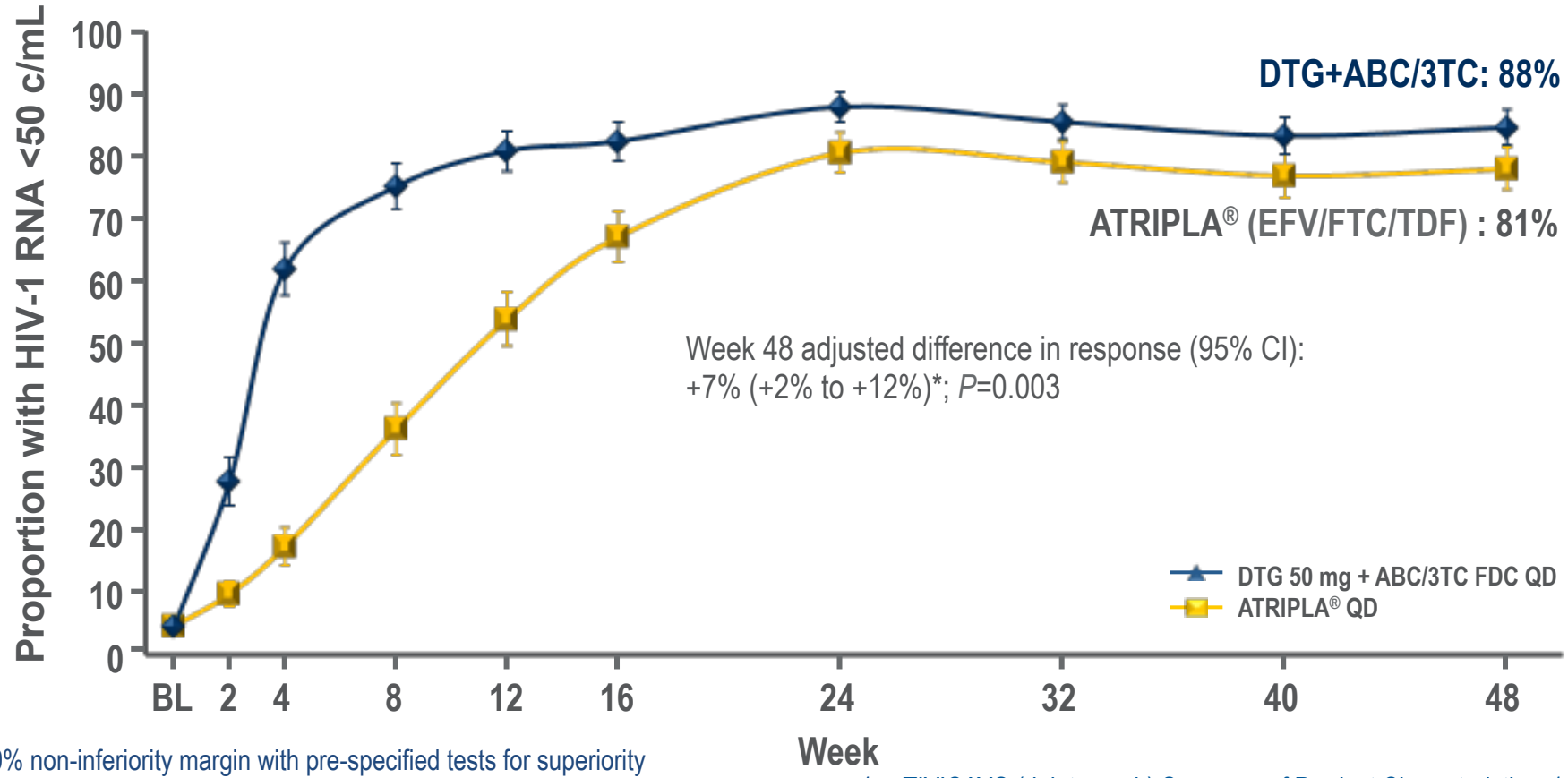
VIKING-3
DTG bid
+optimised regimen

Treatment Naive	Early Treatment	Later Treatment	Resistance INI

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
5. Cahn P, et al. *Lancet* 2013;382(9893):700-708
6. Nichols G, et al. IAS 2013. Poster TULBPE19

IN TREATMENT-NAÏVE PATIENTS, DTG + ABC/3TC HAD STATISTICALLY SUPERIOR EFFICACY VS ATRIPLA®

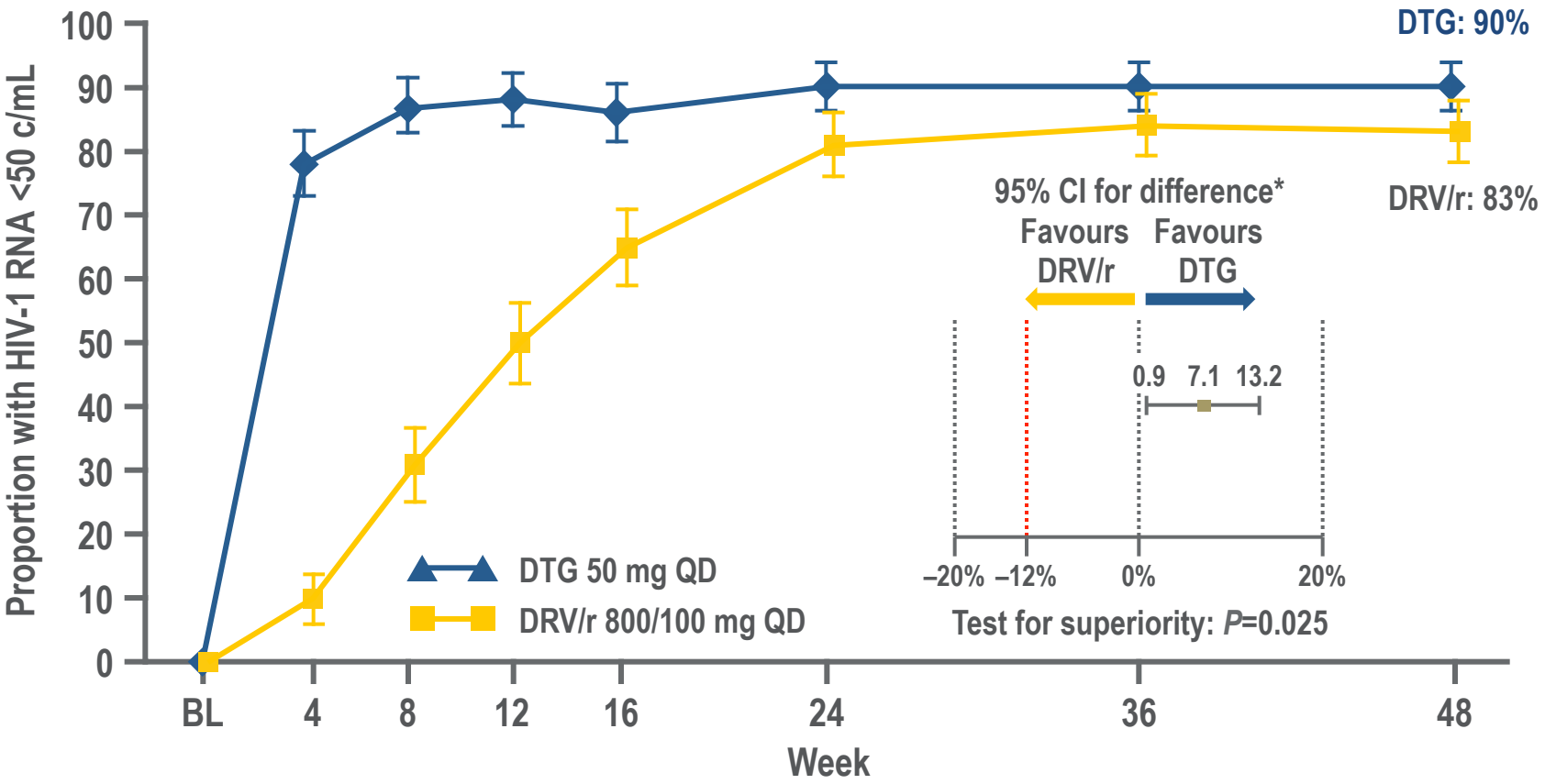
DTG was statistically superior to Atripla® at Week 48
Subjects receiving DTG achieved faster virologic suppression than Atripla® (*P*<0.0001)*[1]



*-10% non-inferiority margin with pre-specified tests for superiority

1. TIVICAY® (dolutegravir) Summary of Product Characteristics, 11/2013
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18

IN TREATMENT-NAIVE SUBJECTS PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS DRV/r



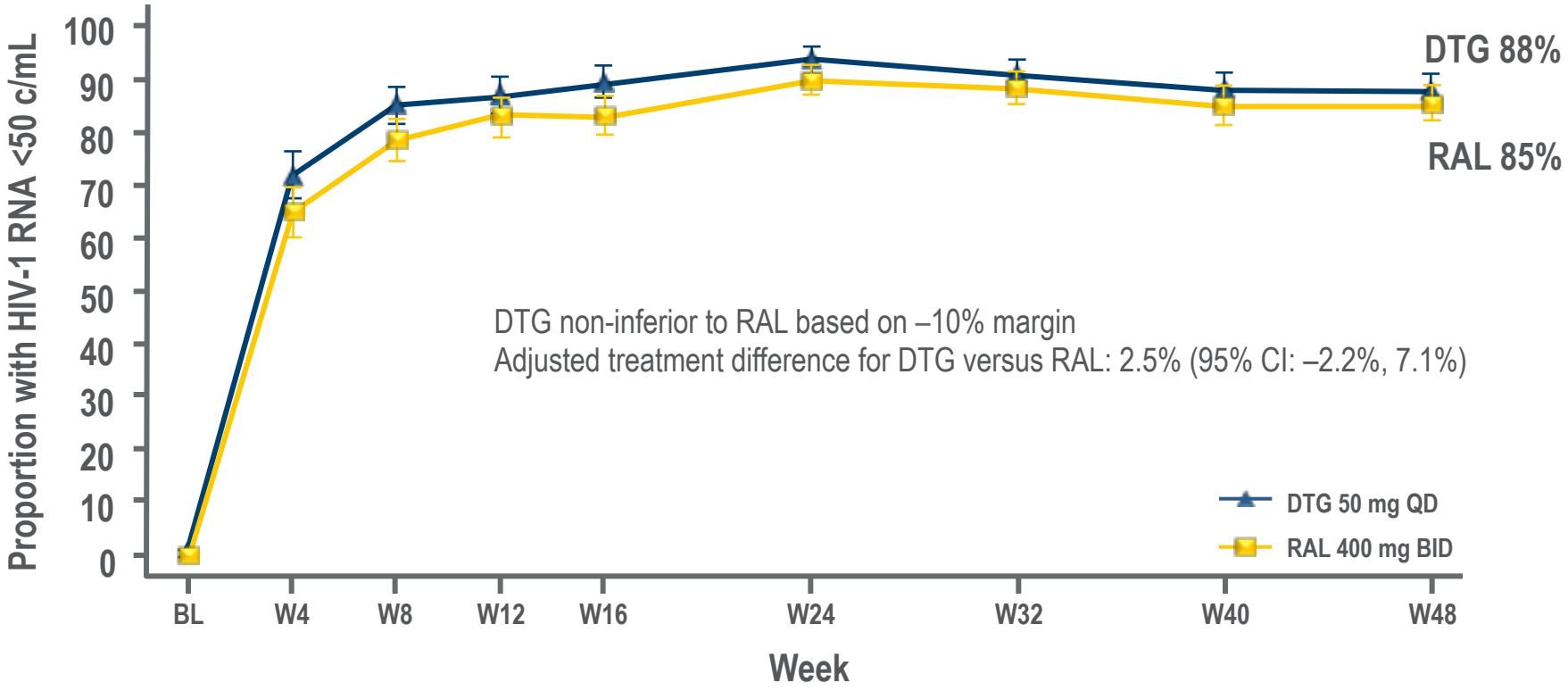
- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy

Week 48 snapshot analysis

Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

IN TREATMENT-NAÏVE PATIENTS, DTG WAS NON-INFERIOR TO RAL AT 48 WEEKS

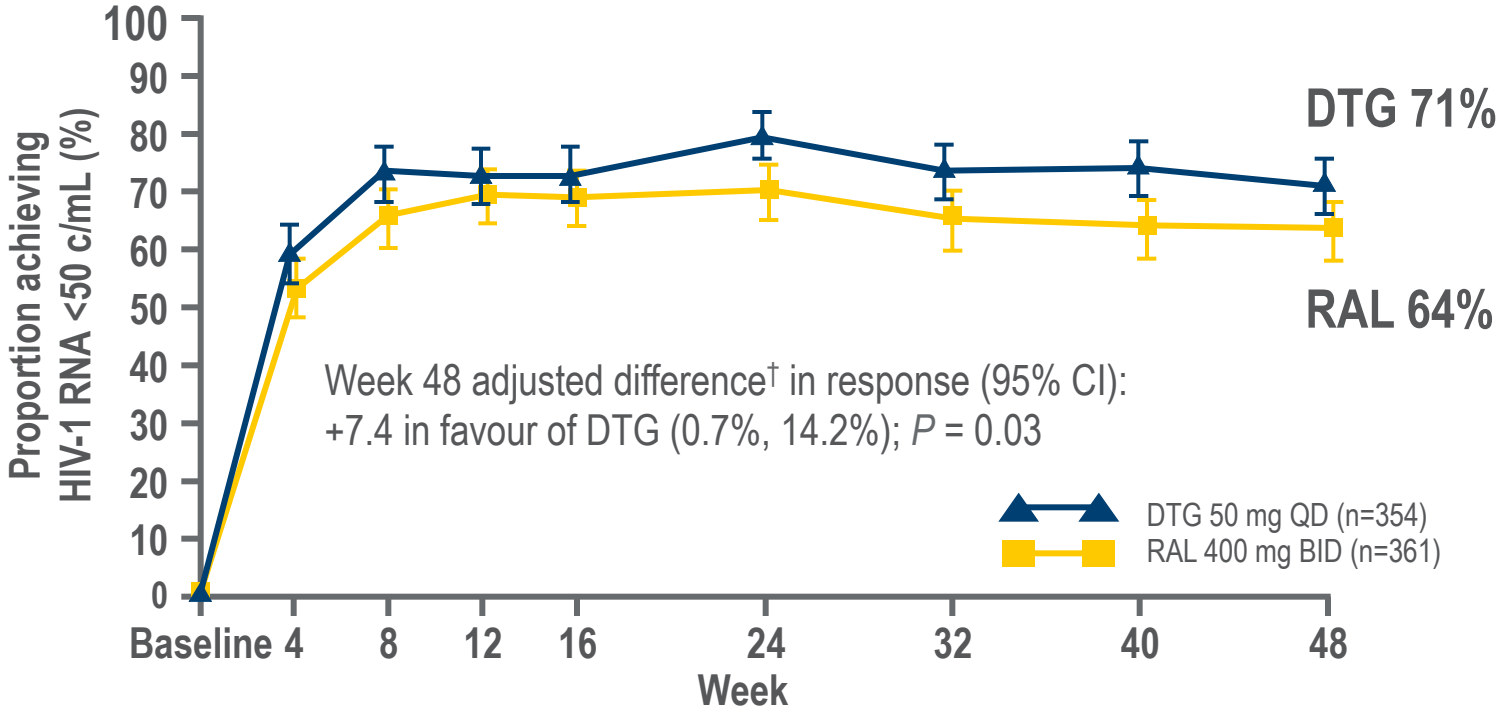


Median (IQR) Change From Baseline CD4+ Cell Count (cells/mm^3)

