Dolutegravir. Novel Therapy Perspectives

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- This event is sponsored by GSK/ViiV, in the interest of advancing the scientific knowledge of healthcare professionals.
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AGENDA

- **Rise of InSTI.** ***Insights based upon recent recommendations*****.**

- **Unmet HIV clinical needs.**

- **Future therapy perspectives with DTG in HIV patients.** ***IAS data***

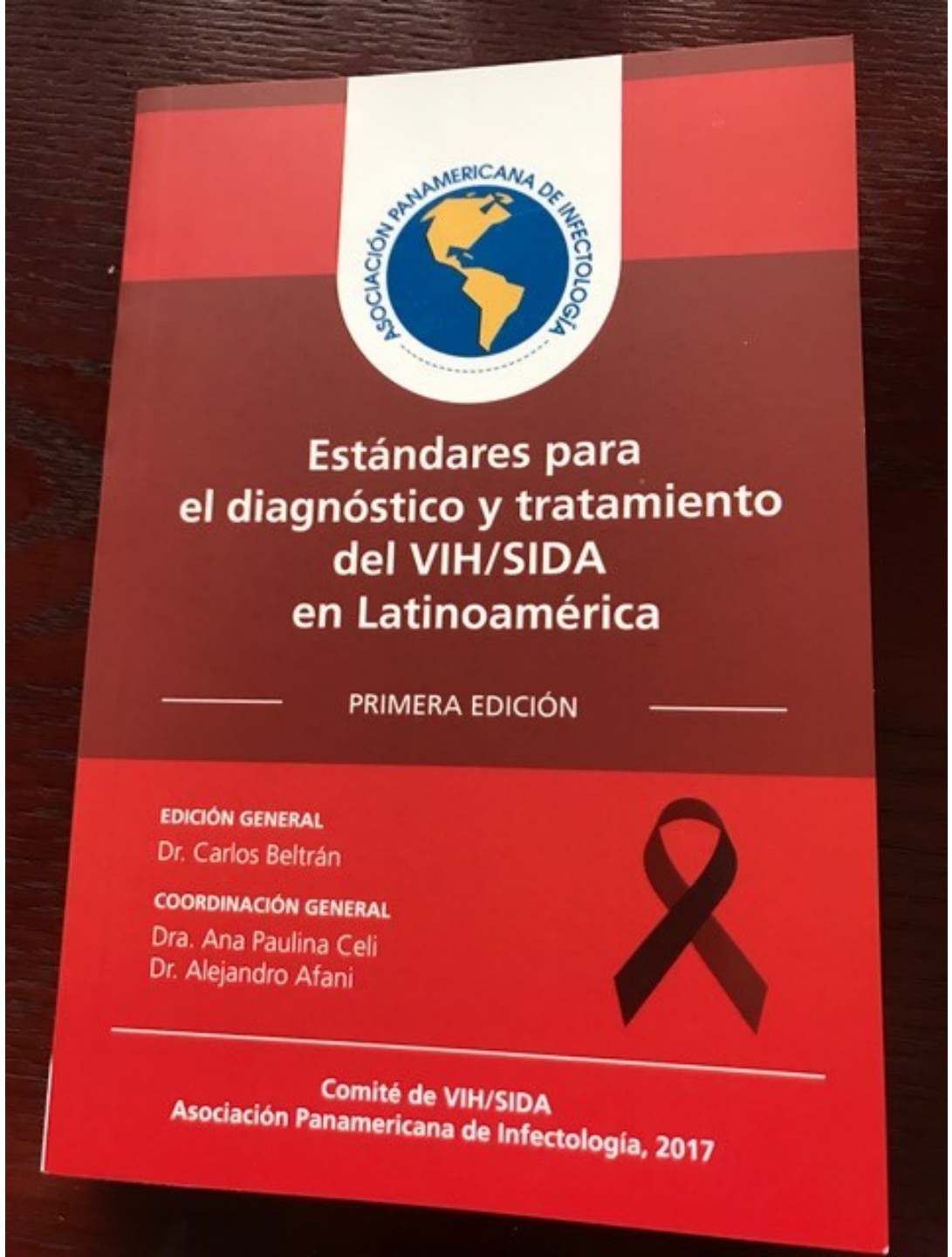
Comparison of Current International Guidelines for Treatment-Naive Pts

Regimen	DHHS[1]	EACS[2]	BHIVA[3]	IAS-USA[4]	GeSIDA[5]	Portugal[6]
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§						

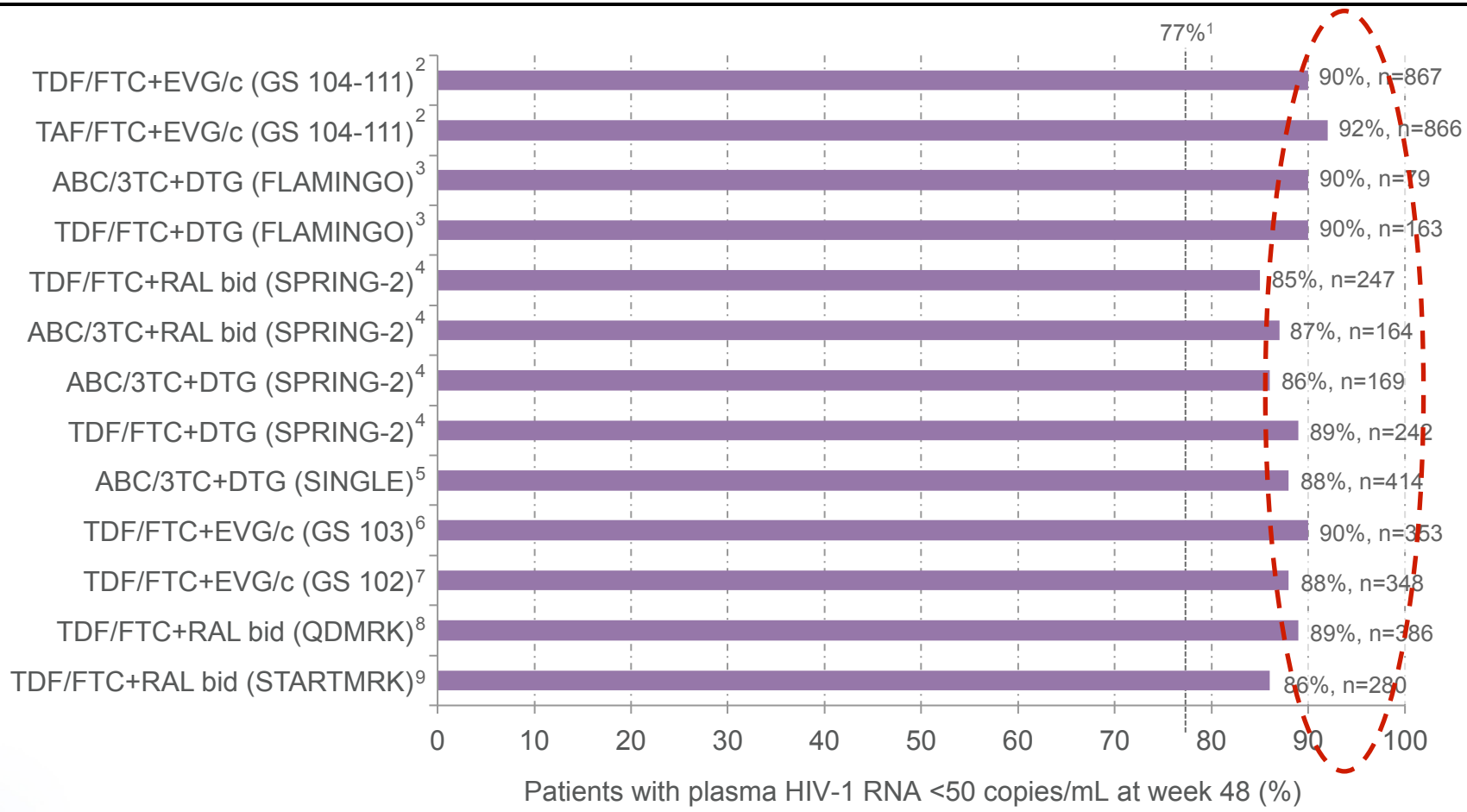
*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. §Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3.

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. January 2016.
6. http://sida.dgs.pt/ Maio 2016


ASOCIACIÓN PANAMERICANA DE INFECTOLOGÍA
Estándares para el diagnóstico y tratamiento del VIH/SIDA en Latinoamérica
PRIMERA EDICIÓN
EDICIÓN GENERAL
Dr. Carlos Beltrán
COORDINACIÓN GENERAL
Dra. Ana Paulina Celi
Dr. Alejandro Afani
Comité de VIH/SIDA
Asociación Panamericana de Infectología, 2017

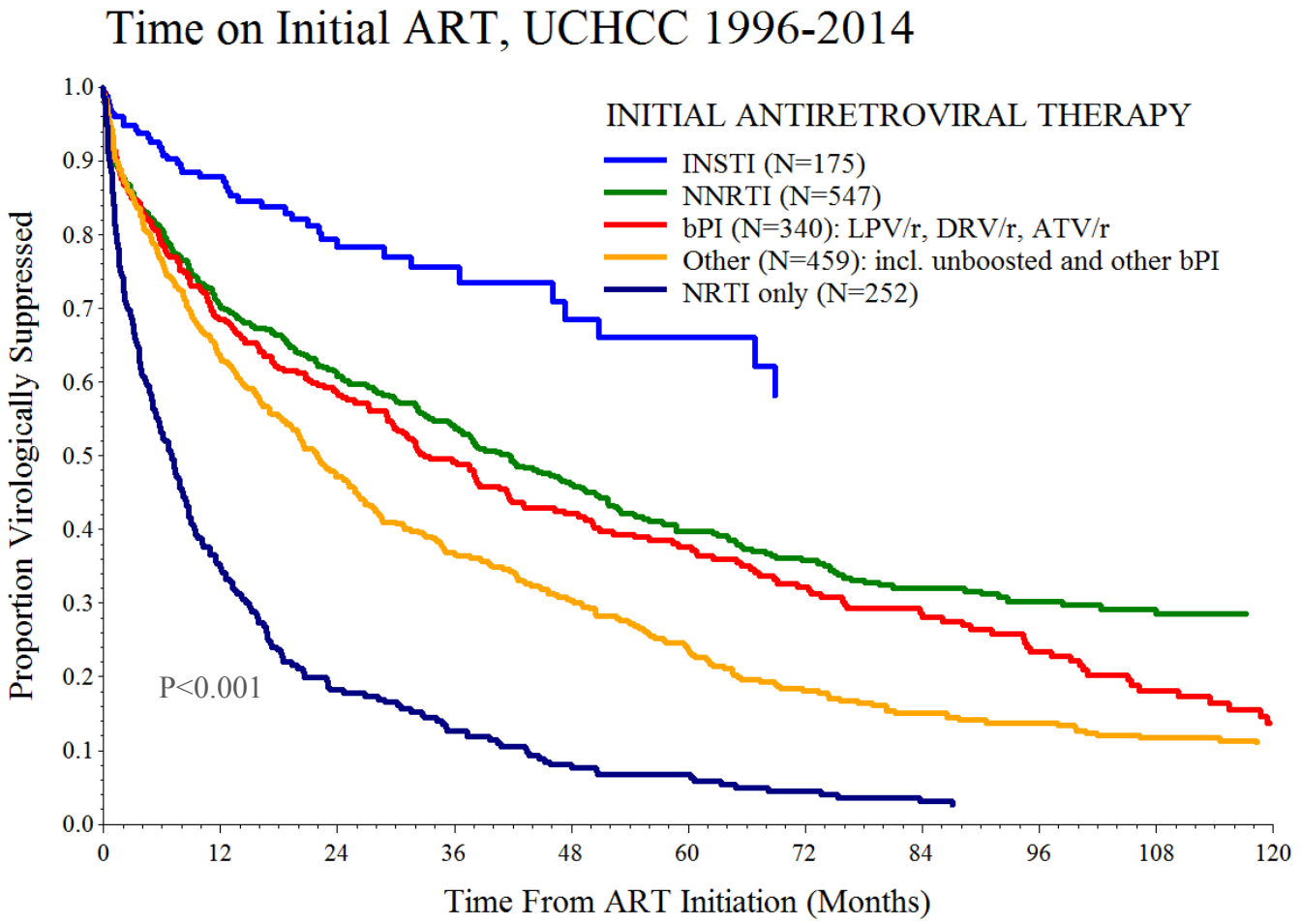
MEAN EFFICACY OF INITIAL REGIMEN CONTINUES TO RISE FROM 77%[1] (2005–2010) TO TODAY'S 48W RESULTS



3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; RAL = raltegravir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate

1. Lee *et al. PLoS ONE* 2014;9:e97482; 2. Wohl *et al.* abstract 113LB presented at CROI 2015; 3. Clotet *et al. Lancet* 2014;383:2222–31; 4. Raffi *et al. Lancet* 2013;381:735–43; 5. Walmsley *et al. N Engl J Med* 2013;369:1807–18; 6. DeJesus *et al. Lancet* 2012;379:2429–38; 7. Sax *et al. Lancet* 2012; 379: 2439–48; 8. Eron Jr *et al. Lancet Infect Dis* 2011;11:907–15; 9. Lennox *et al. Lancet* 2009;374:796–806

Persistence of Initial ART



- **INSTI** hazard ratio: **0,49** (95%CI: 0,35-0,69) for **DC** and **0,70** (95% CI: 0,46-1,06) for **VF** compared to NNRTI. *Davy T, et al. CROI 2017; Abs 465*

Challenging Statements

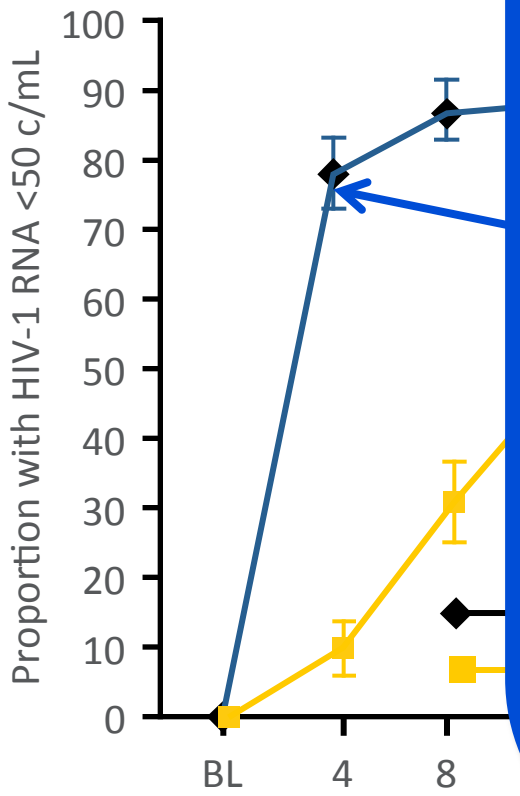
- **"Would not expect that any other regimen show superiority against InSTI".**
  - **NAIVE: InSTI studies. ITT-FDA snapshot 48w analysis**

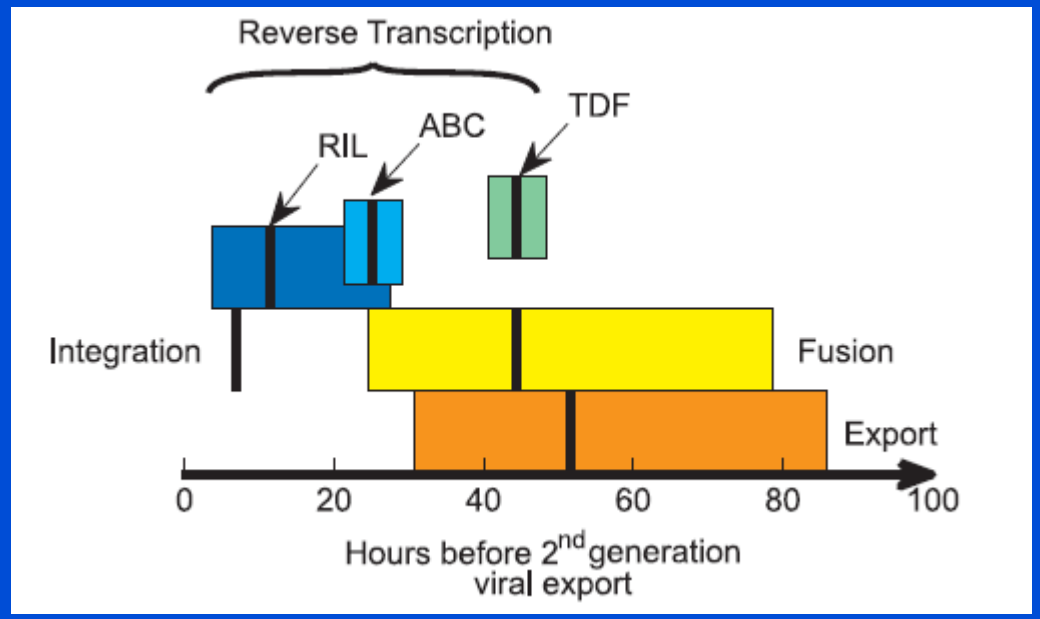
    Superiority hypothesis:

    90% (±2) + 2% DC due to AE/safety + 2-4% VF + 3-5% DC other reasons (lfu) + 6-7% better efficacy >100%.

MATHEMATICALLY IMPOSSIBLE

VIROLO





-Integrase; life cycle. Segadhat A, et al. PNAS 2008

-Active in Monocyte/macrophages. Pollicita M, et al. JAC 2014.

-Deeper phase I VL decay. Gilmore J. PloS comp biol 2013

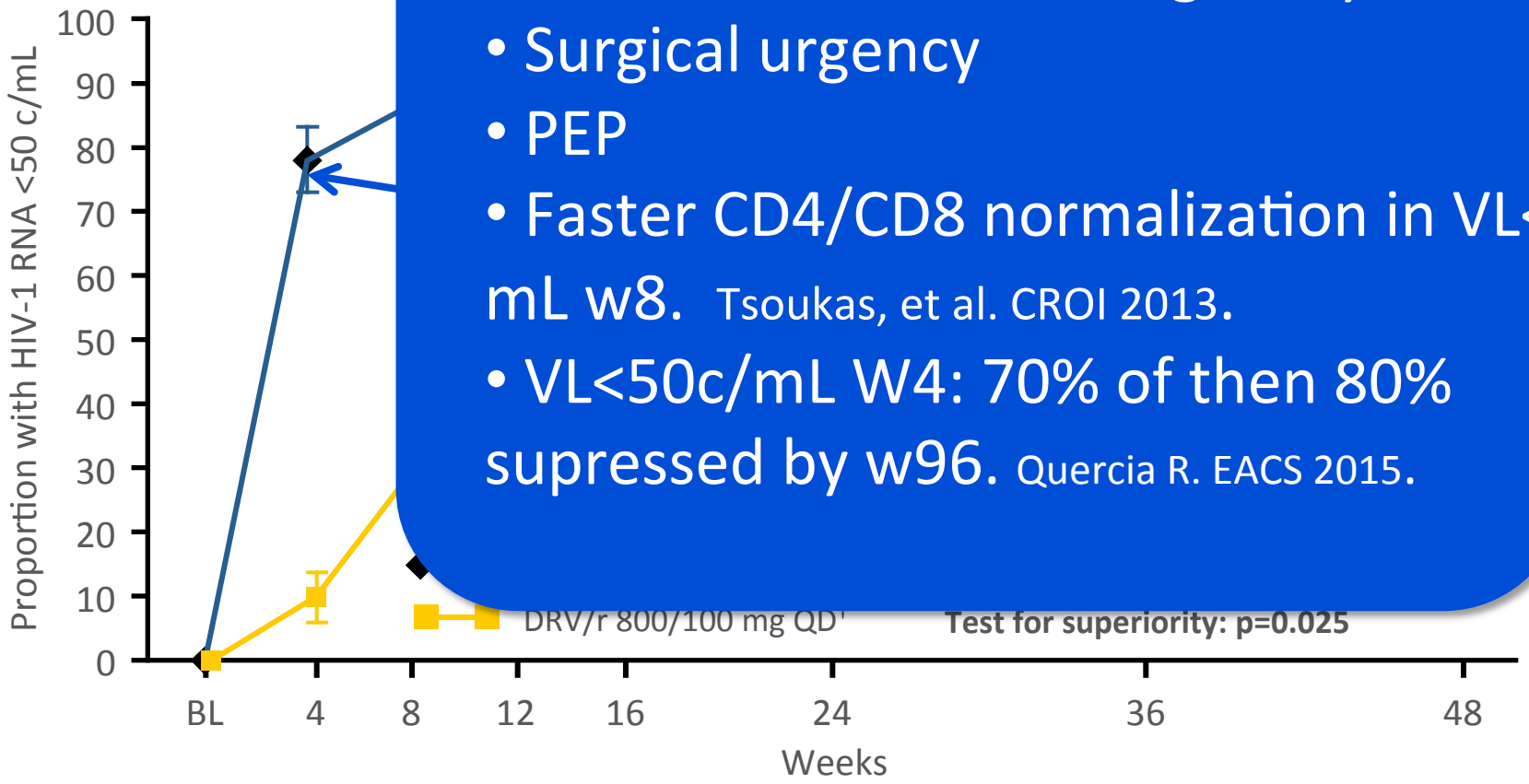
- Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r (difference [95% CI]: 7.4% [1.4–13.3])[2]

*Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI therapy; †plus 2 NRTIs

1. Adapted from Clotet B, et al. Lancet 2014;383:2222–31
2. Clotet B, et al. Lancet 2014;383:2222–31. Supplementary appendix

VIROL

- MDR and Dx late in Pregnancy
- Surgical urgency
- PEP
- Faster CD4/CD8 normalization in VL<5 mL w8. Tsoukas, et al. CROI 2013.
- VL<50c/mL W4: 70% of then 80% supressed by w96. Quercia R. EACS 2015.



