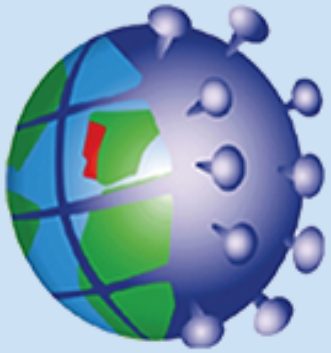
REUNIÃO DE OUTONO

17 de novembro

2ª Reunião de Sócios

APECS
Associação Portuguesa para o Estudo Clínico da SIDA



HIV Drug Therapy GLASGOW 2018

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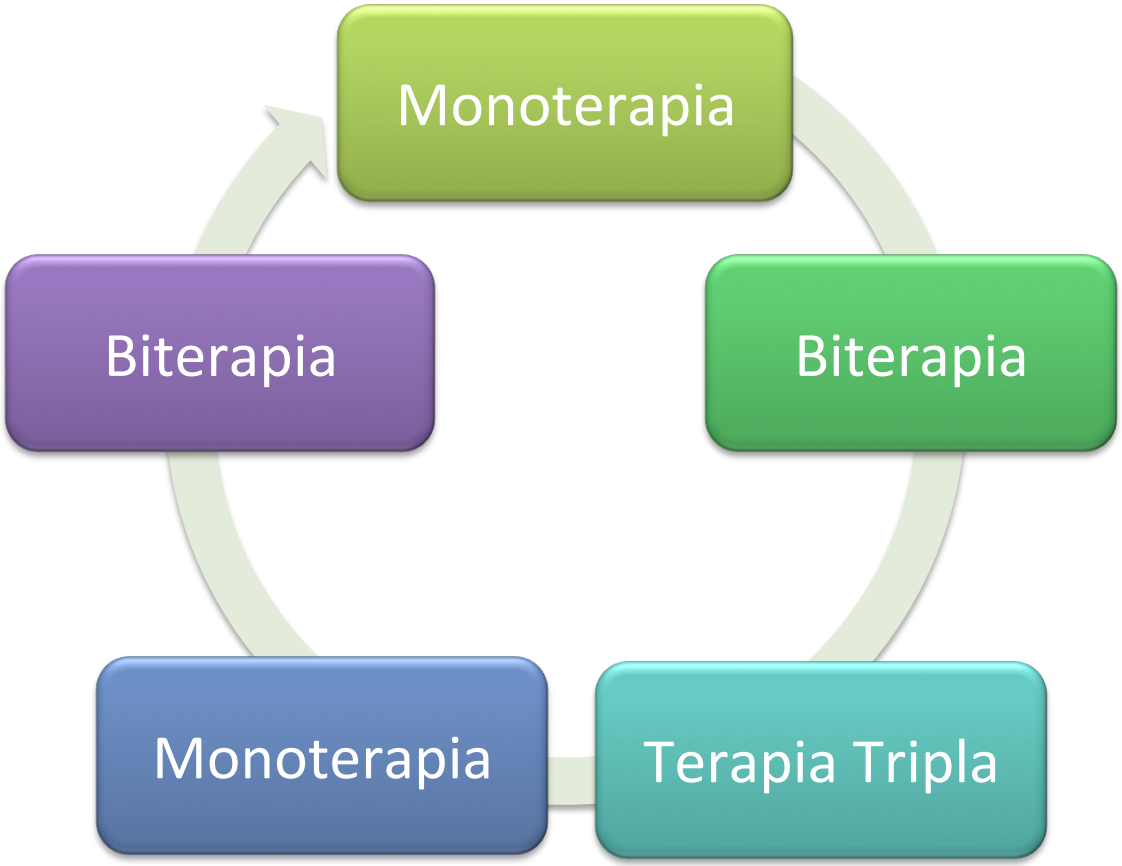
HIV Drug Therapy GLASGOW 2018

Estratégias Terapêuticas

TD vs TT – Oposição ou Complementaridade?


Monoterapia
Biterapia
Terapia Tripla
Monoterapia
Biterapia

Dual therapy with PI/r+3TC or PI/r+TDF shows non-inferior HIV RNA suppression and rates of discontinuation for adverse events, versus triple therapy. Meta-analysis of seven randomised trials in 1635 patients

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HIV Drug Therapy GLASGOW 2018

Dual Therapies – which to choose?

Dual therapy	**DTG + 3TC**	**DTG + RPV**	**PI/r + 3TC or TDF**
Clinical trials	GEMINI 1+2	SWORD 1+2	7 trials
Patients	1433	1024	1635
Naïve/switch	Naïve	Switch	Naïve + Switch
Non-inferior efficacy	Yes	Yes	
Safety benefits (hard endpoints)	No	No	

Aim

To evaluate **safety and efficacy** of dual therapy with **PI/r + NRTI** versus triple therapy

Results: Trial Designs

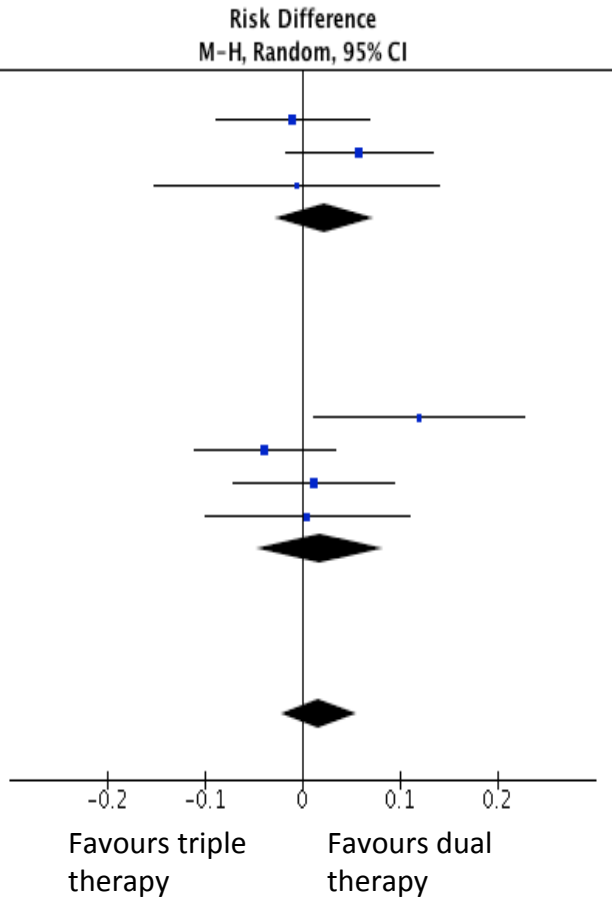
Study	Follow Up Week	Dual	Triple	Treatment History
GARDEL (n=306)	96	LPV/r + 3TC	LPV/r + 2 NRTI	Naïve
KALEAD (n=152)	24	LPV/r + TDF	LPV/r + 2 NRTI	Naïve
ANDES (n=145)	48	DRV/r + 3TC	DRV/r + 3TC/ TDF	Naïve
OLE (n=250)	48	LPV/r + 3TC	LPV/r + 2 NRTI	Switch
ATLAS-M (n=266)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
SALT (n=267)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
DUAL-GESIDA (n=249)	48	DRV/r + 3TC	DRV/r + 2 NRTI	Switch
Total (n=1635)				

Results: HIV-RNA <50 copies/mL

Study	Follow Up Week	Dual	Triple	RD, 95% Confidence Interval
GARDEL (n=306)	96	90.3%	84.4%	+6% (-2%, +13%)
KALEAD (n=152)	24	69.4%	70.0%	-1% (-15%, +14%)
ANDES (n=145)	48	93.3%	94.2%	-1% (-9%, +7%)
OLE (n=250)	48	87.8%	86.6%	+1% (-7%, +9%)
ATLAS-M (n=266)	96	77.4%	65.4%	+12%(+1%, +23%)
SALT (n=267)	96	74.4%	73.4%	+1% (-10%, +11%)
DUAL-GESIDA (n=249)	48	88.9%	92.7%	-4% (-11% , +3%)
Total (n=1635)	**p=0.04**	**83.6%**	**80.6%**	**+2% (-2%, +6%)**

Results: HIV-RNA <50 copies/mL

Study or Subgroup	PI/r Dual Therapy Events	Total	PI/r Triple Therapy Events	Total	Weight	Risk Difference M-H, Random, 95% CI
11.1.1 Naive						
ANDES	70	75	66	70	17.4%	-0.01 [-0.09, 0.07]
GARDEL	149	165	119	141	18.5%	0.06 [-0.02, 0.13]
KALEAD	50	72	56	80	6.4%	-0.01 [-0.15, 0.14]
Subtotal (95% CI)		**312**		**291**	**42.3%**	**0.02 [-0.03, 0.07]**
Total events	269		241			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.72$, df = 2 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 0.87 (P = 0.39)						
11.1.2 Switch						
ATLAS-M	103	133	87	133	10.8%	0.12 [0.01, 0.23]
DUAL-GESIDA	112	126	114	123	19.7%	-0.04 [-0.11, 0.03]
OLE	108	123	110	127	16.1%	0.01 [-0.07, 0.09]
SALT	99	133	99	134	11.2%	0.01 [-0.10, 0.11]
Subtotal (95% CI)		**515**		**517**	**57.7%**	**0.02 [-0.05, 0.08]**
Total events	422		410			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.28$, df = 3 (P = 0.10); $I^2 = 52\%$						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**827**		**808**	**100.0%**	**0.02 [-0.02, 0.06]**
Total events	691		651			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.00$, df = 6 (P = 0.24); $I^2 = 25\%$						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0\%$						