	Week 4		Week 24		Week 48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

1. Raffi F et al. IAS 2012. Abstract THLBB04
2. Adapted from Raffi F et al. Lancet 2013;381:735–43

IN TREATMENT-EXPERIENCED, INI-NAÏVE PATIENTS, DTG HAD STATISTICALLY SUPERIOR EFFICACY VS RAL



DTG mg QD was statistically superior to RAL 400 mg BID based on a pre-specified snapshot analysis* (HIV-1 RNA <50 copies / mL) at Week 48 (*P* = 0.03)

Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm^3; RAL: +153 (144) cells/mm^3

*Analysis based on all subjects randomised who received ≥1 dose of study drug, excluding four subjects at one site with violations of good clinical practice; SD, standard deviation

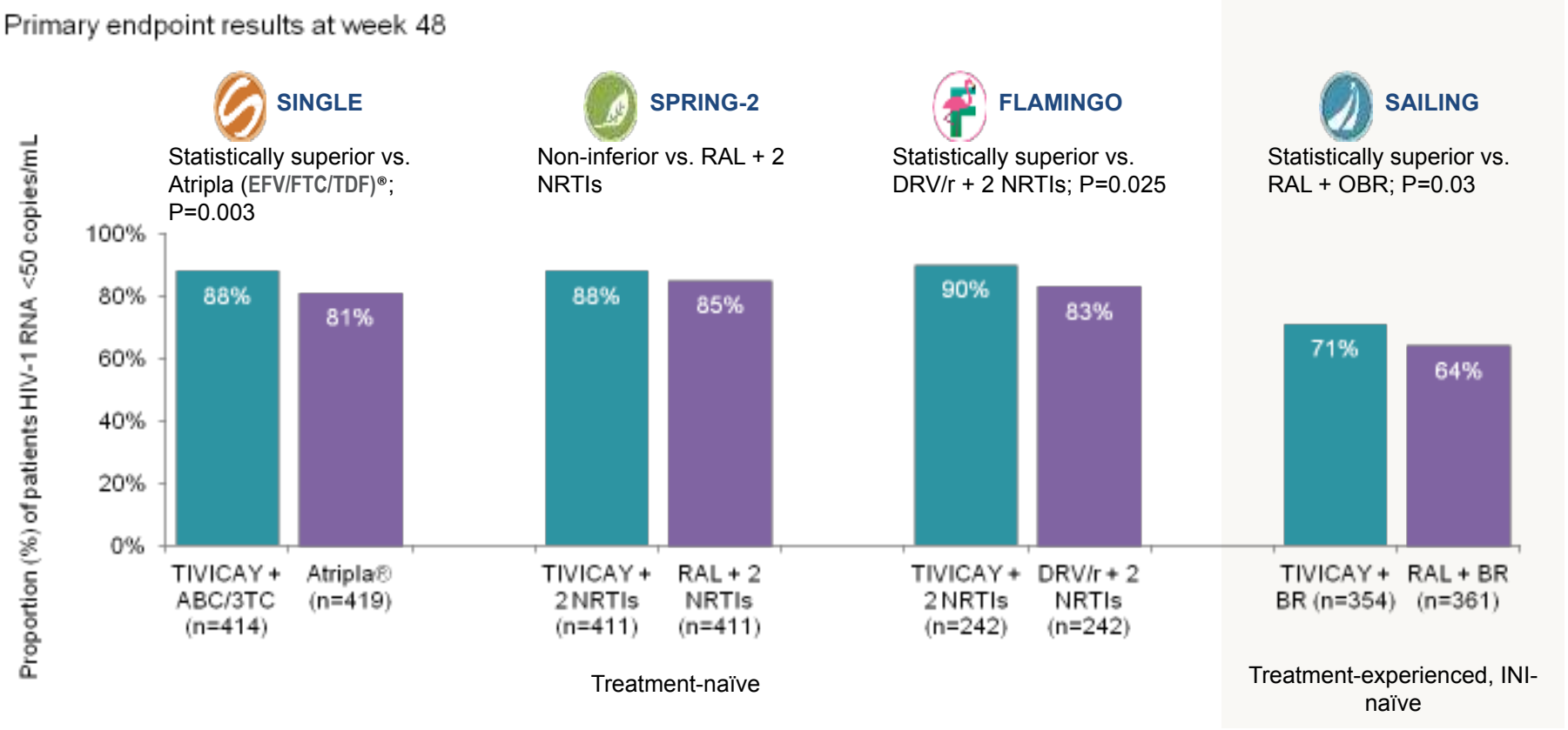
†Adjusted difference based on stratified analysis adjusting for BL HIV-1 RNA (≤50,000 c/mL vs >50,000 c/mL), DRV/r use without primary PI mutations and baseline PSS (2 vs <2)

EA/DLG/0004/14n

Adapted from Cahn P, et al. *Lancet* 2013;382(9893):700-708

Dolutegravir demonstrates superior viral load suppression versus the majority of alternative regimens

- Dolutegravir based treatment regimens have demonstrated **superior viral load suppression** versus EFV and DRV based regimens **in treatment-naïve patients**, and versus RAL **in treatment-experienced but INI-naïve patients**



SPRING-2, SINGLE & FLAMINGO: DTG EFFICACY AT WEEK 48 WITH ABC/3TC OR TDF/FTC, ACCORDING TO BASELINE HIV-1 RNA

ABACAVIR AND BASELINE VIRAL LOAD

n/N (%)	SPRING-2[1,2]		SINGLE[2]		FLAMINGO[3]	
	DTG 50 mg QD + NRTIs*	RAL 400 mg BID + NRTIs*	DTG 50 mg + ABC/3TC QD	EFV/TDF/FTC QD	DTG 50 mg QD + NRTIs*	DRV/r 800/100 mg QD + NRTIs*
≤100,000 copies/mL						
ABC/3TC	115/132 (87)	110/125 (88)	232/280 (90)	–	59/66 (89)	60/68 (88)
TDF/FTC	152/165 (92)	154/170 (91)	--	238/288 (83)	101/115 (88)	97/113 (86)
>100,000 copies/mL						
ABC/3TC	30/37 (81)	32/39 (82)	111/134 (83)	–	12/13 (92)	8/12 (67)
TDF/FTC	64/77 (83)	55/77 (71)	–	100/131 (76)	45/48 (94)	35/49 (71)

*NRTIs were not randomised but investigator selected

1. Raffi F, et al. Lancet 2013;381:735–43
2.Adapted from Eron Jr, J. et al. HIV11 2012. Abstract P204
3.Adapted from Clotet B, et al. Lancet 2014. Epub ahead of print. Supplementary appendix

THE EFFICACY OF DTG/ABC/3TC IN PATIENTS WITH A HIGH BL VL?

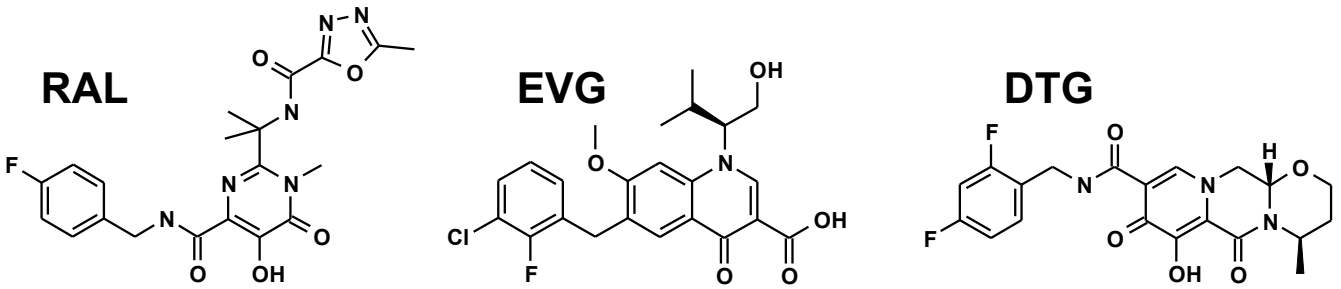
- Findings from the SPRING-2,[1,2] SINGLE[1,3] and FLAMINGO[4,5] studies demonstrated that DTG is effective in combination with ABC/3TC irrespective of BL VL
- In the DHHS, IAS-USA and EACS guidelines, DTG + ABC/3TC is a recommended initial regimen in ARV-naive patients regardless of BL VL[6–8]

1.Eron J, et al. HIV11 2012. Poster P204;
2. Raffi F, et al. Lancet Infect Dis 2013;13:927–35;
3. Walmsley S, et al. J Acquir Immune Defic Syndr 2015;70:515–19;
4. Clotet B, et al. Lancet 2014;383:2222–31;
;
6. Günthard HF, et al. JAMA 2014;312:410–425;
7. DHHS Guidelines for Adults and Adolescents, January 2016;
8. European AIDS Clinical Society Guidelines v8.0, October 2015

HIGH BARRIER TO RESISTANCE

WHAT MAKES DTG DIFFERENT?

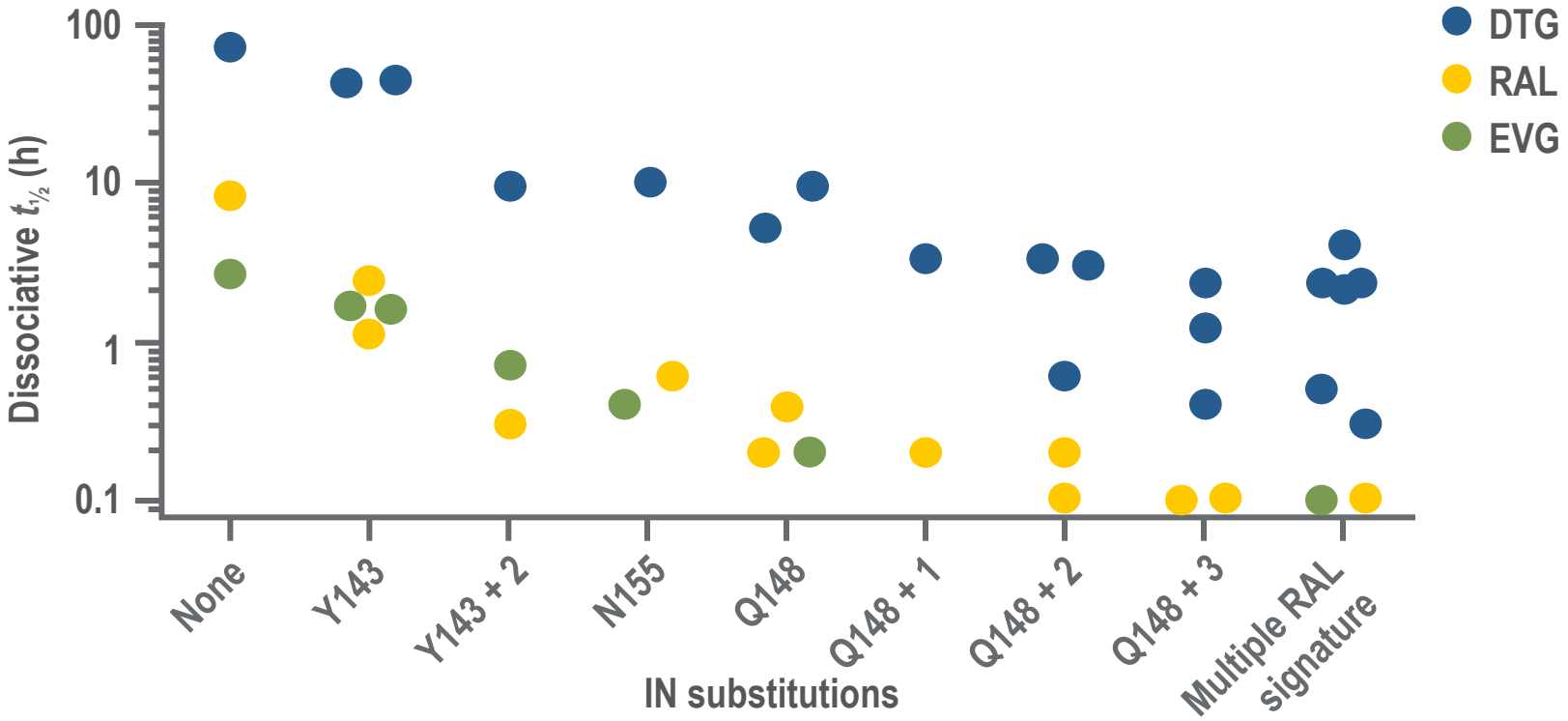
STRUCTURE-BASED RATIONALE FOR DISSOCIATION PROFILES OF DTG, RAL AND EVG



The structural and electronic characteristics of DTG's metal-binding scaffold may contribute to the slower dissociation kinetics of DTG compared with RAL and EVG

Hightower KE, et al. *Antomicrob Agents Chemother* 2011;5:4552–9

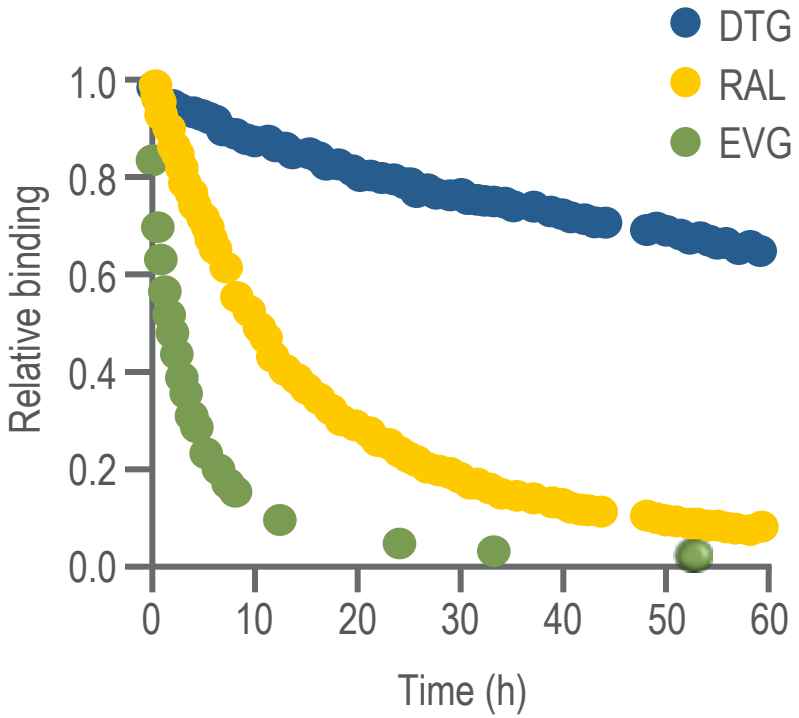
DTG REMAINED BOUND TO HIV INTEGRASE 8 TIMES LONGER THAN RAL AND 26 TIMES LONGER THAN EVG



- DTG dissociation from IN-DNA complexes was slower compared with RAL and EVG
- The combination of multiple RAL signature substitutions or the accumulation of RAL secondary substitutions were needed to impact on DTG dissociation

Hightower KE, et al. *Antimicrob Agents Chemother*.2011;55(10):4552-4559

DTG DISSOCIATED VERY SLOWLY FROM A WILD TYPE IN-DNA COMPLEX AT 37°C



INI	k_{off} (s^{-1})	$t_{1/2}$ (h)
DTG	2.7×10^{-6}	71
RAL	22×10^{-6}	8.8
EVG	71×10^{-6}	2.7

EA/DLG/0004/14n

K_{off}, dissociation rate; $t_{1/2h}$, half-life in hours

Adapted from Hightower KE, et al. *Antimicrob Agents Chemother* 2011;5:4552–9

NO INI OR NRTI RESISTANCE THROUGH 48 WEEKS WITH DTG

n (%)	SPRING-2[1]		SINGLE[2,3,4]		FLAMINGO[5]	
	DTG 50 mg QD (n=411)	RAL 400 mg BID (n=411)	DTG 50 mg +ABC/ 3TC QD (n=414)	ATRIPLA (EFV/FTC/TDF) QD (n=419)	DTG 50 mg (n=234)	DRV/r 800/100 mg QD (n=234)
Subjects with PDVF	20 (5)	28 (7)	18 (4)	17 (4)	2 (<1)	2 (<1)
NRTI-resistant mutations	0	4/19 (21)*	0	1(K65K/R)	0	0
INI-resistant mutations	0	1/18 (6)†	0¶	0	0[a]	0
NNRTI-resistant mutations	–	–	0	4‡	–	–

*One participant had mutation M184M/I; one had mutation A62A/V; and one had mutation M184M/V.