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1. Adapted from Clotet B, et al. Lancet 2014;383:2222–31
2. Clotet B, et al. Lancet 2014;383:2222–31. Supplementary appendix

InSTI- Pathogenic Mechanism

- Naives
  - **Better immune-recovery** (CD4 cell count).
    - Substantial and significant improvement in CD4/CD8 ratio.

  - **Substantial and superior reduction in markers of monocyte activation**: **sCD14**; **sCD163 (ALL)** and also (conflicting) on inflammatory markers : IL-6; hsCRP.
    - Compelling data (few exceptions) in several segment of patients.
- SWITCHING
  - Consistency of significant **decreased** in mainly **monocyte** (sCD14) and **inflammatory activation markers** (hsCRP, IL-6). Also changes in D-dimers
  - Large set of studies **(ALL)** involving several patients segments supressed on several ART regimens.

- **Potential Mechanisms:**
  - Monocyte/Macrophages involvement – large pool of cells **(ALL)**
  - Penetration to Tissues/Reservoirs – GALT **(RAL; DTG)**

1. Pollicita M, et al. JAC 2014;69
2. Thompson C, et al. AIDS Rese and Human Retro 2017;33
3. Greener B, et al. JAIDS 2013;64

DOLUTEGRAVIR-BASED REGIMENS: SUPERIOR EFFICACY IN 4 COMPARATIVE STUDIES

Superior efficacy vs 3 ARV classes: NNRTI, boosted PI and INI[1-5]

Treatment-naïve adults

Superior efficacy vs ATRIPLA®
at weeks 48, 96 and 144
SINGLE[1,2*]:
DTG + ABC/3TC† QD
vs ATRIPLA® QD
(N=833)

Superior efficacy vs darunavir/r
at weeks 48 and 96
FLAMINGO[3,4‡]:
DTG 50 mg + 2 NRTIs QD vs DRV/r 800mg/100mg + 2 NRTIs QD
(N=484)

Comparable efficacy vs raltegravir
at weeks 48 and 96
SPRING-2[6,7§]:
DTG 50 mg QD + 2 NRTIs vs RAL 400 mg BID + 2 NRTIs
(N=822)

Superior efficacy vs ATV/r
at week 48 in **ARIA**[11]
DTG / ABC/3TC FDC† QD
vs ATV/r + TDF/FTC FDC
(N=495)

Treatment-experienced adults

Superior efficacy vs raltegravir
up to week 48
SAILING[5‖]:
DTG 50 mg QD + BR vs RAL 400 mg BID + BR
(N=715)

Maintained efficacy vs continuation of current ARV regimen
up to week 24
STRIVING[8¶]: DTG/ABC/3TC QD vs cART (N=551)

Heavily treatment-experienced adults

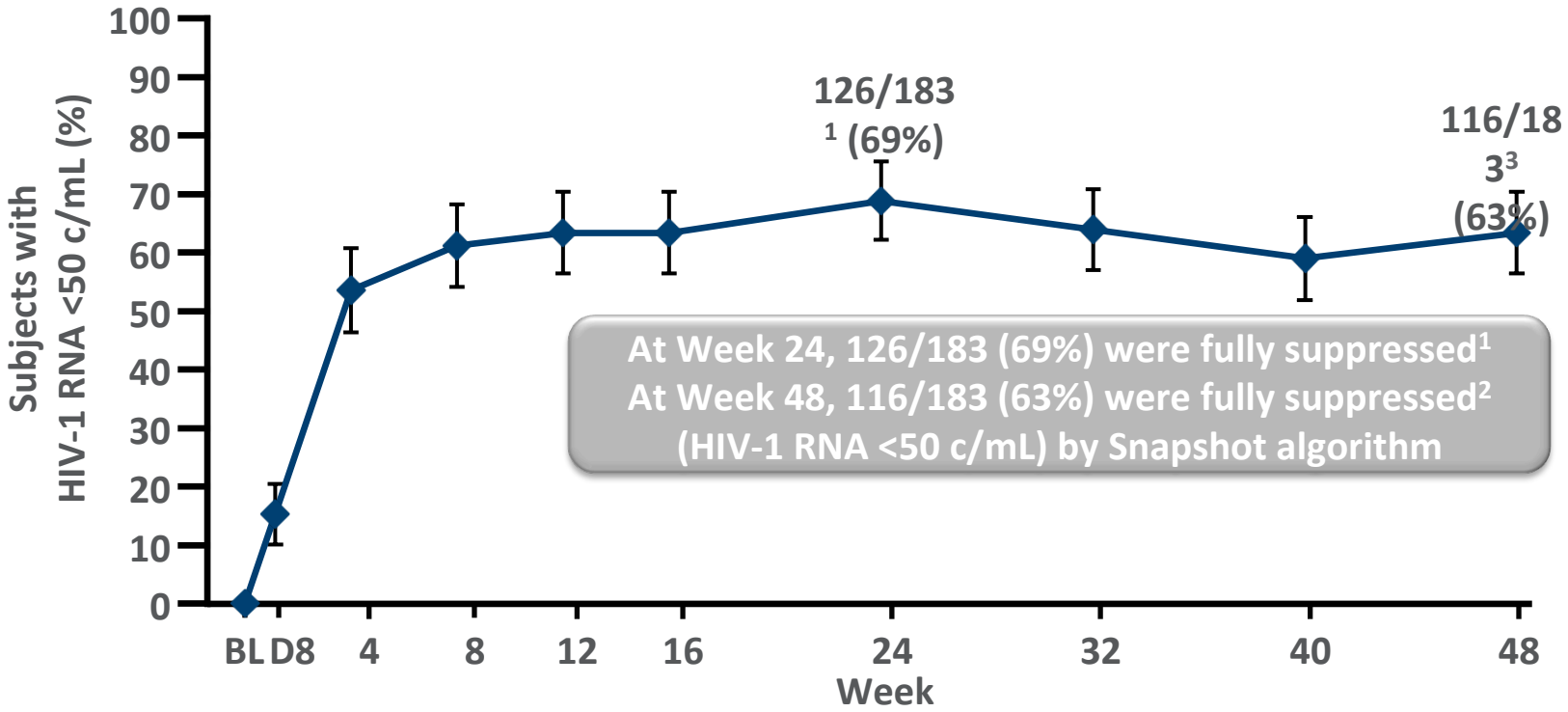
Sustained efficacy
up to week 48
VIKING-3[9,10#]:
DTG 50 mg BID + OBR
(N=183)

Non-comparative
Superior efficacy
Non-inferior

1. Walmsley *et al*. *N Engl J Med* 2013;369:1807-18; 2. Walmsley *et al*. *J Acquir Immune Defic Syndr* 2015;70:515-19; 3. Clotet *et al*. *Lancet* 2014;383:2222-31; 4. Molina *et al*. *Lancet HIV* 2015;2:e127-36; 5. Cahn P *et al*. *Lancet* 2013;382:700-8; 6. Raffi F *et al*. *Lancet* 2013;381:735-43; 7. Raffi *et al*. *Lancet Infect Dis*. 2013;13:927-35; 8. Trottier B *et al*. Presented at: Interscience Conference of Antimicrobial Agents and Chemotherapy; September 17-21, 2015; San Diego, California. Abstract 2015-LB-3271-ASM-ICAAC; 9. Castagna *et al*. *J Infect Dis*. 2014;210:354-62; 10. Vavro *et al*. *Rev Antiviral Ther Infect Dis* 2014;2:Abstract O-10; 11. C. Orrell et al. 21st international AIDS conference, 18-22 July 2016, Durban, South Africa

VIROLOGIC RESPONSE (HIV-1 RNA <50 C/ML) AT WEEK 24 AND WEEK 48 (SNAPSHOT, ITT-E)

- **Day 8 efficacy:** DTG was associated with significant reductions from baseline in HIV-1 RNA: change from baseline: −1.43 $\log_{10}$ c/mL HIV-1 RNA (95% CI: −1.52 to −1.34; p<0.001)[1,2]



- At Week 24,135/183 (74%) achieved HIV-1 RNA <400 c/mL[3]
- At Week 48,125/183 (68%) achieved HIV-1 RNA <400 c/mL[3]

1. Adapted from Castagna A, et al. J Infect Dis 2014;210:354-
2. Nichols G, et al. IAS 2013. Abstract TULBPE19; 3 Vavro CL, et al. EUDRW 2014. Abstract 0_10

VIKING-3

WEEK 24 AND WEEK 48 RESPONSE BY BASELINE INTEGRASE MUTATIONS*

Derived IN mutation group at BL	N	HIV-1 RNA <50 c/mL at Week 24,[1] %	HIV-1 RNA <50 c/mL at Week 48,[2] %
Total	183	69	63
No Q148	126	79	71
Q148 + 1 secondary mutation†	36	58	56
Q148 + ≥2 secondary mutations†	20	24	29

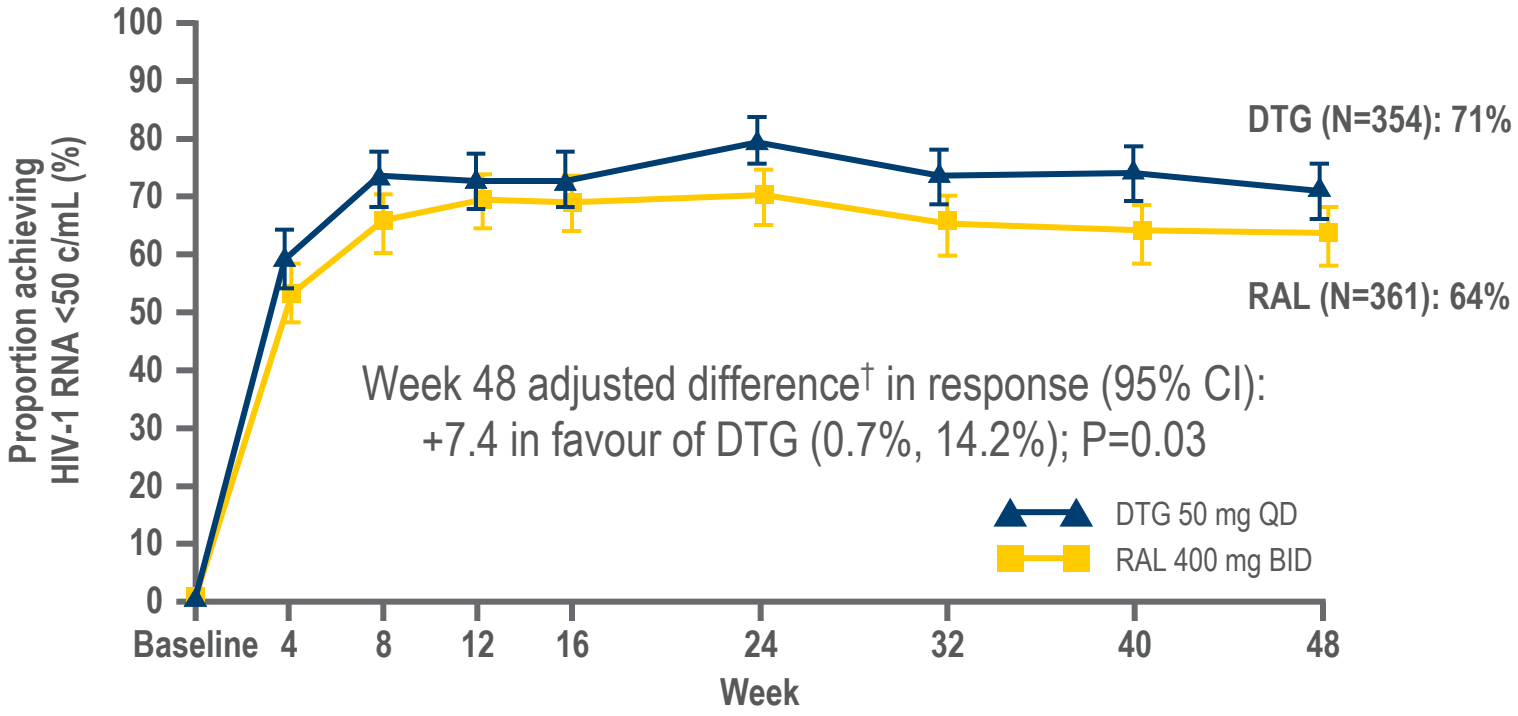
- Antiviral response was sustained through Week 48[2]
- Difference in response rates between Week 24 and Week 48 was primarily for non-virologic reasons[2‡]

*ITT-E, Snapshot algorithm
†Key secondary mutations were G140A/C/S, L74I and E138A/K/T
‡5 subjects became responders and 15 stopped being responders after Week 24; 4/15 subjects had HIV-1 RNA >50 c/mL at Week 48 and non-compliance; 11/15 subjects re-supressed after Week 48, discontinued for non-compliance, withdrew consent while suppressed, or changed background ART while suppressed[3]

1. Castagna A, et al. J Infect Dis 2014;210:354-
2. Vavro CL, et al. EUDRW 2014. Abstract 0_10
3. ViiV data on file (VIKING-3 48-week Clinical Study Report)

PROPORTION OF SUBJECTS WITH HIV-1 RNA <50 C/ML (SNAPSHOT*)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 48



- 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)

Adapted from Cahn P, et al. Lancet 2013;382:700–8

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DTG 50 mg BID + OBR
(N=183)

Non-comparative
Superior efficacy
Non-inferior

Superior response in high VL (>5 logHIV RNA): 78 vs 63%

1. Walmsley *et al*. *N Engl J Med* 2013;369:1807-18; 2. Walmsley *et al*. *J Acquir Immune Defic Syndr* 2015;70:515-19; 3. Clotet *et al*. *Lancet* 2014;383:2222-31; 4. Molina *et al*. *Lancet HIV* 2015;2:e127-36; 5. Cahn P *et al*. *Lancet* 2013;382:700-8; 6. Raffi F *et al*. *Lancet* 2013;381:735-43; 7. Raffi *et al*. *Lancet Infect Dis*. 2013;13:927-35; 8. Trottier B *et al*. Presented at: Interscience Conference of Antimicrobial Agents and Chemotherapy; September 17-21, 2015; San Diego, California. Abstract 2015-LB-3271-ASM-ICAAC; 9. Castagna *et al*. *J Infect Dis*. 2014;210:354-62; 10. Vavro *et al*. *Rev Antiviral Ther Infect Dis* 2014;2:Abstract O-10; 11. C. Orrell et al. 21st international AIDS conference, 18-22 July 2016, Durban, South Africa

No resistance to DTG-based regimens in treatment-naive studies

	SINGLE (144 weeks)[1]		SPRING-2 (96 weeks)[2]		FLAMINGO (96 weeks)[3]		ARIA (48 weeks)[5]	
	DTG 50 mg + ABC/3TC QD (N=414)	EFV/TDF/FTC§ QD (N=419)	DTG 50 mg QD + 2 NRTIs (N=411)	RAL 400 mg BID + 2 NRTIs (N=411)	DTG 50 mg QD + 2 NRTIs (N=242)	DRV/r 800/100 mg QD + 2 NRTIs (N=242)	DTG/ABC/3TC 50/600/300 mg QD (N=248)	ATV/r 300/100 mg QD + TDF/FTC (N=247
Patients with PDVF, n (%)	39 (9)	33 (8)	22 (5)	29 (7)	2 (<1)	4 (2)	6 (2)	4 (2)
NRTI-resistant mutations	0	1 (K65K/R)	0	4/19 (21)*	0	0	0**	1
NNRTI-resistant mutations	0	6‡	–	–	–	–	-	-
INI-resistant mutations	0§	0	0	1/19 (5)†	0	–	0	-
PI-resistant mutations	0	0	–	–	–	0	-	0

*One participant had NRTI-resistance mutation M184M/I; one participant had NRTI-resistance mutation A62A/V; and one participant had NRTI-resistance mutation M184M/V.
†One participant had INI-resistance mutations T97T/A, E138E/D, V151V/I, and N155H, and NRTI-resistance mutations A62A/V, K65K/R, K70K/E, and M184V
‡K101E (n=1); K103N (n=1); K103K/N (n=2); K103N and G190G/A (n=1); and G190G/A (n=1). §E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility. **Two subjects receiving DTG/ABC/3TC had either K219K/Q (TAM) or E138E/G at CVW with no reduced susceptibility to DTG/ABC/3TC. K219K/Q is not selected for by ABC or 3TC nor does it affect their fold change

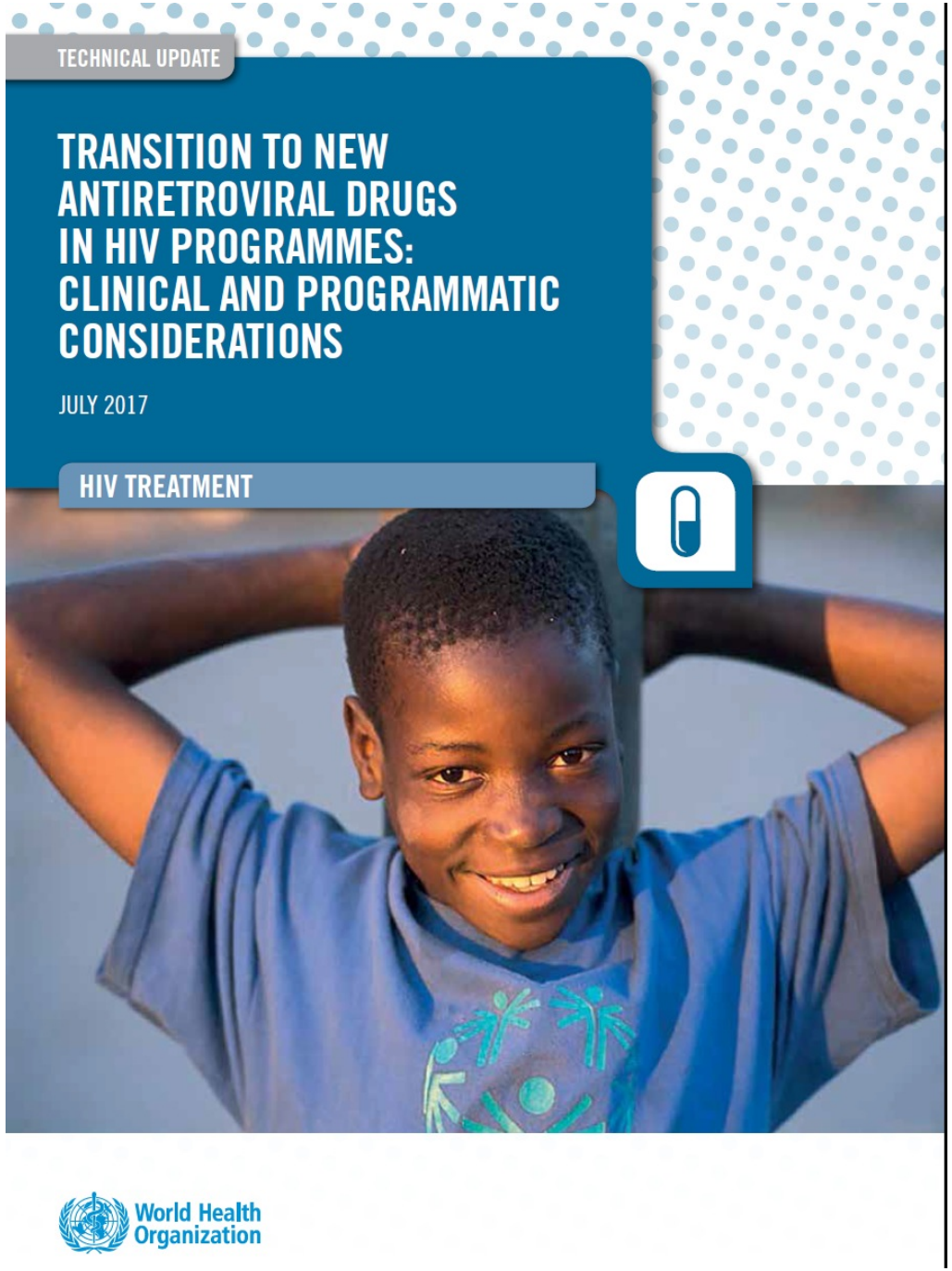
- Backbone was investigator selected in both trials
  - 41% and 33% received DTG with ABC/3TC in SPRING-2 and FLAMINGO, respectively[2,3]

BID, twice daily; DRV/r, darunavir/ritonavir; DTG, dolutegravir; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PDVF, protocol-defined virological failure; PI, protease inhibitor; QD, once daily. $\S$EVFV/TDF/FTC fixed dose combination is not approved in Korea

Adapted from:
1. Adapted from: Walmsley SL et al. CROI 2014; Poster 543;
2. Raffi F et al. Lancet Infect Dis 2013;13:927-35;
3. Molina JM et al. HIV Drug Therapy Glasgow; 2014; presentation O153;
4. Raffi F et al. Lancet 2013;381:735-43
5. Orrell et al. AIDS 2016; Durban, South Africa. Slides THAB0205LB

What are the desired characteristics of an IDEAL cART regimen?