Results: PDVF

Study	Follow Up Week	Dual	Triple	RD, 95% Confidence Interval
GARDEL (n=306)	96	7.3%	6.4%	+1% (-5%, +7%)
KALEAD (n=152)	24	15.3%	8.8%	-7% (-4%, +17%)
ANDES (n=145)	48	0.0%	1.4%	-1% (-5%, +2%)
OLE (n=250)	48	2.4%	2.4%	0% (-4%, +4%)
ATLAS-M (n=266)	96	1.5%	6.8%	-5% (-10%, -1%)
SALT (n=267)	96	6.8%	3.7%	+3% (-2%, +8%)
DUAL-GESIDA (n=249)	48	3.2%	1.6%	+2% (-2%, +8%)
Total (n=1635)	**p=0.98**	**5.0%**	**4.5%**	**0% (-2%,+2%)**

Results: Treatment Emergent Resistance Mutations

Study	Follow Up Week	Dual	Triple	RD, 95% Confidence Interval
GARDEL (n=306)	96	2.4%	2.1%	-1% (-5%, +2%)
KALEAD (n=152)	24	0.0%	1.3%	-1 % (-5%, +2%)
OLE (n=250)	48	0.8%	0.0%	+1% (-1%, +1%)
ATLAS-M (n=266)	96	0.0%	0.0%	0% (-1%, +1%)
SALT (n=267)	96	0.0%	0.7%	-1% (-3%, +1%)
DUAL-GESIDA (n=249)	48	0.0%	0.0%	-1% (-1%, +1%)
Total (n=1490)	**p=0.89**	**0.7%**	**0.7%**	**0% (-1%, +1%)**

Major Mutation Analysis

Dual

NRTI mutations

- **M184V**, n=5

Major PI mutations

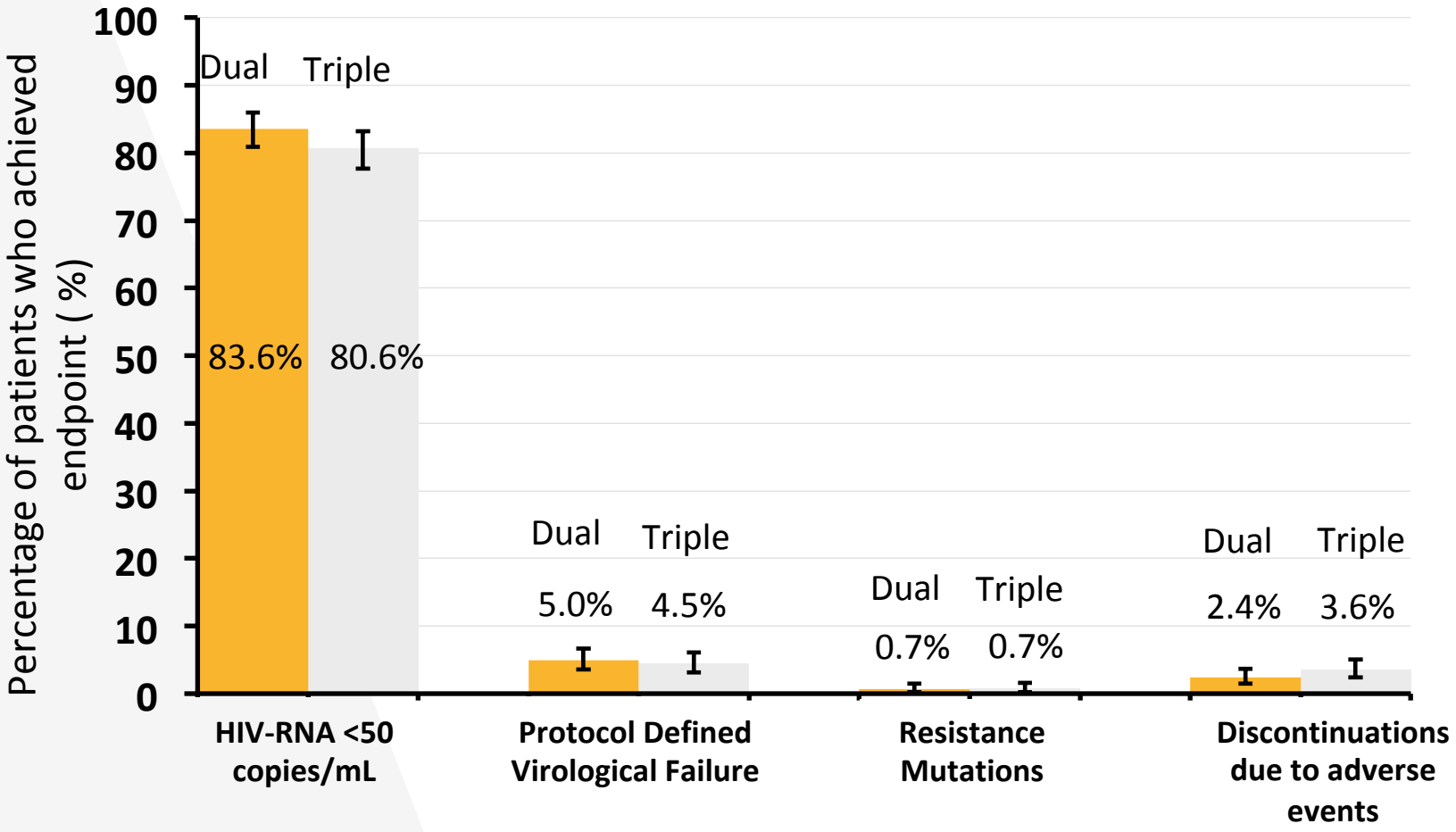
0/52 amplified samples

Triple

NRTI mutations

- **M184V**, n=5;

Summary Findings



Conclusions

- Rates of HIV RNA suppression < 50 copies/mL on PI/r+3TC or PI/r+TDF were non-inferior compared to PI/r + 2 NRTI
- Fewer discontinuations for adverse events but not significant
- No increase risk of treatment emergent resistance mutations
- Generic combinations of DRV/r + 3TC could save significant cost relative to branded triple combinations including TDF/FTC or TAF/FTC

Dual Therapies – which to choose?

Dual therapy	**DTG + 3TC**	**DTG + RPV**	**PI/r + 3TC or TDF**
Clinical trials	GEMINI	SWORD 1+2	7 trials
Patients	1433	1024	1635
Naïve/switch	Naïve	Switch	Naïve + Switch
Non-inferior efficacy	Yes	Yes	**Yes**
Safety benefits (hard endpoints)	No	No	**No**
List price (per person per year in the UK)			

Questões

Doentes Naïve ou após Supressão?

Quanto tempo após Supressão?

Adesão ?

Blips ?

Falência virológica ?

GEMINI-1 and -2

- 2DRs are being evaluated against standard 3-drug regimens for their potential to reduce cumulative drug exposure and drug–drug interactions during lifelong ART in people living with HIV
- We evaluated the 2DR of DTG + 3TC in 2 identical global, double-blind, multicenter, phase III studies GEMINI-1 and -2 (ClinicalTrials.gov: NCT02831673/NCT02831764)

ART, antiretroviral therapy; 2DR, two-drug regimen; DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; 3TC, lamivudine; NRT, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate.

1. Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Abstract TUAB0106LB.

Demographics and Baseline Characteristics: Pooled ITT–E Population

- 1433 adults from 21 countries were randomized and treated in GEMINI-1 and -2

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
>100,000, n (%)	140 (20)	153 (21)
CD4+ cell count, median (range), cells/ mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200, n (%)	63 (9)	55 (8)

DTG, dolutegravir; FTC, emtricitabine; ITT–E, intent-to-treat–exposed; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

Two-Drug Regimen of Dolutegravir Plus Lamivudine (DTG + 3TC) Is Non-Inferior to Dolutegravir Plus Tenofovir/ Emtricitabine (DTG + TDF/FTC) at 48 Weeks in Antiretroviral Treatment–Naive Adults With HIV-1 Infection:

GEMINI Studies

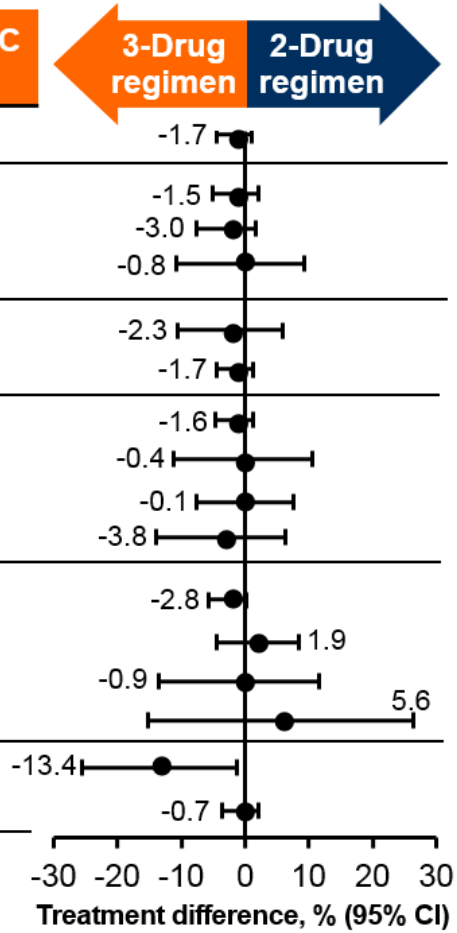
- Study design: Phase III, randomized (1:1), double-blind, parallel-group
  - Participants received either DTG + 3TC (N=716) or DTG + TDF/FTC (N=717)
- Stratification: By Screening plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm3)
- Key eligibility criteria: ≥18 years of age; ART naive (≤10 days of prior ART); no evidence of pre-existing major resistance-associated mutations; no hepatitis B virus infection; HIV-1 RNA 1000 to 500,000 c/mL
- Primary endpoint: Proportion with plasma HIV-1 RNA <50 c/mL at Week 48 using snapshot algorithm; −10% non-inferiority margin
- Subgroup analyses: Snapshot outcomes and AE frequencies by demographic and Baseline HIV-1 RNA and CD4+ cell count
- Statistical analysis: For the primary endpoint, estimates and CIs were based on a stratified analysis using Cochran–Mantel–Haenszel weights. The subgroup analyses were unadjusted

AE, adverse event; ART, antiretroviral therapy; CI, confidence interval.

Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

Snapshot Analysis Outcomes at Week 48 by Subgroups: Pooled ITT–E Population

	Subgroup	DTG + 3TC n/N (%)	DTG + TDF/FTC n/N (%)
	Overall	655/716 (91)	669/717 (93)
Age	<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)
	African heritage	83/99 (84)	64/76 (84)
	Asian	67/71 (94)	68/72 (94)
	Other	58/66 (88)	66/72 (92)
HIV-1 RNA	≤100,000 c/mL	526/576 (91)	531/564 (94)
	>100,000 c/mL	129/140 (92)	138/153 (90)
	>250,000 c/mL	45/51 (88)	41/46 (89)
	>400,000 c/mL	16/18 (89)	20/24 (83)
CD4+ count	≤200 cells/mm^3	50/63 (79)	51/55 (93)
	>200 cells/mm^3	605/653 (93)	618/662 (93)



CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; ITT–E, intent-to-treat–exposed; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

Variable, n (%)	GEMINI 1		GEMINI 2		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

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Snapshot Non-Response in Participants With Baseline CD4+ Cell Count ≤200 cells/mm^3

Participant	Snapshot outcome (Week 48)	Clinical reason for study DC	Study day of DC	Last study VL, c/mL
DTG + 3TC				
1	VL ≥50 c/mL	NA: continued in study	NA	≥50[a,b]
2	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
3	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
4	VL ≥50 c/mL	Protocol-defined virologic withdrawal	205	362
9	VL ≥50 c/mL	NA: Unplanned change in ART	NA	≥50[a,b]
10	VL ≥50 c/mL	PV: randomized in error[c]	15	102
12	VL ≥50 c/mL	Lost to follow-up	356	64366
5	No virologic data	AE: pulmonary TB	206	<50
6	No virologic data	AE: cerebral chagoma	164	507,564[d]
7	No virologic data	Treatment for HCV infection	165	<50
8	No virologic data	Withdrew consent	115	<50
11	No virologic data	PV: randomized in error[e]	28	1,848,435[f]
13	No virologic data	Lost to follow-up	100	<50
DTG + TDF/FTC				
14	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
16	VL ≥50 c/mL	Investigator discretion: incarceration	76	384
15	No virologic data	Withdrew consent	342	<50
17	No virologic data	Lost to follow-up	175	<50

AE, adverse event; DC, discontinuation; DTG, dolutegravir; FTC, emtricitabine; HBV, hepatitis B virus; 3TC, lamivudine; NA, not applicable; PV, protocol violation; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; VL, viral load. [a]VL results from Week 60 shown for participants who continued the study beyond Week 48. [b]Value not provided due to potential for unblinding. [c]Enrolled with HBV coinfection. [d]Participant had discontinued study treatment prior to study DC. [e]Enrolled with Screening VL of >500,000 c/mL. [f]VL result available from Day 1 only.

Orkin et al. HIV Glasgow 2018; Glasgow, UK. Poster P021.

Impact of previous M184V on virological outcome of switch to 3TC-based dual therapies

Retrospective observational study performed in the **ARCA database**

Aim of the study was to compare virological efficacy of bPI or INI +3TC in patients with and without a history of M184V detection.

§ Pts with HIV-RNA ≤50 cps/mL switching to DT (3TC+ PI/r or INI) and with at least one previous genotype were selected

1. **Primary endpoint:**
    1. Time to virological failure in M184V+ and M184V-

2. **Secondary endpoints:**
    1. Predictors of virological failure and virological blips
    2. Time to virological blips in M184V+ and M184V-

Definitions:
Virological failure (VF): 2 VL >50 cp/mL or single value ≥200 cp/mL
Viral blip (VB): single VL 51-199 cp/mL, not confirmed
M184V was assessed in the historical genotypic resistance tests (hGRT) and in the last genotype

Patients baseline characteristics

	M184V- (n=349)	M184V+ (n=87)	p
Age, years*	46 (39; 53)	52 (48; 57)	<0.001
Male sex	257 (72%)	53 (61%)	0.019
Caucasians	308 (88%)	84 (97%)	0.077
Risk factor **Sexual** **IDU** **Other/unknown**	 225 (64%) 40 (11%) 84 (24%)	 56 (64%) 21 (24%) 10 (11%)	0.001
HCV infection	62 (18%)	24 (28%)	<0.001
HBsAg+	12 (3%)	2 (2%)	0.001
Previous AIDS events	40 (12%)	16 (18%)	0.084
HIV-RNA at zenith, cps/mL*	104,750 (35,807;329,250)	107,910 (27,000;252,900)	0.416
Years from HIV diagnosis*	7.8(3.8;13.7)	19.2 (16.1;23.0)	<0.001
Years from first ART initiation *	5.6 (2.8;10.0)	16.6 (12.8;18.9)	<0.001
Duration of viral suppression, years*	3.8 (2.2;6.4)	6.6 (3.7;8.9)	<0.001
Nadir CD4+, cells/µL*	224 (81;313)	147 (57;199)	<0.001
Current CD4+, cells/µL*	620 (453;780)	632 (409; 922)	0.131
Type of DT: **lamivudine+bPI** **lamivudine+INI**	 242 (69%) 107 (31%)	 64 (74%) 23 (26%)	0.441
Calendar year*	2014 (2013; 2015)	2014 (2012; 2015)	0.121
GSS of the 2nd drug **	0.99 (0.07)	0.91 (0.20)	<0.001

Data are shown as n (%); * median (IQR), ** mean (SD).

Notes: IDU, injecting drug users; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; ART, antiretroviral therapy; BL, baseline; DT, dual therapy; lamivudine; bPI, boosted protease inhibitors; INI, integrase inhibitor; GSS, genotypic sensitivity score.

Gagliardini R et als- Impact of previous M184V on virological outcome of switch to 3TC-based dual therapies. CROI 2018. Poster 498

Estimated probability of remaining free from VF according to previous M184V detection

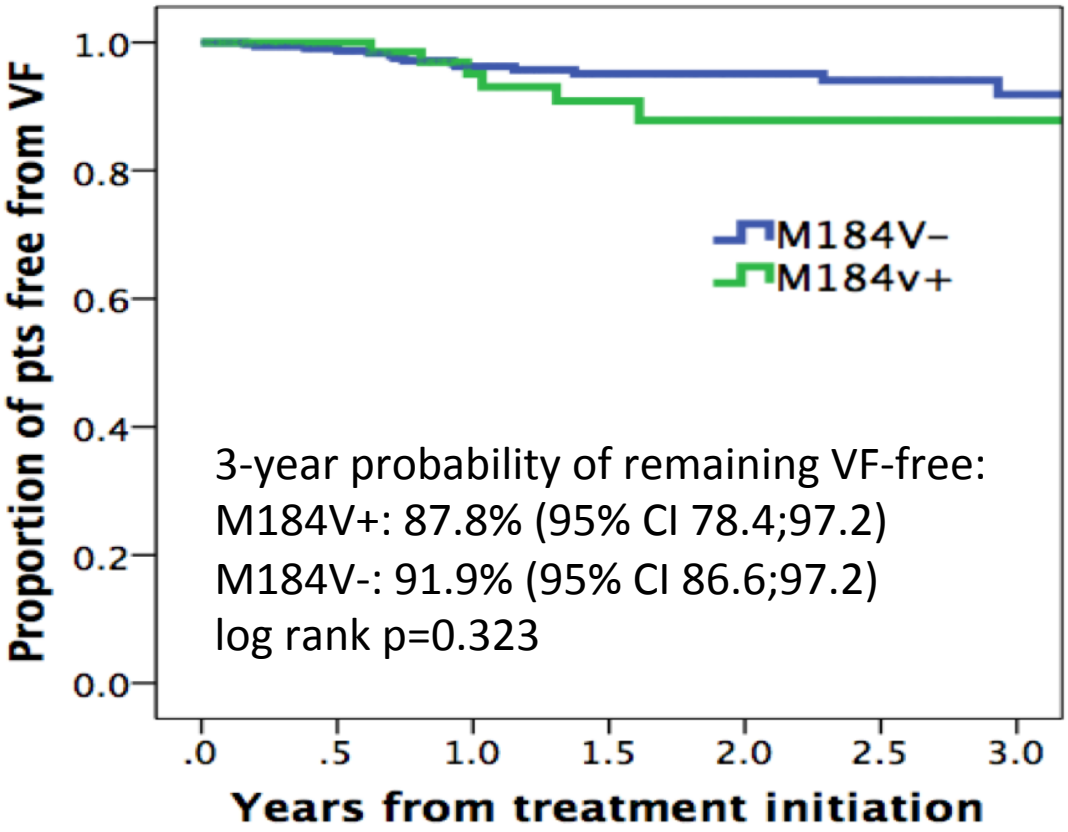
Incidence of virological failure during 693 person-years of follow-up (PYFU):