† One participant had integrase mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI mutations A62A/V, K65K/R, K70K/E, and M184V

¶E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

‡n=1 with K101E, n=1 with K103K/N, n=1 with G190G/A and n=1 with K103N+G190G/A

[a]One subject in the DTG treatment group had phenotypic resistance to nelfinavir. This subject had secondary PI resistance mutations L10V, I13V, K20R, E35D, M36I, I62I/V, L63T and L89M at baseline and at PDVF

BL, baseline; c/mL, copies/mL; INI, integrase inhibitor
PDVF, protocol defined virologic failure

1. Adapted from Raffi F, et al. *Lancet* 2013;381:735–43
2. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
3. Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b
4. Adapted from Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18 (suppl appendix)
5. Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

RESISTANCE PROFILE OF DTG: IN VITRO
DTG VIROLOGY STUDIES

DTG has a distinct *in vitro* resistance profile compared with RAL or EVG.

DTG demonstrated **limited cross-resistance to RAL- and EVG-resistant mutants**[1]

In vitro experiments support the potential for DTG to have a higher barrier to resistance compared with RAL and EVG[1,2]

In vitro passage studies showed that DTG leads to a distinct resistance profile, with lower FC compared with RAL and EVG[1-3]
Highly resistant mutants were not isolated. Only mutations which conferred low FC IC_{50} ≤4.1 were identified within the IN-active site[1]

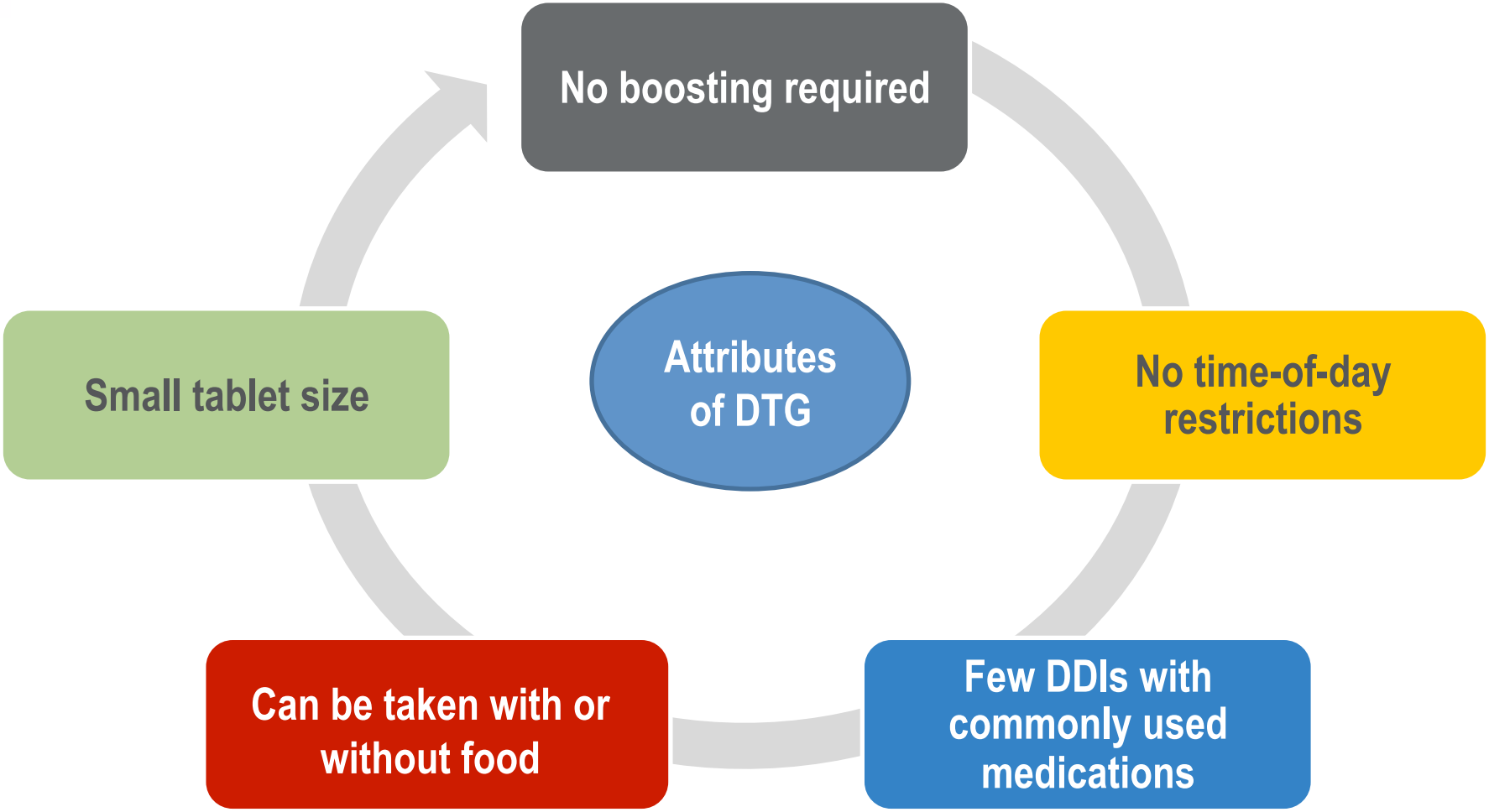
DTG showed reduced activity against E138K/Q148K, G140S/Q148R, and Q148R/N155H[2]

- For details: See Tivicay medical core deck, Chapter 6 (virology)
IN, integrase

- 1. Sato A et al. IAS 2009. Abstract WEPEA097; 2. Seki T et al. CROI 2010. Abstract 555;
3. Kobayashi M et al. Antimicrob Agents Chemother 2011;55:813-821

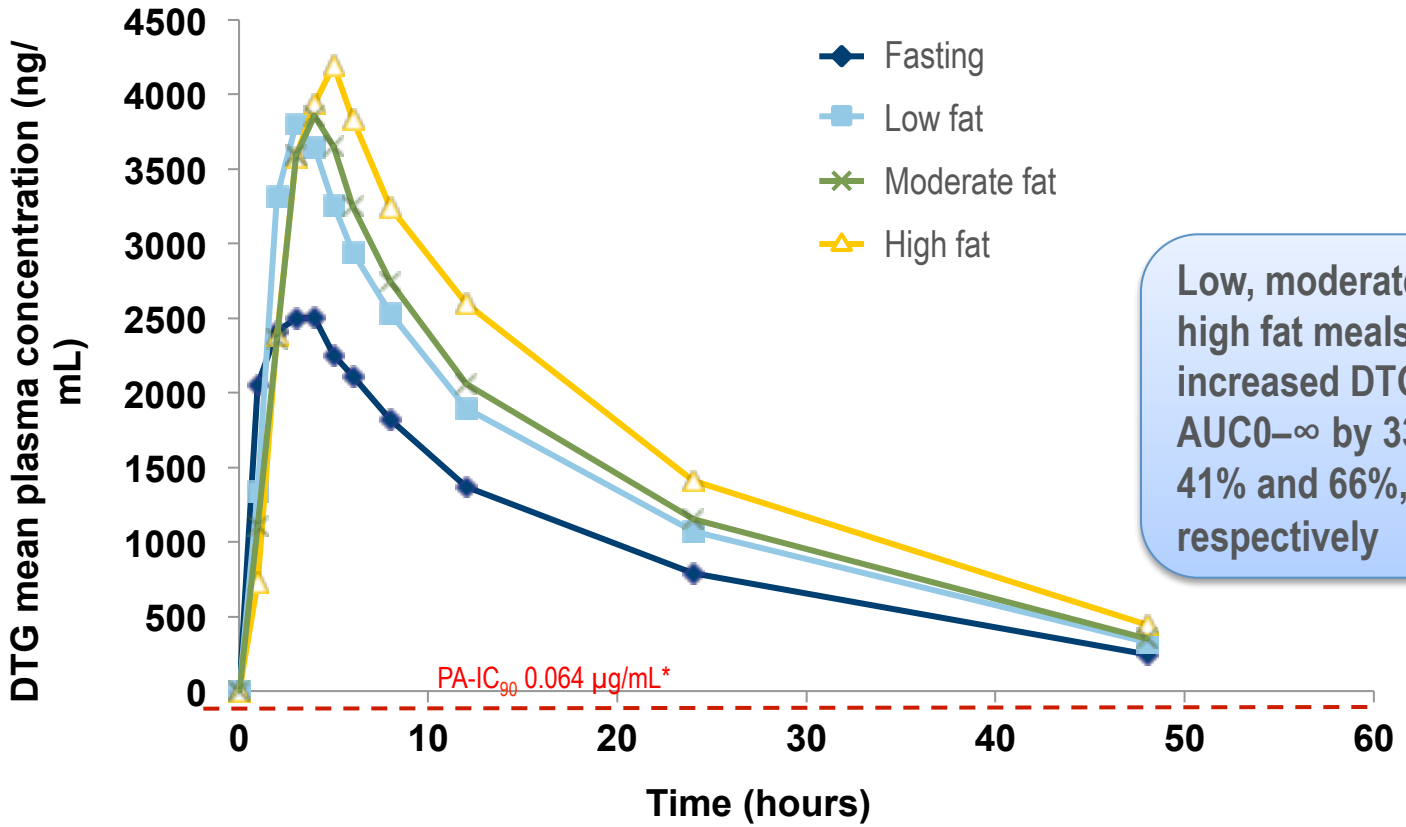
WHAT ABOUT DRUG-DRUG INTERACTION ?

CONVENIENCE BEYOND ONCE-DAILY DOSING



TIVICAY (dolutegravir) Summary of Product Characteristics, 11/2013

DTG CAN BE TAKEN WITH OR WITHOUT FOOD



Low, moderate and high fat meals increased DTG* AUC0–∞ by 33%, 41% and 66%, respectively

Administration with food increased DTG exposure, but this was not clinically significant and therefore DTG can be taken without regard to meals

*PA-IC_{90} is the protein-adjusted 90% inhibitory concentration;
†Phase III (50 mg) formulation

EA/DLG/0004/14n

Adapted from Song I, et al. *Antimicrob Agents Chemother* 2012;56:1627–9

PK/PD PROFILE OF DTG VERSUS ELVITEGRAVIR AND RALTEGRAVIR

	DTG[1–3]	RAL[4]	EVG[5,6]
Clinical dose	50 mg QD (INI-naïve), 50 mg BID (INI-resistant)	400 mg BID	150 mg QD boosted (quad pill)
$t_{1/2}$	~14 hours	~9 hours	~12.9 hours (boosted)
PK variability	Low to moderate	High	Low (with boosting)
Food effect	Can be taken with or without food	No food restriction, but fat content affects absorption and increases PK variability	Taken with food
Protein binding	High: 99.5–99.7%	Moderate: 83%	High: 98–99%
Metabolism and excretion	UGT1A1 (major), CYP3A (minor), renal elimination <1%	UGT1A1, renal elimination ~9%	CYP3A (major), UGT1A1/3 (minor), renal elimination 6.7%
PK/PD relationship	Yes, C_{trough}-driven efficacy	No	Yes, C_{trough}-driven efficacy

DTG has a favourable PK/PD profile compared with other INIs, including EVG and RAL

1. TIVICAY (dolutegravir) Summary of Product Characteristics, 11/2013
2. Min S, et al. *Antimicrob Agents Chemother* 2010;54:254–8
3. Min S, et al. *AIDS* 2011;25:1737–45; 4. Isentress prescribing information (April 2013)
5. Stribild prescribing information (August 2012); 6. Ramanathan S, et al. *Clin Pharmacokinet* 2011;50:229–44

DTG HAS FEW INTERACTIONS WITH COMMONLY USED MEDICATIONS[1,2,3]

Commonly used medications	Dose adjustment required
Oral contraceptives	No
Proton pump inhibitors	No
H_2 antagonists (including cimetidine, famotidine, nizatidine, ranitidine)	No
Methadone	No
Hepatitis B transcriptase inhibitor (adefovir)	No*
Hepatitis C protease inhibitors (telaprevir, boceprevir)	No
Antidepressants	No*
Statins	No*
Rifampicin	Dose DTG 50 mg BID Avoid in INI-class resistance
Magnesium/aluminium-containing antacids Calcium and iron supplements Multivitamins	Dose separate DTG 2 hours before or 6 hours after these medicines
EFV, NVP, and TPV/r	Dose DTG 50 mg BID Avoid in INI-class resistance
ETV	Must only be used in combination with ATV/r, DRV/r or LPV/r at a dose of 50 mg QD

- DTG and dofetilide co-administration contraindicated due to potential life-threatening toxicity caused by high dofetilide concentration
- DTG is not primarily metabolised via the CYP450 pathway†
- List is not complete, and for further information the TIVICAY SmPC should be consulted

* Based on results from other drug interaction trials, DTG is not expected to affect the pharmacokinetics of these drugs

† DTG is metabolised by the UGT1A1 pathway

1. TIVICAY (dolutegravir) Summary of Product Characteristics, 11/2013
2. Fantauzzi A et al. *HIV/AIDS (Auckl)* 2013;5:29-40
3. Teixeira R et al. *Braz J Infect Dis* 2013;17(2):194-204)

WHAT ABOUT TOLERABILITY ?