- ✓ Highly Efficacious
- ✓ Safe and Well Tolerated
- ✓ High Genetic Barrier to Resistance
- ✓ Convinience
- ✓ DDI- no/few



http://www.who.int/hiv/pub/en

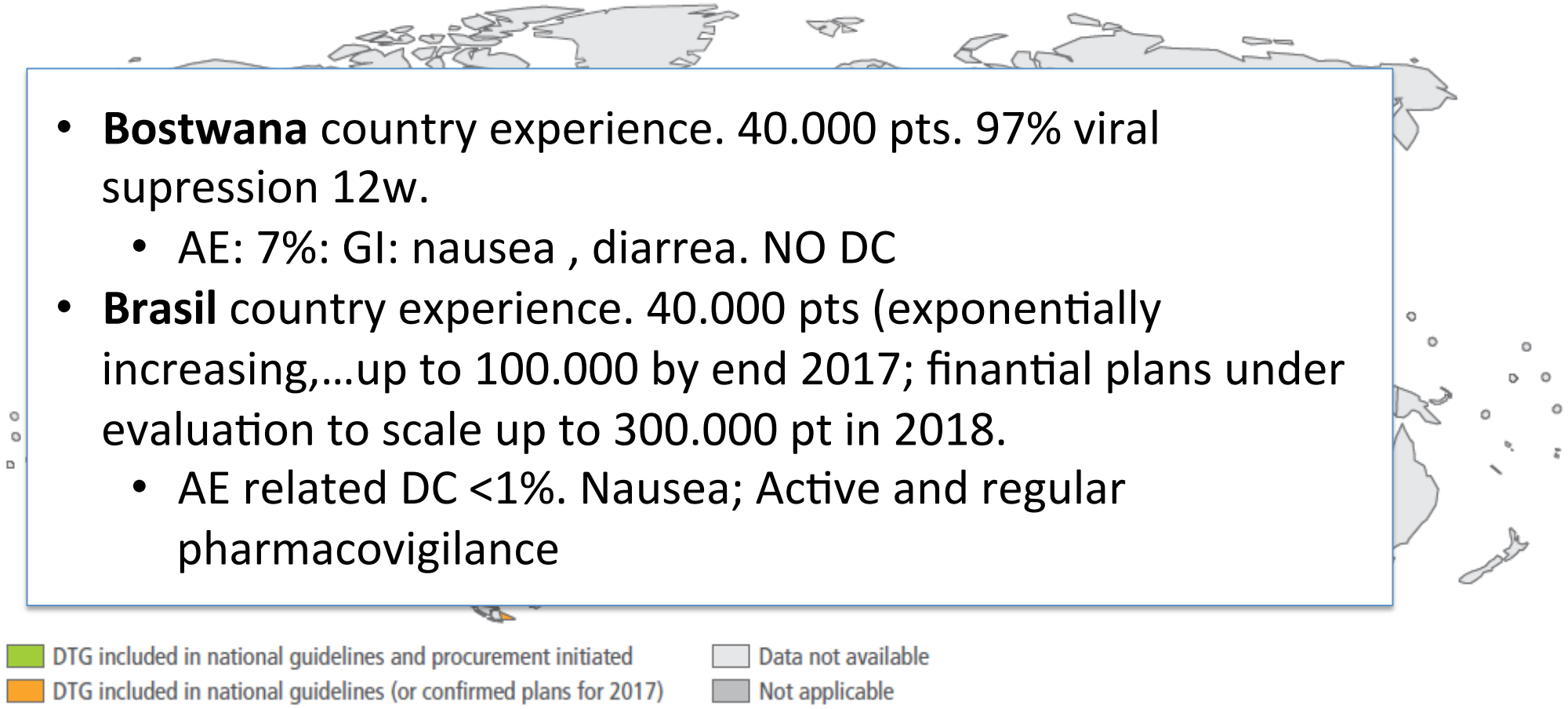
Table 1. Information and guidance on new ARV drugs according to the 2016 WHO consolidated ARV guidelines

New ARV option	Adults and adolescents	Pregnant women	Children	HIV-associated TB
Efavirenz, 400 mg (EFV400)	Recommended as alternative first-line option	Limited efficacy data (ongoing pharmacokinetic studies)	Dose reduction in children not needed (already pharmacokinetically adjusted)	No clinical data (ongoing pharmacokinetic studies)
Dolutegravir (DTG)	Recommended as alternative first- and third-line option	Used only if benefits outweigh the risk Limited efficacy and safety data (ongoing pharmacokinetic and clinical studies)	Recommended as third-line (approved for children >6 years old)	No clinical data (ongoing pharmacokinetic studies) Increased dose may be needed with use of rifampicin
Darunavir/ritonavir (DRV/r)	Recommended as alternative second- and third-line option (dose adjustment needed in third-line ART)	As recommended for adults but limited use in low- and middle-income countries	Recommended as third-line ART (approved for children >3 years old)	Not recommended with concomitant use of rifampicin
Raltegravir (RAL)	Recommended as alternative second- and third-line option	As recommended for adults but limited use in low- and middle-income countries	Recommended as second- and third-line option	Increased dose needed with concomitant use of rifampicin
Tenofovir alafenamide fumarate (TAF)*	Not recommended	No data available	No data available	No data available

http://www.who.int/hiv/pub/en

WHO – Guidelines
Policy Implementation. DTG country report

Figure 1. Adoption of DTG as a first-line option in low- and middle-income countries, June 2017



- **Bostwana** country experience. 40.000 pts. 97% viral supression 12w.
  - AE: 7%: GI: nausea , diarrea. NO DC
- **Brasil** country experience. 40.000 pts (exponentially increasing,…up to 100.000 by end 2017; finantial plans under evaluation to scale up to 300.000 pt in 2018.
  - AE related DC <1%. Nausea; Active and regular pharmacovigilance

Source: Global AIDS Monitoring [online database] (*6*).

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Maintained efficacy vs continuation of current ARV regimen
up to week 24
STRIVING[8¶]: DTG/ABC/3TC QD vs cART (N=551)

Second-line:Superior efficacy vs lopinavir/r
up to week 24
DAWNING[12‖]:
82% vs 69%
DTG 50 mg QD + OBR vs LPV/r BID + OBR
(N=624)

Heavily treatment-experienced adults

Sustained efficacy
up to week 48
VIKING-3[9,10#]:
DTG 50 mg BID + OBR
(N=183)

Non-comparative

Superior efficacy

Non-inferior

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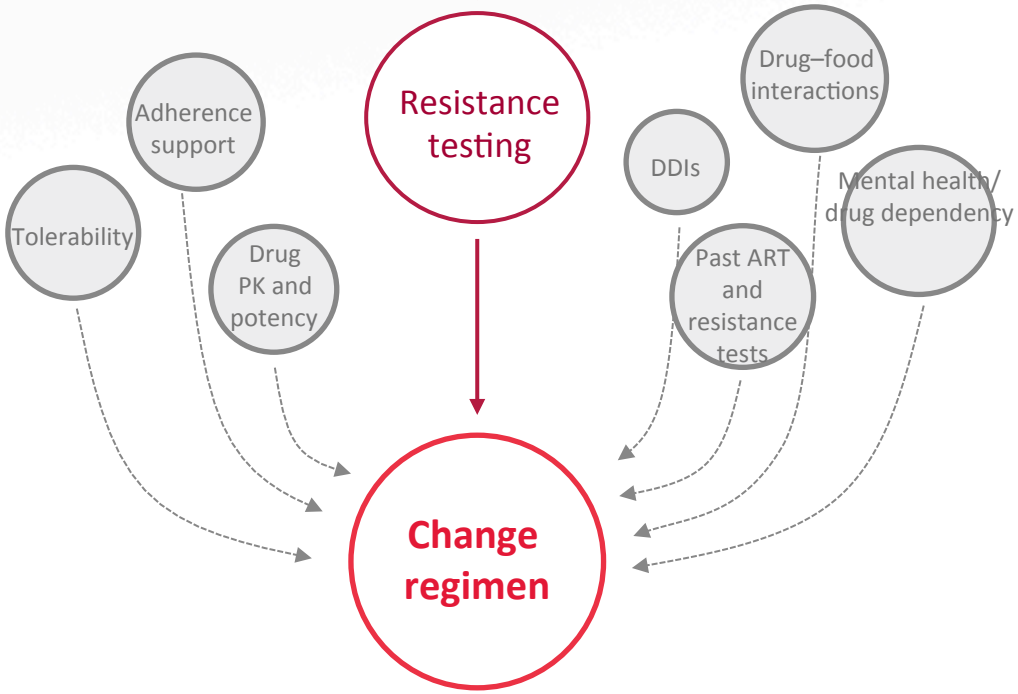
DHHS recommends genotypic resistance testing prior to second-line regimen switch, WHO does not

IAS–USA International Antiviral Society–USA

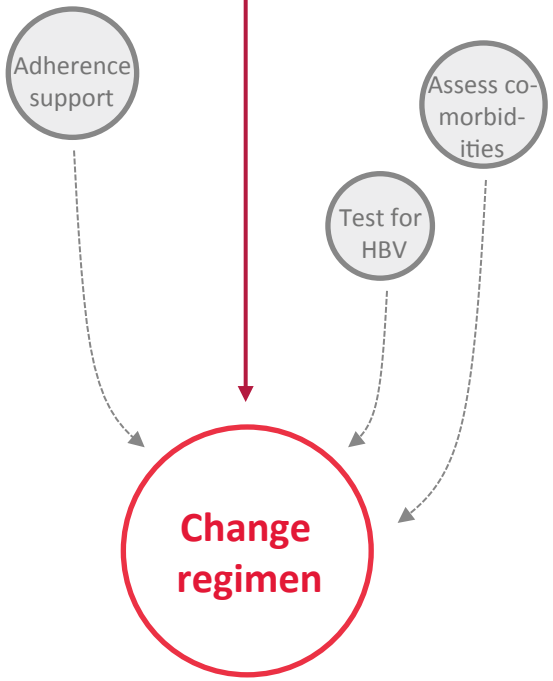
EACS European AIDS Clinical Society

World Health Organization

Failure: **HIV viral load >200 copies/mL** (EACS >50 copies/mL)



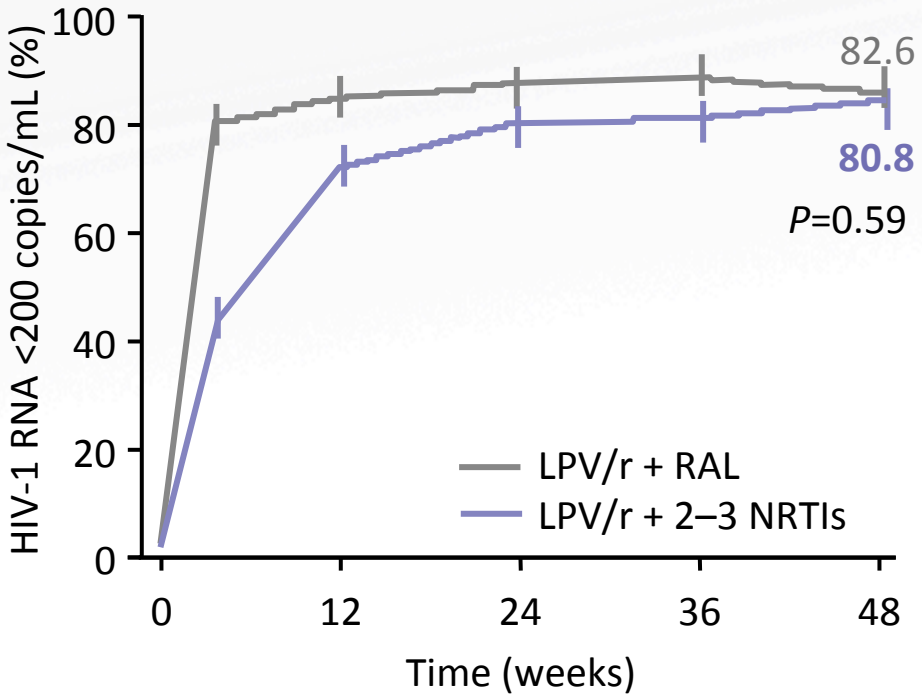
Failure: **HIV viral load >1000 copies/mL**



1. Günthard HF *et al. JAMA* 2016;316:191–210; 2. DHHS guidelines 2016;
3. EACS HIV guidelines 2017; 4. WHO consolidated guidelines 2016

DDI, drug–drug interaction;
HBV, hepatitis B virus; PK, pharmacokinetics

SECOND-LINE: Non-inferiority of LPV/r + RAL versus LPV/r + NRTIs at Week 48



Similar high levels of virological suppression with each strategy in primary mITT analysis

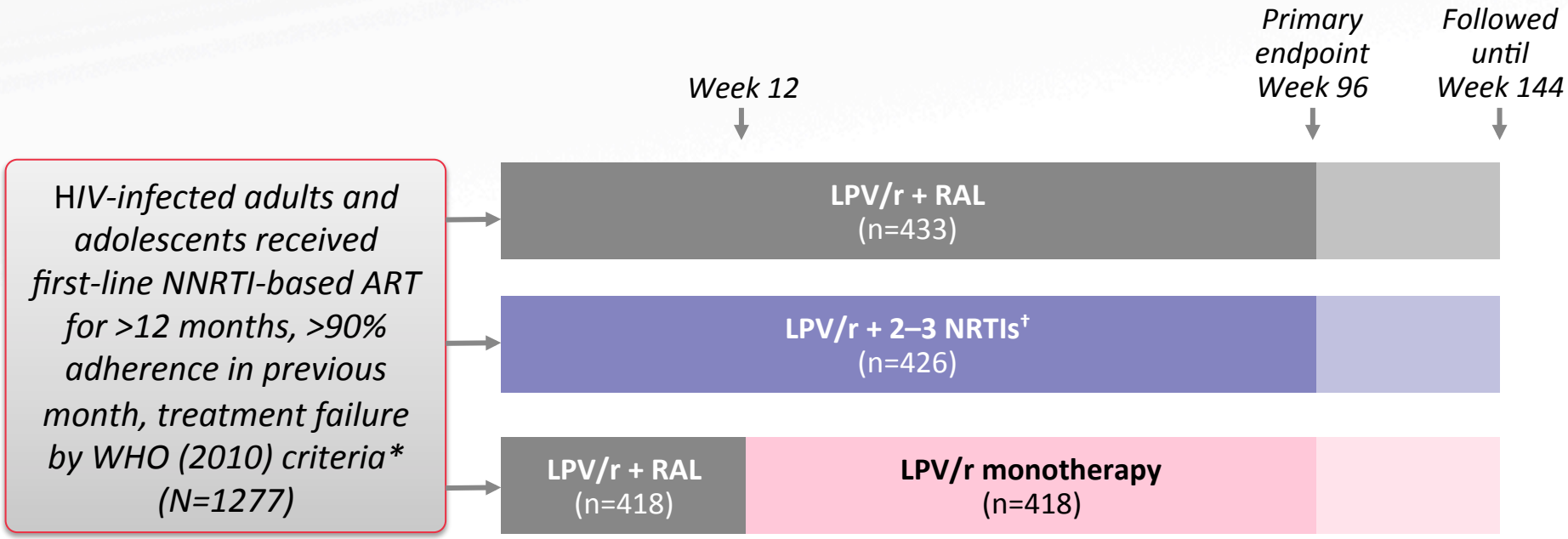
- **At 48 weeks: 219/271 (81%)** patients in the NRTI group had viral load <200 copies/mL compared with **223/270 (83%)** in the RAL group (difference 1.8%, 95% CI –4.7 to 8.3), fulfilling criteria for **non-inferiority**
- **Median time to reach primary endpoint: 12.0 weeks** (IQR 4.0–23.1) in the control group and **4.1 weeks** (IQR 4.0–7.6) in the RAL group (HR 1.41, 95% CI 1.2–1.7; *P*=0.0001)
- RAL was associated with observed **faster initial reduction** in plasma viral load but no difference in clinical outcomes

SECOND-LINE study group. *Lancet* 2013;381:2091–2099

CI, confidence interval; HR, hazard ratio; mITT, modified intention to treat

EARNEST: Study design

Randomised, controlled, open-label, Phase III trial

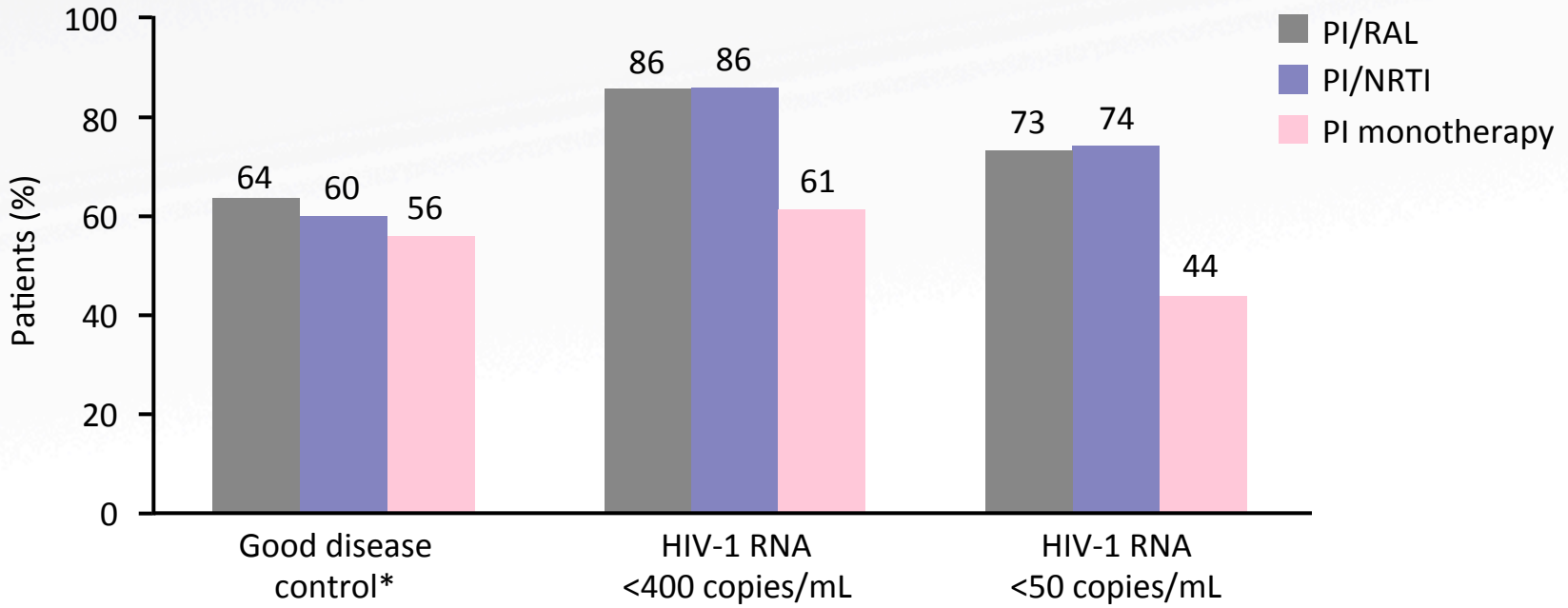


- Baseline demographics (median): HIV-1 RNA 69,782 copies/mL; CD4+ 71 cells/mm^3; time on ART 4 years

Paton NI *et al. N Engl J Med* 2014;371:234–247

*Including clinical, CD4+ cell count (HIV-1 RNA confirmed), or virological criteria;
†Selected by physician according to local standard of care