- 5.1 per 100 PYFU in M184V+
- 3.1 per 100 PYFU in M184V-

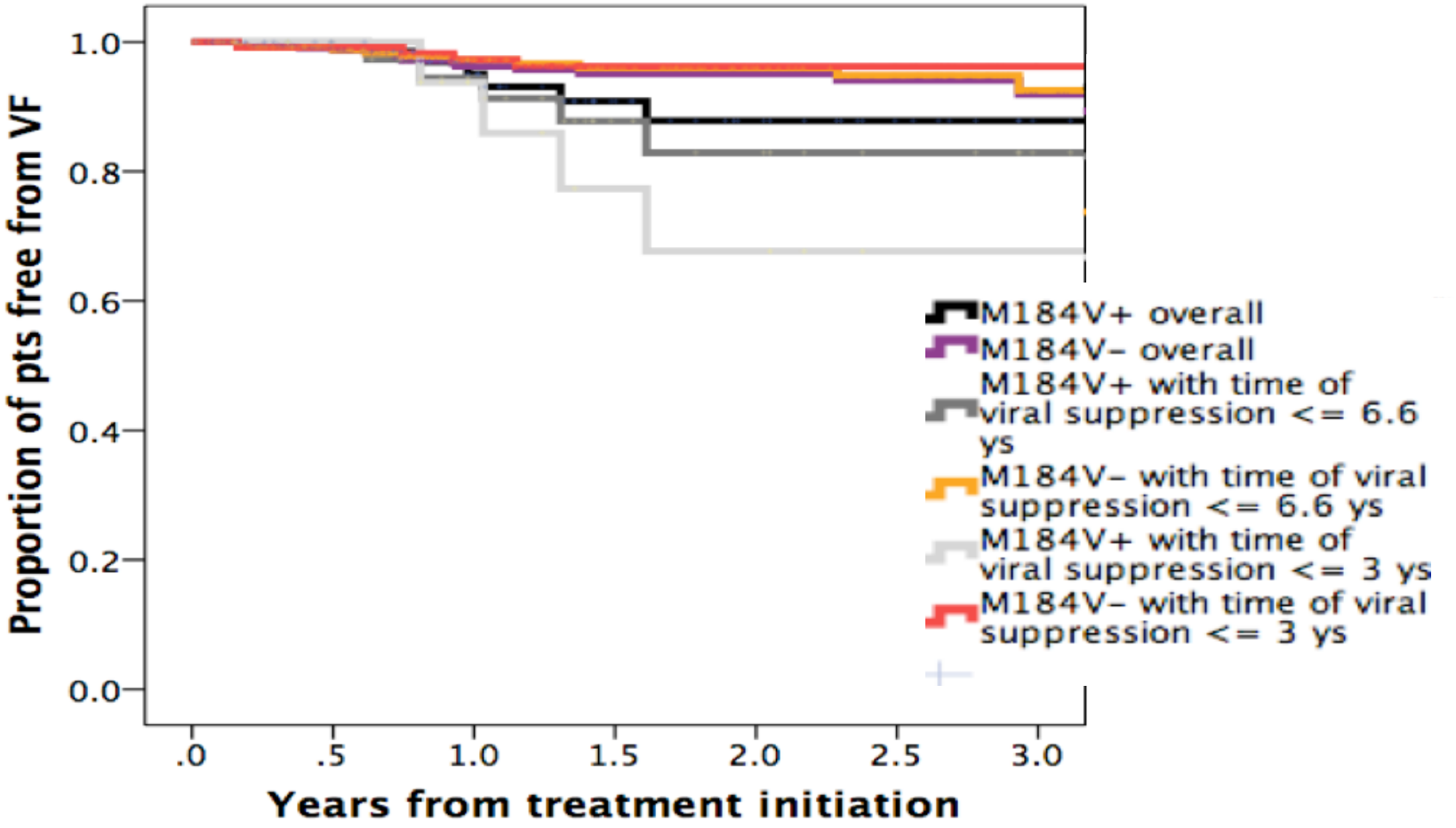
Virological failures:

-**in the M184V+ group:**
-4 on 3TC+atazanavir/r
-3 on 3TC+darunavir/r;

-**in the M184V- group:**
-7 on 3TC+atazanavir/r,
-5 on3TC+darunavir/r,
-3 on 3TC+lopinavir/r
-2 on 3TC+dolutegravir.

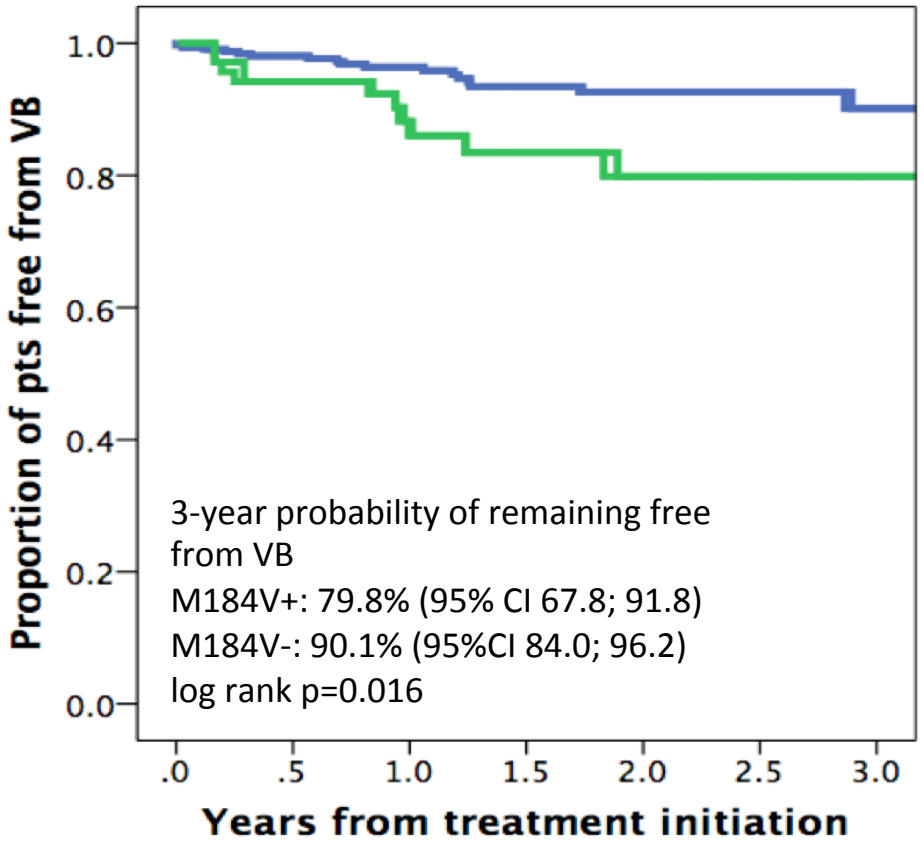


Estimated probability of remaining free from VF in dual therapy for different time of viral suppression



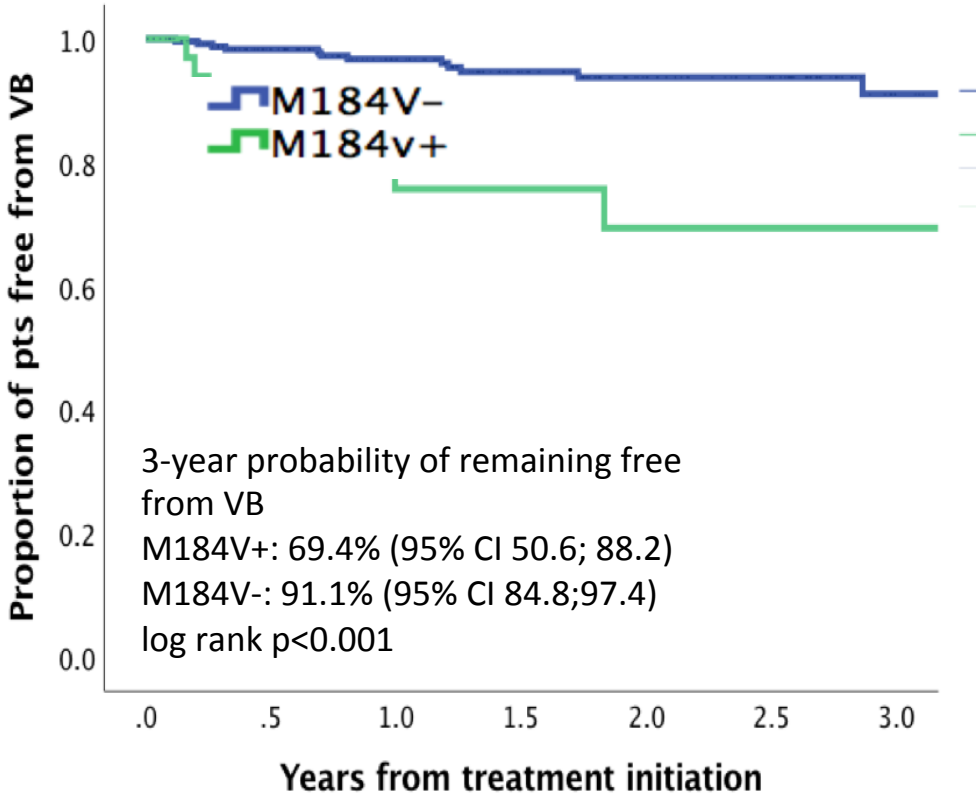
Gagliardini R et als- Impact of previous M184V on virological outcome of switch to 3TC-based dual therapies. CROI 2018. Poster 498

Estimated probability of remaining free from viral blips



3-year probability of remaining free from VB
M184V+: 79.8% (95% CI 67.8; 91.8)
M184V-: 90.1% (95%CI 84.0; 96.2)
log rank p=0.016

Estimated probability of remaining free from VB in patients with viral suppression ≤6.6 years



3-year probability of remaining free from VB
M184V+: 69.4% (95% CI 50.6; 88.2)
M184V-: 91.1% (95% CI 84.8;97.4)
log rank p<0.001

Discussion and conclusions

Prior selection of M184V did not seem to play a significant role on virological efficacy with 3TC+bPI or DTG as switch regimens.