TREATMENT-RELATED ADVERSE EVENTS OVER 144 WEEKS

	DTG + ABC/3TC 50 mg QD (N=414)		EFV/TDF/FTC QD (N=419)	
Adverse event*	Week 96 (%)	ΔWeek 144	Week 96 (%)	ΔWeek 144
Any	44	+1	67	+1.2
Dizziness	7	+0	33	+0.2
Abnormal dreams	7	+0	16	+0.2
Nausea	11	+0.2	12	+0
Insomnia	10	+0	6	+0.7
Diarrhoea	6	+0	8	+0
Fatigue	7	+0	7	+0
Headache	6	+0	7	+0
Rash	<1	+0	8	+0

EA/DLG/0004/14n

* Reported in ≥5% of subjects in either treatment group

Adapted from Pappa K, et al. ICAAC 2014. Abstract H-647a

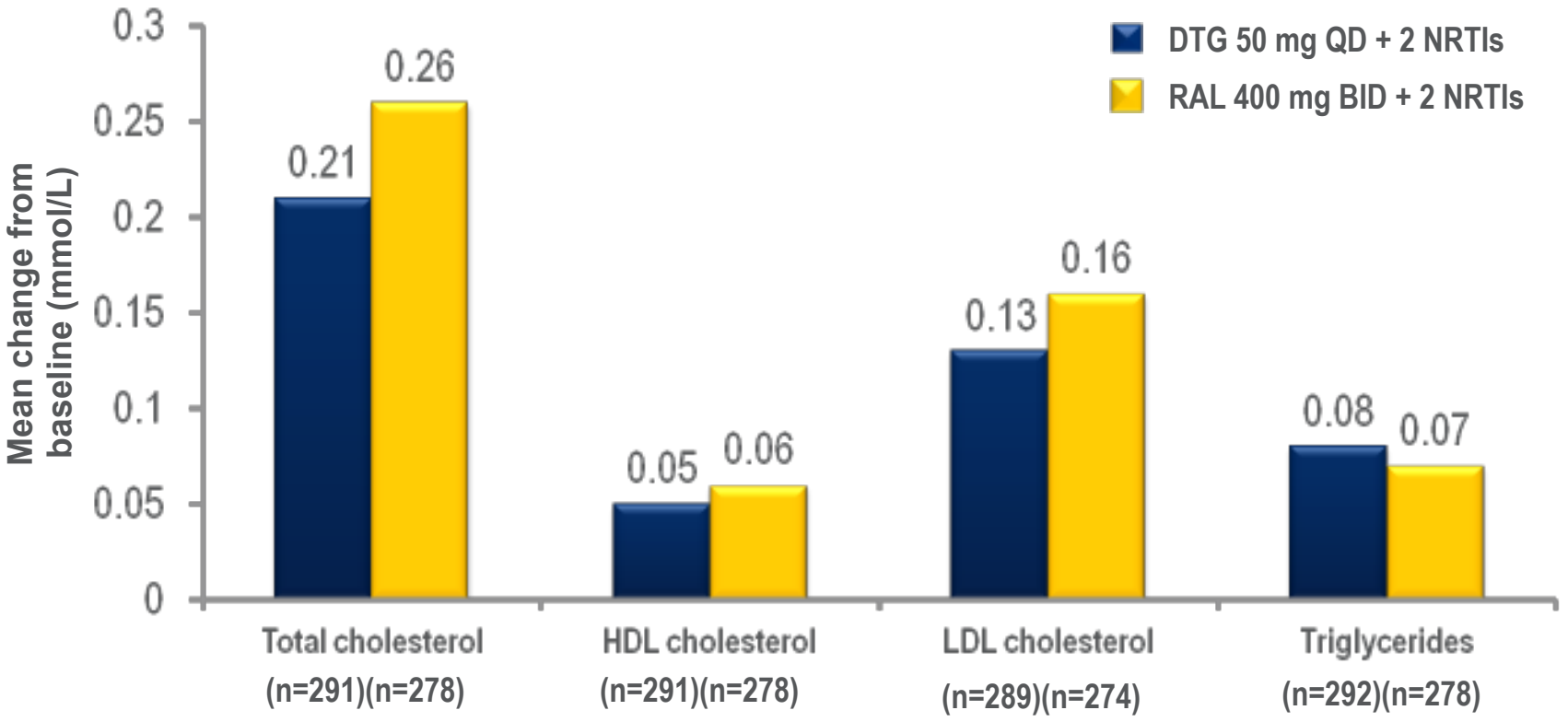
MOST COMMON CLINICAL ADVERSE EVENTS TO WEEK 96

AEs, n (%)	DTG 50 mg QD (N=411)	RAL 400 mg BID (N=411)
WEEK 48[1,2]		
Any event	**339 (82)**	**340 (83)**
Nausea	59 (14)	53 (13)
Headache	51 (12)	48 (12)
Nasopharyngitis	46 (11)	48 (12)
Diarrhoea	47 (11)	47 (11)
WEEK 96[3]		
Any event	**349 (85)**	**349 (85)**
Nausea	60 (15)	56 (14)
Nasopharyngitis	55 (13)	58 (14)
Diarrhoea	57 (14)	55 (13)
Headache	56 (14)	55 (13)

1. Adapted from Raffi F, et al. IAS 2012. Abstract THLBB04
2. Adapted from Raffi F, et al. Lancet 2013;381:735–43
3. Adapted from Raffi F, et al. Lancet Infect Dis 2013;13:927–35; Supplementary appendix

DTG HAD A LIPID-NEUTRAL PROFILE

No evidence of clinically significant impact on lipid profile (i.e. total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides) at 96 weeks[1]



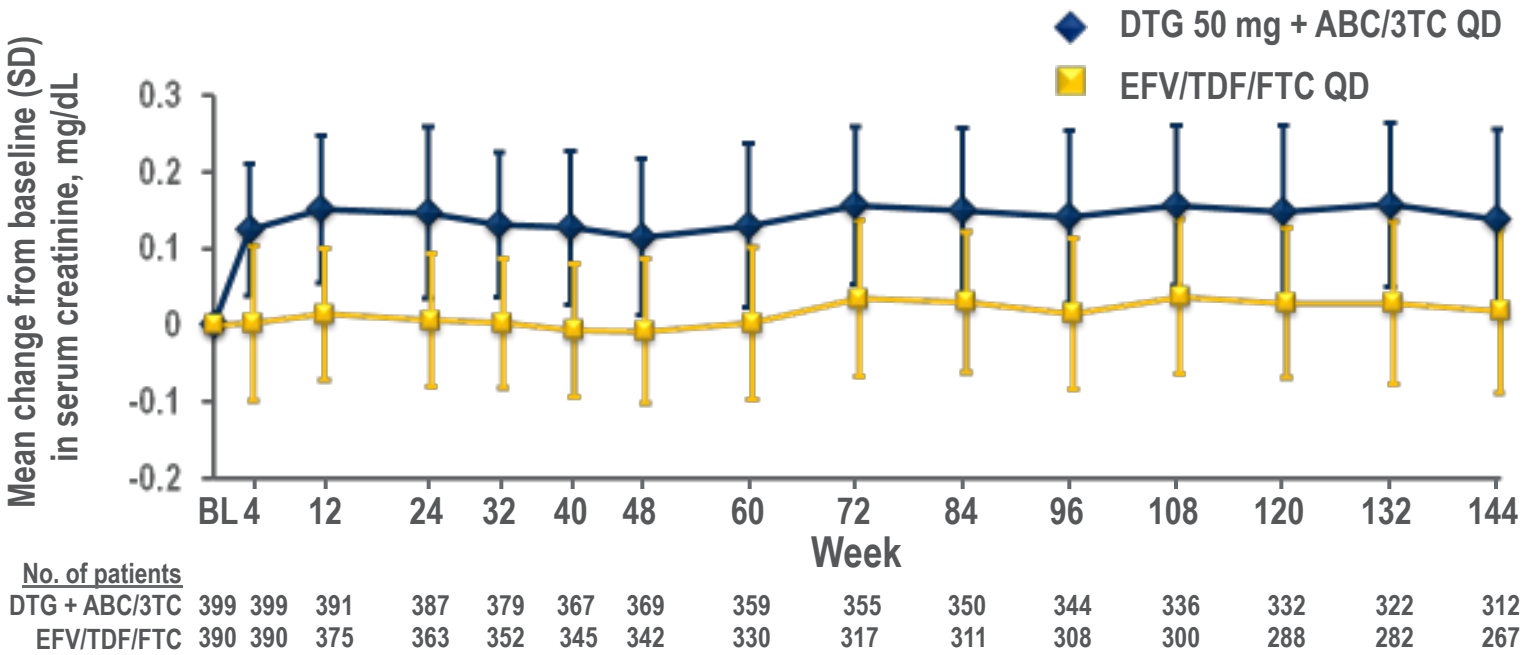
Median changes at Week 48 in mmol/L: Total cholesterol, DTG, +0.18 mmol/L, RAL +0.23 mmol/L; Triglycerides, DTG +0.10 mmol/L, RAL +0.10mmol/L

IQR, interquartile range

1. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
2. Data on file. UK/DLG/0028/13,01/11/13

RENAL SAFETY OF DTG

CHANGE FROM BASELINE TO 144 WEEKS IN RENAL PARAMETERS

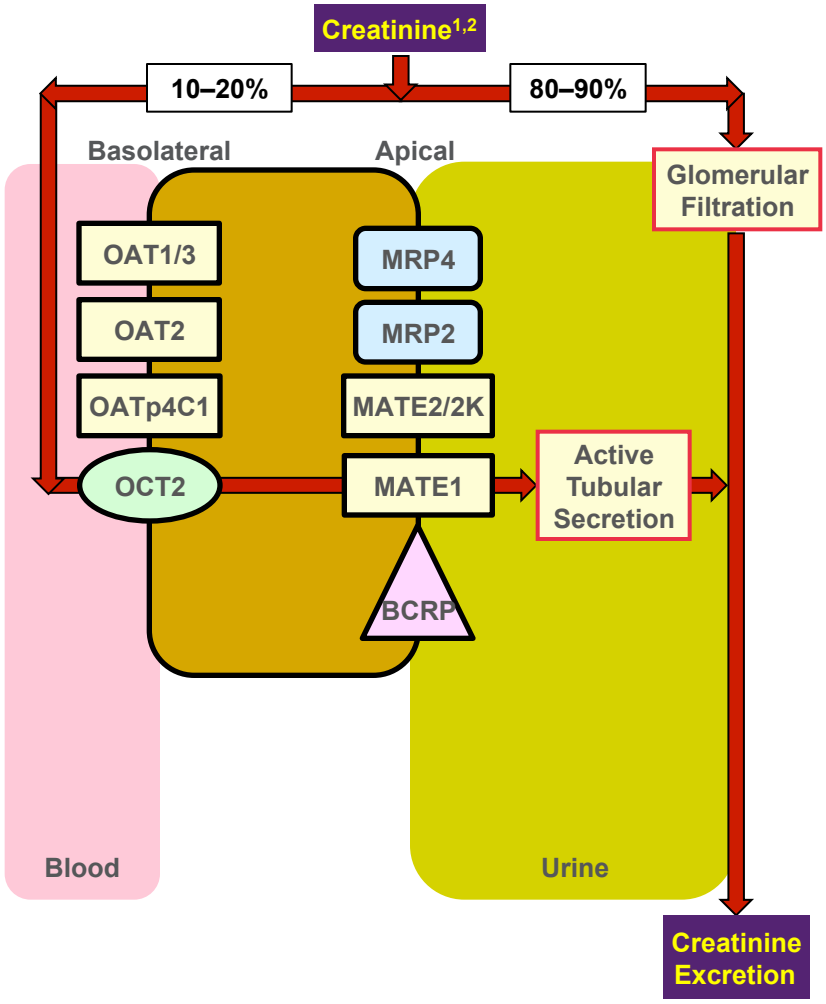


	DTG + ABC/3TC QD			EFV/TDF/FTC QD		
Parameter	**Week 48**	**Week 96**	**Week 144**	**Week 48**	**Week 96**	**Week 144**
Urine albumin/creatinine ratio (mg/mmol)	0	0	0	0.05	0.05	0.10
Median change (IQR)	(-0.3, -0.3)	(-0.3, 0.2)	(-0.4, 0.2)	(-0.2, 0.3)	(-0.2, 0.3)	(-0.2, 0.4)

Adapted from Pappa K, et al. ICAAC 2014. Abstract H-647a

DRUGS THAT INTERFERE WITH CREATININE TUBULAR TRANSPORTERS

- In addition to glomerular filtration, creatinine is excreted into urine by active secretion (10–20%) in the proximal renal tubules
- OCT2 on the basolateral membrane is responsible for creatinine influx
  - Drugs that inhibit OCT2 include DTG and rilpivirine
- MATE1 on the apical membrane is responsible for creatinine efflux
  - Drugs that inhibit MATE1 include cimetidine, cobicistat, trimethoprim, ritonavir, and DTG



Shemesh O et al. Kidney Int 1985;28:830-838; Sato T et al. Biochem Pharmacol 2008;76:894-903; Mills A et al. ICAAC 2011 Abstract H2-794c; Lepist EI et al. ICAAC 2011. Abstract A1-1724; Yombi JC et al. AIDS 2014;28:621-632

RENAL SAFETY OF DTG: SUMMARY

The effect of DTG on serum creatinine is not clinically relevant

- DTG inhibits OCT2,[1] but without affecting glomerular filtration[2]
  - this is similar to other drugs such as trimethoprim or cimetidine
  - these drugs decrease tubular secretion of creatinine and therefore increase concentrations of serum creatinine without affecting glomerular filtration
- In Phase III trials, a small initial increase in creatinine was observed with DTG, due to this blockade of creatinine secretion[3–5]
  - no patients discontinued treatment in Phase III trials because of a renal AE

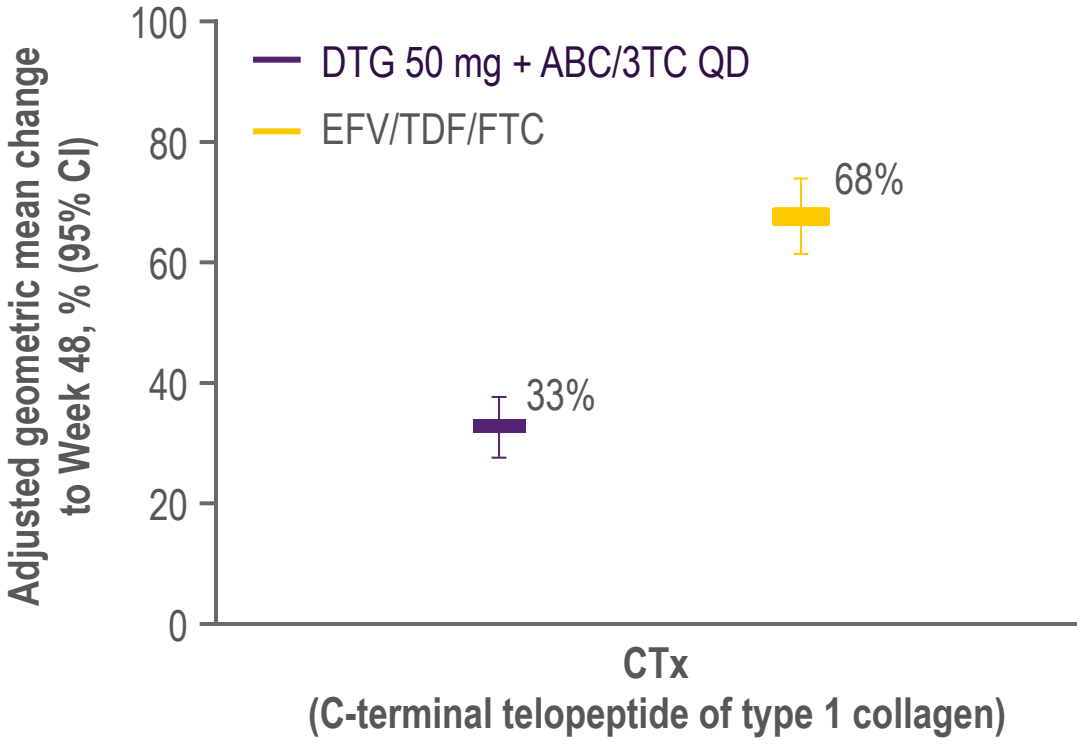
1. Koteff J, et al. ICAAC 2011. Abstract A1–1728
2. Koteff J et al. *Br J Clin Pharmacol*. 2013;75(4):990-996
3. Raffi F, et al. *Lancet* 2013;381:735–43]
4. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
5. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