EARNEST: Non-inferiority of LPV/r + RAL versus LPV/r + NRTIs at week 96



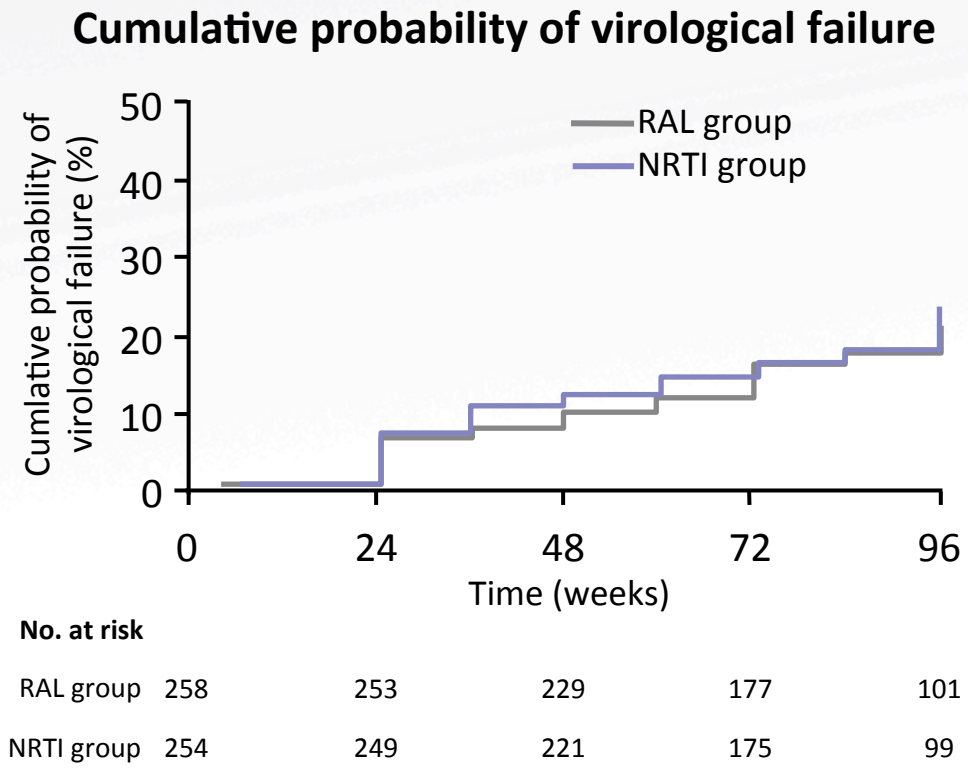
- **No significant difference** in 96-week resistance rates between LPV/r + NRTIs and LPV/r + RAL (**although borderline CD4 advantage with RAL** – 144-week follow-up to assess clinical benefit and cost effectiveness)
- **Similar rates of grade 3/4 AEs** across treatment arms (range: 22–24%)
- **PI monotherapy is inferior to PI/NRTI:** Lower viral load suppression and more resistance; PI monotherapy is unsuitable for public health approach
- PI/NRTI had excellent outcomes (**90% WHO grade 4 event-free survival**) and viral load suppression (**86% <400 copies/mL**) at week 96, even in advanced first-line failure (minus resistance testing/viral load monitoring)

*'Good disease control' at week 96 defined as patient alive, no new WHO grade 4 events from weeks 0 to 96, *and* CD4+ cell count >250 cells/mm^3, *and* HIV-1 RNA <10,000 *or* >10,000 copies/mL without PI resistance

AE, adverse event

Paton NI *et al. N Engl J Med* 2014;371:234–247

SELECT ACTG A5273: Non-inferiority of LPV/r + RAL versus LPV/r + NRTIs at week 96



Similar high levels of virological suppression with each strategy in primary mITT analysis

- **Cumulative probability of virological failure at week 48: 10.3%** (95% CI 6.5–14.0) for RAL and **12.4%** (95% CI 8.3–16.5) for NRTIs
- Weighted analysis showed a small difference of **–3.4% (95% CI –8.4 to 1.5) favouring RAL**, indicating **non-inferiority** (not superiority) to NRTIs
- **No difference observed** between the probability of virological failure between groups by any of the stratification factors
- **Significant**, albeit modest, **increases in concentrations of total cholesterol**, LDL cholesterol, and triglycerides were noted in the RAL group

ACTG A5273 study group. *Lancet HIV* 2016;3:e247–e258

LDL, low-density lipoprotein

SELECT ACTG A5273: Virological failure during follow-up and emergent resistance data

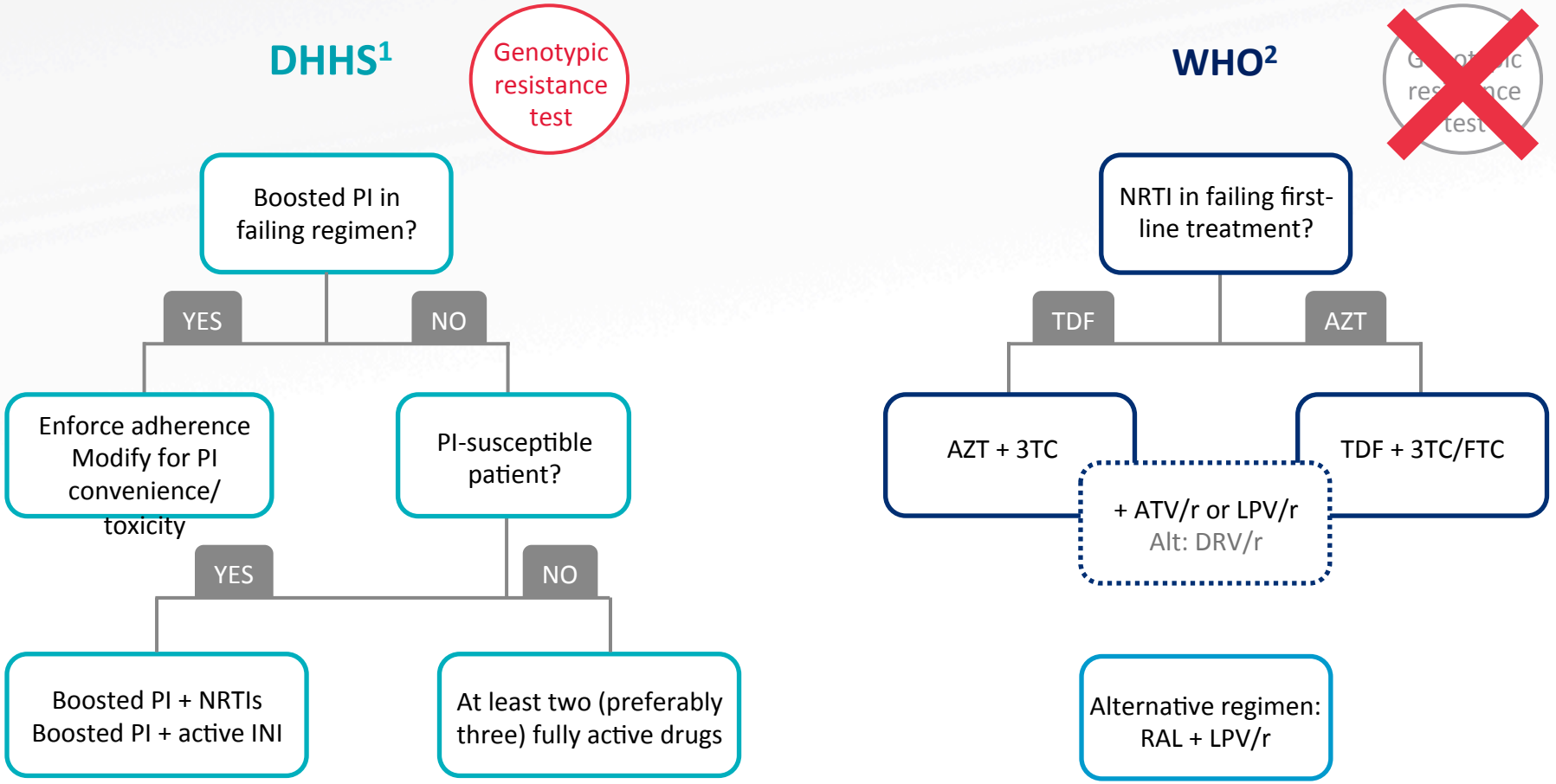
	LPV/r + **RAL** n=258	LPV/r + **2–3 NRTIs** n=254*
Protocol-defined virological failure (PDVF), n	46	50
Any mutation, n (%)[†]	39 (85)	45 (90)
New NRTI mutations, n/N (%)		
M184V/I	1/39 (3)	1/45 (2)
K65R	0	0
TAMS	0	4/45 (9)
Q151M	0	0
T69N	0	1/45 (2)
Major protease inhibitor mutations, n/N (%)		
M46I	0	3/45 (7)
L76V	0	2/45 (4)
V82A	0	2/45 (4)
Integrase mutations, n/N (%)		
T66A	1/39 (3)	0
T97A	3/39 (8)	0
Y143C/R	2/39 (5)	0
N155H	6/39 (15)	0

Codon mixtures are counted as mutant

ACTG A5273 study group. *Lancet HIV* 2016;3:e247–e258

*Not available for one participant who did not start treatment in the NRTI arm;
[†]Number of participants with paired study entry and failure genotypes

DHHS and WHO have different approaches to selection of a second-line regimen



DHHS guidelines base second-line regimen choice on resistance testing results, emphasising choice of active drugs. WHO recommendations centre on NRTI cycling, with no requirement for resistance testing

1. DHHS guidelines 2016;
2. WHO consolidated guidelines 2016

WHO recommends simple, fixed-dose combinations of NRTIs and PI/r for second-line treatment

Preferred approach: NRTI backbone as a fixed-dose combination

Strong recommendation

Boosted PI: Heat-stable fixed-dose combinations of ATV/r and LPV/r

Strong recommendation

Boosted PI alternative: Heat-stable fixed-dose combinations of DRV/r

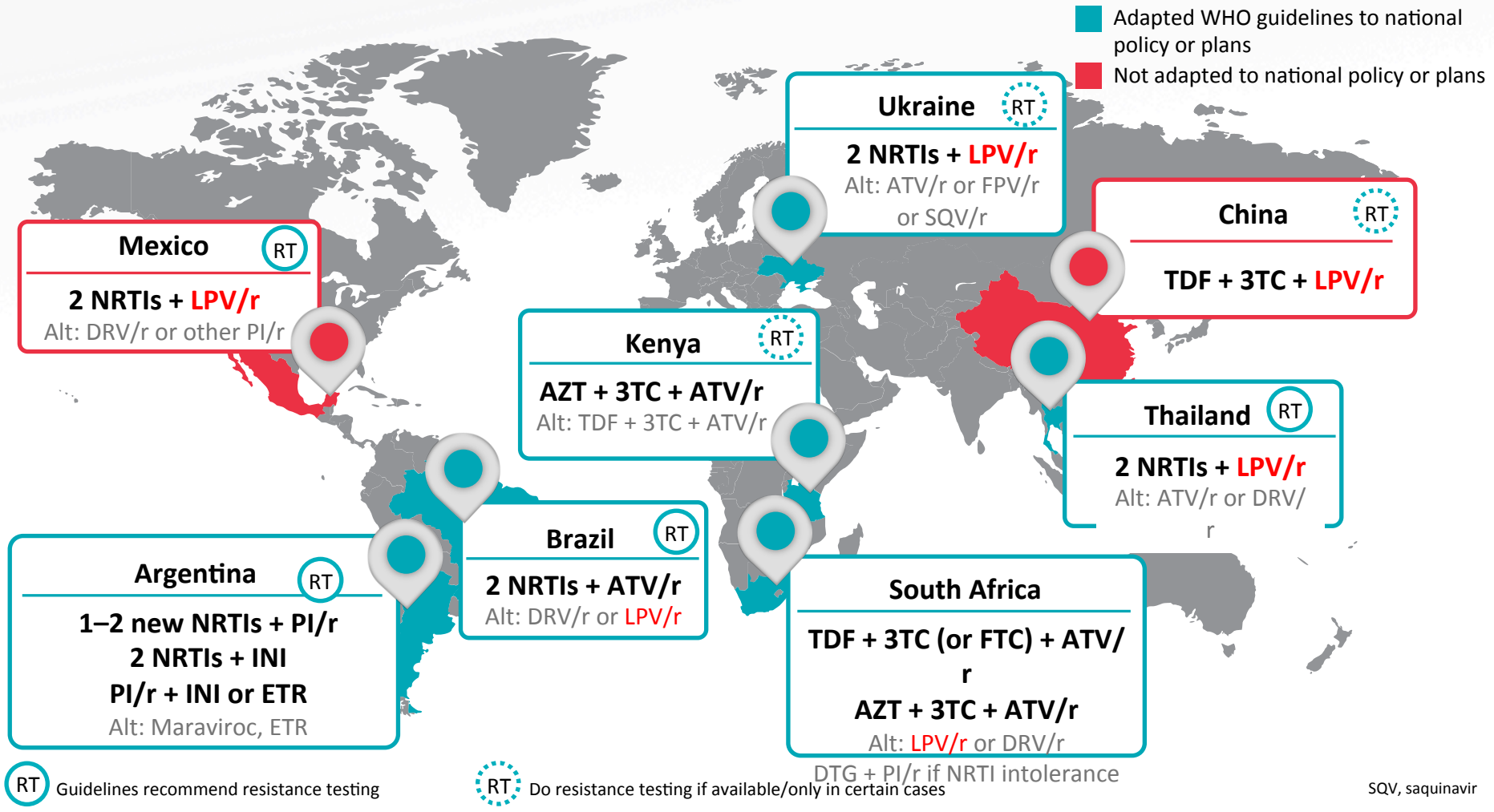
Conditional recommendation

Alternative regimen: RAL + LPV/r

Conditional recommendation

Majority of guidelines recommend LPV/r or ATV/r with two NRTIs for second-line treatment

Majority of guidelines in low- and middle-income settings recommend 2 NRTIs + PI/r, whether or not resistance testing is available



RT Guidelines recommend resistance testing

RT Do resistance testing if available/only in certain cases

SQV, saquinavir

ETV (no PI) 2nd line rescue regimen showed high rate of viral failure

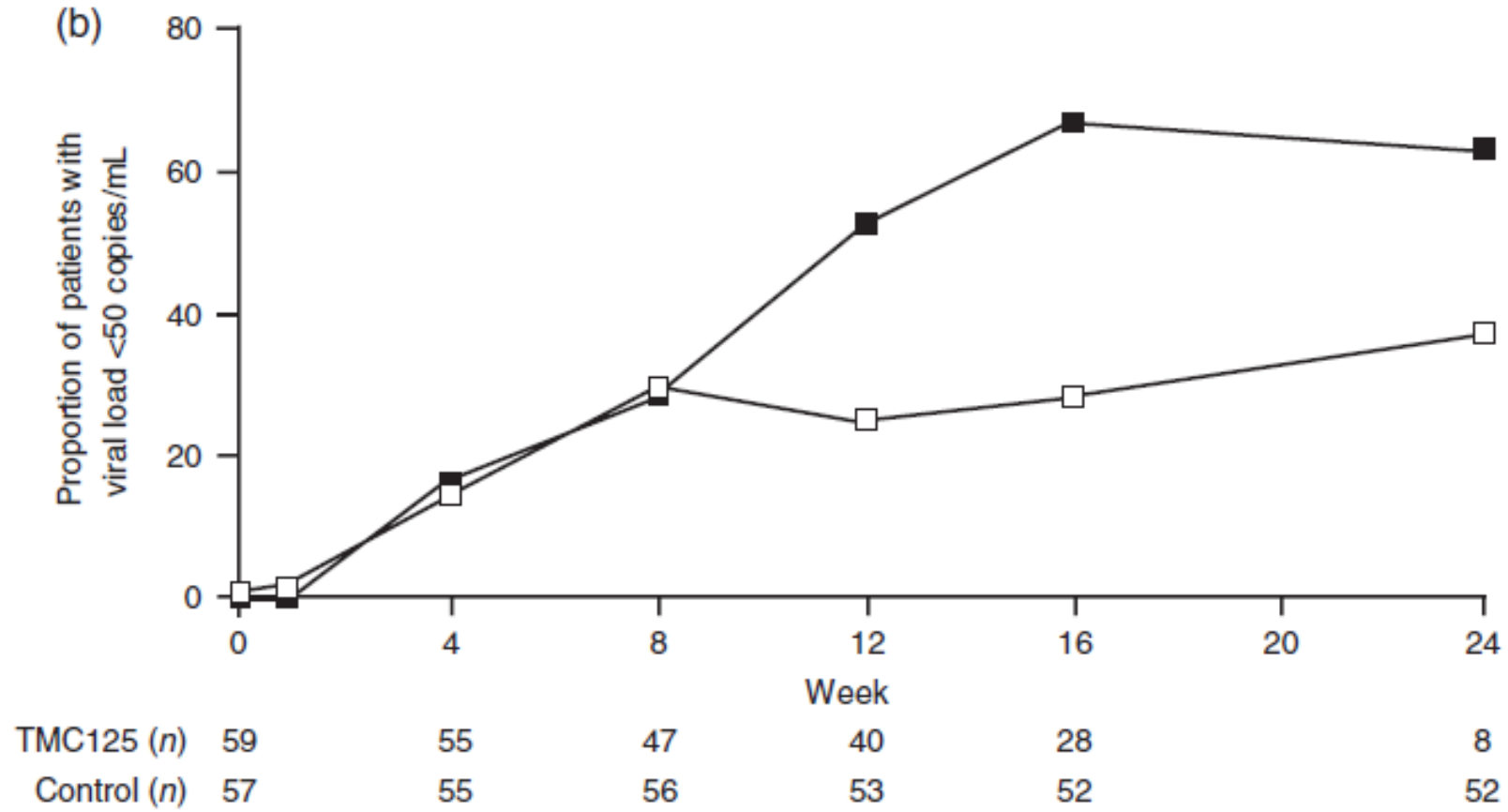


Fig. 3 Virological responses from baseline up to week 24 (observed data). (a) Mean change from baseline in plasma viral load. (b) Proportion of patients with viral load <50 copies/mL. bid, twice a day; SE, standard error.

Ruxrungtham X, et al. HIV Medicine 2008;9:883

Superior Efficacy of Dolutegravir (DTG) Plus 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Compared With Lopinavir/Ritonavir (LPV/RTV) Plus 2 NRTIs in Second-Line Treatment: Interim Data From the DAWNING Study

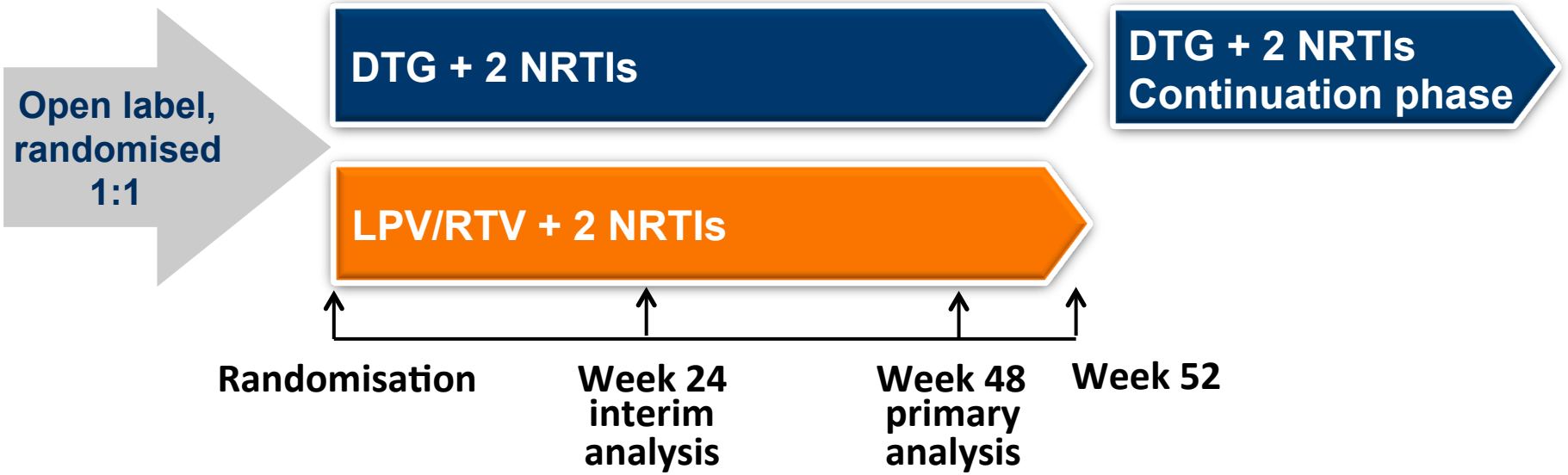
Michael Aboud,[1] Richard Kaplan,[2] Johannes Lombaard,[3] Fujie Zhang,[4] José Hidalgo,[5] Elmira Mamedova,[6] Marcelo Losso,[7] Ploenchan Chetchotisakd,[8] Jörg Sievers,[1] Dannae Brown,[9] Judy Hopking,[10] Mark Underwood,[11] Maria Claudia Nascimento,[1] Martin Gartland,[11] Kimberly Smith[11]

[1]ViiV Healthcare, Brentford, UK; [2]Desmond Tutu HIV Foundation, Cape Town, South Africa; [3]Josha Research, Bloemfontein, South Africa; [4]Beijing Ditan Hospital, Beijing, China; [5]VÍA LIBRE, Lima, Peru; [6]Kiev AIDS Centre, Kiev, Ukraine; [7]Hospital J M Ramos Mejía, Buenos Aires, Argentina; [8]Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand; [9]ViiV Healthcare, Abbotsford, Australia; [10]GlaxoSmithKline, Stockley Park, UK; [11]ViiV Healthcare, Research Triangle Park, NC, USA

9th IAS Conference on HIV Science; July 23-26 2017; Paris, France

Study Design

Open-label randomised noninferiority phase IIIb study



- **Key eligibility criteria:** on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥400 c/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 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

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

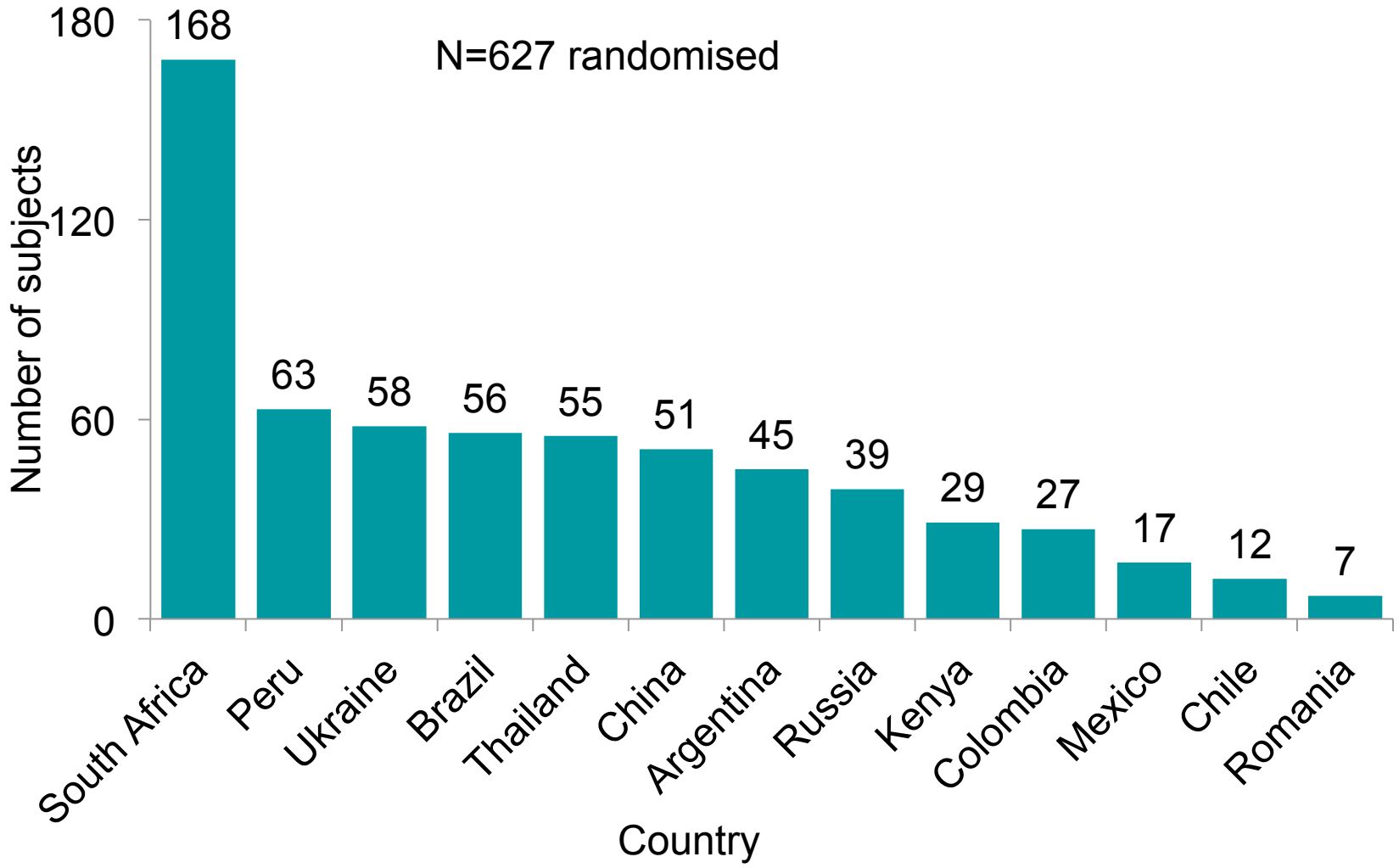
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

IDMC Recommendation

- The IDMC completed 2 of 3 pre-planned analyses, and the study continued according to the study protocol
- Following their second pre-planned analysis, the IDMC conducted an ad hoc review of Week 24 data and large subsets of data from Weeks 36 and 48
- The IDMC recommended discontinuation of the LPV/RTV arm because of differences in rates of virologic nonresponse (FDA snapshot) and increasing differences in rates of protocol-defined virologic failure (PDVF) favouring the DTG arm.
- The study protocol has been amended to allow ongoing LPV/RTV subjects to switch to the DTG arm

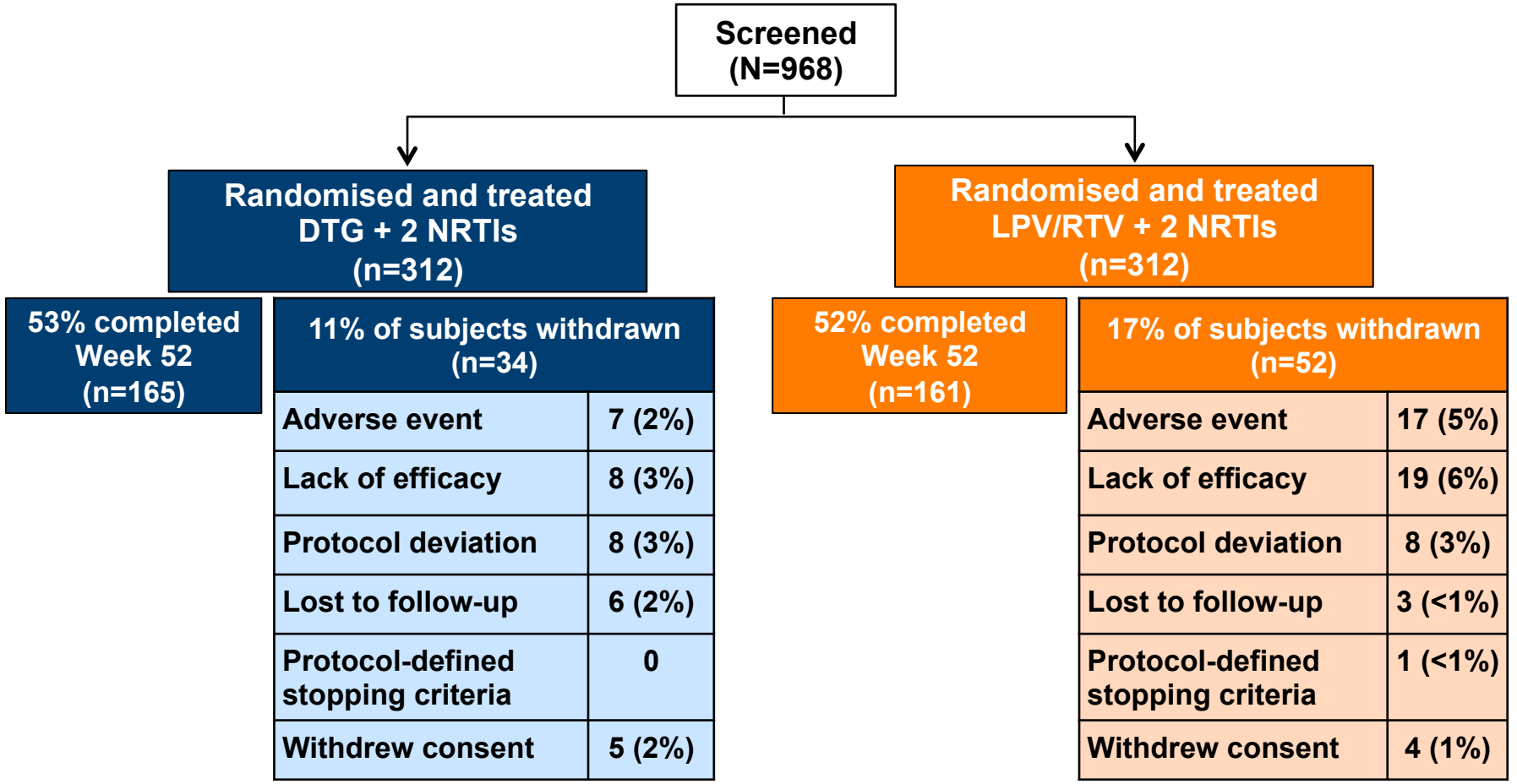
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

Global Enrolment



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

Study Disposition



5 DTG subjects (2%) and 2 LPV/RTV subjects (<1%) became pregnant during the randomised phase and were withdrawn from the study.

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

Demographics and Baseline Characteristics

	DTG + 2 NRTIs (n=312)	LPV/RTV + 2 NRTIs (n=312)
Age, median (range), years	37.0 (19-64)	37.0 (18-72)
Female, n (%)	116 (37)	103 (33)
Race/Ethnicity, n (%)		
African heritage	130 (42)	112 (36)
American Indian	42 (13)	53 (17)
White	90 (29)	91 (29)
Asian	50 (16)	56 (18)
Hepatitis B, n (%)	13 (4)	16 (5)
Hepatitis C, n (%)	25 (8)	25 (8)
CDC category, n (%)		
C: AIDS	106 (34)	95 (30)
HIV-1 RNA, mean, log c/mL	4.21	4.22
>100,000 c/mL, n (%)	70 (22)	63 (20)
CD4+ cell count, cells/mm^3		
<200, n (%)	166 (53)	151 (48)
Duration of first antiretroviral regimen, mean, months	37	35
Prior therapy agent, n (%)		
EFV	242 (78)	242 (78)
TDF	181 (58)	186 (60)
AZT	89 (29)	89 (29)

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

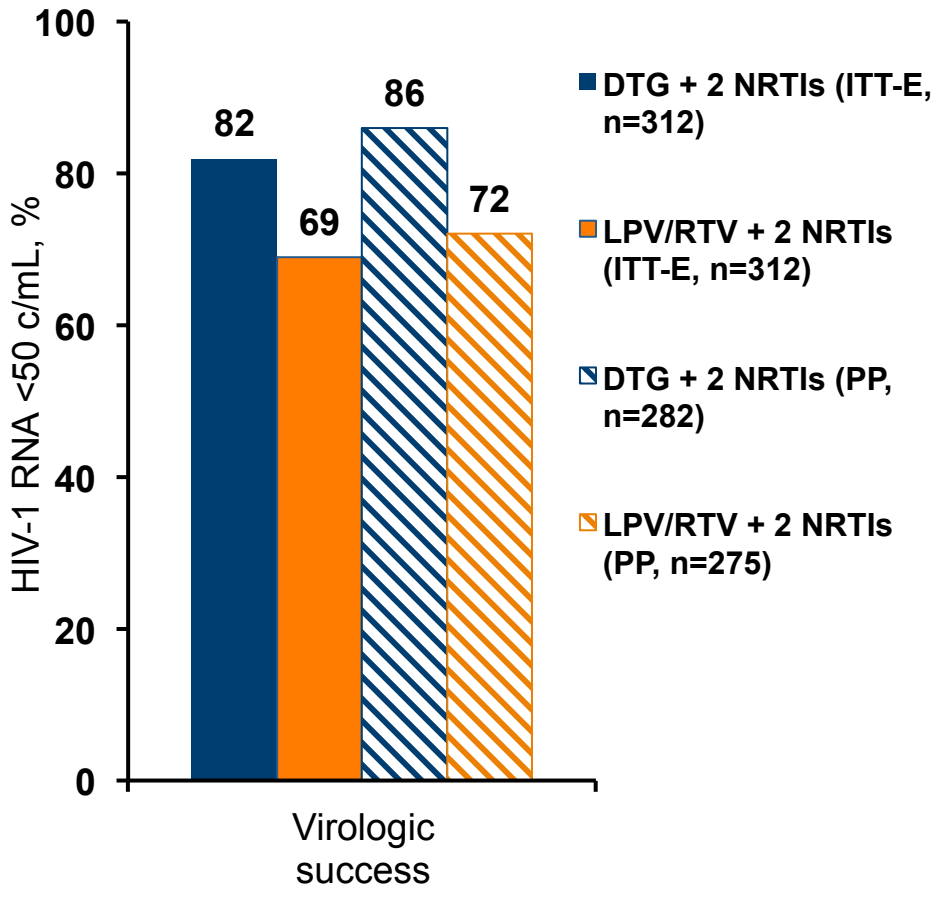
NRTI Background Regimen Post Randomisation

	DTG + 2 NRTIs (n=312)	LPV/RTV + 2 NRTIs (n=312)
NRTI background regimen, n (%)		
AZT + 3TC	131 (42)	121 (39)
TDF + 3TC or FTC	128 (41)	134 (43)
TDF + AZT	36 (12)	40 (13)
ABC + 3TC	7 (2)	7 (2)
Other	10 (3)	10 (3)

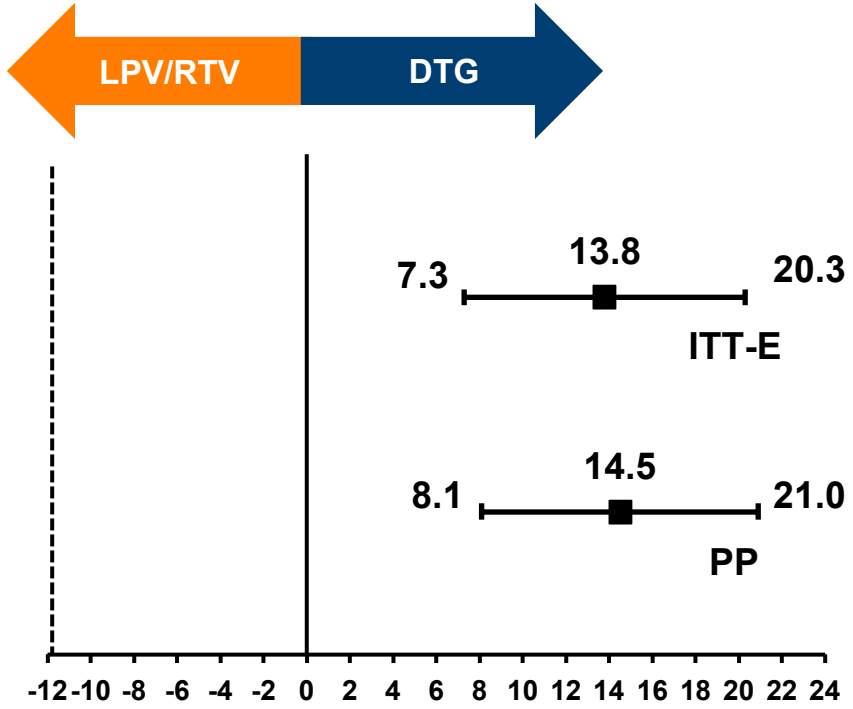
Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.

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.

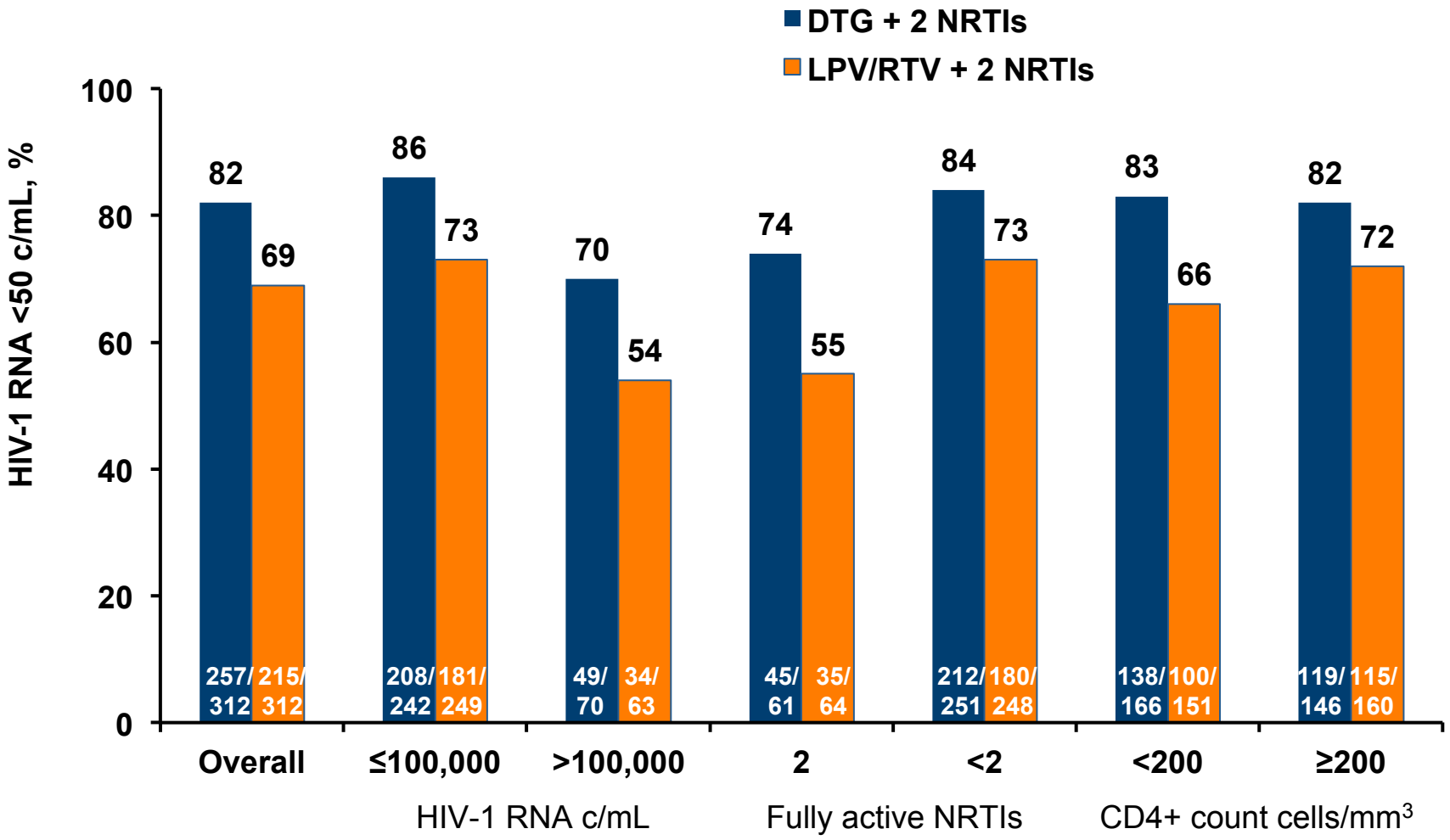
Snapshot Outcomes at Week 24: ITT-E

n (%)	DTG + 2 NRTIs (n=312)	LPV/RTV + 2 NRTIs (n=312)
Virologic response	257 (82)	215 (69)
Virologic nonresponse	37 (12)	77 (25)
Data in window not below <50 c/mL	32 (10)	67 (21)
Discontinued for other reason while not <50 c/mL	1 (<1)	4 (1)
Change in ART	4 (1)	6 (2)
No virologic data	18 (6)	20 (6)
Discontinued study due to AE or death	4 (1)	12 (4)
Discontinued study for other reasons	12 (4)	4 (1)
Missing data during window but on study	2 (<1)	4 (1)

AE, adverse, event; ART, antiretroviral therapy; ITT-E, intent-to-treat exposed

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

Snapshot Outcomes by Key Baseline Subgroups at Week 24: ITT-E



ITT-E, intent-to-treat exposed.

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

Snapshot Virologic Response (<50 c/mL) at Weeks 24, 36 and 48: ITT-E

		DTG + 2 NRTIs	LPV/RTV + 2 NRTIs	Treatment differences (95% CI)
Week 24	Interim	257 / 312 (82%)	215 / 312 (69%)	13.8 (7.3, 20.3)
Week 36[a]	Interim	230 / 293 (78%)	203 / 293 (69%)	9.8 (2.7, 16.8)
Week 48[a]	Interim	199 / 247 (81%)	161 / 243 (66%)	15.4 (7.8, 23.1)

[a]Subjects who have been in the study at least 36/48 weeks are included in this population.