Nonetheless a virological signal was observed with **M184V+ patients showing a higher probability of VB and shorter time of prior viral suppression appearing to increase the risk of VF and of VB** in this group. However, **duration of viral suppression was not a predictor of VF or VB**.

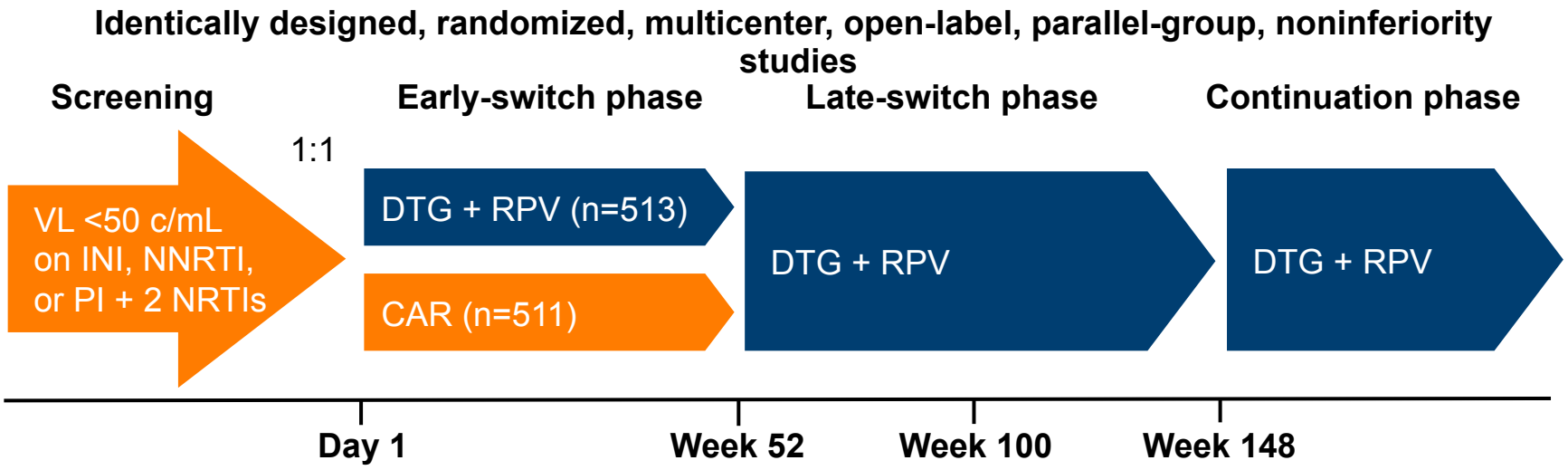
Limitations of the study: retrospective design, limited statistical power, no data about adherence, different characteristics of the two groups at BL.

Hypothesis/explanation:

- decreased viral fitness does not allow viral rebound;
- protective role of M184V against the selection of dolutegravir resistance mutations (no failure detected in n=21 patients on 3TC+DTG followed a median of 10 months [IQR 6; 14]);
- longer duration of viral suppression could disproportionally reduce the size of the reservoir of replication-impaired viruses such as M184V-carrying viral variants.

SWORD-1 and SWORD-2 Phase III Study Design

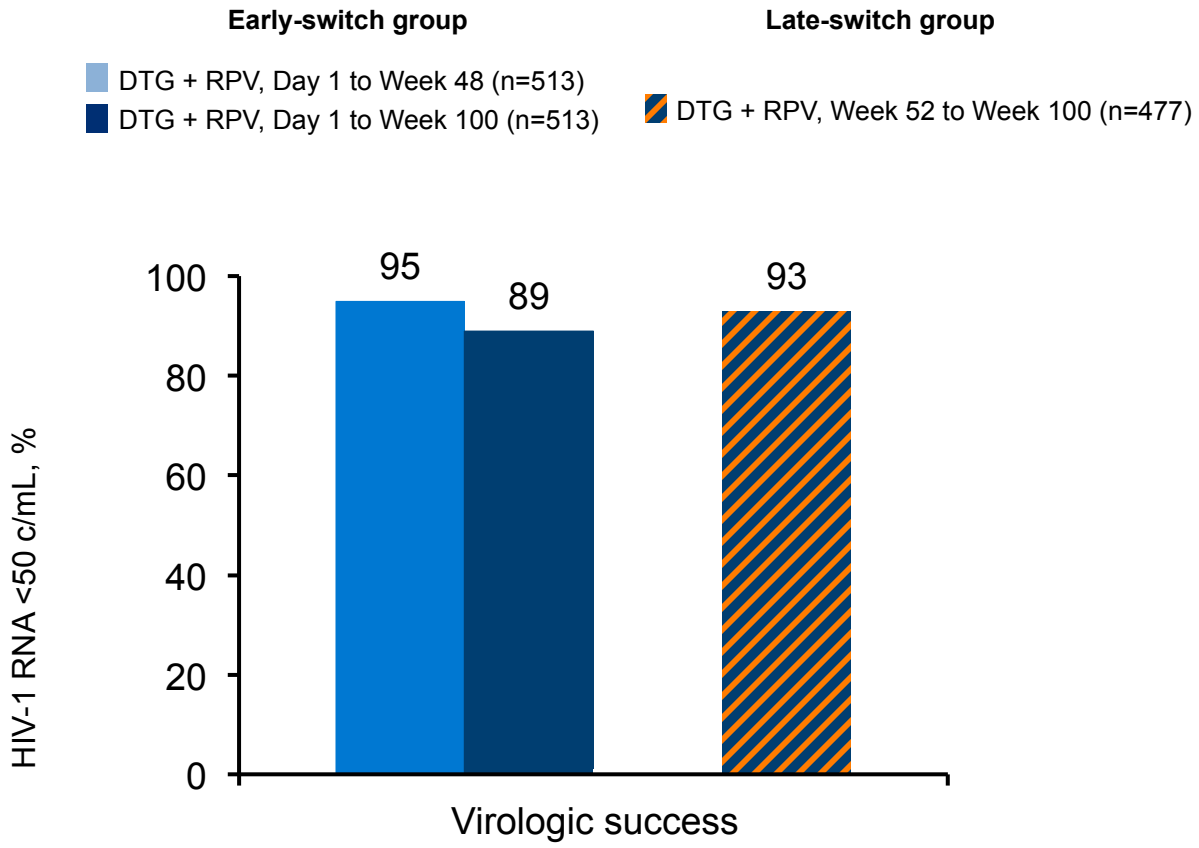
- SWORD-1 and SWORD-2 were identically designed, randomized, multicenter, open-label, parallel-group, noninferiority phase III studies



Llibre et al. *Lancet*. 2018;391:839-849.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

DTG + RPV efficacy at 100 weeks of treatment



[a]Other reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

Llibre et al. *Lancet*. 2018;391:839-849.

DTG + RPV efficacy at 100 weeks of treatment

Early-switch group

DTG + RPV, Day 1 to Week 48 (n=513)

DTG + RPV, Day 1 to Week 100 (n=513)

Late-switch group

DTG + RPV, Week 52 to Week 100 (n=477)

n, %	Early-switch group: DTG + RPV Week 48	Early-switch group: DTG + RPV Week 100	Late-switch group: DTG + RPV Week 100
Virologic success	486 (95)	456 (89)	444 (93)
Virologic nonresponse	3 (<1)	13 (3)	10 (2)
Data in window, not <50 c/mL	0	5 (<1)	3 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	3 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	0
Change in ART	0	0	4 (<1)
No virologic data	24 (5)	44 (9)	23 (5)
Discontinued because of AE or death	17 (3)	27 (5)	11 (2)
Discontinued for other reasons[a]	7 (1)	17 (3)	9 (2)
Missing data during window but on study	0	0	3 (<1)

[a]Other reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

Llibre et al. *Lancet*. 2018;391:839-849.

DTG + RPV: Confirmed Virologic Withdrawal Through Week 100

Week of failure	Previous regimen	Viral loads, copies/mL[b]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[c])	Confirmed virologic withdrawal	
Week 24	EFV/TDF/FTC	88; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	1,059,771; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64[d]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	———
Week 76[d]	ATV, ABC/3TC	79; 162; 217	———	Test not performed[e]	———
Week 88	DTG/ABC/3TC	278; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	147; 289	———	Test not performed[e]	———
Week 100	EFV/TDF/FTC	651; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	280; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	———

[a]Shading represents participants with treatment-emergent NNRTI resistance–associated mutations. [b]Underlined value denotes viral load when participant met virologic withdrawal. [c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [d]Participants in the late-switch group. [e]Resistance testing not performed because of low viral load.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

DTG + RPV: Confirmed Virologic Withdrawal Through Week 100

Previous Regimen	Week of Fail.	Viral Load			Resistance mutations[a]							
		VW	Confirmat. Test	Dis. visit	Baseline (GenoSur[c])		Fenotipic sensibility		Confirmed virologic withdrawal		Fenotipic sensibility	
					NNRTI	INSTI	RPV	DTG	NNRTI	INSTI	RPV	DTG
EFV/TDF/FTC	24	88	466	-	none	G193E			none	G193E		1.21
EFV/TDF/FTC	36	1,059,771	1018	<50	none	none			K101K/E	none	1.21	
DTG/ABC/3TC	64[d]	833	1174	<50	none	N155N/H, G163G/R			Test failed			
ATV, ABC/3TC	76[d]	79	162	217	Not reported				Test not performed [e]			
DTG/ABC/3TC	88	278	2571	55	none	none			E138E/A	none	1.61	0.72
RPV/TDF/FTC	88	147	289	-	Not reported				Test not performed [e]			
EFV/TDF/FTC	100	651	1105	300	K101E E138A	G193E			K101E, E138A, M230M/L	Test failed	31	
ATVr+TDF/FTC	100	280	225	154	none	none			none	none		

[a]Shading represents participants with treatment-emergent NNRTI resistance–associated mutations. [b]Underlined value denotes viral load when participant met virologic withdrawal. [c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences,South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [d]Participants in the late-switch group. [e]Resistance testing not performed because of low viral load.