48 WEEK BONE MARKER CHANGES IN DOLUTEGRAVIR (GSK1349572) PLUS ABACAVIR/LAMIVUDINE VERSUS TENOFOVIR/EMTRICITABINE/EFAVIRENZ: THE SINGLE TRIAL

P Tebas,[1] P Kumar,[2] C Hicks,[3] C Granier,[4] B Wynne,[5] K Pappa,[6] S Min[6]

[1]University of Pennsylvania, Philadelphia, PA, USA; [2]Georgetown University School of Medicine, Washington, DC, USA; [3]Duke University Medical Center, Durham, NC, USA; [4-6]GlaxoSmithKline, [4]London, UK; [5]Philadelphia, PA, USA; [6]Research Triangle Park, NC, USA

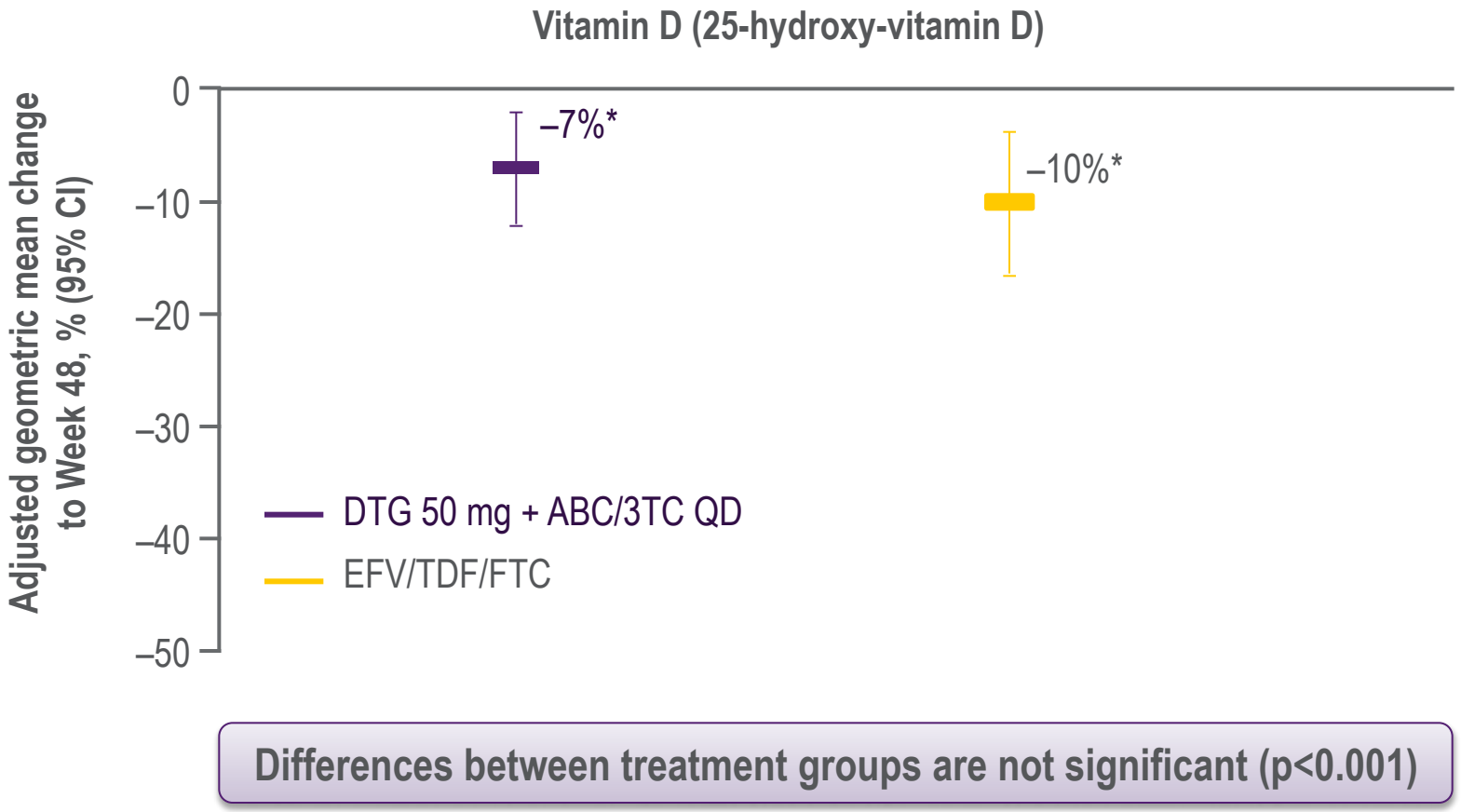
PERCENT CHANGE FROM BASELINE AT WEEK 48 IN BONE RESORPTION BIOMARKERS



Differences between treatment groups was significant ($p<0.001$)

Adapted from Tebas P, et al. ICAAC 2013. Abstract H-1461

PERCENT CHANGE FROM BASELINE AT WEEK 48 IN VITAMIN D



Differences between treatment groups are not significant (p<0.001)

Adapted from Tebas P, et al. ICAAC 2013. Abstract H-1461

CONVENIENCE BEYOND ONCE-DAILY DOSING

Challenge	Characteristics of DTG	
Equivalent or statistically superior efficacy	DTG delivers rapid and sustained efficacy	
Drug resistance	DTG has a high barrier to resistance	
Tolerability	DTG is well tolerated with few discontinuations	
Convenience	Small tablet size Can be taken with or without food No time-of-day restrictions No boosting required Few DDIs with commonly used medications	

1. Walmsley S, et al. *N Engl J Med* 2013; 369:1807-18
2. Raffi F et al. *Lancet* 2013;381:735–43
3. Raffi F, et al. *Lancet Infect Dis* 2013; 13:927-35
4. Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a
5. Cahn P, et al. *Lancet* 2013;382(9893):700-708

ABACAVIR: HLA-B*5701 CARRIAGE & RISK OF MI

Warning Regarding Abacavir and Risk of Myocardial Infarction

Section 4.4: Myocardial infarction

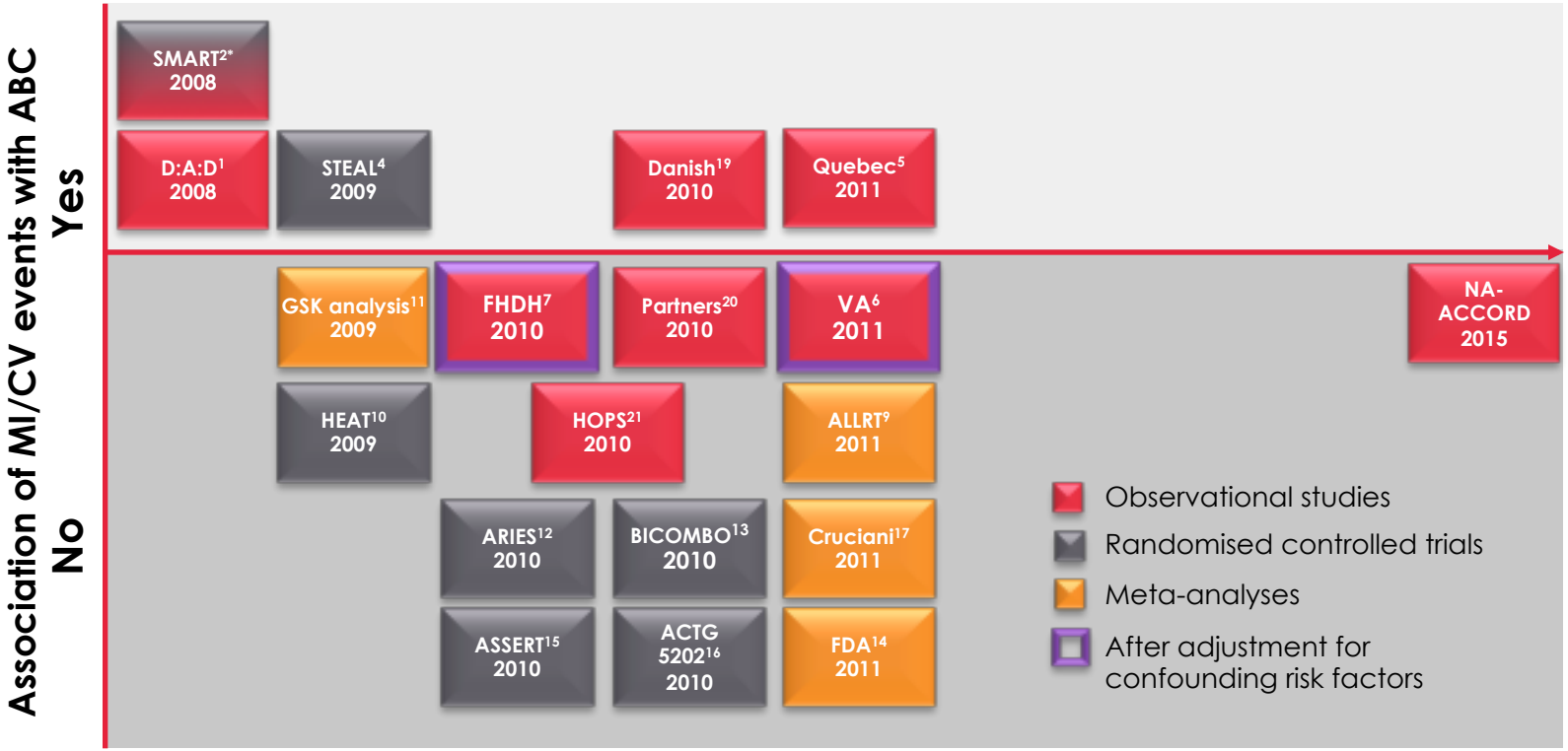
Observational studies have shown an association between myocardial infarction and the use of abacavir. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction.

To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Kivexa, action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia)

ViiV Healthcare

Conflicting Evidence on Risk of Myocardial Infarction (MI) / Cardiovascular (CV) Events Associated with Abacavir (ABC) Treatment

Studies measured either myocardial infarction (MI) risk or cardiovascular (CV) event risk: No consistent endpoint assessed across all studies

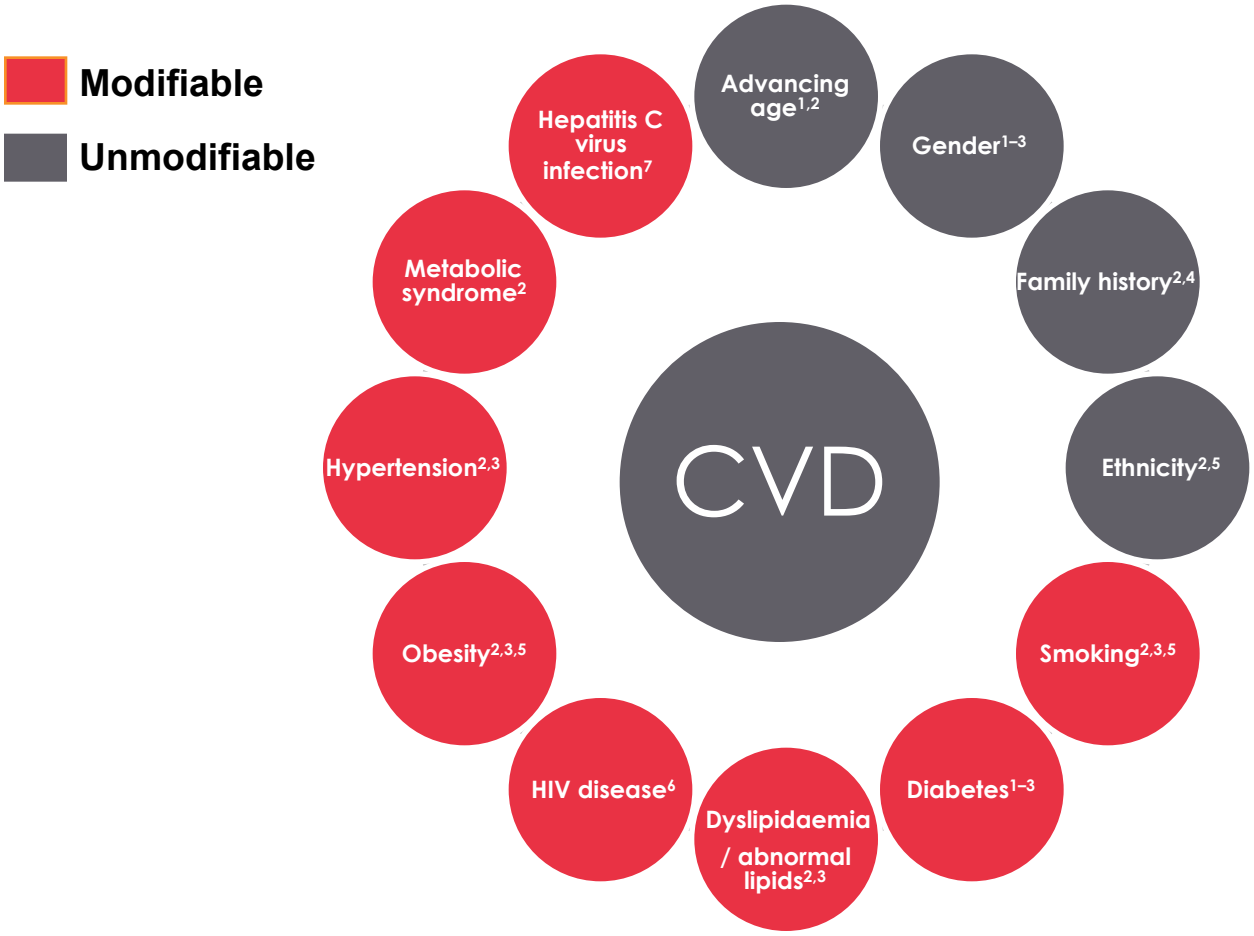


*Dates represent publication or presentation at a major congress. *Observational substudy of SMART RCT.*

1. Sabin CA et al. Lancet 2008;371:1417–26; 2. SMART Study Group. AIDS 2008;22:F17–F24; 3. Worm SW et al. J Infect Dis 2010;201:318–30;
4. Martin A et al. CID 2009; 49:1591–1601; 5. Durand M et al. JAIDS 2011;57:245–53; 6.Bedimo RJ et al. Clin Infect Dis 2011;53:84–91;
7. Lang S et al. Arch Intern Med 2010;170:1228–38; 8. Sabin CA et al. 21st CROI, 2014; Abstract 747LB;
9. Ribaudo HJ et al. Clin Infect Dis 2011;52:929–40; 10. Smith KY et al. AIDS 2009;23:1547–56; 11. Brothers CH et al. JAIDS 2009;51;20–8;
12. Squires K et al. AIDS 2010;24:2019–27; 13. Martinez E et al. AIDS 2010;24:F1–F9; 14. Ding X et al. JAIDS 2012;61:441–7;
15. Moyle G et al. Antivir Ther 2013;18:905–13; 16. Sax P et al. J Infect Dis 2011;204:1191–201; 17. Cruciani M et al. AIDS 2011;25:1993–2004;
18. Choi AI et al. AIDS 2011;25:1289–98; 19. Obel N et al. HIV Med 2010;11:130–6; 20. Triant V et al. JAIDS 2010;55:615–9;
21. Lichtenstein K et al. Clin Infect Dis 2010;51:435–47.