- Week 36 and Week 48 results are consistent with Week 24.

CI, confidence interval; ITT-E, intent-to-treat exposed

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

Proportion of Subjects meeting Confirmed Virologic Withdrawal criteria

	DTG + 2 NRTIs (N=312) n (%)	LPV/RTV + 2 NRTIs (N=312) n (%)
Week 16	**1 (<1)**	**1 (<1)**
Week 24[a]	**6 (2)**	**18 (6)**
Any time[b]	**10 (3)**	**28 (9)**

[a]Cumulative; includes subjects meeting confirmed virologic withdrawal criteria at Week 16.
[b]Any time includes data up to Week 52

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

Treatment-Emergent Mutations in Patients With Confirmed Virologic Withdrawal

- The resistance analysis was performed on subjects meeting confirmed virologic withdrawal (HIV-1 RNA decrease <1 $\log_{10}$ c/mL by Week 16, HIV-1 RNA rebound to ≥400 c/mL after prior confirmed suppression, confirmed ≥400 c/mL on or after Week 24)

Resistance analysis	DTG + 2 NRTIs (n=8)	LPV/RTV + 2 NRTIs (n=24)
INSTI	**0**	**0**
NRTI	**0**	**3***
K70R	0	2
M184V	0	1
K219Q	0	1
K219E	0	1
PI	**0**	**0**

* Both K70R and M184V developed in one subject, K70R and K219E in another.

- No subject receiving DTG + 2 NRTIs developed INSTI or NRTI resistance-associated mutations.

INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

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

SAILING subanalysis: DTG-based regimens are active in INI-naïve patients with NRTI resistance

- **DTG, superior efficacy** compared with RAL (+OBR) in heavily treated patients.
- In INI-naïve patients with resistance to at least two drug classes, **none (0/32)** receiving DTG + 2 NRTIs experienced PDVF, even if **both NRTIs were not fully active**
- In contrast, **7/32 (22%)** patients receiving RAL + 1–2 NRTIs experienced PDVF

Protocol-defined virological failure in patients by type of background regimen (SAILING week 48)

	DTG n with PVDF*/N (%)	RAL n with PVDF*/N (%)
Overall	21/354 (6)	43/361 (12)
NRTI-only background regimens*	0/32	7/32 (22)
PI-containing background regimens	18/300 (6)	36/305 (12)

Demarest J *et al*. IAC 2014. Abstract TUAB0104

*PDVF defined as plasma HIV-1 RNA decrease <$\log_{10}$ copies/mL (unless <400 copies/mL by week 16 or HIV-1 RNA ≥400 copies/mL on or after week 24) or virological rebound (plasma HIV-1 RNA ≥400 copies/mL after confirmed HIV-1 RNA <400 copies/mL or >$\log_{10}$ copies/mL increase above any nadir of ≥400 copies/mL)

Summary of Adverse Events (Randomised Phase)

	DTG + 2 NRTIs (n=314)[a]	LPV/RTV + 2 NRTIs (n=310)
Any adverse event, n (%)	204 (65)	231 (75)
Most common AEs (≥5% in either arm)		
Diarrhoea	28 (9)	98 (32)
Upper respiratory tract infection	37 (12)	34 (11)
Nausea	11 (4)	28 (9)
Headache	22 (7)	16 (5)
Lower respiratory tract infection	11 (4)	14 (5)
Vomiting	5 (2)	17 (5)
Any neuropsych AE	19 (6)	15 (5)
Drug-related AE	47 (15)	113 (36)
All drug-related grade 2-4 AEs	9 (3)	40 (13)
Diarrhoea	1 (<1)	22 (7)
Serious AEs or death[b]	17 (5)	18 (6)
Drug-related serious AEs	2 (<1)	2 (<1)
AEs leading to withdrawal	7 (2)	17 (5)

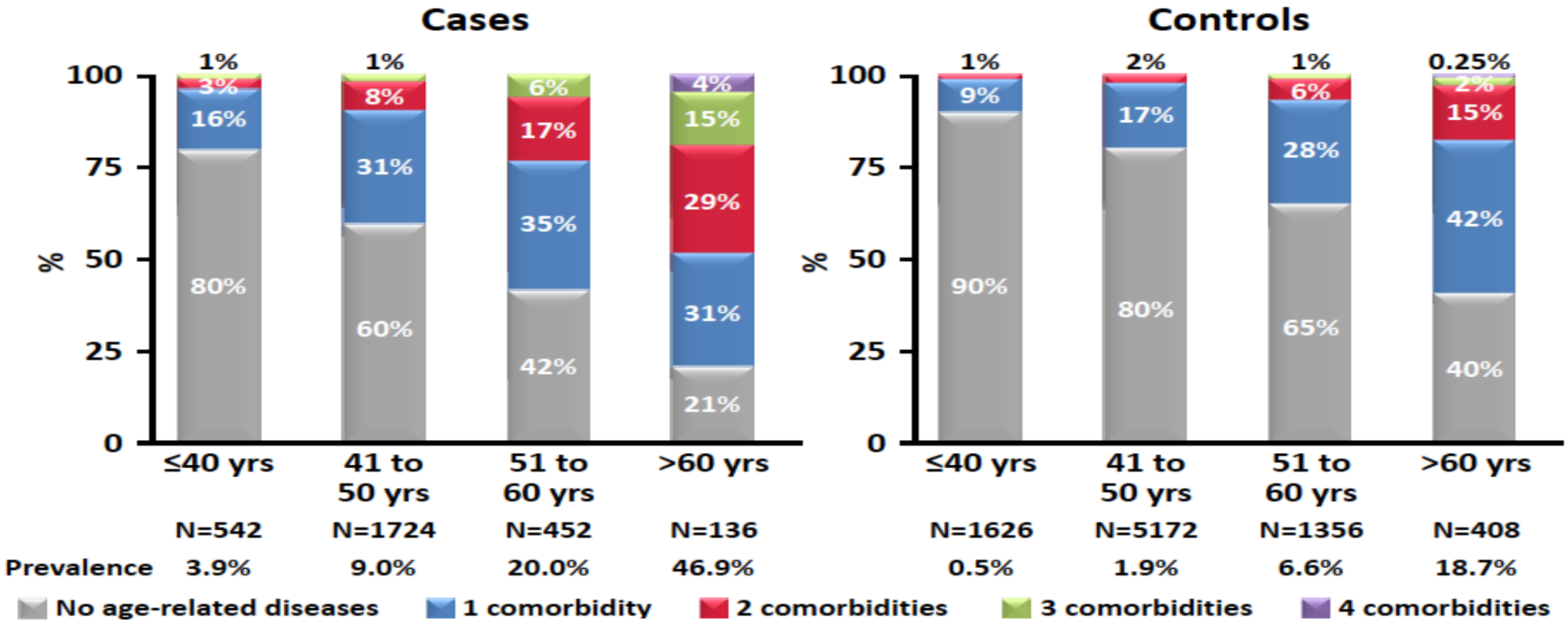
[a]Two patients received LPV/RTV instead of DTG + 2 NRTIs. [b]Four fatal SAEs: DTG + 2 NRTIs, n=1 (pneumonia); LPV/RTV, n=3 (pneumonia, encephalitis/IRIS, encephalitis).

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

What are the desired characteristics of an IDEAL cART regimen?

- ✓ Highly Efficacious
- ✓ Safe and Well Tolerated
- ✓ High Genetic Barrier to Resistance
- ✓ Convinience
- ✓ DDI- no/few

HIV Gray Epidemic Spectrum



Significantly more hypertension, angina, MI, peripheral vascular disease, liver dysfunction, chronic renal failure and cancer in people living with HIV

1. Guaraldi G *et al. Clin Infect Dis.* 2011;cid.cir627

DOLUTEGRAVIR-BASED REGIMENS: BOOSTER-FREE WITH FEW SIGNIFICANT INTERACTIONS WITH COMMONLY USED MEDICATIONS

Selected **miscellaneous drugs** – Drug-drug interactions between ARVs and non-ARVs[1†]

	BOOSTED FREE AGENTS					BOOSTED AGENTS	
	DTG[‖]	RAL	EFV	ETV	RPV	EVG/c	DRV/r
antacids	■	■	◆	◆	■	■	◆
PPIs	◆	◆	◆	◆	●	◆	◆
H2-blockers	◆	◆	◆	◆	■	◆	◆
beclometasone inhaler	◆	◆	◆	◆	◆	◆	◆
buprenorphine	◆	◆	■	■	◆	◆	■
budesonide inhaler	◆	◆	■	■	◆	■	■
ergot derivative[a]	◆	◆	●	●	■	●	●
ethinyl estradiol	◆	◆	■	◆	◆	■	■
Fluticasone inhaler	◆	◆	■	■	◆	■	■
Methadone	◆	◆	■	■[b]	■	◆	■
Salmeterol inhaler	◆	◆	■	■	◆	■	■
Sildenafi (erectile dysuntion)	◆	◆	■	■	◆	■	■
St. John's Wort[§]	●	◆	●	●	●	●	●
varenicline	◆	◆	◆	◆	◆	◆	◆

***Key to symbols*[#]**
Further information (in vivo, in vitro, or from label) at www.hiv-druginteractions.org

- ● These drugs should not be co-administered
- ■ Potential interaction-may require close monitoring, alteration of drug dosage or timing of administration
- ◆ No clinically significant expected

a Ergot derivative interactions may vary with individual products and should be individually checked before prescribing.
b According to the Intelence® Summary of Product Characteristics, no changes in methadone dosage were required based on clinical status during or after the period of etravirine co-administration.[2]
†This table is based on data provided by the University of Liverpool and summarises the drug-drug interactions between HIV therapy and some commonly prescribed co-medicines as well as the drug-drug interactions of particular clinical relevance. This table is not exhaustive; for additional drug-drug interaction data and dosage adjustments, see www.hiv-druginteractions.org (University of Liverpool).
§According to the TIVICAY SPC, the recommended dose of dolutegravir is 50 mg twice daily when co-administered with this drug. Alternative combinations should be used where possible in INI-resistant patients.[3]
‖ According to the TIVICAY SPC, metformin concentrations may be increased by dolutegravir. Patients should be monitored during therapy and a dose adjustment of metformin may be required.[3]
#The symbols (green, amber, red) used to rank the clinical significance of the drug interaction are based on www.hiv-druginteractions.org.

1. University of Liverpool. Drug interactions chart. October 2015. www.hiv-druginteractions.org. Accessed November 2015
2. Intelence® Summary of Product Characteristics. June 2014
3. TIVICAY (dolutegravir) Summary of Product Characteristics. September 2015

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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

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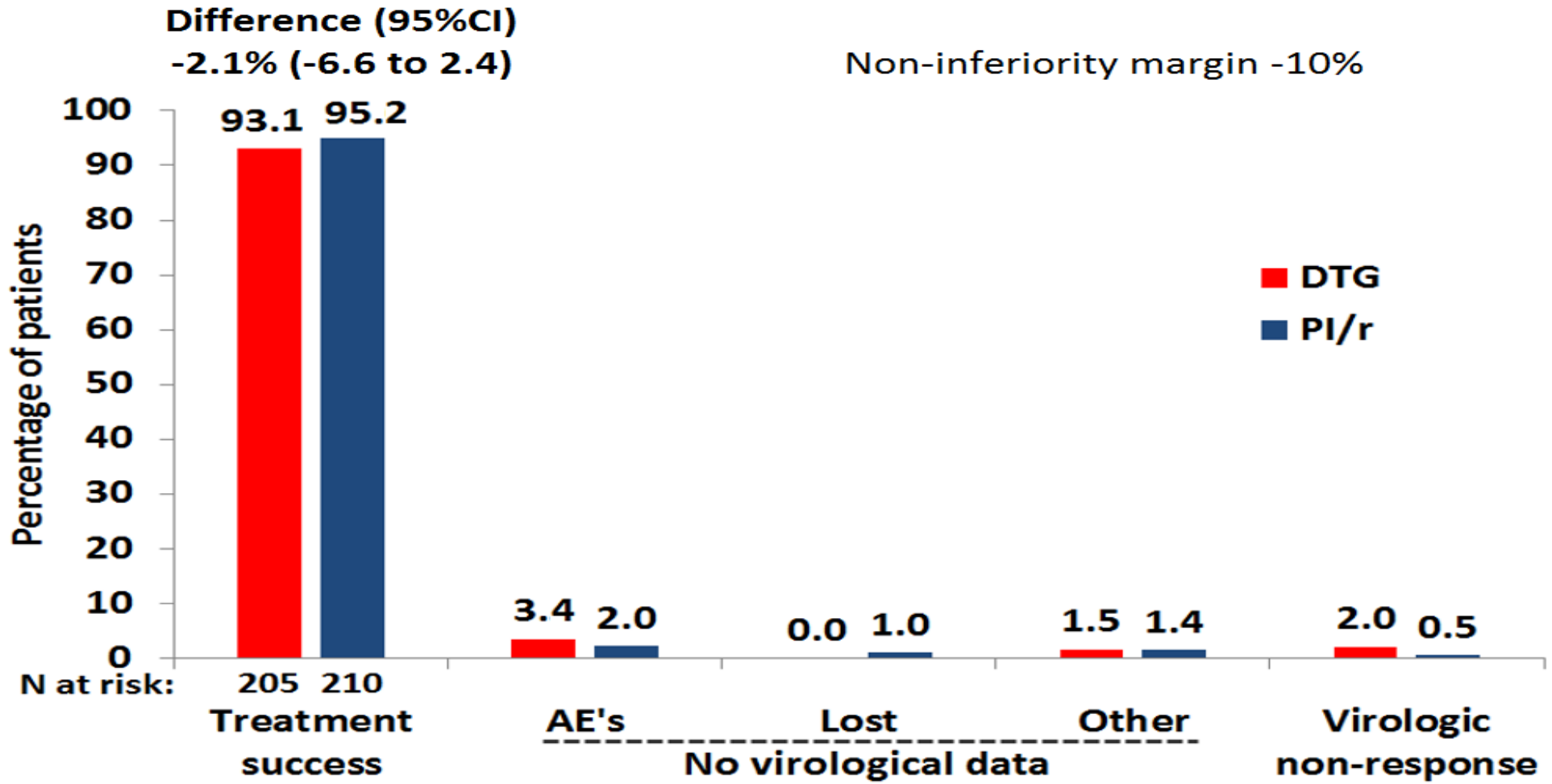
Baseline characteristics (I): n(%) or median (IQR)

	DTG (n=205)	PI/r (n=210)	Total (n=415)
Age > 50 years	179(87.3)	184(87.6)	363(87.5)
Framingham score > 10% at 10 years	155(75.6)	151(71.9)	306(73.7)
Male gender	181(88.3)	189(90.0)	370(89.2)
White race	173(84.4)	180(85.7)	353(85.1)
Mode of HIV transmission			
Male homosexual sexual intercourse	130(63.4)	131(62.4)	261(62.9)
Heterosexual sexual intercourse	43(23.9)	48(22.9)	97(23.4)
Other	26(12.7)	31(14.8)	57(13.7)
CD4 count; cells per µL	635(495-819)	585(471-830)	617(477-820)
HIV RNA >50 copies/ml	7(3.4)	1(0.5)	8(2)
Hepatitis C IgG antibodies	27(13.4)	24(11.6)	51(12.5)
Time since undetectable viral load (< 50 copies per ml); years	4.9(2.5-9.1)	5.3(2.3-8.5)	5(2.4-8.8)
Current Smokers	78(38)	79(37.8)	157(37.9)
Diabetes	11(5.5)	13(6.3)	24(5.9)
Family history of cardiovascular disease	87(43.3)	89(43.4)	176(43.3)
>= 1 CVD risk factor	151(73.7)	154(73.3)	305(73.5)
Receiving lipid lowering agents	63(30.7)	60(28.6)	123(29.6)
Daily exercise	64(32.5)	59(28.9)	123(30.5)
Fasting plasma lipids			
Total cholesterol; mmol/L	5.2(4.5-5.8)	5.1(4.5-5.6)	5.1(4.5-5.7)
Triglycerides; mmol/L	1.6(1.2-2.3)	1.6(1.2-2.2)	1.6(1.2-2.2)

Baseline characteristics (II): n (%)

	DTG (n=205)	PI/r (n=210)	Total (n=415)
Backbone nucleos(t)ides			
TDF / FTC	134 (65.4)	135 (64.3)	269 (64.8)
Abacavir/ 3TC	63 (30.7)	67 (31.9)	130 (31.3)
Other	8 (3.9)	8 (3.8)	16 (3.9)
PI/r at baseline			
Darunavir/r	105 (51.5)	107 (51.0)	212 (51.2)
Atazanavir/r	77 (37.7)	74 (35.2)	151 (36.5)
Other	22(10.7)	29(13.8)	51(12.3)

Results (I): Co-primary efficacy endpoint

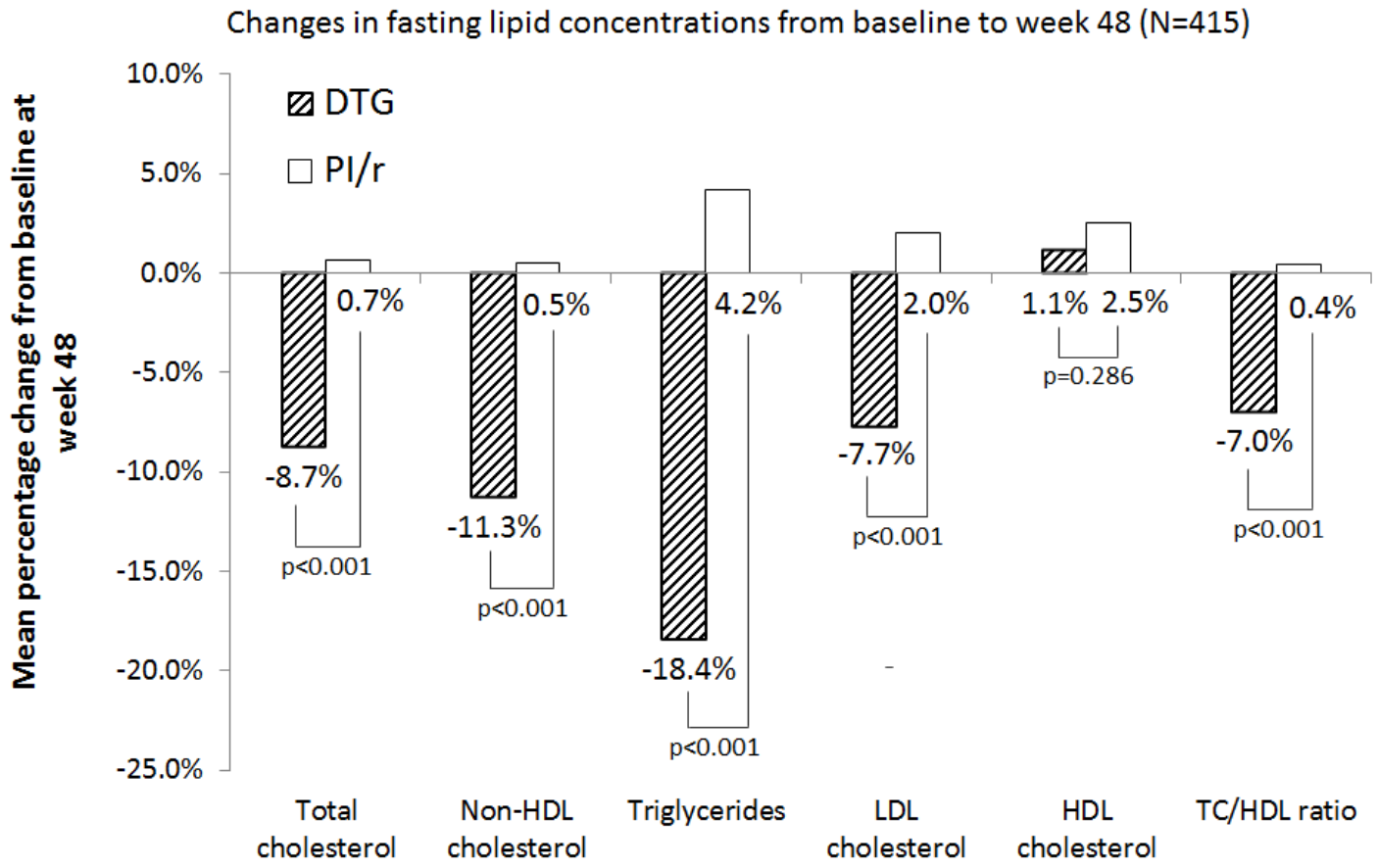


ITT population

ITT

NEAT22/SSAT060 week 48 data

DTG HAS A SIGNIFICANT IMPROVEMENT IN HIGH RISK HIV PATIENTS. NEAT 22

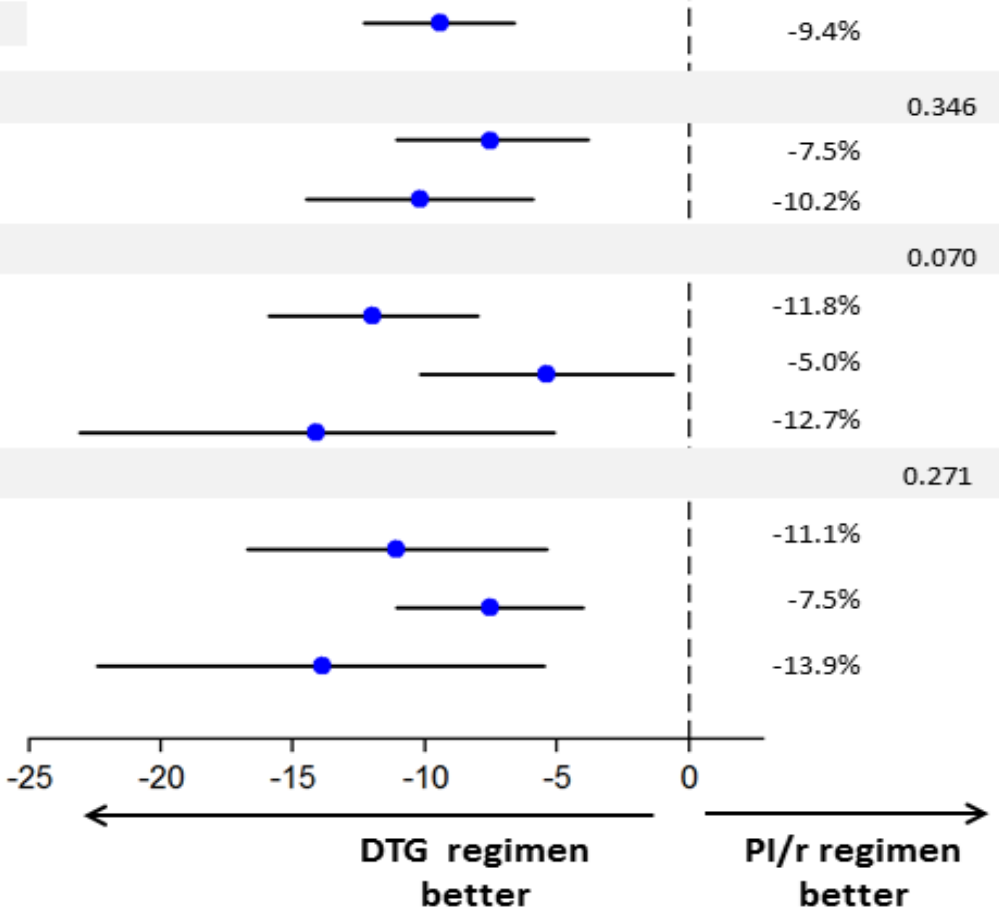


- **Ageing HIV patients with moderate-high CV risk (Framingham risk score >10%)**

