Viroteam 2019
Table ronde

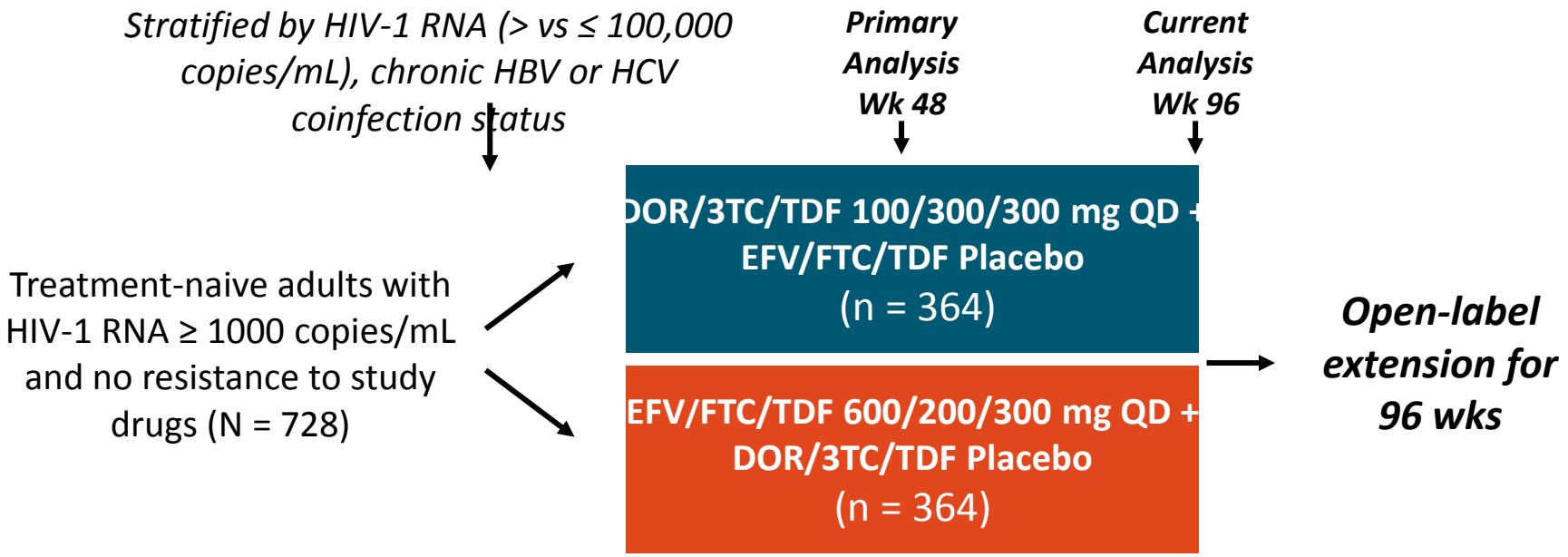
Actualités Thérapeutiques ARV 2018

P de Truchis

Traitements initiaux

DRIVE-AHEAD: DOR/3TC/TDF vs EFV/FTC/TDF in Treatment-Naive Adults at Wk 96

- Multicenter, randomized, double-blind phase III noninferiority trial[1]

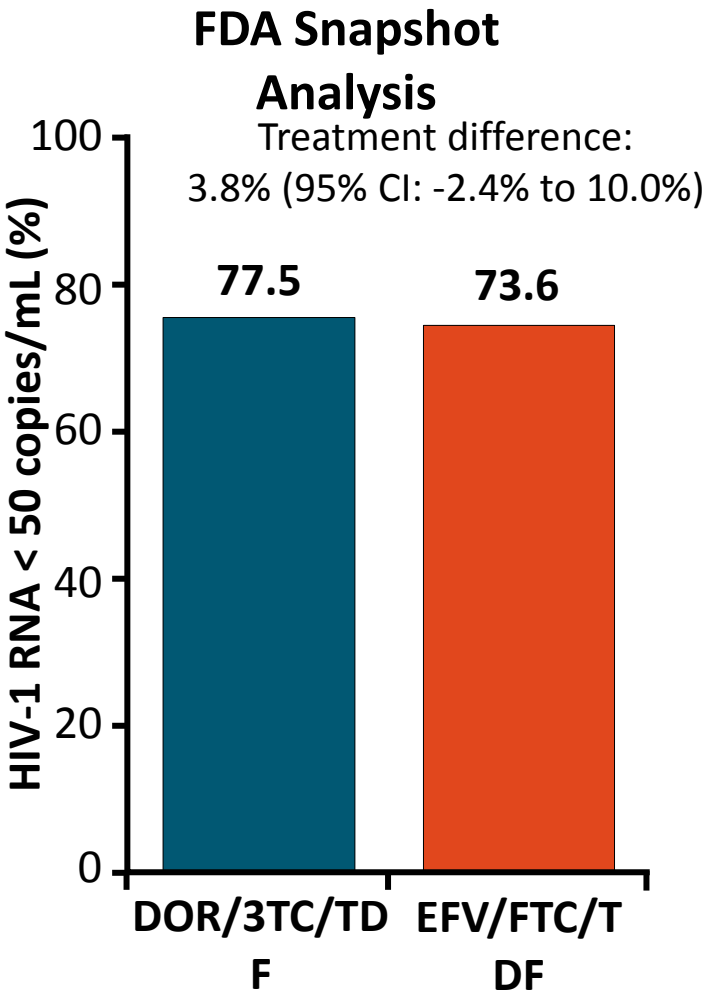


- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -10%)[2]
  - **DOR/3TC/TDF** vs **EFV/FTC/TDF**: **84.3%** vs **80.8%** (difference: 3.5%; 95% CI: -2.0% to 9.0%)
  - Neuropsychiatric events less frequent with **DOR/3TC/TDF**

1. Orkin. IDWeek 2018. Abstr LB1. 2. Orkin. Clin Infect Dis. 2018;[Epub].

Slide credit: clinicaloptions.com

DRIVE-AHEAD: Virologic Outcomes at Wk 96



HIV-1 RNA < 50 copies/mL by Observed Failure Analysis, % (n*)	DOR/3TC/TDF	EFV/FTC/TDF
All participants	83.7 (337)	85.9 (312)
BL HIV-1 RNA, copies/mL		
▪ ≤ 100,000	86.9 (268)	87.5 (248)
▪ > 100,000	71.0 (69)	79.7 (64)
BL CD4+ cell count, cells/mm^3		
▪ ≤ 200	65.0 (40)	82.1 (39)
▪ > 200	86.2 (297)	86.4 (273)

*n refers to total number of participants per subgroup.

- Resistance:
  - DOR-R in 6 patients (1.6%) in DOR arm vs EFV-R in 13 patients (3.8%) in EFV arm
  - NRTI-R in 1.4% vs 1.6%, respectively
- Small decreases in fasting LDL-C, non–HDL-C with DOR vs increases with EFV

Orkin. IDWeek 2018. Abstr LB1. Reproduced with permission.

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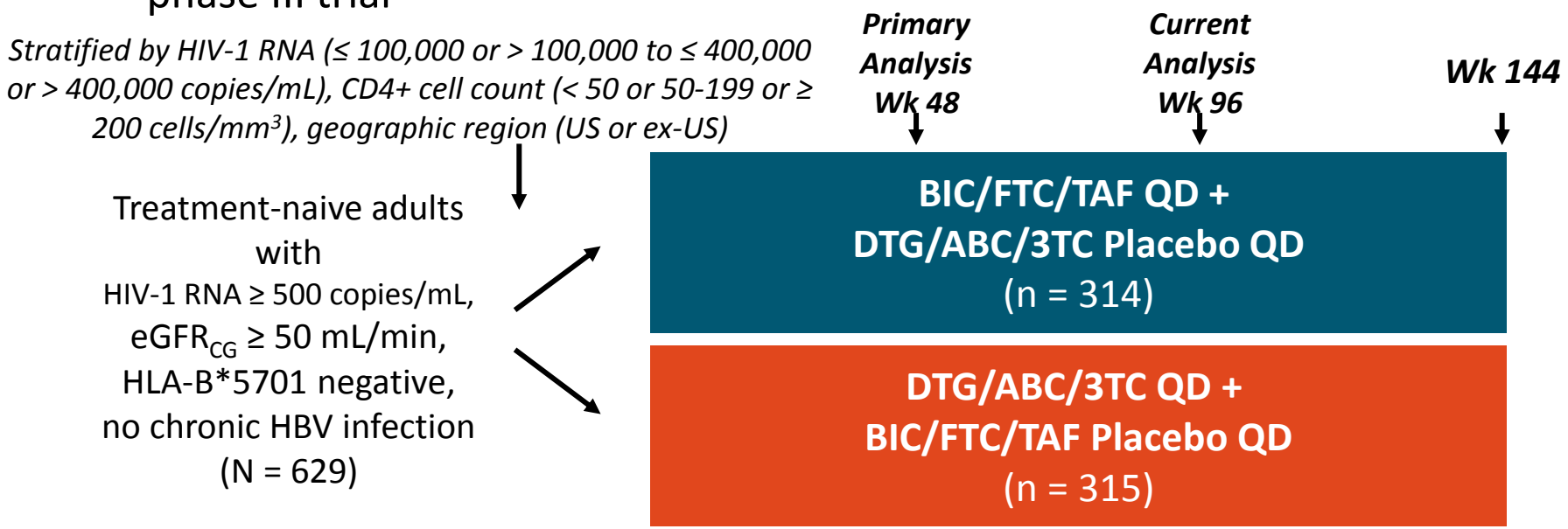
GS-1489: BIC/FTC/TAF vs DTG/ABC/3TC in Treatment-Naive Adults at Wk 96

- Multicenter, randomized, double-blind, active-controlled noninferiority phase III trial[1]

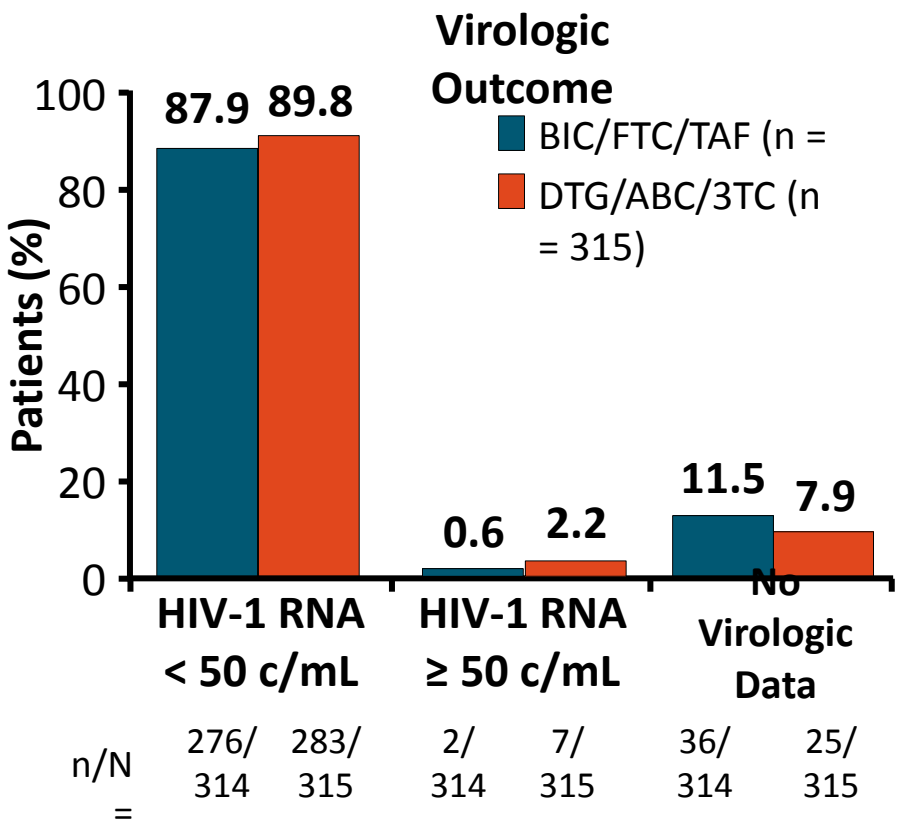


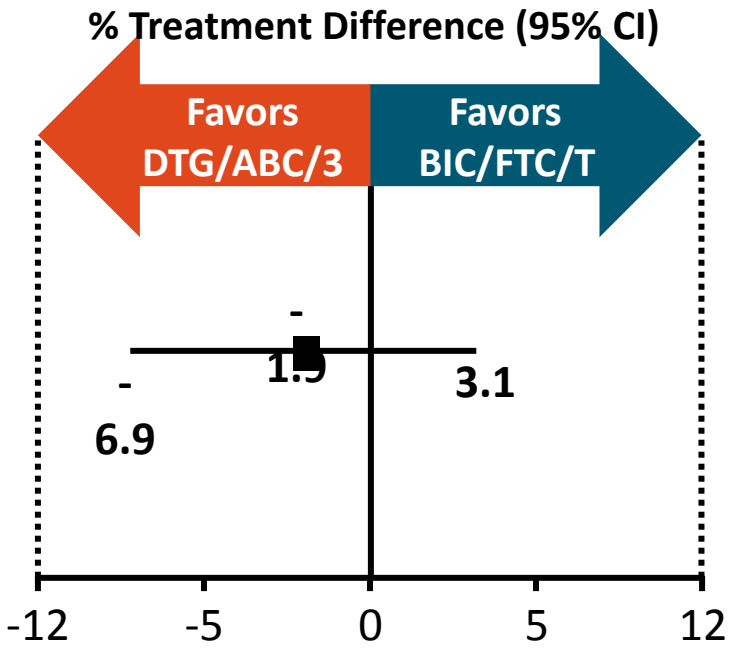
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -12%)[2]
  - **BIC/FTC/TAF** vs **DTG/ABC/3TC**: **92.4%** vs **93.0%** (difference: -0.6%; 95% CI: -4.8% to 3.6%; *P* = .78)
  - Nausea less frequent with **BIC/FTC/TAF** vs **DTG/ABC/3TC** (10% vs 23%; *P* < .0001)

Slide credit: clinicaloptions.com

1. Wohl. IDWeek 2018. Abstr LB4. 2. Gallant. Lancet. 2017;390:2063.

GS-1489: Virologic Outcomes at Wk 96





- Noninferiority of **BIC/FTC/TAF** vs **DTG/ABC/3TC** confirmed in additional analyses
- No treatment-emergent resistance detected in any patient through Wk 96

Wohl. IDWeek 2018. Abstr LB4. Reproduced with permission.

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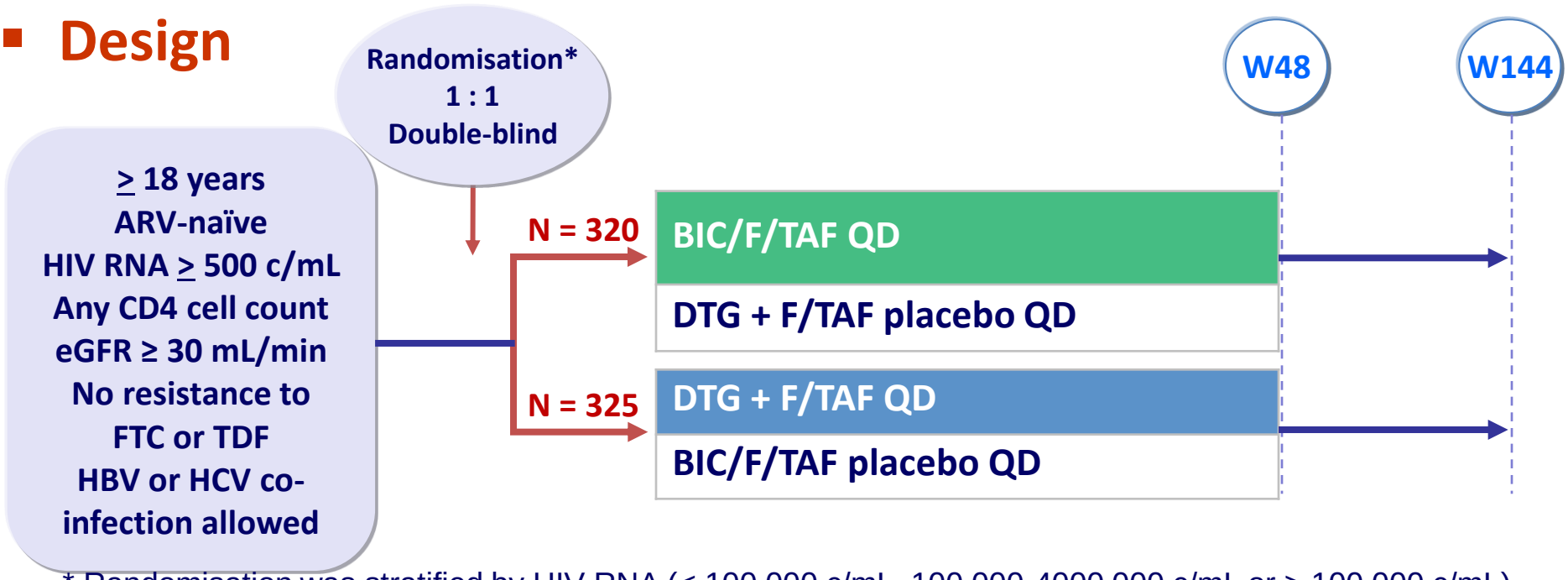
Study GS-US-380-1490: BIC/F/TAF QD vs DTG + F/TAF QD W96 results

Design



* Randomisation was stratified by HIV RNA (≤ 100 000 c/mL, 100 000-4000 000 c/mL or > 100 000 c/mL), CD4 (< 50/mm^3, 50-199/mm^3 or ≥ 200/mm^3) at screening and geographic region (USA vs non-USA)

BIC/F/TAF : 50/200/25 mg, as STR

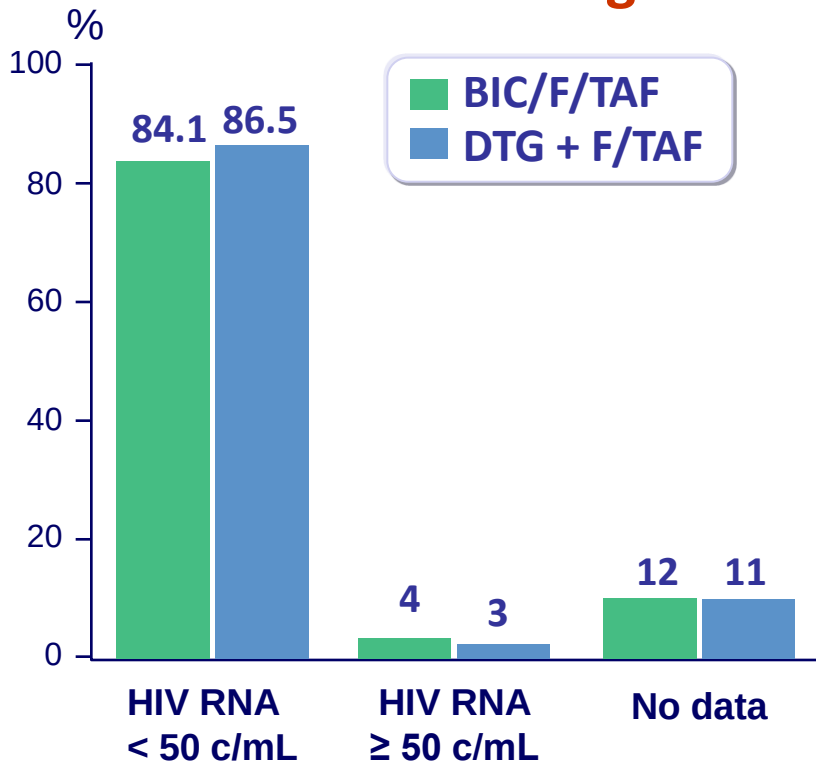
Objective

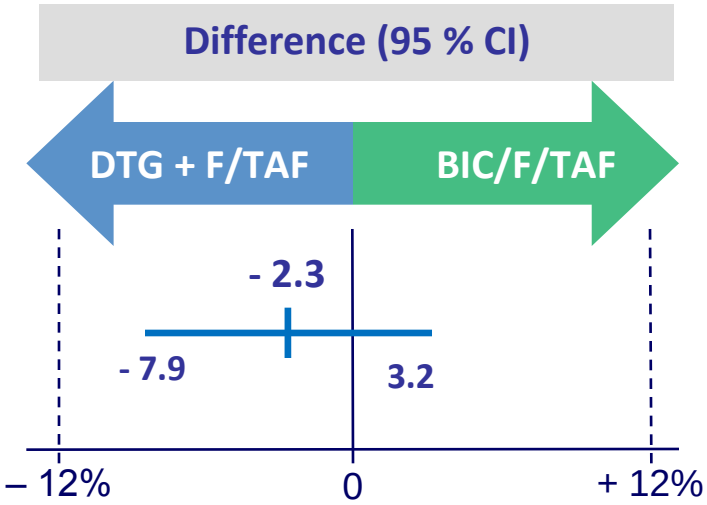
- Non inferiority of BIC/F/TAF at W48: % HIV RNA < 50 c/mL by intention to treat, snapshot analysis (lower margin of the 2-sided 95.002% CI for the difference= -12%, 95% power)

Sax PE. Lancet. 2017 Nov 4;390(10107):2073-2082.

Study GS-US-380-1490: BIC/F/TAF QD vs DTG + F/TAF QD

Virologic outcome at week 96





- **HIV RNA < 50 c/mL (per-protocol)**
  - BIC/F/TAF: 100%
  - DTG + F/TAF: 98.2%

- **Met criteria for resistance testing (HIV RNA ≥ 200 c/mL)**
  - BIC/F/TAF: 7 vs DTG + F/TAF: 6
  - No resistance emergence
- **Mean CD4 increase at W96**
  - BIC/F/TAF: + 237/mm^3
  - DTG + F/TAF: + 281/mm^3

Stellbrink H (Abs. 0211). JIAS 2018; 21, suppl. 8: 8

Study GS-US-380-1490: BIC/F/TAF QD vs DTG + F/TAF QD

Adverse events at week 96

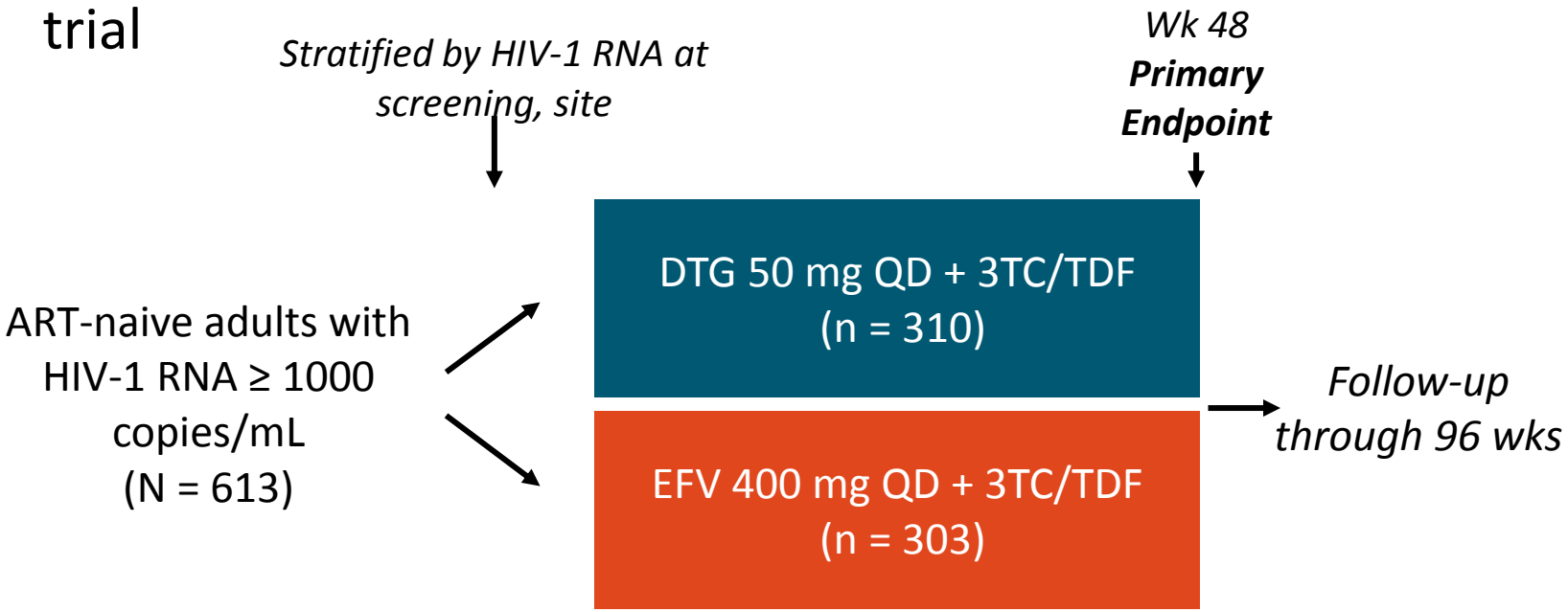
	BIC/F/TAF N = 320	DTG + F/TAF N = 325
Treatment-related	**20%**	**28%**
Leading to discontinuation	**N = 6 (2%)**	**N = 5 (2%)**
Before W48	**5**	**1**
After W48	**1**	**4**
Most common adverse events		
Diarrhea	**18%**	**16%**
Headache	**16%**	**15%**

- Lipid changes were not significantly different between groups
- No renal discontinuations
- No cases of proximal renal tubulopathy

Stellbrink H (Abs. 0211). JIAS 2018; 21, suppl. 8: 8

NAMSAL: DTG- vs EFV 400 mg–Based ART in Treatment-Naive Patients in Cameroon

- Multicenter, randomized, open-label phase III noninferiority trial



- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (FDA Snapshot)
  - Noninferiority tested with 10% margin

NAMSAL: Efficacy at Wk 48 (FDA Snapshot)

Outcome at Wk 48	DTG + 3TC/TDF (n = 310)	EFV 400 + 3TC/TDF (n = 303)	Treatment Difference DTG - EFV (95% CI), %
HIV-1 RNA < 50 c/mL (virologic success), n (%)	231 (74.5)	209 (69.0)	5.5 (-1.6 to 12.7)
HIV-1 RNA < 200 c/mL/< 1000 c/mL, %	89.0/91.9	83.5/86.5	--
HIV-1 RNA > 50 c/mL (virologic failure), n	62	70	--
▪ D/c for death	6	7	--
▪ D/c other reasons (LTFU, withdrawn)	9	15	--
HIV-1 RNA < 50 c/mL by BL VL, n/N (%)			
▪ HIV-1 RNA < 100,000 c/mL	94/103 (91.3)	86/103 (83.5)	7.8 (-1.2 to 16.8)
▪ HIV-1 RNA > 100,000 c/mL	137/207 (66.2)	123/200 (61.5)	4.7 (-4.6 to 14.0)
▪ HIV-1 RNA > 500,000 c/mL	51/93 (54.8)	55/95 (57.9)	--

- AEs: DTG 11% vs EFV 400 8%; AIDS-defining events: DTG 8% vs EFV 400 10%
- Virologic failure (HIV-1 RNA > 1000 c/mL) observed in 19 pts; emergent resistance in 0/3 DTG failures vs 9/10 EFV 400 failures

Slide credit: clinicaloptions.com

Cournil. Glasgow 2018. Abstr O342.

le meilleur ...de la CROI 2018

Essai ANDES : bithérapie DRV/r + 3TC en 1ère ligne – Résultats à S48

- Schéma : essai randomisé, ouvert, multicentrique (Argentine)
- Critères d'inclusion
  - Adultes VIH, naïfs d'ARV, Ag HBs-, CV > 1 000 c/ml
  - Absence de résistance aux INTI et IP

S48
critère principal

Randomisation
1:1
stratifiée sur CV
< ou > 100 000 c/ml

- **DRV/r 800/100 mg qd + 3TC 300 mg qd (n = 75)**
- **DRV/r 800/100 mg qd + 3TC/TDF 300/300 mg qd (n = 70)**

DRV/r coformulation (générique)

- Caractéristiques à l'inclusion : âge médian : 33 ans, hommes : 91 %, CV médiane : 4,5 $\log_{10}$ c/ml, CV > 100 000 c/ml : 24 %, CD4, médiane : 383/mm^3

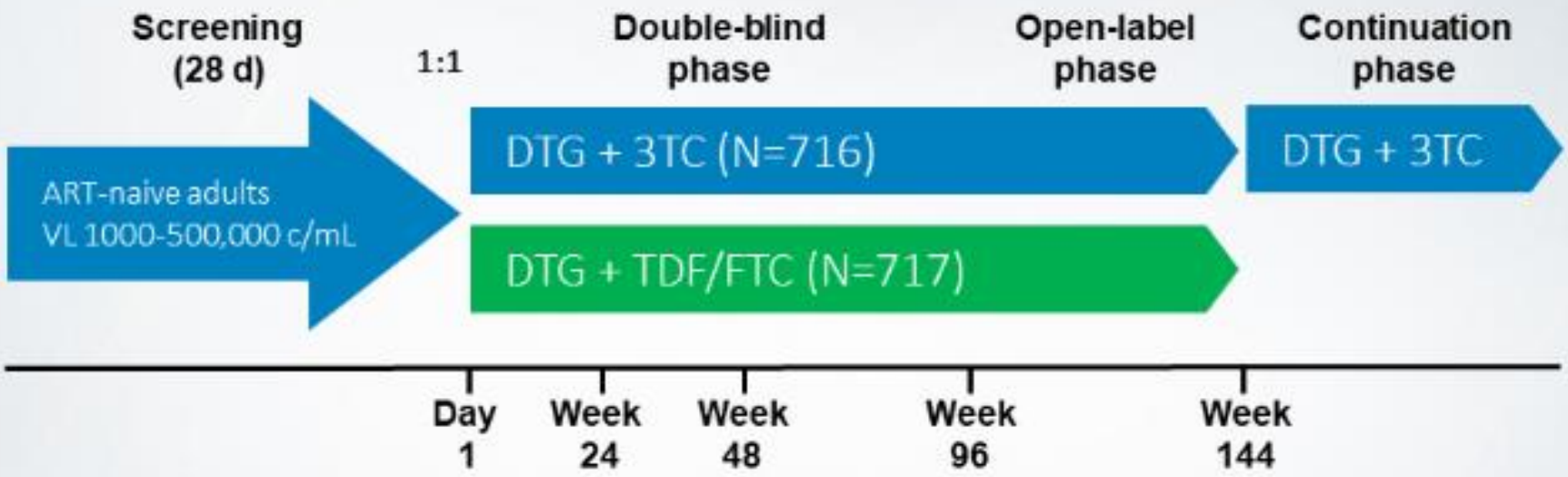
% CV < 50 c/ml à S48

	DRV/r + 3TC	DRV/r + 3TC/TDF
ITT- Tous patients	93	94
ITT – CV J0 > 100 000 c/ml	91	92
Per protocole	100	99

- Evénements indésirables les plus fréquents : gastro-intestinaux
  - Bithérapie : 7 %
  - Trithérapie : 14 %
- ↗ lipides (cholestérol total, LDL-cholestérol, triglycérides) moindre dans le groupe trithérapie

Figueroa MI, CROI 2018, Abs. 489

GEMINI 1 AND 2: STUDY DESIGN

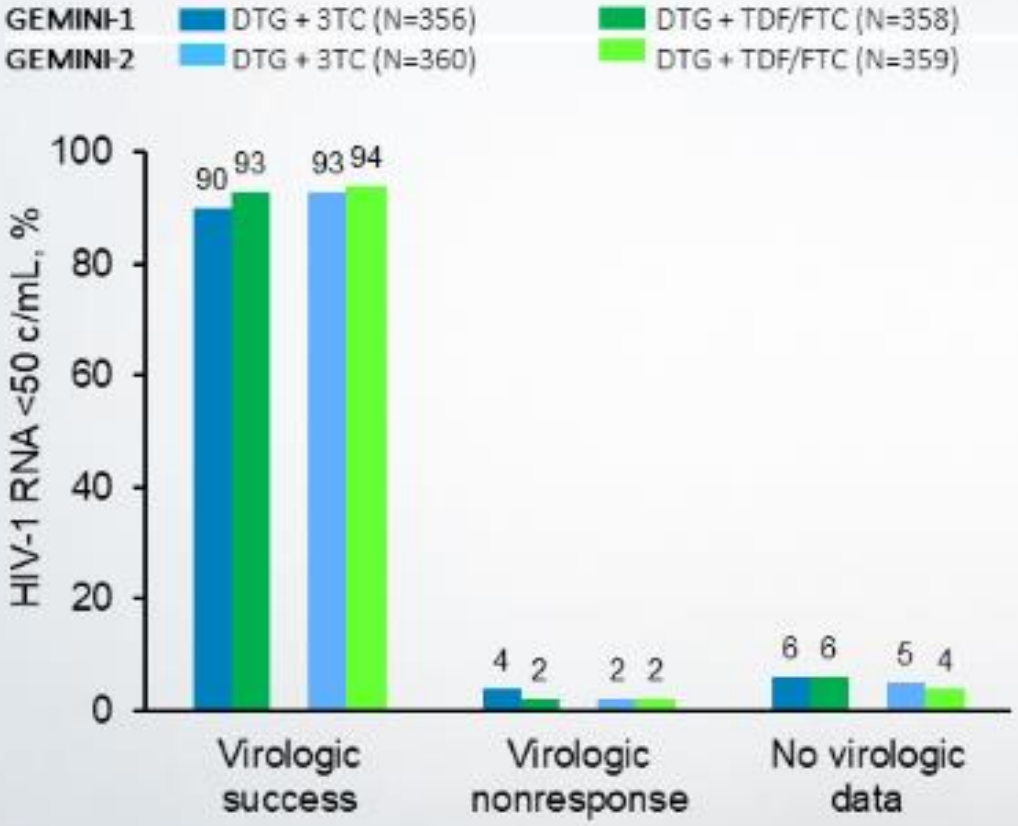


- Eligibility criteria
  - ≤10 days of prior ART
  - No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
  - No HBV infection or need for HCV therapy

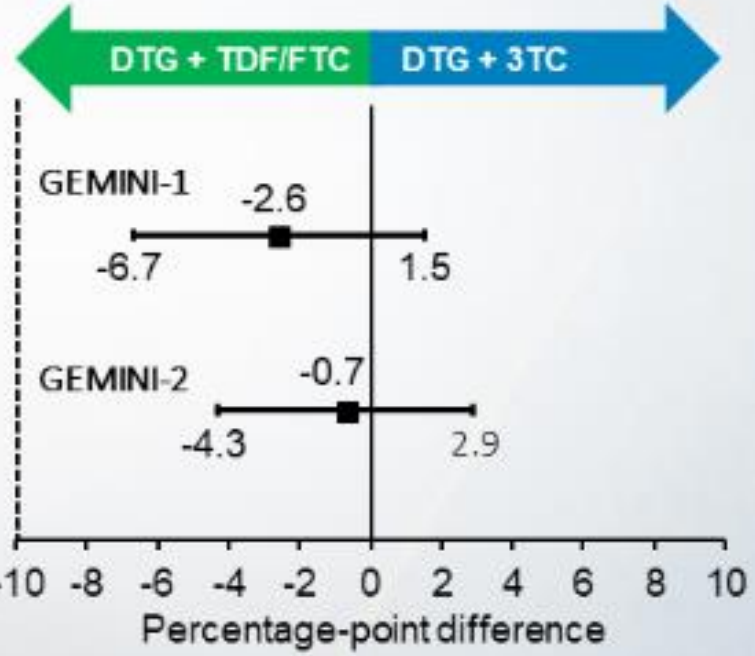
Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.

GEMINI 1 AND 2: SNAPSHOT OUTCOMES AT WEEK 48

Virologic outcome



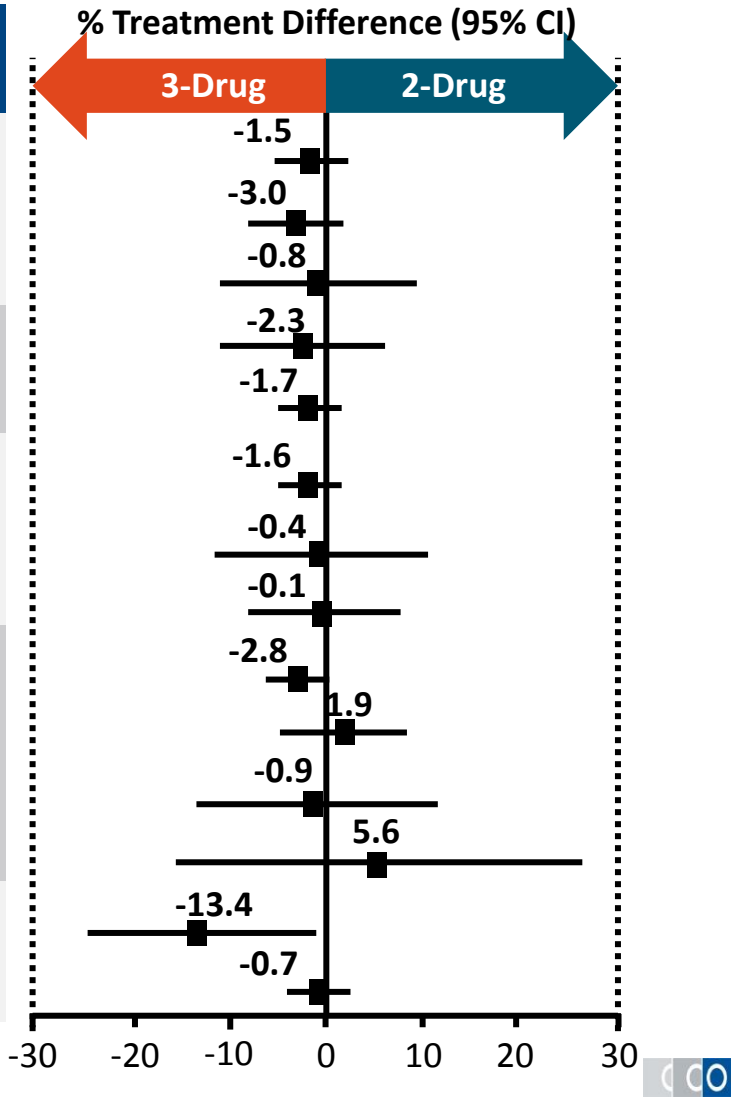
Adjusted treatment difference (95% CI)[a]



Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.

GEMINI-1 and -2: Wk 48 Subgroup Analysis

HIV-1 RNA < 50 copies/mL, n/N (%)		DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)
Age, yrs	▪ < 35	386/420 (92)	381/408 (93)
	▪ 35 to < 50	211/231 (91)	216/229 (94)
	▪ ≥ 50	58/65 (89)	72/80 (90)
Sex	▪ Female	100/113 (88)	89/98 (91)
	▪ Male	555/603 (92)	580/619 (94)
Race	▪ White	447/480 (93)	471/497 (95)
	▪ Black	83/99 (84)	64/76 (84)
	▪ Asian	67/71 (94)	68/72 (94)
HIV-1 RNA, copies/mL	▪ ≤ 100,000	526/576 (91)	531/564 (94)
	▪ > 100,000	129/140 (92)	138/153 (90)
	▪ > 250,000	45/51 (88)	41/46 (89)
	▪ > 400,000	16/18 (89)	20/24 (83)
CD4+ count, cells/mm^3	▪ ≤ 200	50/63 (79)	51/55 (93)
	▪ > 200	605/653 (93)	618/662 (93)



Orkin. Glasgow 2018. Abstr P021. Reproduced with permission.

Slide credit: clinicaloptions.com

Viral decay with DTG+ 3TC in naive patients

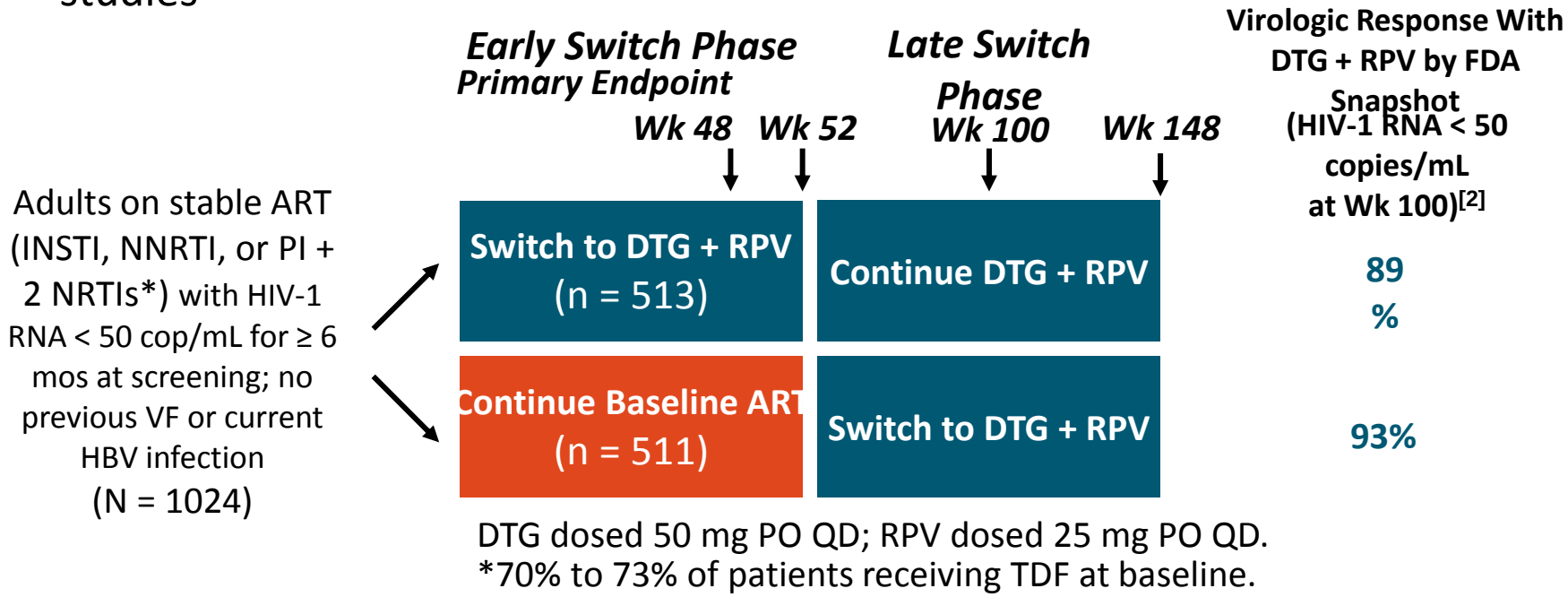
- Retrospective analysis
  - 120 patients initiating DTG + 3TC (ACTG 5353)
  - 468 patients initiating DTG + 2 NRTI (SPRING-1 + SINGLE)

- **Results**
  - Faster initial viral decay with DTG + 3TC (W0-W2)
  - Globally, decay rate similar W0-W24 between 2 DR and triple ART even if baseline VL up to 500,000 c/mL
  - Slower initial decay rate when baseline VL > 100 000 c/mL with no difference between DTG + 3TC and DTG triple

Stratégies thérapeutiques switches

SWORD-1 and -2: Switch to DTG + RPV vs Continuation of Baseline ART in Virologically Suppressed Adults

- Parallel, randomized, open-label, multicenter phase III noninferiority studies[1]



DTG dosed 50 mg PO QD; RPV dosed 25 mg PO QD.
*70% to 73% of patients receiving TDF at baseline.

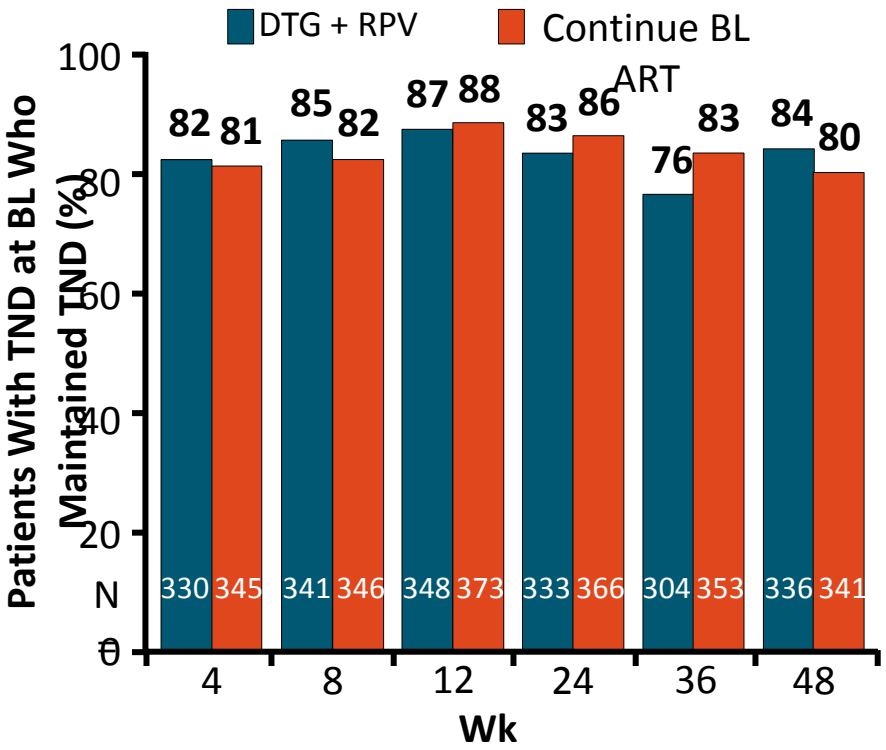
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (noninferiority margin: -8%)[3]
  - 95% in each arm at Wk 48 (adjusted treatment difference: -0.2%; 95% CI: -3.0% to 2.5%)
- Wk 100: 1% confirmed virologic withdrawal; emergent NNRTI resistance in 3/10, all early switch arm[2]

1. Underwood. Glasgow 2018. Abstr P311. 2. Aboud. AIDS 2018. Abstr THPEB047. 3. Llibre. Lancet. 2018;391:839.

Slide credit: clinicaloptions.com

SWORD-1 and -2: Viral Replication With HIV-1 RNA < 50 copies/mL

- Current analysis used viral load assay that reports qualitative target detected or target not detected for HIV-1 RNA < 40 copies/mL
- Patients with TND at baseline: 78% for DTG + RPV arm, 83% for continue BL ART arm



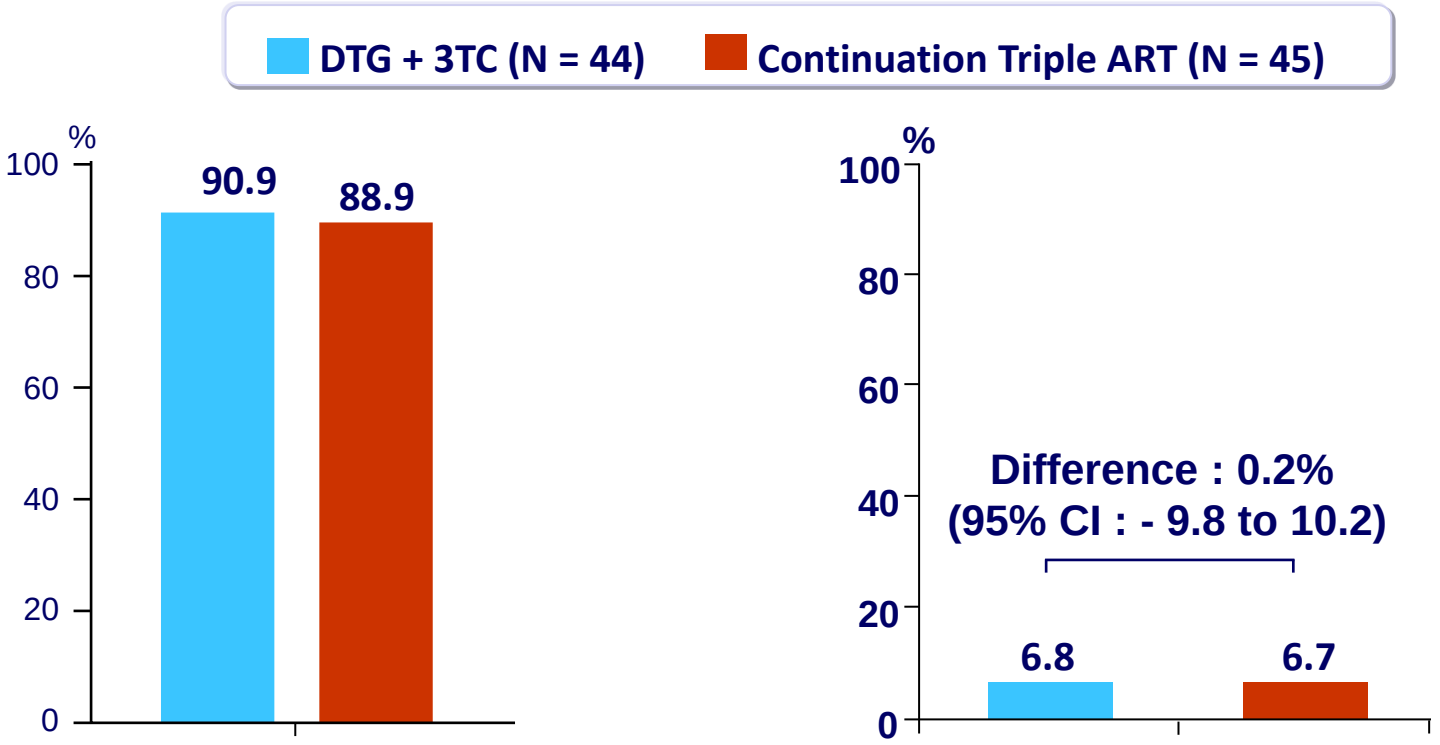
- Similar rate of post-BL TD and TND categories by BL category across arms
- Qualitative viremia by TD more common with BL TD vs BL TND
- No difference between arms in virologic success by TND at Wk 48 (FDA Snapshot)
  - DTG + RPV 84% vs continued BL ART 80% (adjusted difference: 3.1%; 95% CI: -2.2% to 8.3%)

Underwood. Glasgow 2018. Abstr P311.

ASPIRE Study: switch to DTG + 3TC

HIV RNA < 50 c/mL at W48 (ITT, snapshot)

Primary endpoint: Treatment failure t W48



LATTE-2 – W160 results

Week 160 Snapshot study outcomes (ITT-ME)[a]	CAB LA + RPV LA Q8W[b] (N = 115)	CAB LA + RPV LA Q4W[c] (N = 115)
% HIV-1 RNA < 50 copies/ml at W160	90 %	83 %
Snapshot virologic non-response	4 %	0
Data in window not < 50 copies/ml	< 1 %	0
Discontinued due to lack of efficacy	< 1 %	0
Discontinued due to other reasons while not suppressed	3 %	0
Snapshot no virologic data	5 %	17 %
Discontinued due to AE or death	< 1 %	10 %
Discontinued due to other reasons while suppressed	4 %	7 %

a : ITT-maintenance exposed following 20W induction with oral CAB + ABC/3TC
b : Q8W : CAB LA 600 mg + RPV LA 900 mg IM ; c : Q4W : CAB LA 400 mg + RPV LA 600 mg IM

- Discontinuation for AE : Q8W : 3% vs Q4W : 10%
- Differences in outcomes between Q8Wand Q4W due to non-virologic reasons
- Both regimens are under evaluation in phase 3 studies

Margolis D. (Abs. P118). JIAS 2018; 21 , suppl. 8:87-88

Schémas de bithérapies initiales

Essai (n pts)	Bras allégé	Comparateur	Situation	Recul, sem.	Efficacité virol.
GARDEL (426)	LPV/r + 3TC	LPV/r +2NRTI	Induction	48	88% vs83 (Non-inf.)
ANDES (145)	DRV/r + 3TC	DRV/r+ TDF-3TC	Induction	48	93% vs94 (Non-inf.)
NEAT 01 (805)	DRV/r + RAL	DRV/r+TDF-FTC	Induction	96	81%vs85 (Non-inf)*
GEMINI 1-2 (1400)	DTG + 3TC	DTG+TDF/FTC	Induction	48	Non inf
PADDLE (20)	DTG + 3TC	-	Induction	48	90% succès
ACTG5353 (120)	DTG + 3TC	-	Induction	48	90% succès**

* Moins bien si nadir <200; apparition de résistance aux INIs

* * Un cas de résistance émergente chez un patient « chaotique » (R263K + M184V)

Conclusion : IP ou INI + 3TC…

Schémas de bithérapies en maintenance

Essai (n pts)	Bras allégé	Comparateur	Situation	Recul, sem.	Succès virol.
OLE (250)	LPV/r+3TC	LPV/R+2NRTI	Maintenance	48	87.8% vs86.6% (Non-Inf)
ATLAS-M (266)	ATV/r + 3TC	ATV/r+2 NRTI	Maintenance	48	90% vs. 80 (Sup.)
SALT (286)	ATV/r + 3TC	ATV/r+2 NRTI	Maintenance	96	74% vs. 74 (Non-inf)
DUAL (249)	DRV/r+3TC	DRV/r+2NRTI	Maintenance	48	89% vs93 (Non-inf)
SWORD 1-2 (1024)	DTG + RPV	Trithérapie	Maintenance	48	95%vs95 (Non-inf.)**
ASPIRE (89)	DTG+3TC	tri	Maintenance	48	91%vs89%
LAMIDOL (104)	DTG + 3TC	-	Maintenance	48	97% succès
TRULIGHT (222)	TDF/FTC	TDF/FTC + x	Maintenance	24(an.I)	91% succès ?
ETRAL (160)	ETV + RAL	-	Maintenance	48	95% succès
LATTE 2 (309)	CABO + RPV IM / 8 ou 4s	CABO + ABC/3TC	Maintenance	96	94%/87%/84% succès

** 1 cas de résistance émergente (K101K/E)

→ stratégies comprenant 1 inhibiteur RT + (IP ou INI)