ViiV Healthcare

Cardiovascular Disease (CVD) Risk Factors in HIV



1. Booth GL et al. Lancet 2006;368:29–36; 2. WHO CVD Guidelines. Available at http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf (accessed Sept 2014); 3. Yusuf S et al. Lancet 2004; 364: 937–52; 4. Hunt SC et al. Am J Prev Med 2003;24:136–142; 5. NICE CVD Guidelines 2010. Available at: http://www.nice.org.uk/guidance/ph25 (accessed Sept 2014); 6. Klein D et al. 18th CROI, 2011; Abstract 810; 7. Butt AA et al. Clin Infect Dis 2009; 49:225–232.

Results: Cardiovascular Biomarkers After Switching to ABC/DTG/3TC

- Multivariate analysis of change from baseline showed statistically greater declines in sCD14 levels in men and non-white persons
- In a sensitivity analysis using a model that also adjusted for BMI, patients with BMIs ≥25 kg/m^2 saw slightly larger declines in sCD14 and I-FABP levels

Percent Change From Baseline in I-FABP and sCD14 by BMI

Model, including baseline BMI	Adjusted geometric mean change*100 (%)	Adjusted geometric mean ratio; 95% CI for ratio	*P* value
I-FABP (ng/L)			0.078
<25 kg/m^2	-10%		
≥25 kg/m^2	-20%	1.12 (0.99; 1.26)	
sCD14 (ng/L)			0.031
<25 kg/m^2	-19%		
≥25 kg/m^2	-22%	1.05 (1.00; 1.09)	

Lake et al. CROI 2016; Boston, MA. Poster 660.

ASSOCIATION BETWEEN ABC USE AND MI RISK

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Adverse Effects:

Hypersensitivity Reactions:

- Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele.[15,16] HLA-B*5701 testing should precede use of ABC. ABC should not be given to patients who test positive for HLA-B*5701 and based on a positive test result, ABC hypersensitivity should be noted on a patient's allergy list. Patients who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR should never be re-challenged, regardless of their HLA-B*5701 status.

Cardiovascular Risk:

- An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational observational study group found that recent (within 6 months) or current use of ABC was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.[17,18]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association;[19-22] others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[23-27]
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association

Panel's Recommendations:

- ABC should only be prescribed for patients who are HLA B*5701 negative.
- On the basis of clinical trial safety and efficacy data, experience in clinical practice, and the availability of ABC/3TC as a component of co-formulated products, the Panel classifies ABC/3TC plus DTG as a Recommended regimen **(AI)** (see discussion regarding DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG) .

What's New in the Guidelines? (Last updated April 8, 2015; last reviewed April 8, 2015)

Revisions to the May 1, 2014, version of the guidelines include key updates to several existing sections and the addition of two new tables. Significant updates are highlighted throughout the document.

Key Updates

The following are key updates to existing sections of the guidelines.

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient

Since the last version of these guidelines, data from clinical trials and cohort studies, as well as experience in clinical practice, have prompted significant changes to the list of Recommended, Alternative, and Other regimens for treatment-naive patients (Table 6). Additionally, a new table, titled "Antiretroviral (ARV) Regimen Considerations as Initial Therapy Based on Specific Clinical Scenarios," has been created to guide clinicians on the selection of an initial ARV regimen based on specific clinical scenarios and ARV-related considerations (Table 7).

- There are now five Recommended regimens for antiretroviral therapy (ART)-naive patients—four integrase strand transfer inhibitor (INSTI)-based regimens and one ritonavir-boosted protease inhibitor (PI/r)-based regimen, as listed below:

  INSTI-Based Regimens:

  - Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)—only for patients who are HLA-B*5701 negative (**AI**)
  - DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (**AI**)
  - Elvitegravir/cobicistat/TDF/FTC (EVG/c/TDF/FTC)—only for patients with pre-ART CrCl >70 mL/min (**AI**)
  - Raltegravir (RAL) plus TDF/FTC (**AI**)

ABC and MI ViiV Healthcare

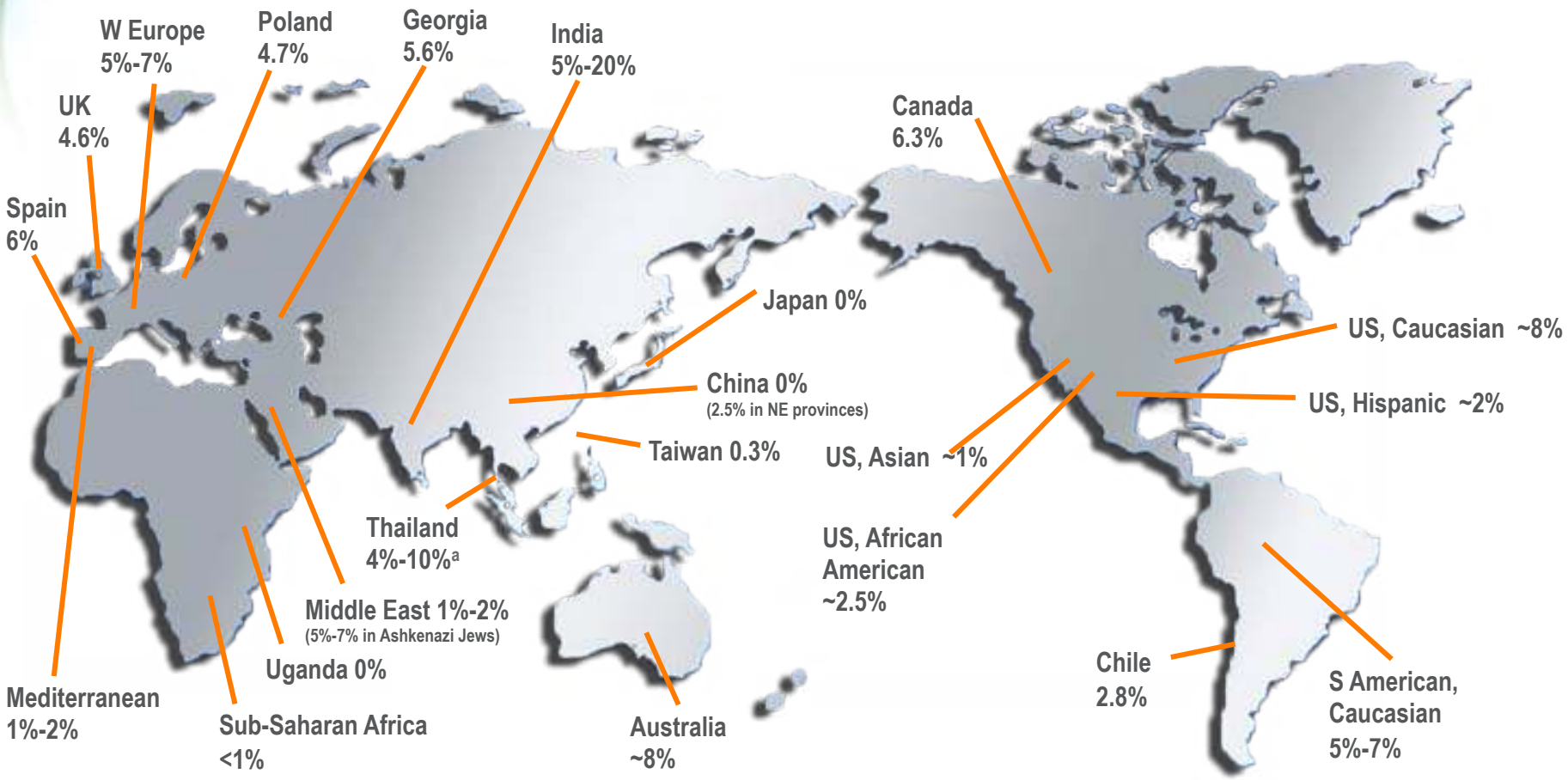
- ViiV Healthcare continually monitors and reviews the most recent and historical data regarding ABC and MI. Although a link between ABC and increased risk of MI cannot be specifically disproven, the majority of recent RCT data, cohort analyses that control for known risk factors and mechanistic data have not supported an association. However, these studies were not prospectively designed to measure risk of MI
- When looking at data regarding MI risk, healthcare providers should take into consideration all data – RCTs cohorts and biomarker studies – and recognise the advantages and limitations of each

ViiV Healthcare

Medical Comment HIV 14.04. ABC and Risk of Cardiovascular Disease. March 2014.

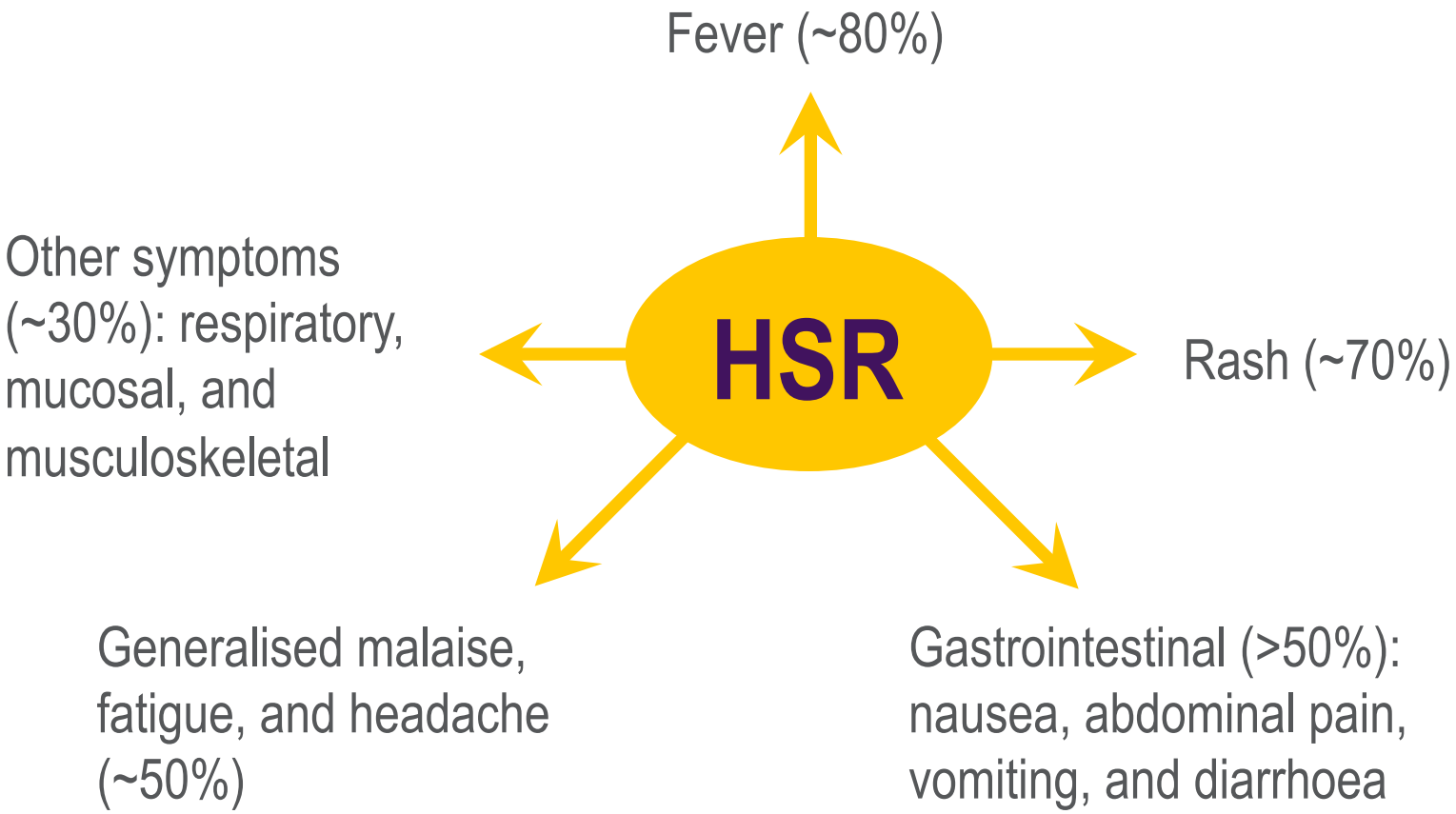
ABC USE AND HLA-B*5701 CARRIAGE

HLA-B*5701 CARRIAGE FREQUENCY[1-9]



- [a] Thailand B*57 carriage: Thai Dai Lue (NE Thai), ~11%; Urban Bangkok, 3.6%; Southern Thai Muslim, 3%.
- **1.** Nolan et al. *J HIV Ther*. 2003;8:36-41. **2.** Lalonde et al. *Tissue Antigens*. 2010;75:12-18. **3.** Poggi et al. *Braz J Infect Dis*. 2010;14:510-512. **4.** Dvali et al. *Georgian Med News*. 2010;12:16-20. **5.** Parczewski et al. *HIV Med*. 2010;11:345-348. **6.** Arrizabalaga et al. *HIV Clin Trials*. 2009;10:48-51. **7.** Sun et al. *J Antimicrob Chemother*. 2007;60:599-604. **8.** Munderi et al. *Trop Med Int Health*. 2011;16:200-204. **9.** Orkin et al. *HIV Med*. 2010;11:187-192.