José Gatell, et al. IAS 2017

Results (VII): Subgroup analysis for total cholesterol

Subgroup	Percentage in group	DTG mean (SE)	PI/r mean (SE)	Mean difference (95% CI)	P Value for interaction
All participants	100.0	-8.7% (1.0)	+0.7 (1.0)	-9.4%	
Framingham Cardiovascular risk score					0.346
<15%	53.0	-5.6% (1.3)	+1.8% (1.3)	-7.5%	
≥15%	47.0	-11.4% (1.6)	-1.2% (1.5)	-10.2%	
PI/r regimen					0.070
Darunavir	51.5	-10.8% (1.4)	+1.0% (1.4)	-11.8%	
Atazanavir	37.7	-5.6% (1.7)	-0.6% (1.7)	-5.0%	
Others	10.8	-9.9% (3.2)	+2.8% (2.8)	-12.7%	
Age and Framingham Cardiovascular (CVS) risk					0.271
Age≥50yr and CVS<10%	26.0	-5.6% (2.1)	+5.5% (1.9)	-11.1%	
Age≥50yr and CVS≥10%	61.4	-8.9% (1.3)	-1.4% (1.3)	-7.5%	
Age<50yr and CVS≥10%	12.3	-14.0% (2.9)	-0.1 (3.0)	-13.9%	



Total cholesterol

NEAT22/SSAT060 week 48 data

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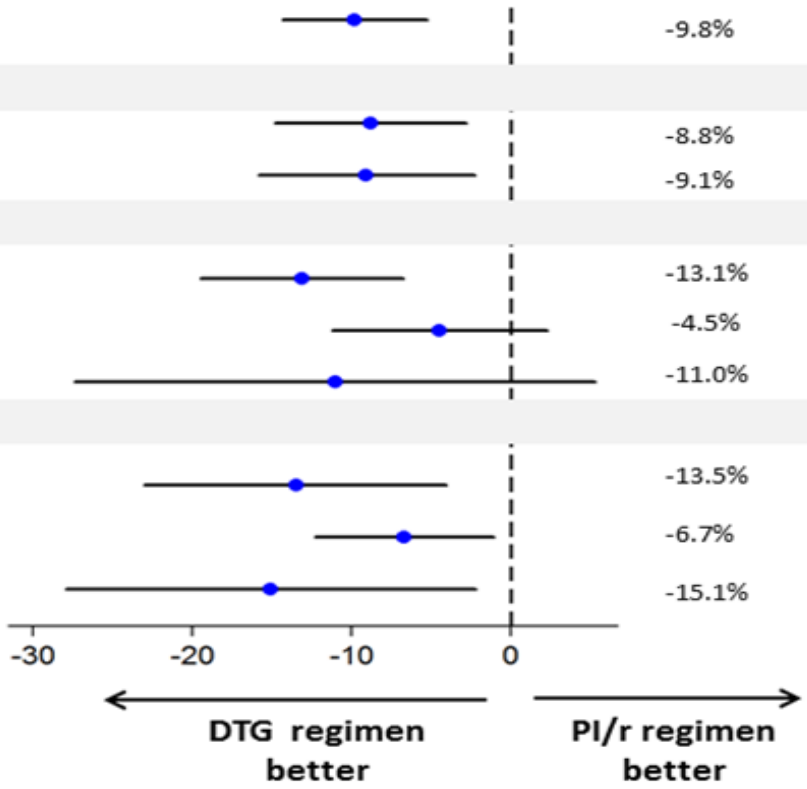
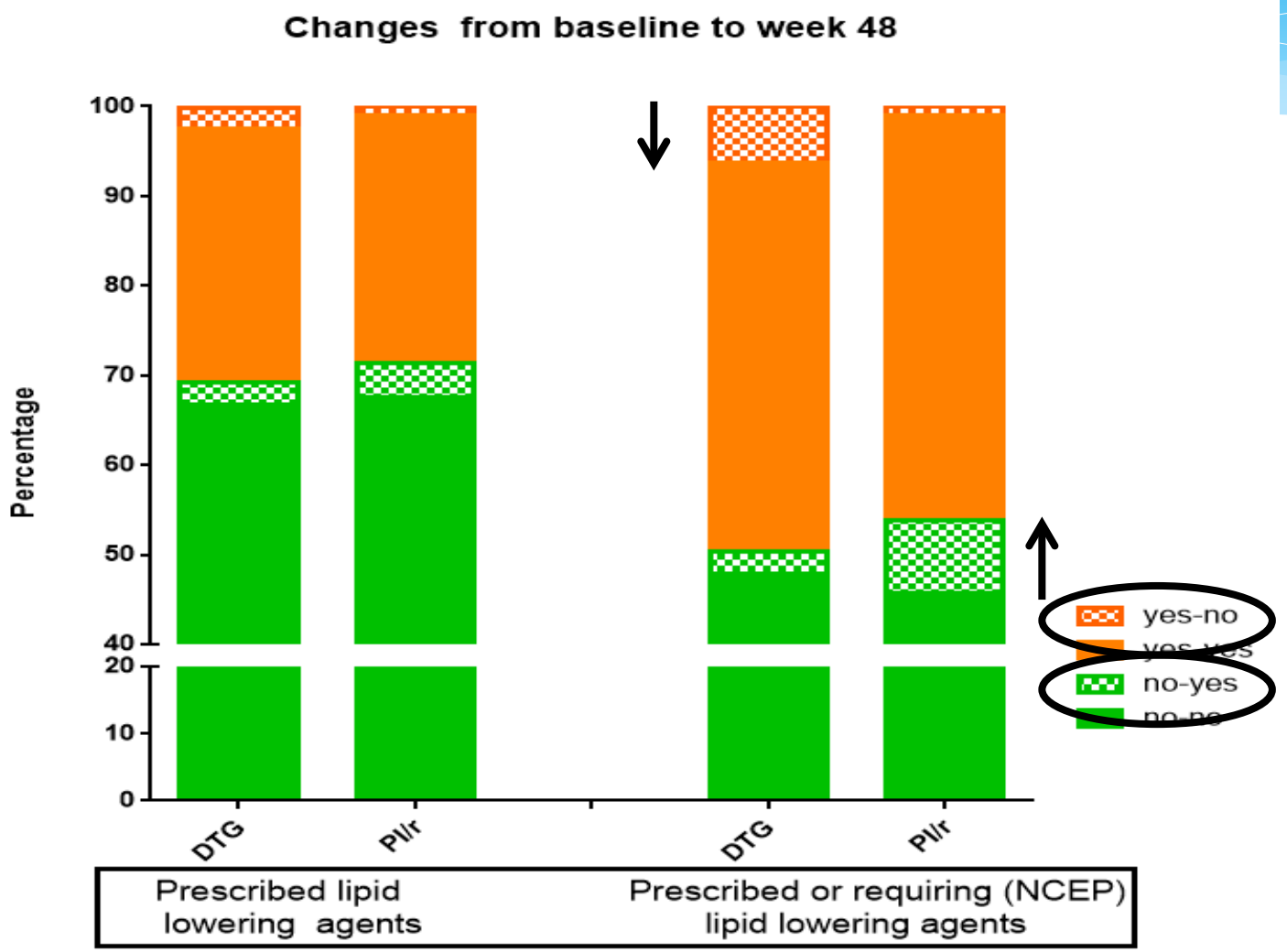
Results (VIII): Subgroup analysis for LDL-cholesterol

Subgroup	Percentage in group	DTG mean (SE)	PI/r mean (SE)	Mean difference (95% CI)	P Value for interaction
All participants	100.0	-7.8% (1.6)	+2.0 (1.6)	-9.8%	
Framingham Cardiovascular risk score					0.959
<15%	53.0	-5.2% (2.2)	+3.6% (2.2)	-8.8%	
≥15%	47.0	-11.4% (1.6)	-1.2% (1.5)	-9.1%	
PI/r regimen					0.215
Darunavir	51.5	-11.3% (2.3)	+1.8% (2.3)	-13.1%	
Atazanavir	37.7	-2.8% (2.4)	+1.7% (2.4)	-4.5%	
Others	10.8	-7.5% (6.0)	+3.5% (5.5)	-11.0%	
Age and Framingham Cardiovascular (CVS) risk					0.291
Age≥50yr and CVS≤10%	26.0	-5.1% (23.5)	+8.5% (3.2)	-13.5%	
Age≥50yr and CVS>10%	61.4	-7.6% (2.0)	-0.9% (2.0)	-6.7%	
Age<50yr and CVS>10%	12.3	-13.5% (4.4)	+1.5% (4.7)	-15.1%	



Results: Co-primary lipids endpoint



Conclusions

- **InSTI** has become the **new Recommended Agent** for the majority of Guidelines.
- **DTG** has been shown to be **superior** than comparators (EFV, DRV, ATV) and virological better response in hVL naive patients compared to RAL.
- **DTG** is **replacing** (slowly in some countries) **EFV as recommended regimen** in low-middle income countries. **WHO endorse** it´s use and provided guidelines for immediate incorporation.
- **InSTI** is **essential** across patient treatment history. **DTG** has demostrated to be a valid option for **2nd line therapy** (superior than LPV/r).
- Due to convinience and DDI profile (glucuronidation), **DTG** is an **excellent** treatment option for **HIV ageing patients** with **comorbidities.**

MUCHAS GRACIAS

MUCHAS GRACIAS

F A R M A C O V I G I L A N C I A

La seguridad de los pacientes es responsabilidad de todos

Notifique eventos adversos y/o información de seguridad a través de los siguientes medios:

TELÉFONO:

01 800 APOYAME (276-9263)
Call Center 24 horas

EMAIL:

farmacovigilancia.mx@gsk.com

INTERNET:

Salud GSK
https://salud.gsk.com.mx/

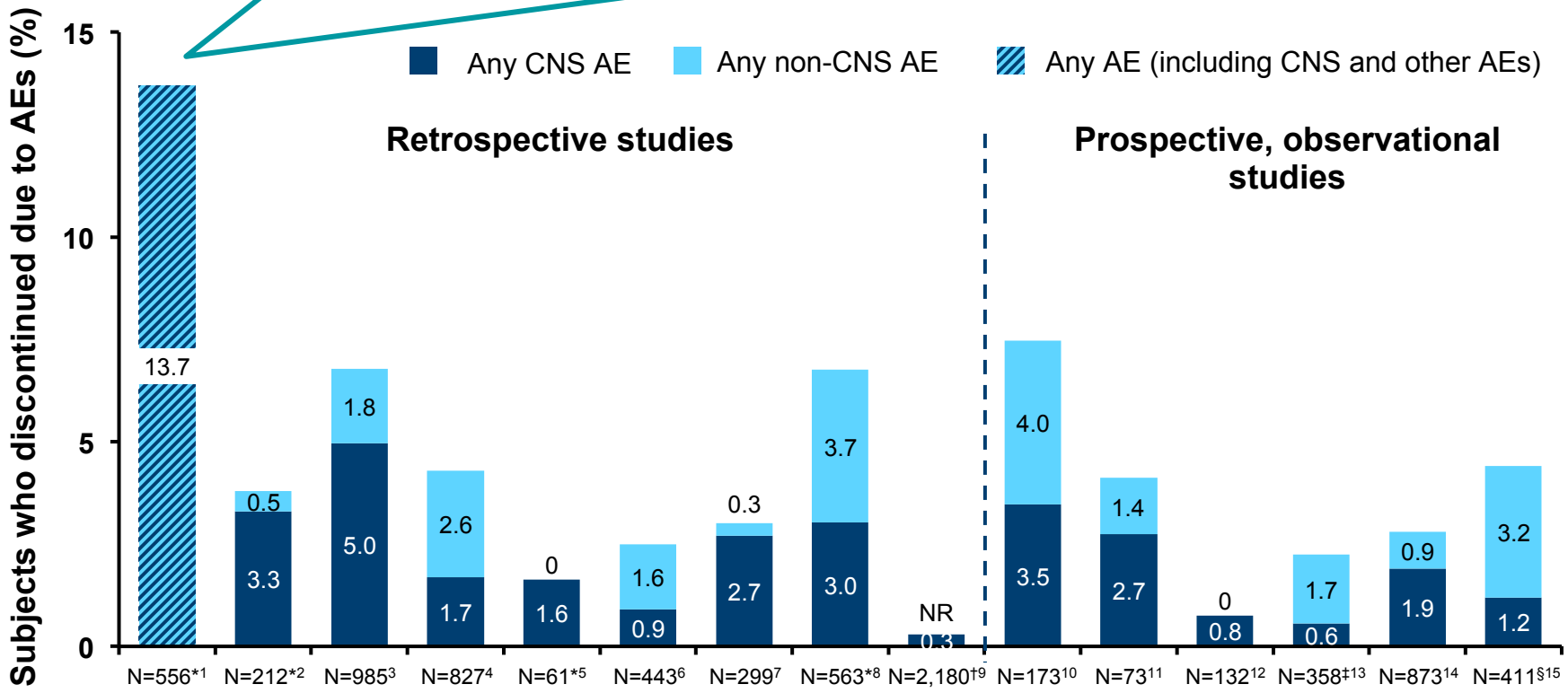
DIRECCIÓN:

Calz. México-Xochimilco 4900
Col. San Lorenzo Huipulco
Delegación Tlalpan C.P. 14370, CDMX

Back up

DTG Discontinuation Due to CNS AEs

- A Dutch study reported that 85/556 (15.3%) subjects discontinued DTG for any reason and that 76/556 (13.7%) subjects discontinued DTG due to an adverse drug reaction[1]
- These 76 subjects experienced 125 adverse reactions, 31 (39%) had multiple adverse reactions and 11 (14%) had >2 adverse reactions[1]
- Of adverse reactions contributing to discontinuation, 55/125 were CNS adverse reactions[1]

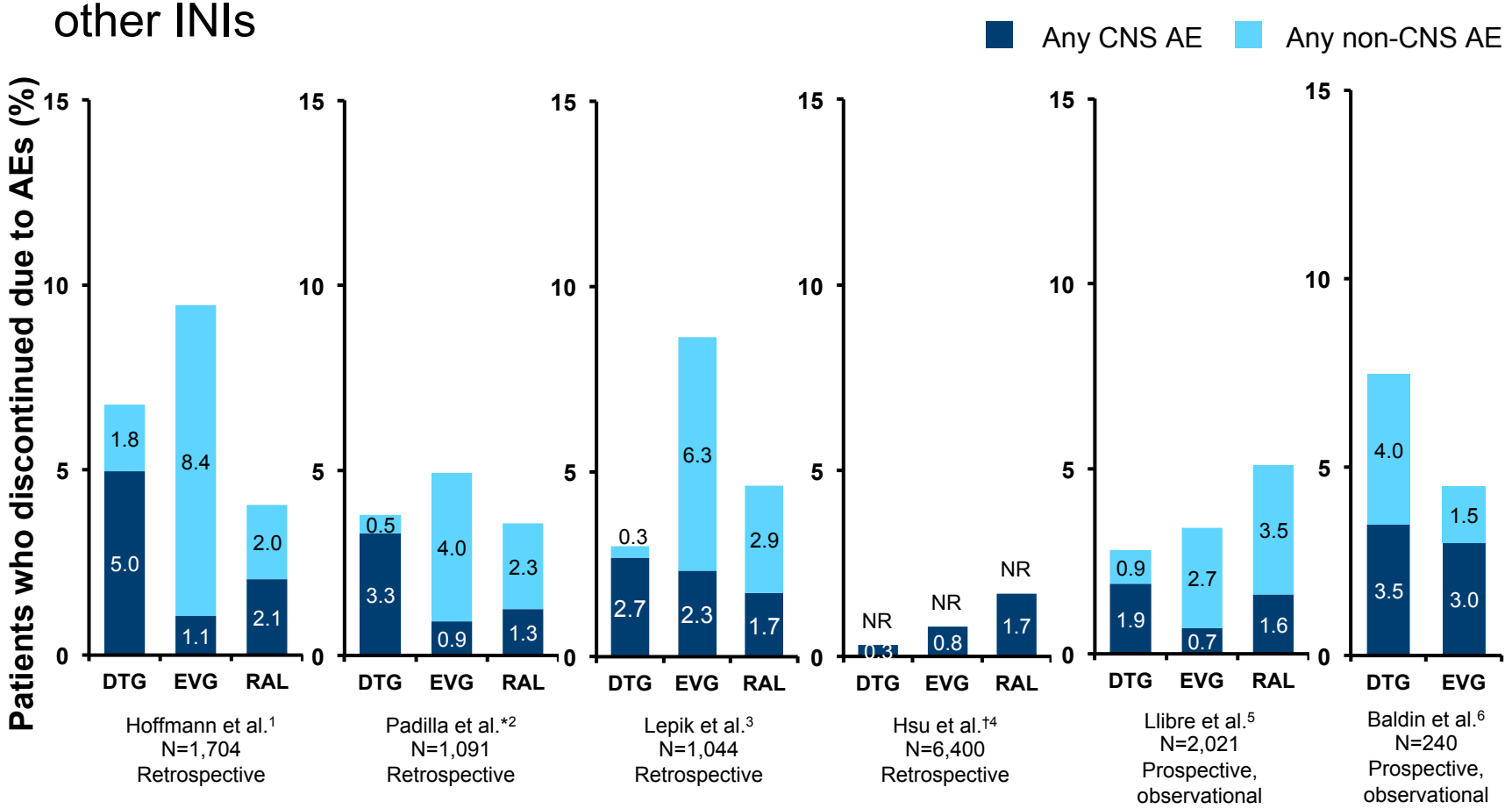


*>1 AE reported for some subjects. †Discontinuation within 14 days of diagnosis of a psychiatric disorder, excluding subjects with a history of the relevant disorder at baseline. ‡8 subjects (2.2%) discontinued DTG due to any AE, 2 (0.56%) due to CNS AEs and 6 (1.68%) due to non-CNS AEs §1.2% of subjects reported depression, overall frequency of CNS AEs not reported