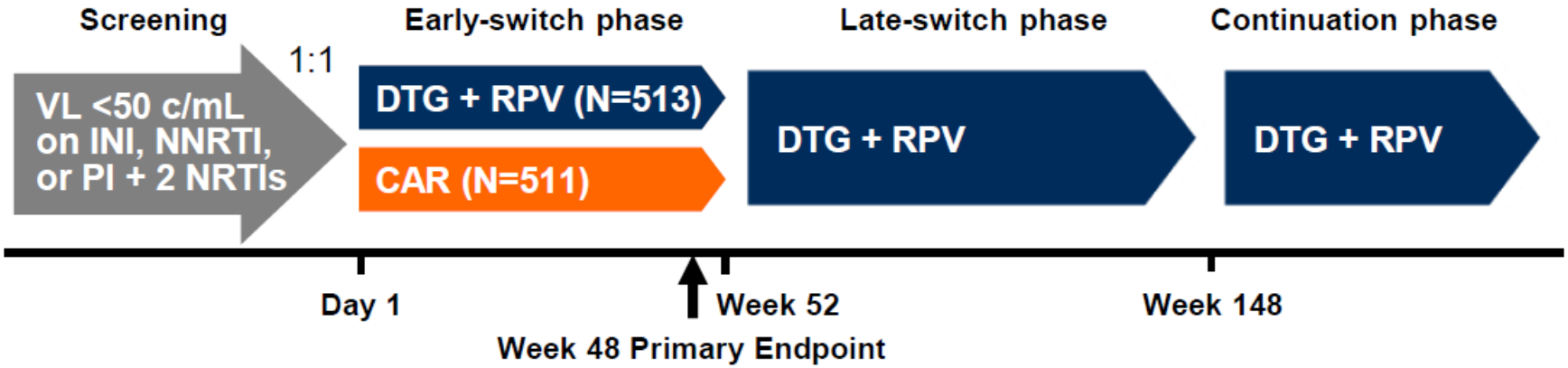
Comparison of Viral Replication Below 50 c/mL for Two-Drug (DTG + RPV) Versus Three-Drug Current Antiretroviral Regimen (CAR) Therapy in the SWORD-1 and SWORD-2 Studies

- SWORD-1 and SWORD-2 are identical, open-label, multicentre, global, phase III, non-inferiority studies1 evaluating efficacy and safety of switching from CAR to DTG + RPV once daily in HIV-1–infected adults, with HIV-1 RNA <50 c/mL (VL <50 c/mL) for at least 6 months and no history of virologic failure
- FDA Snapshot algorithm uses 50 c/mL as cutoff. The clinical significance and subject management implications of low-level quantitative and qualitative VL data remain controversial

CAR, current antiretroviral regimen; DTG, dolutegravir; RPV, rilpivirine; FDA, US Food and Drug Administration; VL, viral load.

Underwood et al. HIV Glasgow; Glasgow, UK. Poster P311.

Study Design



- 95% of participants suppressed by Snapshot VL <50 c/mL (ITT–E)[1]
- 1024 participants were randomized and exposed across both studies
- At Week 48, 95% of participants in each arm had Snapshot VL <50 c/mL[1] in the ITT–E population
- The Abbott RealTime HIV-1 assay measures quantitative HIV-1 RNA VL from 40 c/mL to 10,000,000 c/mL and generates qualitative TD or TND results for VL <40 c/mL
- We assessed the number of participants having 40 c/mL ≤ VL <50 c/mL, or TD or TND for those with VL <40 c/mL, over 48 weeks for the DTG + RPV two-drug regimen vs CAR (PI-, NNRTI-, or INSTI-based three-drug CAR)

1. Llibre et al. *Lancet*. 2018;391:839-849.

Underwood et al. HIV Glasgow; Glasgow, UK. Poster P311.

Methods

- We explored shifts from Baseline (Day 1), cumulative, and per visit classification of participants into >50 c/mL, 40 c/mL ≤ VL <50 c/mL, or TD/TND when <40 c/mL, across arms throughout 48 weeks

TD, target detected; TND, target not detected; VL, viral load.

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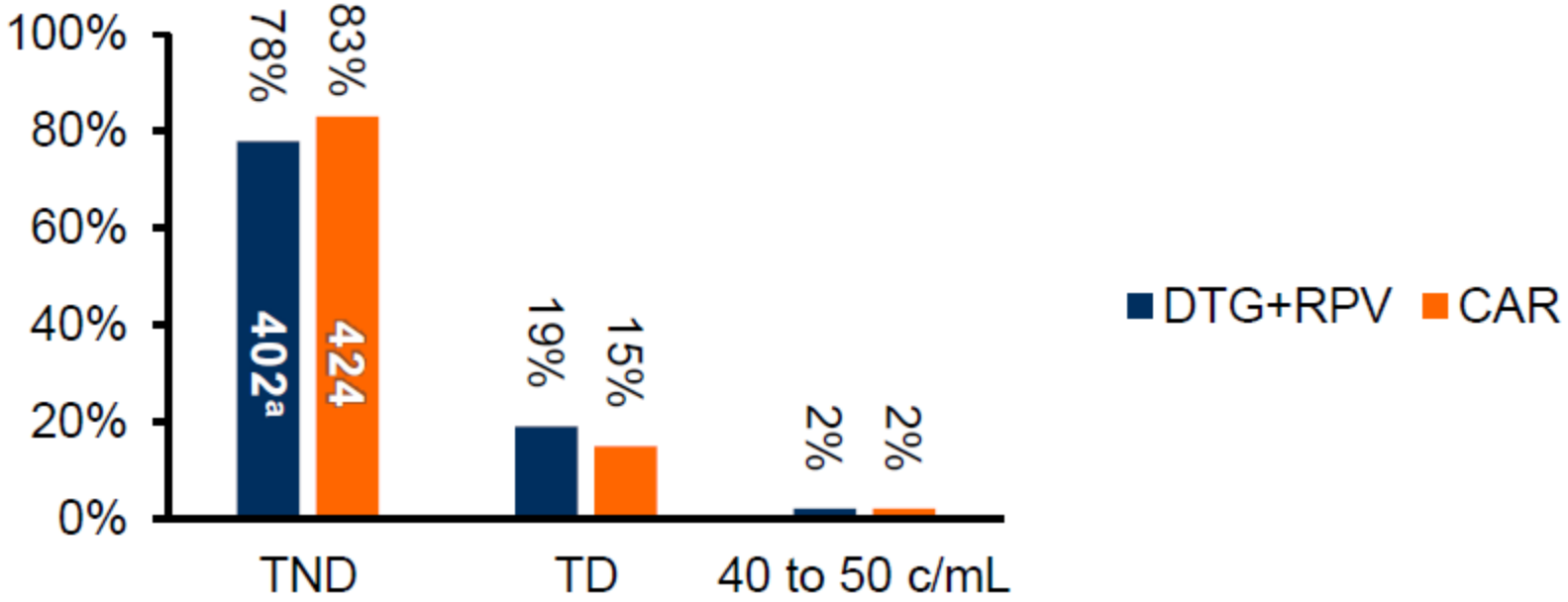
Proportions by VL Category <50 c/mL at Baseline



- At Baseline, slight numerical differences were observed within the VL categories <50 c/mL between the DTG + RPV and CAR arms

[a]The number of participants per category. Of four participants in the DTG + RPV arm with no Post-Baseline data, three had TND and one had TD at Baseline. Two with Baseline TND in CAR had no Post-Baseline VL, and are included here and per Snapshot algorithm in Table 2 (N=402 and N=424), but not in Table 1 analyses (TND DTG + RPV, N=399 and CAR, N=422).

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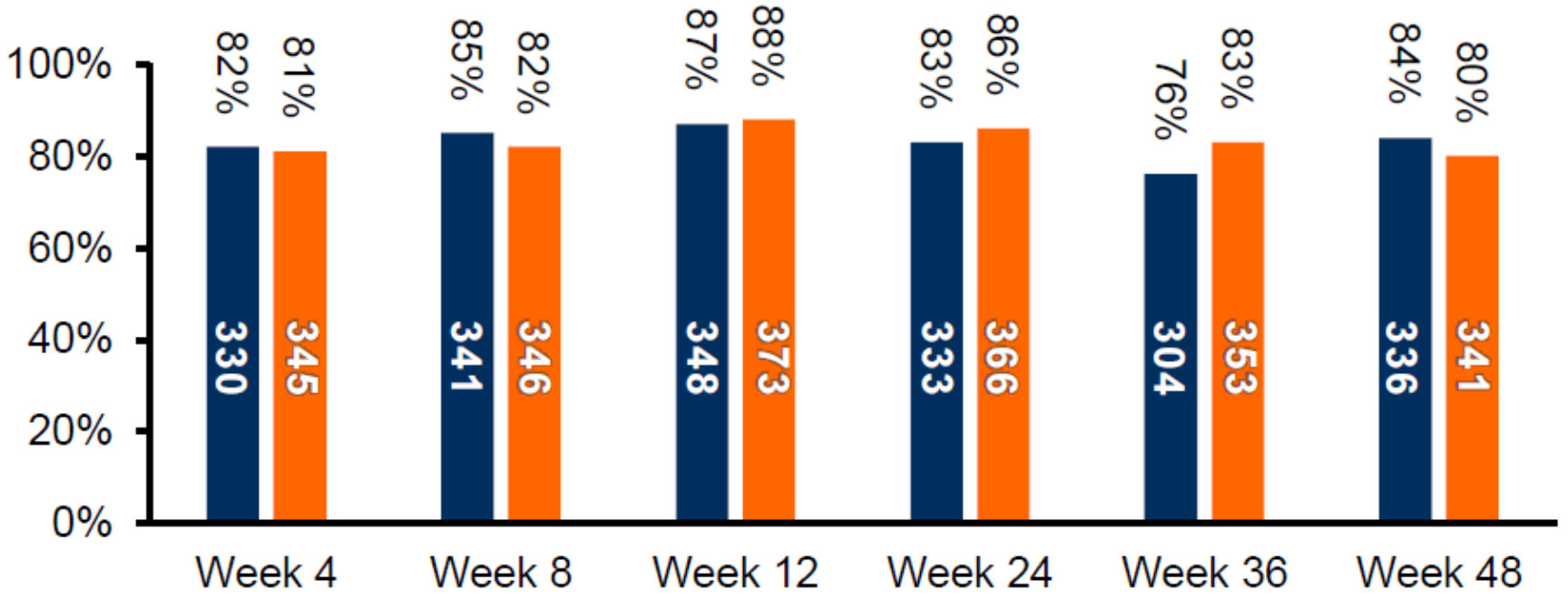
Proportions of TND by Week for Participants With Baseline TND