HYPERSENSITIVITY TO ABC IS A MULTI-ORGAN CLINICAL SYNDROME USUALLY CHARACTERISED BY A SIGN OR SYMPTOM IN TWO OR MORE OF THE FOLLOWING GROUPS



Hetherington S, et al. Clin Ther 2001;23:1603–14

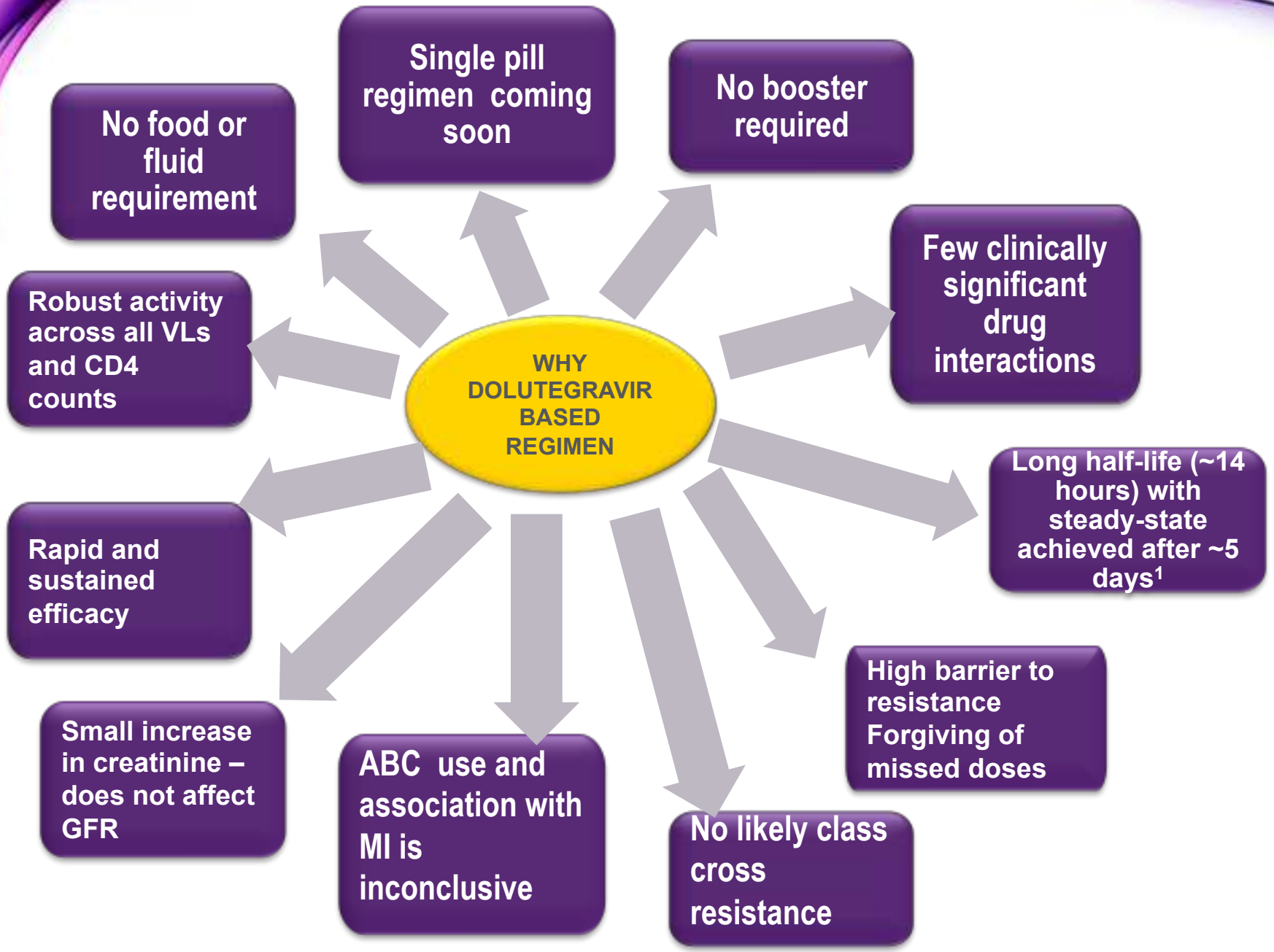
Q: WHAT IS THE RISK OF HYPERSENSITIVITY REACTION TO ABC WITH DTG/ABC/3TC?

A: Patients receiving any regimen containing ABC should be screened for the HLA-B*5701 allele to assess for risk of potential hypersensitivity reactions[1,2]

From the Phase IIb and III clinical programme, the rate of hypersensitivity reaction with DTG+ABC/3TC is <1% and is similar to the rates seen in comparator arms. All subjects in these trials were HLA-B*5701 negative[3–8]

If a suspected hypersensitivity reaction occurs with DTG/ABC/3TC, discontinue the entire regimen immediately and NEVER restart DTG/ABC/3TC or any other DTG- or ABC-containing regimen[1,2]

1. KIVEXA EU Summary of Product Characteristics, January 2016
2. TRIUMEQ EU Summary of Product Characteristics, January 2016
3. Stellbrink H-J, et al. AIDS 2013;27:1771–78; 4. Raffi F, et al. Lancet 2013;381:735–43
5. Walmsley S, et al. N Engl J Med 2013;369:1807–18;
6. Walmsley S, et al. J Acquir Immune Defic Syndr 2015;70:515–9
7. Clotet B, et al. Lancet 2014;383:2222–31
8. Molina JM, et al. Lancet HIV 2015;2:e127–36. Suppl. appendix


WHY DOLUTEGRAVIR BASED REGIMEN
Single pill regimen coming soon
No booster required
No food or fluid requirement
Few clinically significant drug interactions
Robust activity across all VLs and CD4 counts
Long half-life (~14 hours) with steady-state achieved after ~5 days[1]
Rapid and sustained efficacy
High barrier to resistance Forgiving of missed doses
Small increase in creatinine – does not affect GFR
ABC use and association with MI is inconclusive
No likely class cross resistance

PREFERRED INITIAL REGIMENS FOR ARV-NAÏVE PATIENTS

DHHS[1] 2015 (Dept. of Health and Human Services)	IAS-USA[2] 2014 (International Antiviral Society USA Panel)	EACS[3] 2015 (European AIDS Clinical Society)	WHO[4] 2015 (World Health Organization)
NNRTI-based therapy			
~~EFV + TDF/FTC~~	EFV +TDF/FTC	~~EFV + TDF/FTC~~	TDF + 3TC (or FTC) + EFV
	EFV+ABC/3TC	RPV[y] + TDF/FTC or ABC/3TC	TDF + 3TC (or FTC) + EFV*[400]
	RPV + TDF/FTC		
Ritonavir-boosted PI-based therapy			
	ATV/r + TDF/FTC	ATV/r + TDF/FTC or ABC/3TC	
DRV/r + TDF/FTC	ATV/r + ABC/3TC	DRV/r + TDF/FTC or ABC/3TC	
	DRV/r + TDF/FTC		
INI-based therapy			
RAL + TDF/FTC **ELV/c/TDF/FTC**	RAL +TDF/FTC **ELV/c/TDF/FTC**	RAL +TDF/FTC **ELV/c/TDF/FTC**	**DTG + TDF + 3TC or FTC***
DTG + TDF/FTC **DTG + ABC/3TC**	DTG + TDF/FTC **DTG + ABC/3TC**	DTG + TDF/FTC **DTG + ABC/3TC**	

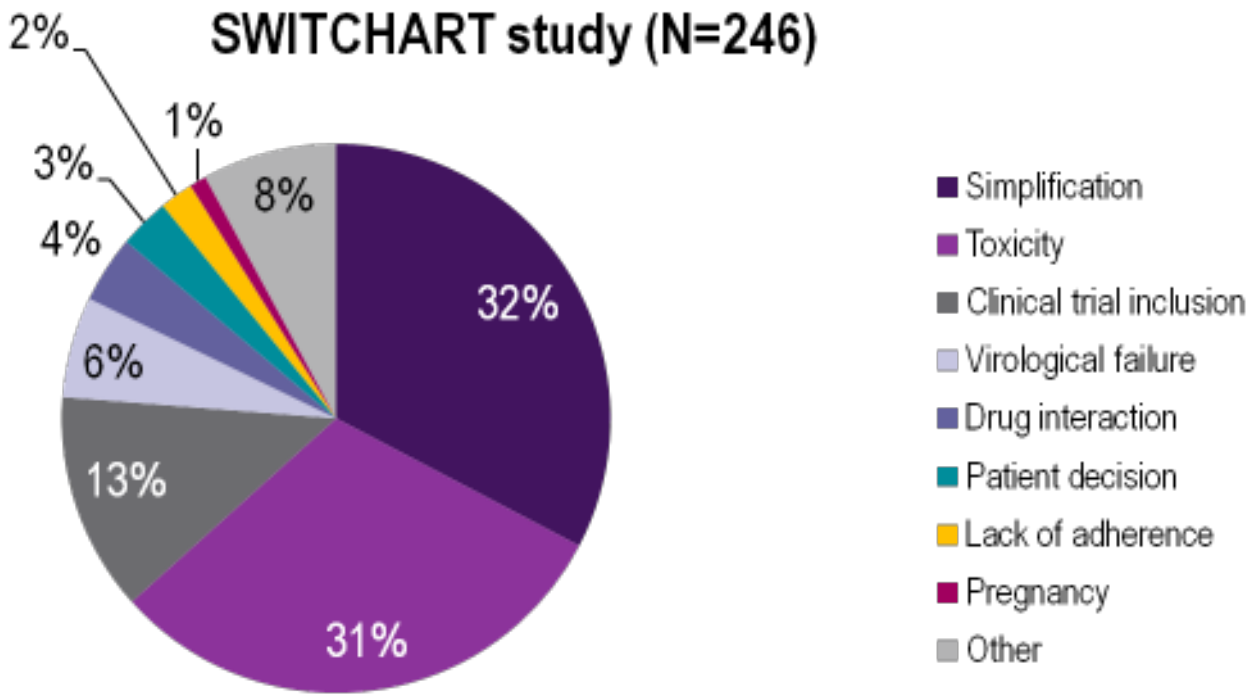
* Alternative * Single Pill Regimen

1. http://aidsinfo.nih.gov/guidelines
2. https://www.iasusa.org
3. http://www.europeanaidsclinicalsociety.org

STRIIVING STUDY – SWITCH STUDY

62

MAIN REASONS FOR SWITCHING ART ARE SIMPLIFICATION AND TOXICITY



- Renal (25%) and CNS (18%) toxicities were the main reasons for ART switch, followed by diarrhoea (16%), liver enzyme elevation (ALT 10%; AST 9%; bilirubin 7%), lipid elevation (cholesterol 5%; triglycerides 8%), nausea (7%) and other (5%)

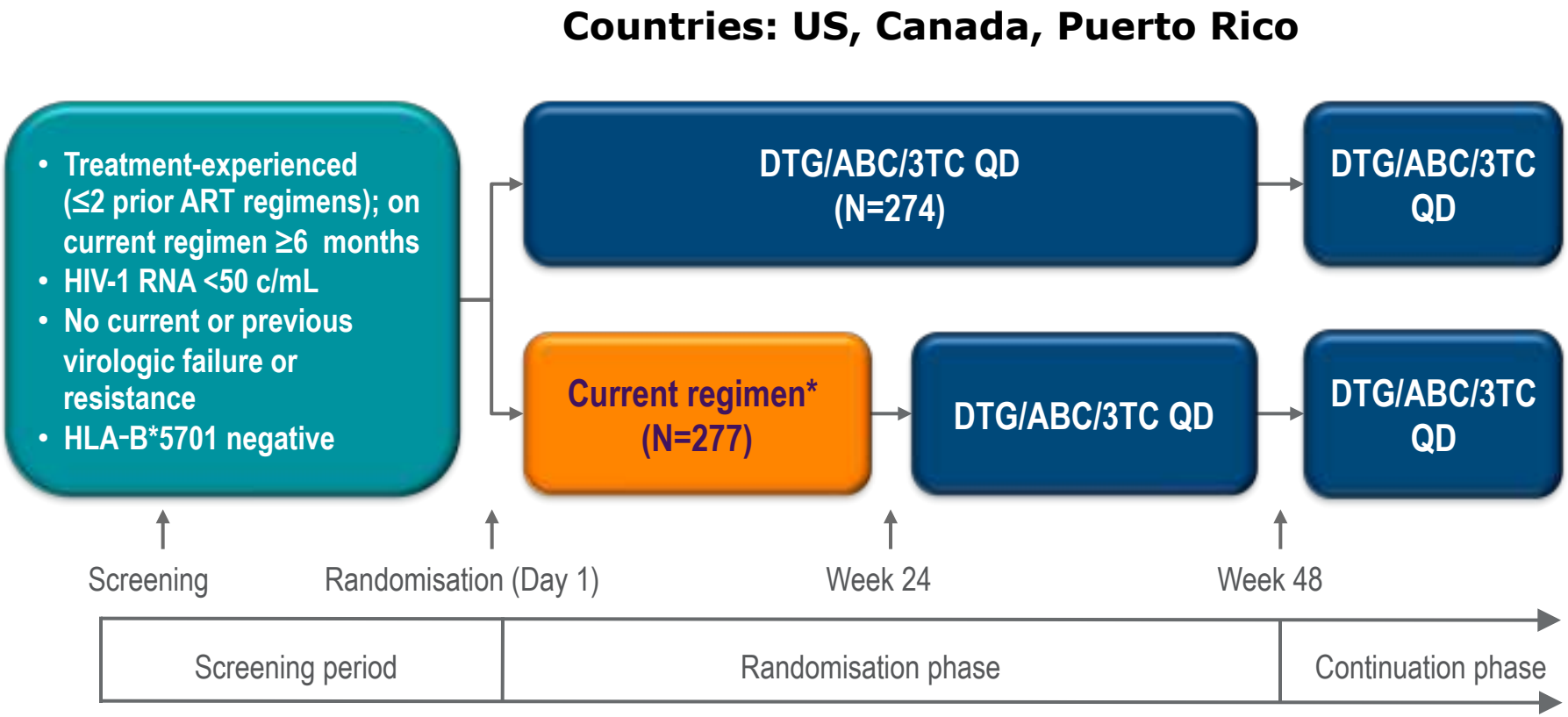
Carrero-Gras A, et al. J Int AIDS Soc 2014;17(Suppl 3):19819

SWITCHING: THE CASE FOR DOLUTEGRAVIR

Efficacious	Well tolerated	"Forgiving"	High barrier to resistance	Few drug interactions	Convenient
•Phase 3 comparisons against NNRTI, PI/r and INSTI	•Few discontinuations for AEs and no apparent signature toxicities	•High inhibitory quotient •Long plasma half-life (~14 h); long binding half-life to wild-type HIV-1 integrase (~71 h) •Wide exposure window for antiviral effect; low inter-patient PK variability	•No treatment emergent resistance to DTG or its NRTI backbone in any clinical study in INSTI-naïve patients to date	• No booster • Primarily metabolised through UGT 1A1: little or no CYP450-mediated interaction	•Low dose (50 mg) and small tablet •No food or timing requirements •Available as a single-tablet regimen with ABC/3TC[a]

1. Walmsley SL, et al. N Engl J Med 2013;369:1807-18; 2. Walmsley S, et al. JAIDS 2015; Aug 9 (E-pub ahead of print); 3. Raffi F et al. Lancet Infect Dis 2013;13:927-35;
4. Molina JM, et al. Lancet HIV 2015; 2(4): e127-e136; 5. van Lunzen J, et al. Lancet Infect Dis 2012;12:111–8; 6. Min S, et al. AIDS 2011;25:1737–45;
7. Llibre JM, et al. AIDS Rev 2015;17:56-64; 8. Tivicay EU SmPC; 9. Triumeq EU SmPC.