See slide notes for references and additional notes

Cohort Data: INI Discontinuation Due to AEs

- 0.3–5% of subjects discontinued DTG due to CNS AEs vs 0.7–3% with other INIs



*More than 1 AE reported for some subjects. † Discontinuation within 14 days of diagnosis of a psychiatric disorder, excluding subjects with a history of the relevant disorder at baseline. See slide notes for further study information

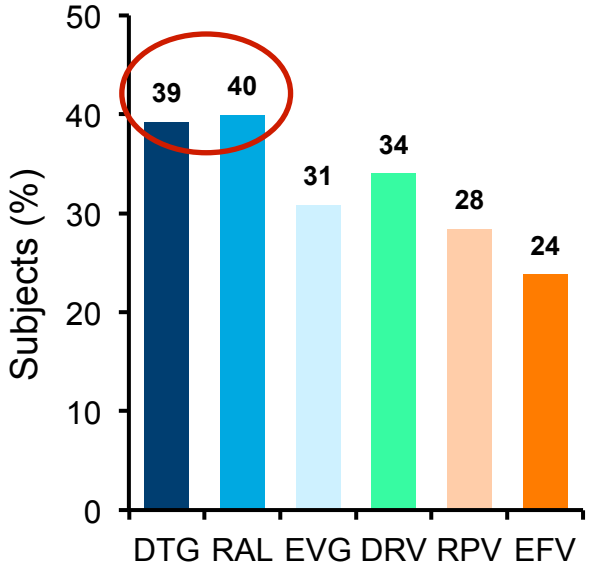
1. Hoffmann C, et al. HIV Med 2017;18:56–63; 2. Padilla M, et al. International Workshop on Comorbidities and ADRs in HIV 2016; 3. Lepik KJ, et al. IAS 2015. Abstract TUPEB256; 4. Hsu R, et al. CROI 2017. Abstract 664; 5. Llibre JM, et al. CROI 2017. Poster 651; 6. Baldin G, et al. HIV Glasgow 2016. Poster P106

OPERA Cohort: Incidence of CNS Disorders by Event History

- OPERA database* analysis: 11,539 subjects in routine US practice who received regimens† containing DTG (19%), EFV (14%), RAL (8%), DRV (15%), RPV (15%) or EVG (29%)

Baseline

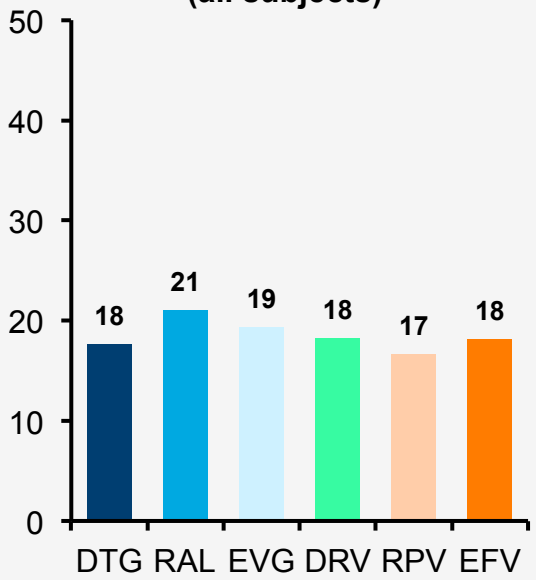
Subjects with history of CNS disorders‡



DTG prescriptions included a high proportion of subjects with a history of CNS disorders‡ at baseline

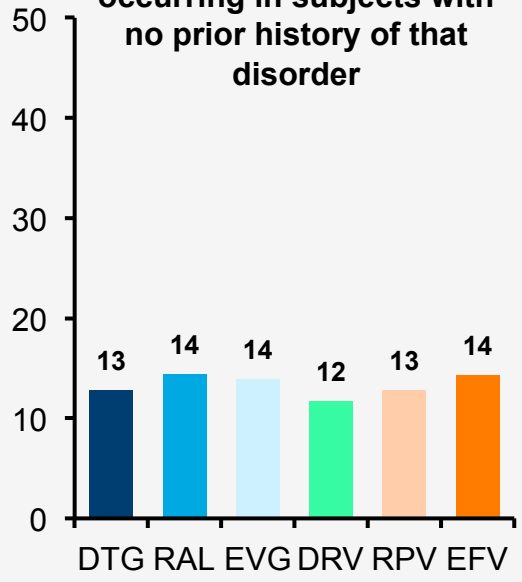
On-study

CNS disorders‡ (all subjects)



More subjects experienced CNS disorders‡ during treatment with RAL than DTG

'New' CNS disorders‡ occurring in subjects with no prior history of that disorder



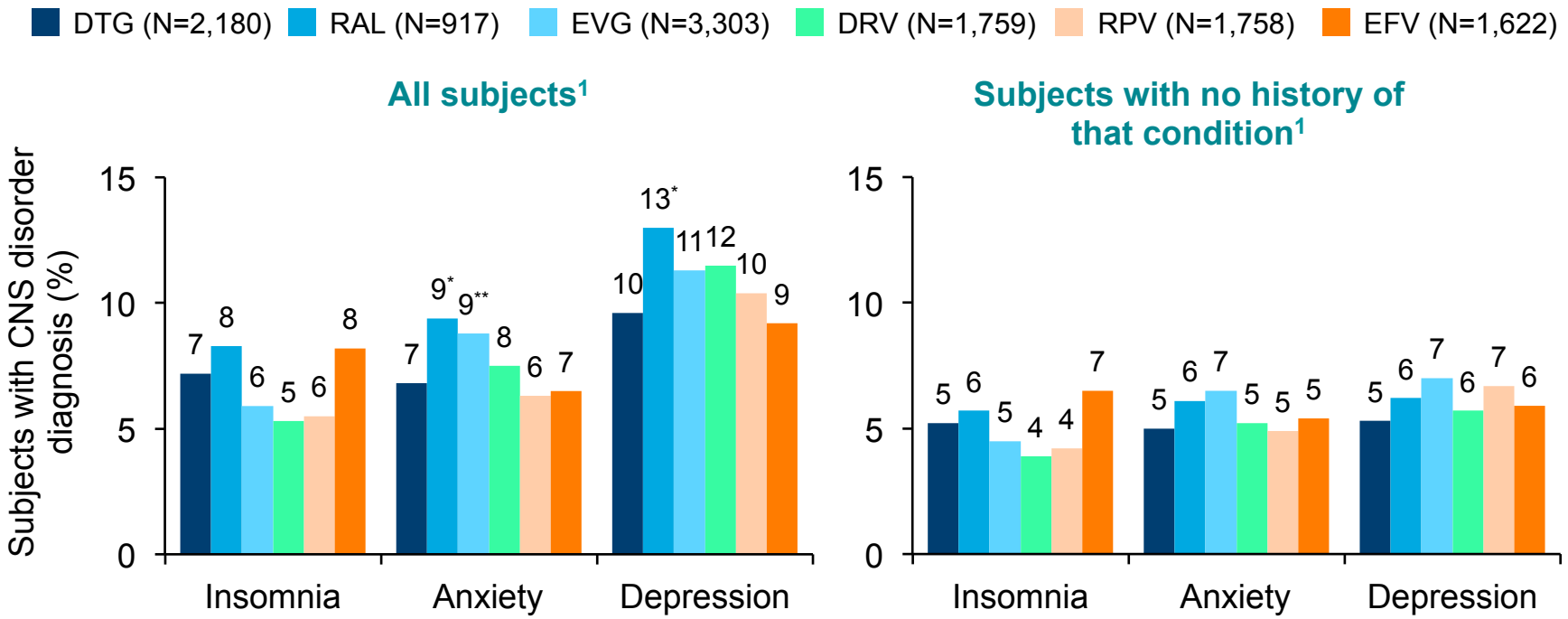
Frequency of 'new' CNS disorders similar across regimens

*Prospectively-captured, routine clinical data (electronic medical records) from 79 outpatient clinics across 15 states in the USA. †All agents listed were given with other ARVs; ‡anxiety, depression insomnia, or suicidality

Hsu R, et al. CROI 2017. Abstract 664

OPERA Cohort: CNS AEs According to Medical History

- Data† from large, diverse US cohort; diagnoses prospectively captured by HCPs[1,2]
- DTG use not associated with increased risk of CNS AEs or discontinuation due to CNS AEs, despite more patients with history of psychiatric disorders being prescribed DTG[1,2]



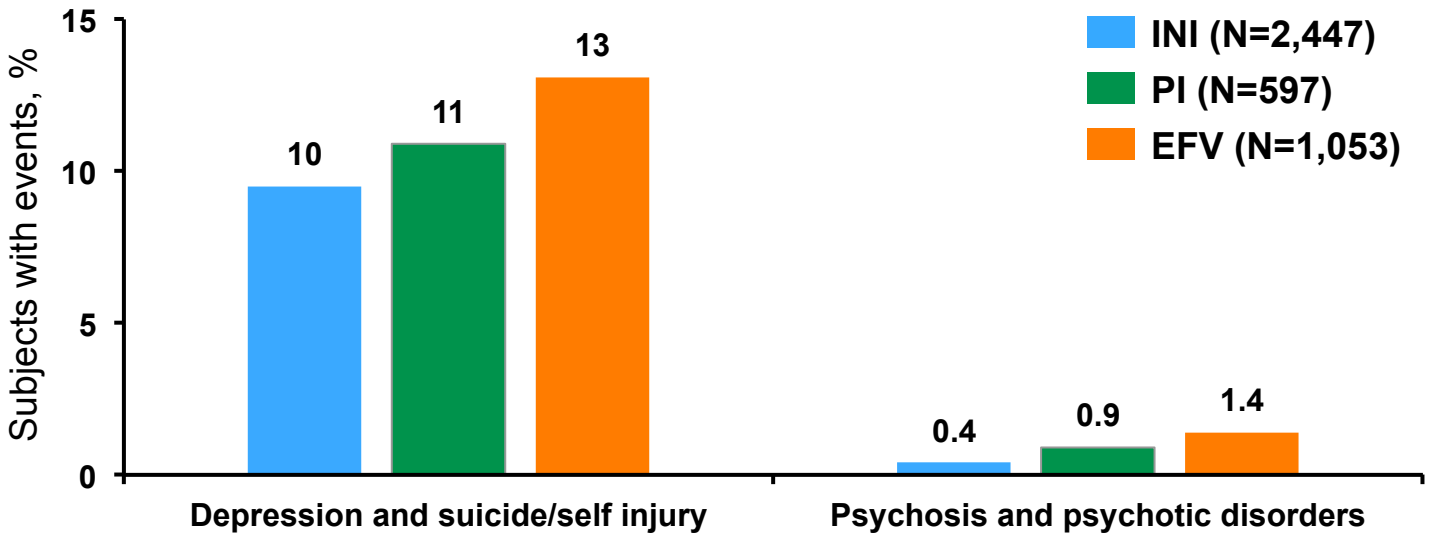
- Subjects using DTG least likely to discontinue within 14 days of CNS disorder diagnosis[1]

Suicidality described in a separate slide. p-values vs. DTG: *p=0.01; **p=0.006. †Electronic medical records

1. Hsu R, et al. CROI 2017. Poster 664
2. Fettiplace A, et al. J Acquir Immune Defic Syndr 2017;74:423–31

FDA Phase III Clinical Trial Meta-analysis: Risk of CNS Events in ART-naïve Subjects

CNS AEs were infrequent over 96 weeks and risk was not increased with INIs* vs PIs† or NNRTIs‡



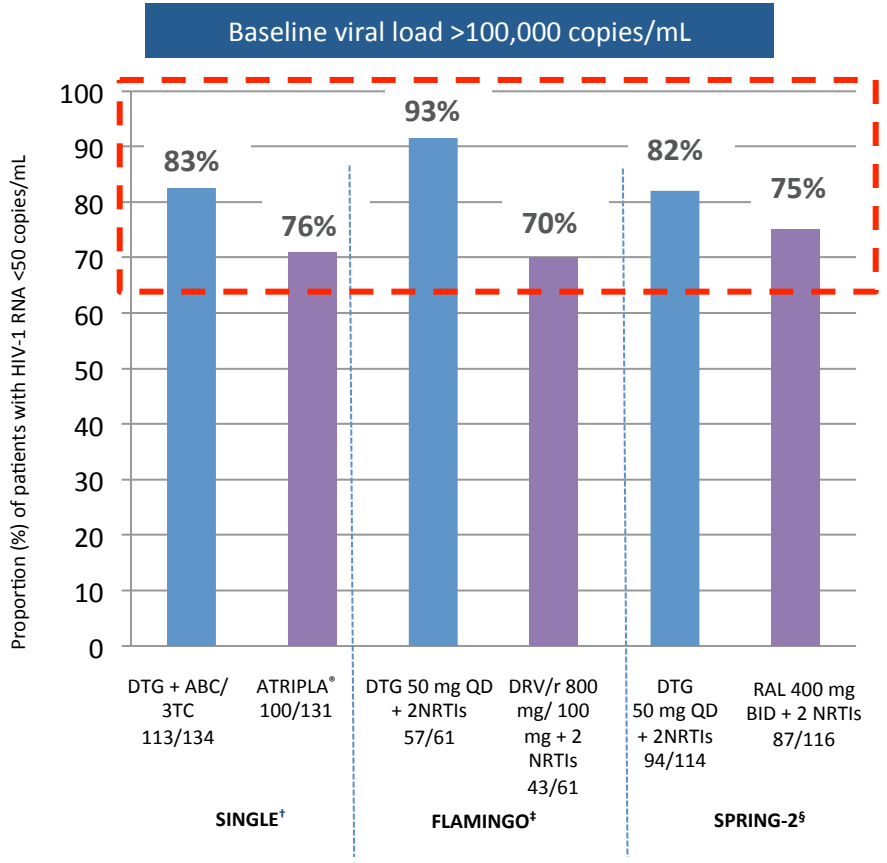
- Relationship between ART and CNS AEs potentially confounded by factors that were not evaluated, such as non-ART medications, pre-existing CNS illness and social stressors

FDA meta-analysis of 6 Phase III trials supporting approval of INIs; CNS AEs identified using Standardised MedDRA Query Version 18.0 terms in the categories: depression and suicide/self-injury; psychosis and psychotic disorders. *DTG, RAL or EVG; †ATV/r or DRV/r; ‡EFV. ART, antiretroviral therapy; MedDRA, medical dictionary for regulatory activities; NNRTI, non-NRTI; PI, protease inhibitor

Viswanathan P, et al. CROI 2017. Poster 372

DOLUTEGRAVIR . POST HOC ANALYSIS BASED ON BASELINE VIRAL LOAD

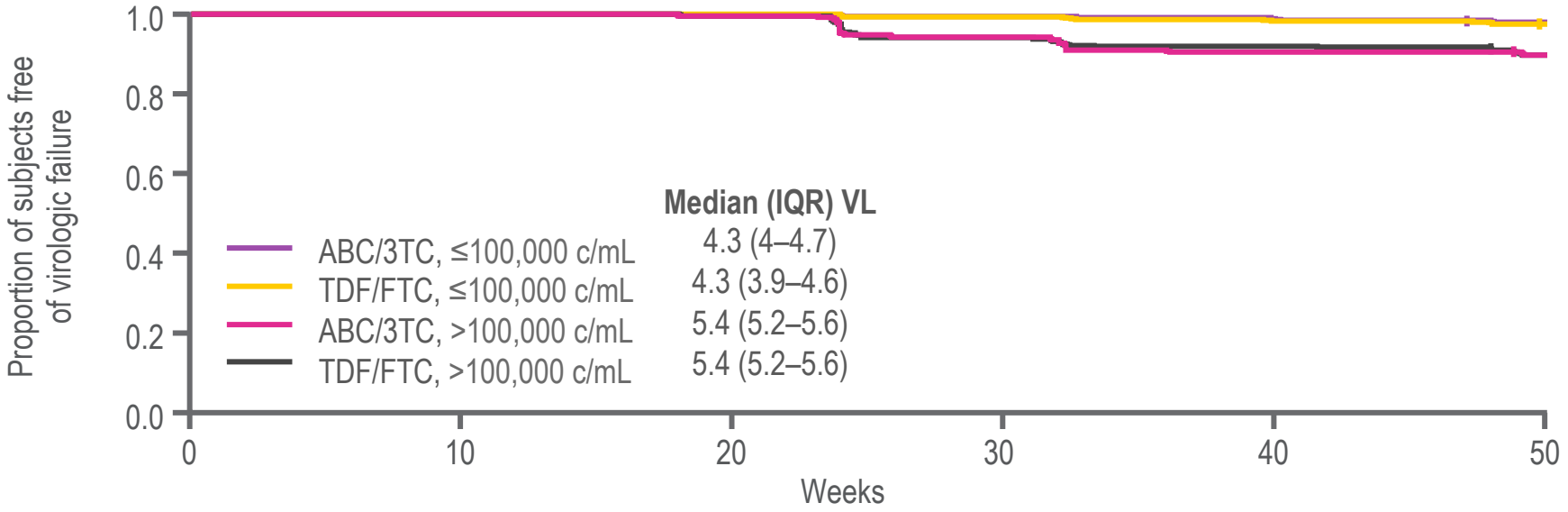
Week 48 snapshot analysis



† 32% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL
‡ 25% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL
§ 28% of treatment-naïve patients had a baseline viral load > 100,000 copies/mL

Adapted from Walmsley S *et al.* 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b
TIVICAY (dolutegravir) Summary of Product Characteristics, 06/2014
Adapted from Walmsley S *et al. N Engl J Med* 2013; 369:1807-18
Adapted from Walmsley S *et al. N Engl J Med* 2013; 369:1807-18 (appendix)
Adapted from Clotet B *et al. Lancet* 2014;383:2222-31
Adapted from Clotet B *et al. Lancet* 2014;383:2222-31(Supplementary Appendix)
Adapted from Raffi F *et al. Lancet* 2013;381:735–43

SPRING-2, SINGLE, AND FLAMINGO: ERDF KM ESTIMATES AT WEEK 48 BY BASELINE VIRAL LOAD AND NRTI BACKBONE



	Events/censored/at risk, n				
	Day 0	Week 12	Week 24	Week 32	Week 48
ABC/3TC, ≤100,000 c/mL	0/0/671	0/23/648	3/33/635	5/42/624	12/293/366
ABC/3TC, >100,000 c/mL	0/0/235	0/8/227	11/13/211	17/15/203	21/84/130
TDF/FTC, ≤100,000 c/mL	0/0/851	0/38/813	6/59/786	10/65/776	19/382/450
TDF/FTC, >100,000 c/mL	0/0/382	0/22/360	15/29/338	26/34/322	31/158/193

Adapted from Raffi F, et al. AIDS 2015:29:167-174

GESIDA 2015. Adherencia

Recomendaciones

- Antes de iniciar el TAR se debe preparar al paciente, identificar y corregir las causas potenciales de adherencia incorrecta ***(A-III)***
- Una vez iniciado el TAR se recomienda efectuar un control a las 2-4 semanas para comprobar la adherencia y eventualmente corregirla **(*A-III*)**
- La adherencia debe monitorizarse y reforzarse coincidiendo con las visitas clínicas **(*A-III*)**
- El control de la adherencia debe realizarse por un equipo multidisciplinar, adaptado a la disponibilidad de cada centro, que incluya a médicos, personal de enfermería, profesionales de apoyo psicológico y farmacia hospitalaria **(*A-III*)**
- En pacientes con cumplimiento irregular es preferible utilizar pautas basadas en IP/r (y probablemente dolutegravir) para prevenir la selección de resistencias **(*A-III*)**. A pesar de la poca experiencia clínica disponible, los datos iniciales parecen apoyar que las pautas basadas en dolutegravir pueden ser también útiles en este tipo de pacientes ***(B-III)***

Documento de consenso de GeSida/PNS sobre TAR (enero 2015)

DTG DISTRIBUTION

- Plasma protein binding: ≥98.9%[1].
- A Phase IIIb study assessed the distribution of DTG in CSF[3]
  - DTG concentrations observed in CSF at both Week 2 and Week 16 exceeded the in-vitro IC_{50} against wild-type viruses (0.2 ng/mL)[3] for all subjects, suggesting that DTG was able to **achieve therapeutic concentrations in the CSF**
- The estimated DTG Free concentrations in **Seminal plasma** at weeks 4 and 24 exceed 170-fold and 280-fold the *in vitro* unbound EC_{50} for wild type HIV-1 (0.21 ng/mL)[4].
- **Rectal tissue** concentration is 2 fold higher than PA-IC90[5]. Ileum terminal concentrations slightly lower than plasma but >IC-90.
- No adjustment in patients with hepatic (up to Child B) or renal insufficiency (CreaCl>30 mL/min)[1].

1. DTG US Prescribing Information. ViiV Healthcare, August 2015
2. DTG EU Summary of Product Characteristics, August 2015
3. Letendre S, et al. CROI 2013. Poster 178LB
4. Imaz A, et al, J Infec Dis 2016
5. Greener B, et al. JAIDS 2013;64