- Similar proportions of participants with TND were observed at each visit in the DTG + RPV and CAR arms through Week 48 among participants with TND at Baseline

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Changes in Quantifiable and Non-Quantifiable VL Levels by Baseline VL Category Through Week 48

		DTG + RPV (N=513)			CAR (N=511)		
	Baseline	TND	TD	40-50 c/mL	TND	TD	40-50 c/mL
		399 (78%)	98 (19%)	12 (2%)	422 (83%)	76 (15%)	11 (2%)
Post-Baseline	≥50 c/mL[a]	21 (5%)	14 (14%)	4 (33%)	22 (5%)	13 (17%)	2 (18%)
	≥40-<50 c/mL[a]	12 (3%)	4 (4%)	2 (17%)	5 (1%)	6 (8%)	1 (9%)
	VL <40 & TD[a]	177 (44%)	61 (62%)	4 (33%)	172 (41%)	43 (57%)	7 (64%)
	VL <40 & TND[b]	189 (47%)	19 (19%)	2 (17%)	223 (53%)	14 (18%)	1 (9 %)

Post-Baseline categories are mutually exclusive; inclusion of participants into a category is based on highest VL observed (ie, from top to bottom rows). The percentages for Post-Baseline below solid line are calculated from the percentages at Baseline for categories above solid line. Four participants with TND and one with TD in the DTG + RPV arm and two with TND in the CAR arm at Baseline had no Post-Baseline on-treatment VL data and thus are not included here in Baseline totals. [a]In at least one time point after Baseline through Week 48. [b]In all time points Post-Baseline.

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Changes in Quantifiable and Non-Quantifiable VL Levels by Baseline VL Category Through Week 48 (cont)

- By Baseline VL category, there were similar proportions of Post-Baseline categories between the DTG + RPV and CAR arms
  - The proportions with TND at Baseline were 78% for DTG + RPV vs 83% for CAR
- Post-Baseline TD was more common with Baseline TD vs Baseline TND

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Snapshot Analysis for Participants With TND at Baseline Using <50 c/mL or TND as Endpoint at Week 48

Outcome	DTG + RPV (N=402)[a]	CAR (N=424)[a]	Crude diff. Prop. (95% CI)[b]	Adjust. diff. Prop. (95% CI)[c]
Virologic Success				
VL <50 c/mL[d]	383 (95%)	405 (96%)	—	—
VL <40 c/mL & TND	336 (84%)	341 (80%)	3.2% (-2.1%, 8.4%)	3.1% (-2.2%, 8.3%)
Virologic Failure[e]	47 (12%)	66 (16%)		
VL <40 & TD at Week 48 visit	45 (11%)	59 (14%)		
40 ≤ VL <50 at Week 48 visit	2 (<1%)	5 (1%)		
VL ≥50 at Week 48 visit	0	2 (<1%)		
No Virologic Data	19 (5%)	17 (4%)		
Disc. study due to AE or death	15 (4%)	3 (1%)		
Disc. study for other reasons while VL below 50 c/mL	4 (1%)	13 (3%)		
Missing data during window but on study	0	1 (<1%)		

Note: [a]Participants having TND at Baseline. [b]Difference: Proportion on DTG + RPV − Proportion on CAR. [c]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for stratifications factors: Baseline age (< or ≥50 years) and Baseline third agent (PI, NNRTI, INI). [d]Endpoint VL <50 c/mL in participants with Baseline TND; details on virologic failures and no virologic data for this endpoint are not provided. [e]There were no virologic failures due to disc. for lack of efficacy, disc. for other reasons while VL not below 50 c/mL, or change in ART.

- Week 48 Snapshot success by VL measurement <50 c/mL was similar for participants with TND at baseline between the DTG + RPV and CAR arms
- Week 48 Snapshot success by TND was similar across the DTG + RPV and CAR arms

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Conclusions

- Similar proportions of participants with TND were observed at each visit through Week 48 for the DTG + RPV and CAR arms
- There were similar proportions of participants in the DTG + RPV and CAR arms with Post-Baseline TD and TND categories by Baseline category
- Qualitative viremia by the TD measure was more common with Baseline TD than with Baseline TND
- Using the more stringent TND data, there was no difference by Snapshot for the DTG + RPV two-drug regimen versus the CAR three-drug regimen at Week 48

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Comparison of HIV-1 Intermittent Viremia for Two Drug (DTG+RPV) vs Three Drug Current Antiretroviral Therapy in the SWORD-1 and SWORD-2 Studies

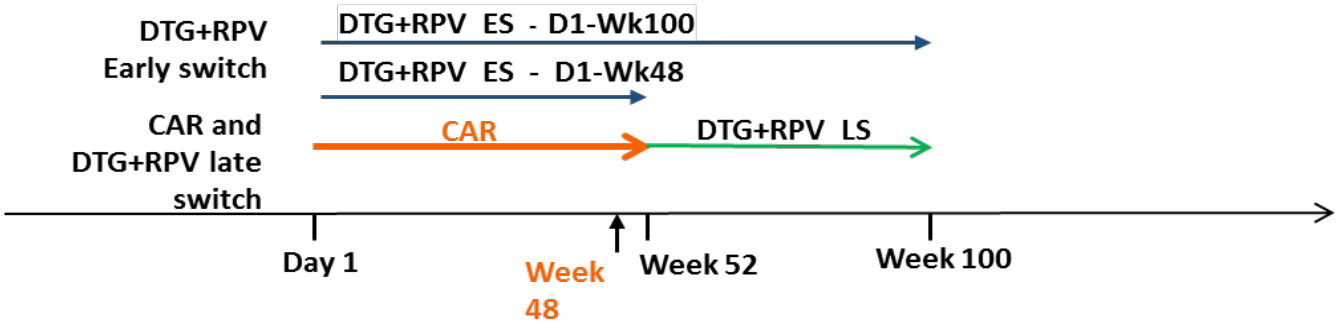
- The overall goal of HIV therapy is to maintain lifelong virologic suppression over the entire course of a patient's treatment
- The clinical significance and management of subjects who have transient "blips" remains controversial; however, their appearance may lead to concerns about the durability of an ART regimen
- We assessed elevated viral loads over 2 years of therapy with the 2-drug regimen (2DR) of DTG+RPV vs remaining on 3-drug current antiretroviral regimen (CAR)

- SWORD-1 and SWORD-2 are identical open-label, multicentre, global, phase III, non-inferiority studies evaluating efficacy and safety of switching from CAR to DTG+RPV once daily in
  HIV-1-infected adults, with HIV-1 RNA <50 c/mL (viral load [VL] <50 c/mL) and no history of virologic failure

Wang et al. HIV Glasgow; Glasgow, UK. Poster P313.

Study Design

Viral Load Category Windows



- Subjects either switched to DTG+RPV on Day 1 (Early Switch [ES] DTG+RPV arm) or remained on CAR (CAR arm) and switched to DTG+RPV at Week 52 (Late Switch [LS] DTG+RPV arm) if still on study and suppressed
- ES DTG+RPV D1–Week 100 represents subjects randomized to DTG+RPV at Day 1 with cumulative data from Day 1 through Week 100

- US Food and Drug Administration Snapshot algorithm uses 50 c/mL as a cutoff for viral suppression
- We divided subjects within each of the following groups with ≥1 post-Baseline on-treatment VL ≥50 c/mL into 2 major categories:
  - (1) Subjects with ≥1 VL between 50 and 200 c/mL and no VL ≥200 c/mL
  - (2) Subjects with ≥1 VL ≥200 c/mL

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Viral Load Categories and Subjects Observed per Category

Study regimen and time frames VL categories	ES DTG+RPV D1–Wk48 N = 513	CAR D1–Wk48 N = 511	LS DTG+RPV Wk52–Wk100 N = 477	ES DTG+RPV D1–Wk100 N = 513
1.VL between 50 and 200 c/mL and no VL ≥200 c/mL				
1a. ≥1 VL ≥50 and <200 c/mL, and adjacent VL <50 c/mL (**"blip"**)	34 (6%)	28 (5%)	20 (4%)	48 (9%)
1b. ≥2 consecutive VL between 50 and 200 c/mL	1 (<1%)	1 (<1%)	3 (1%)	4 (1%)
2.VL ≥200 c/mL				
2a. 1 VL ≥200 c/mL and no 2 consecutive VL ≥50 c/mL	2 (<1%)	5 (1%)	5 (1%)	5 (1%)
2b. 2 consecutive VL ≥50 c/mL with ≥1 VL ≥200 c/mL	2 (<1%)	3 (1%)	4 (1%)	6 (1%)
Total (all categories)	39 (8%)	37 (7%)	32 (7%)	63 (12%)

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Occurrence of Blips Prior to Participants Meeting CVW

- Through Week 100 across treatment groups, 10 subjects met CVW criteria[1]
  - 6 out of 10 CVW subjects had no intermittent blips; 3 had a single blip; and only 1 subject had 2 blips (Subject A) before having a VL measurement meeting SVW criterion that was subsequently confirmed

Subject ID	A	B	C	D	E
Treatment arm	CAR	CAR	ES DTG+RPV	ES DTG+RPV	LS DTG+RPV
# of Blips	2	1	0	0	0

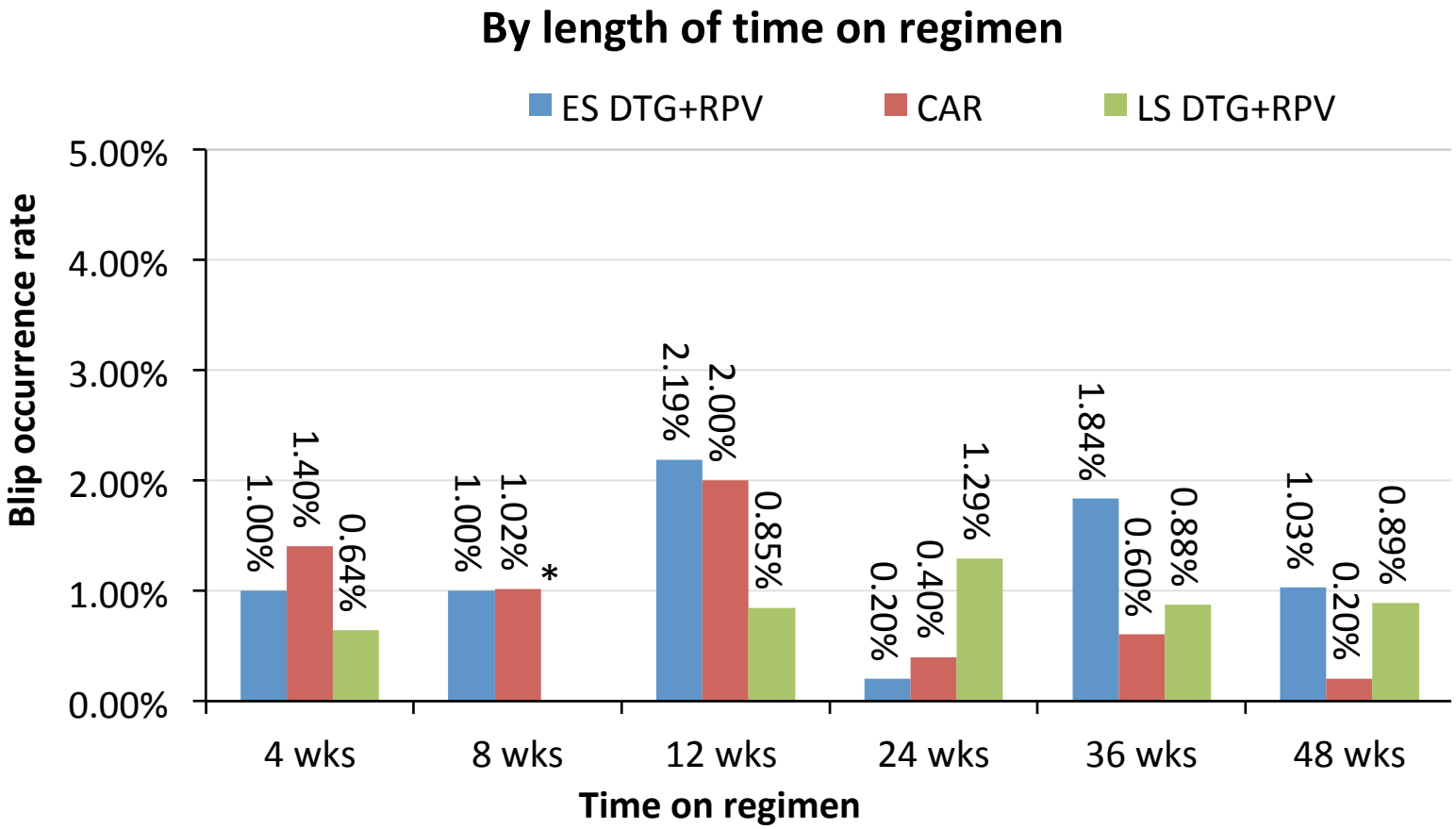
Subject ID	F	G[a]	H[a]	I[a]	J[a]
Treatment arm	LS DTG+RPV	ES DTG+RPV	ES DTG+RPV	ES DTG+RPV	ES DTG+RPV
# of Blips	0	1	0	1	0

[a]Subjects in DTG+RPV arm that met CVW in year two.

CVW, confirmed virologic withdrawal: HIV-1 RNA ≥200 c/mL following prior VL ≥50 c/mL.

1. Aboud et al. AIDS 2018; Amsterdam, the Netherlands.

Rates of Blips Through Week 100



*There was no Week 8 visit for the late switch subjects.

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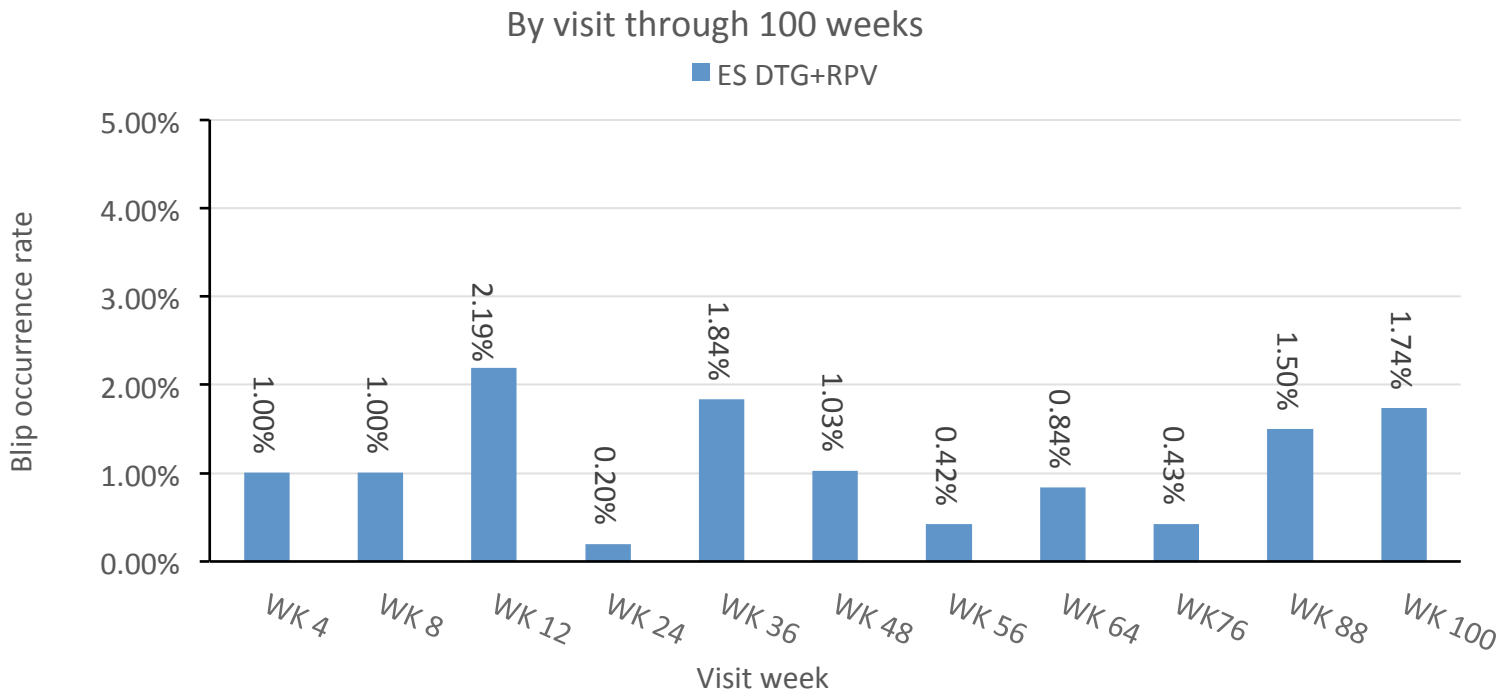
Rates of Blips Through Week 100 (cont)



- Blip occurrences by treatment arm over time demonstrate overall diverse numbers as expected for virologic blips caused by stochastic non-adherence, intercurrent illness,[1] or immunizations[2]

1. Donovan et al. *J Infect Dis*. 1996;174:401-403. **2.** Günthard et al. *J Infect Dis*. 2000;181:522-531.

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Conclusions

- The incidence of blips was low, fluctuated, and occurred at a similar rate among subjects receiving DTG+RPV 2-drug regimen and subjects receiving 3-drug (CAR) regimen
- All other categories of VL >50 c/mL occurred infrequently in all groups
- Viral blips were not associated with CVW
- DTG+RPV 2DR is as effective at preventing intermittent low-level viremia as 3-drug ART

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REUNIÃO DE OUTONO

17 de novembro

2ª Reunião de Sócios

APECS
Associação Portuguesa para o Estudo Clínico da SIDA

HIV Drug Therapy GLASGOW 2018

Estratégias Terapêuticas

TD vs TT – Oposição ou Complementaridade?