STRIIVING study design



Primary endpoint: HIV-1 RNA <50 c/mL (Snapshot) at 24 weeks
Secondary endpoints: CD4 cell count changes; clinical and laboratory safety; lipids, renal, bone, and cardiovascular changes; development of resistance; treatment satisfaction

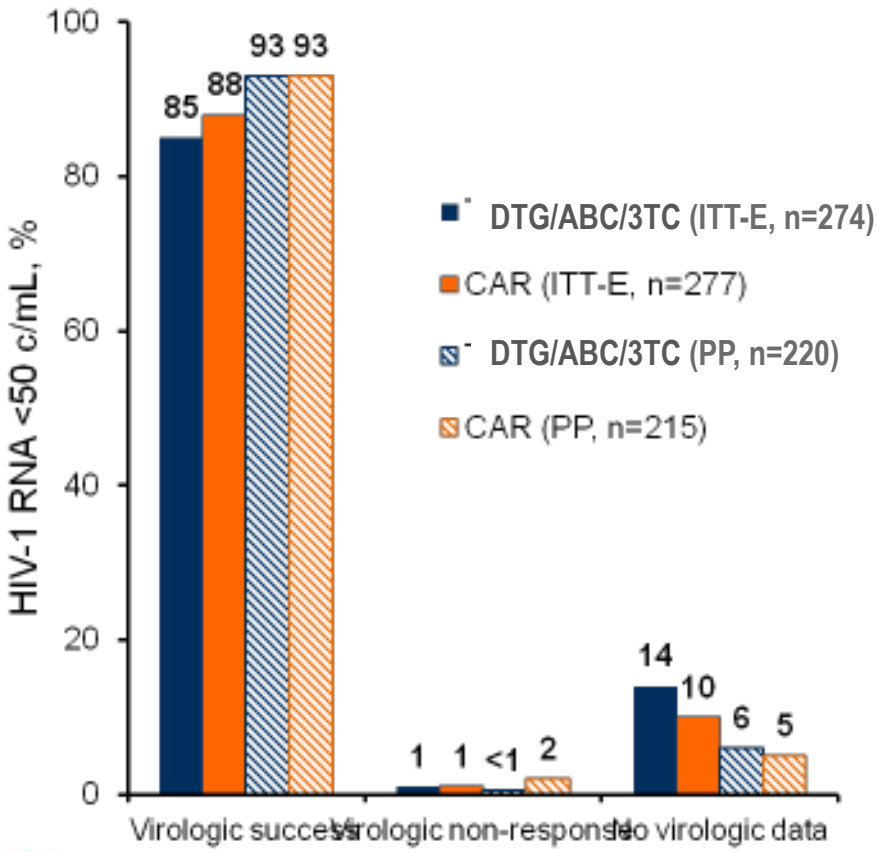
*Stable suppressive ART regimen with 2 NRTIs plus either a PI, an NNRTI, or an INI; ≥40% PIs, at least 25% INIs
90% power based on 10% non-inferiority margin (estimated response rate = 85%)

ART, antiretroviral; c/mL, copies/mL; INI, integrase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; VL, viral load.

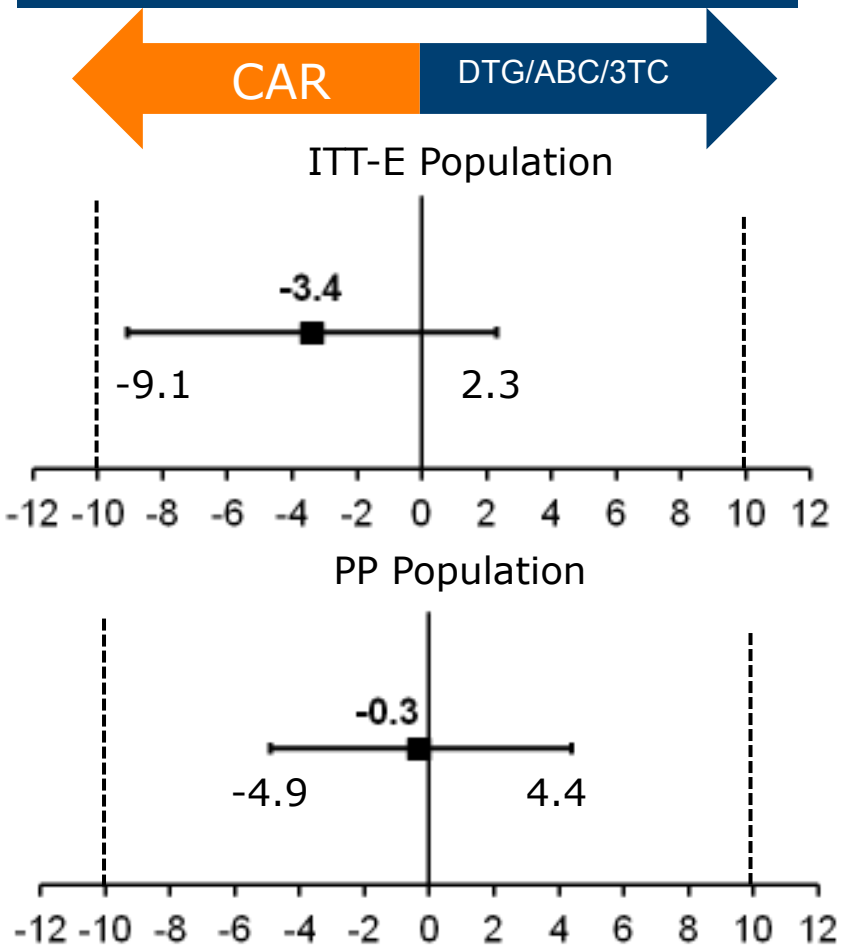
Trottier B, et al. Presented at ICAAC, 17-21 September 2015, San Diego.

STRIIVING: snapshot outcomes at week 24 (ITT-E and PP populations)

Virological outcomes



Treatment differences (95% CI)



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

Trottier B, et al. Presented at ICAAC, 17-21 September 2015, San Diego.

STRIIVING: virological endpoints

- No subjects met protocol-defined virological failure in either study arm

	DTG/ABC/3TC (n=274)	CAR (n=277)
PDVF	0	0
VL ≥50 in W24 window	3 (1%)[a]	4(1%)[b]

[a] DTG/ABC/3TC VLs: 58, 64, 71 c/mL
[b] CAR VLs: 55, 55, 61, 85 c/mL

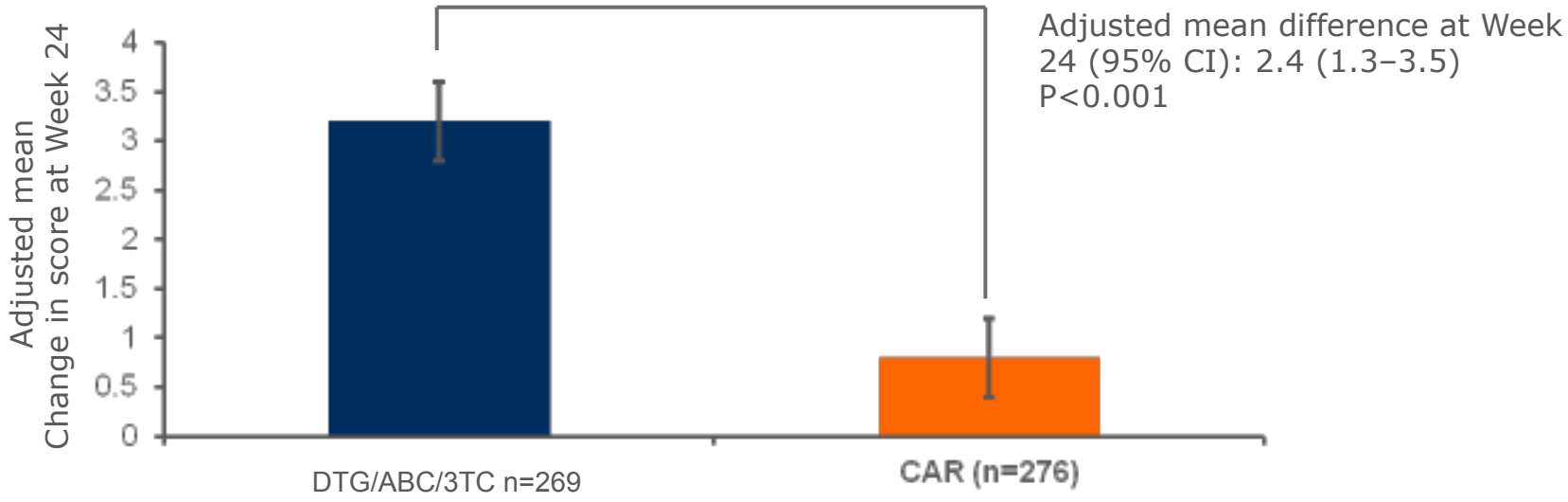
- Subjects with HIV-1 RNA ≥50 c/mL at any visit (scheduled or unscheduled) will require further testing
- Subjects with HIV-1 RNA ≥400 c/mL on 2 consecutive assessments any time after randomization are withdrawn = meets "confirmed virological withdrawal criterion"

c/mL, copies/mL; CAR, current antiretroviral therapy; PDVF, pre-defined virological failure.

ViiV Healthcare

Trottier B, et al. Presented at ICAAC, 17-21 September 2015, San Diego.

STRIIVING: treatment satisfaction–total score



- At baseline, overall treatment satisfaction scores were similar between groups.
- **HIV TSQ total scores increased in both groups, with a statistically significant difference favouring DTG/ABC/3TC**.

CAR, current antiretroviral therapy; TSQ, treatment satisfaction questionnaire.

Trottier B, et al. Presented at ICAAC, 17-21 September 2015, San Diego.

STRIIVING: conclusions

- Switching to DTG/ABC/3TC from a variety of regimens was demonstrated to be safe and effective
- Switching to DTG/ABC/3TC met non-inferiority endpoints for all population analyses
- No subjects met the protocol-defined virological failure endpoint through 24 weeks
- Discontinuations due to AEs in the DTG/ABC/3TC arm were infrequent and mostly due to low grade adverse events
- Greater improvements in treatment satisfaction were demonstrated in subjects switching to DTG/ABC/3TC
- No worsening of markers associated with cardiovascular disease was observed following switch to DTG/ABC/3TC as compared with CAR
  - Cardiovascular biomarker data may suggest reduced microbial translocation and monocyte activation following switch to DTG/ABC/3TC

ViiV Healthcare

AEs, adverse events.

Trottier B, et al. Presented at ICAAC, 17-21 September 2015, San Diego. Lake et al. CROI 2016; Boston, MA. Poster 660.

COMBINATION REGIMEN COMPARISON

Red, negative trait; **green**, positive trait; **orange**, may be positive or negative

	ATRIPLA[1]	EVIPLERA/ COMPLERA[2]	STRIBILD[3]	Tivicay+ABC/3TC[4]	TAF-STRIBILD[5]	TAF+FTC +DRV/ COBI[6]	TAF+FTC+ RPV[7]	Generic SPRs?
Broad indication	Yes	No	No	Yes	?	?	?	?
Boosting requirement	No	No	Yes	No	Yes	Yes	No	?
DDIs	Few	Few	Many	Few	Many	Many	Few	?
Food restrictions	Yes	Yes	Yes	No	Yes?	No?	Yes	?
Efficacy in high VL	Yes	No	Yes	Yes	Yes?	Yes?	?	?
Resistance profile – barrier to resistance	Low	Low	Moderate	Probable high?	Moderate*	Probable high?	Low	?
Class cross resistance	Yes	Yes	Yes	No	Yes?	No?	Yes	?
Percentage of Grade 2–4 ADRs reported at 96 wks	Moderate (0–9%)	Low (1–2%)	Moderate (1–16%)	Low (0–3%)	Moderate?	Moderate?	Low	
Effect on lipids	Negative	Positive	Negative	Neutral	Neutral?	Negative?	Negative?	?
Link to CV, bone, renal toxicity	Renal/bone	Renal/bone	Renal/bone	CV	No?	No?	No?	?
Requires additional renal monitoring	No	No	Yes	No	No?	No?	No?	?
Requires screening genetic test	No	No	No	Yes	No	No	No	?
Contains tenofovir	Yes	Yes	Yes	No	No	No	No	?

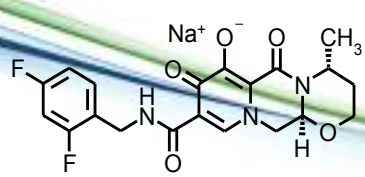
Table not meant to imply that head-to-head safety and efficacy studies have been conducted. Note: efficacy takes in to account reduction in VL, CD4+ count, duration of response and speed of action (updated on 28 Aug 2014)

Slide based on feedback from advisory boards and internal communications

'?' after a characteristic denotes that it is currently unknown, but has been assumed based on available data

ADR, adverse drug reaction; CV, cardiovascular; DDI, drug–drug interaction; VL, viral load; TAF, tenofovir alafenamide

1. ATRIPLA Prescribing Information, October 2013; 2. COMPLERA Prescribing Information, June 2014; 3. STRIBILD Prescribing Information, August 2012; 4. TRIUMEQ Prescribing Information, August 2014; 5. Sax PE, et al. ICAAC 2013. Abstract H-146d; 6. Mills A et al. ICAAC 2014. Abstract H-647c; 7. Personal communication, ViiV Healthcare



ATTRIBUTES OF DOLUTEGRAVIR

Attributes of DTG

- Highly potent antiviral activity[1]
- Generally well tolerated[1,2]
- Distinct in-vitro resistance profile, with an apparent high barrier to resistance[3]
- Low potential for drug interactions[2] (favourable drug interaction profile)
- Diffusion & Control of VL in CSF and Genital track
- Low PK variability and predictable exposure-response relationship[1,2]
- Can be taken without regard to meals, no significant food effect[4]
- Once daily administration without a PK enhancer[2]
- Size: Very small pill

Long half-life (~14 hours) with steady-state achieved after ~5 days[1]

- Efficacy
- Tolerability
- Resistance
- PK Profile
- Convenience
- Specific population

Metabolised primarily by UGT1A1 pathway; it does not impact on other drugs and has few DDIs

PK, pharmacokinetics

1. Min, S. et al. AIDS 2011;25:1737–45
2. Min, S. et al. Antimicrob Agents Chemother. 2010;54:254–8
3. Kobayashi, M. et al. Antimicrob Agents Chemother 2011;55:813–21
4. Song, I. et al. Antimicrob Agents Chemother 2012;56:1627–9

THANK YOU

FDA Pregnancy categories for Antiretroviral Therapy (1)

FDA Pregnancy Categories

Category A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters)

Category B: Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate, but well-controlled, studies of pregnant women have not been conducted

Category C: Safety in human pregnancy has not been determined; animal studies either are positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus

Category D: There is positive evidence of human fetal risk that is based on adverse-reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women might be acceptable despite its potential risks

Category X: Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit