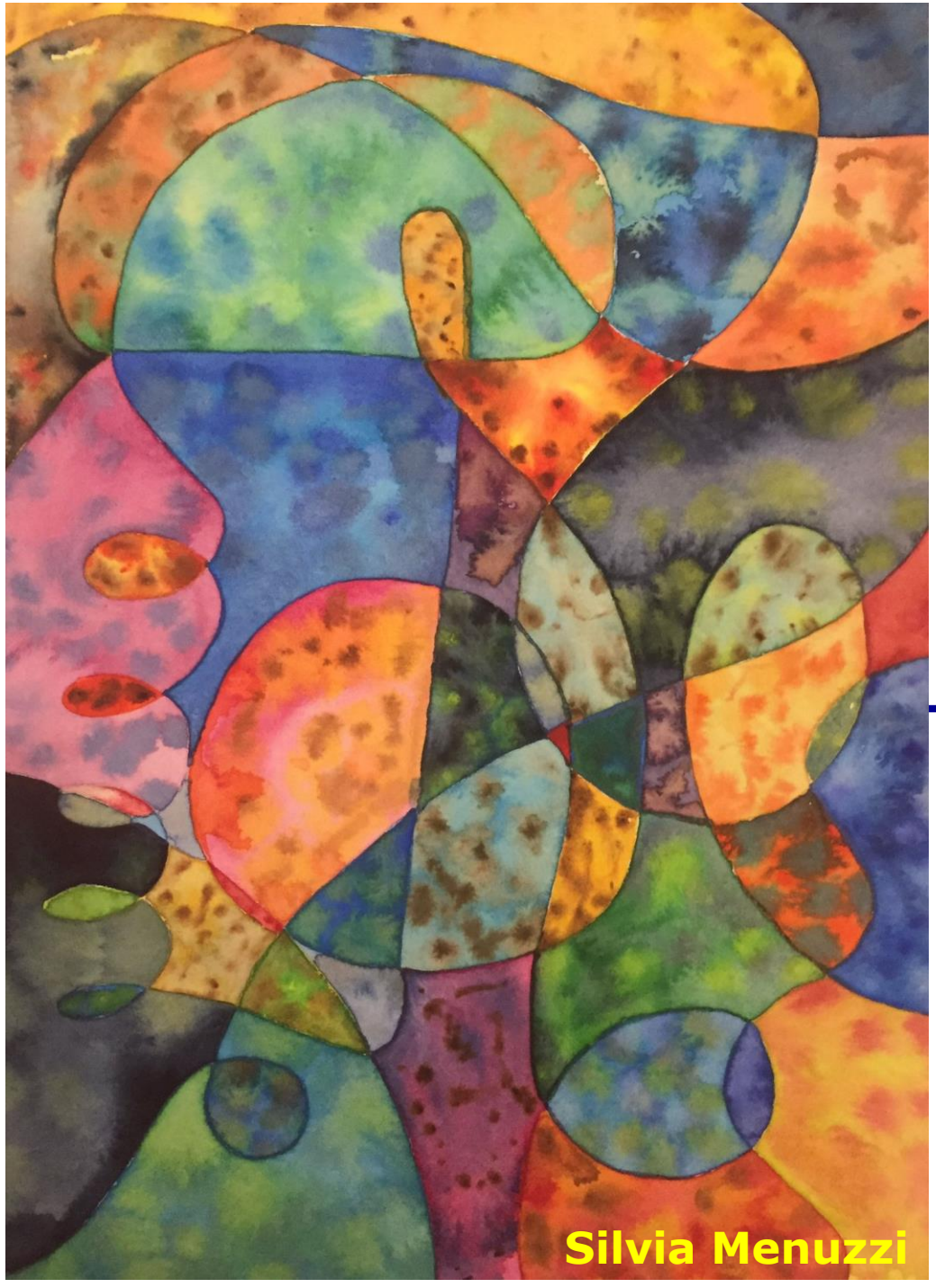

SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 23

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

Triplice o duplice? Il dilemma della cART oggi

Stefano Rusconi

Sistema Socio Sanitario
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MEDICI CON L'AFRICA CUAMM

Therapeutic strategies in naïve subjects (EACS guidelines version 11.1, October 2022)

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	II (Weight increase (TAF) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0, dosing)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/XTC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (DRV/r: cardiovascular risk) X (Boosted regimens and drug-drug interactions)

Switch strategies in virologically suppressed subjects (EACS guidelines version 11.1, October 2022)

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

Dual therapies

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is
a) no historical resistance and
b) HBV immunity or if non-immune concomitant HBV Vaccination

Dual therapies supported by large randomized clinical trials or meta-analyses:

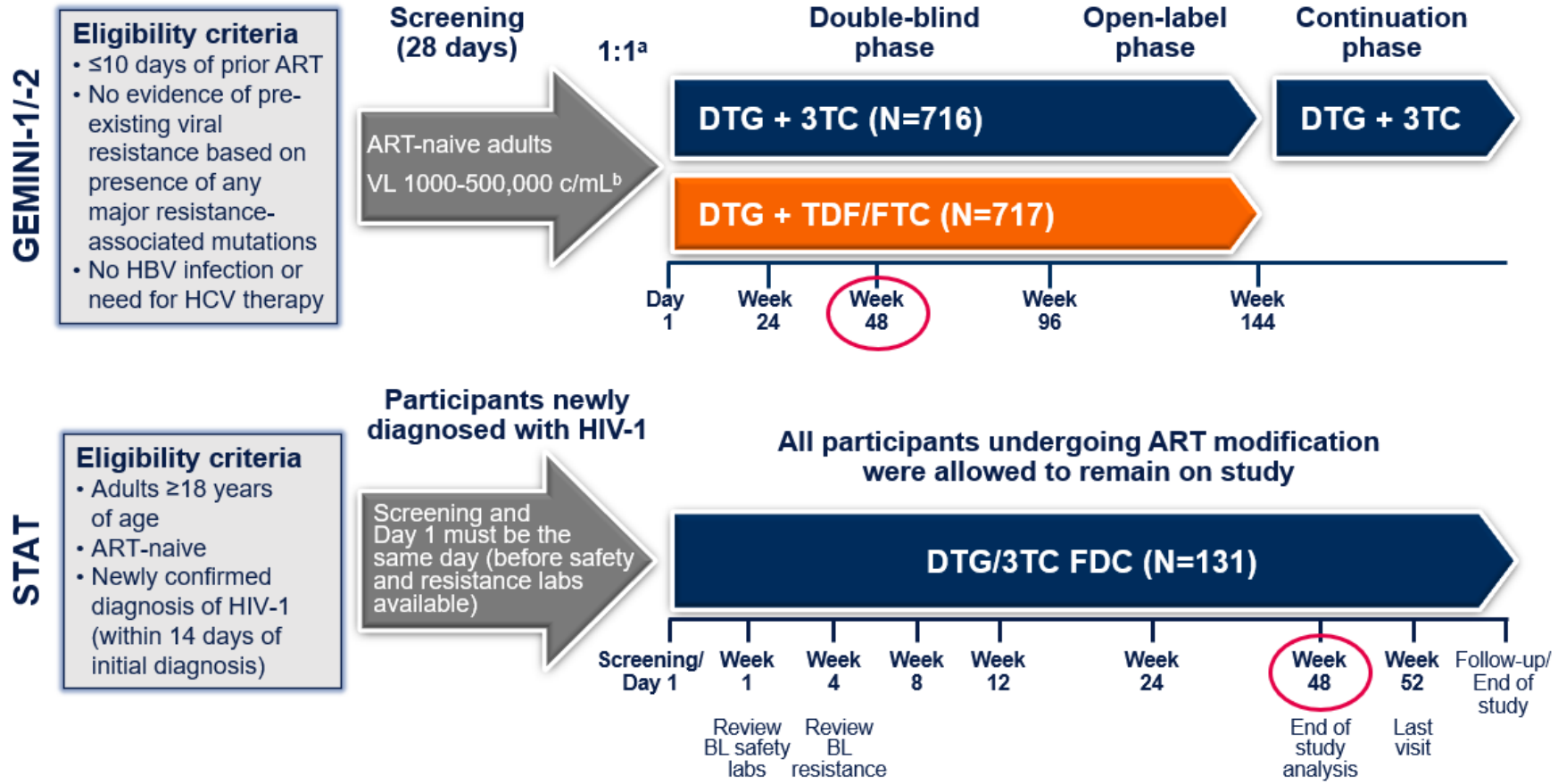
DTG + RPV
XTC + DTG
XTC + DRV/b
Long-acting CAB + RPV bi-monthly injections

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV and CAB + RPV

Dual therapy options supported only by small trials:
These regimens should be indicated only in persons not eligible for other treatment combinations due to intolerance or resistance to other drugs

DRV/b + RPV
DRV/b + DTG

GEMINI-1/-2 and STAT Study Designs

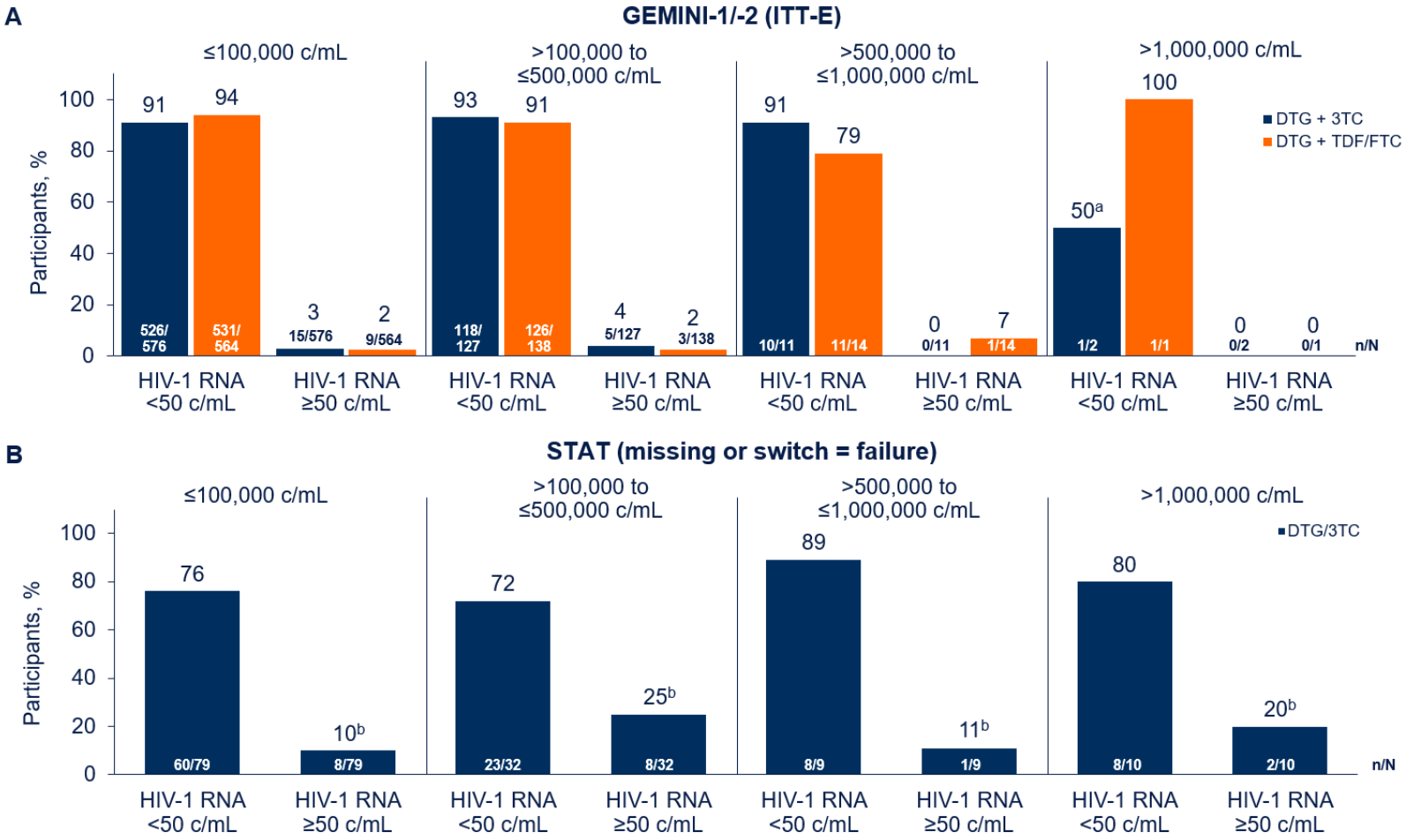


[a]Randomization in GEMINI-1/-2 stratified by baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm3). [b]Participants with VL ≤500,000 c/mL at screening but >500,000 c/mL at baseline (Day 1) were allowed to continue the study.

Rolle et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Poster P056.

Virologic Snapshot Outcomes at Week 48 by Baseline Viral Load in (A) GEMINI-1/-2 and (B) STAT

- Proportions of participants with HIV-1 RNA <50 c/mL were high across all studies, including in participants with high and very high baseline VL
- Few participants with baseline VL >500,000 c/mL had HIV-1 RNA ≥50 c/mL (GEMINI-1/-2, n=1 in the DTG + TDF/FTC group; STAT, n=3)
- In STAT, VL non-suppression rates were driven by non-virologic reasons, including study withdrawals (eg, withdrawn consent, lost to follow-up; n=6) and ART modifications (n=10)
- At Week 48, no treatment-emergent HIV resistance was detected in participants with confirmed virologic failure across GEMINI-1/-2 (DTG + 3TC, n=6; DTG + TDF/FTC, n=4) and STAT (n=2), including in 1 participant with high or very high baseline VL (>1,000,000 c/mL in STAT)



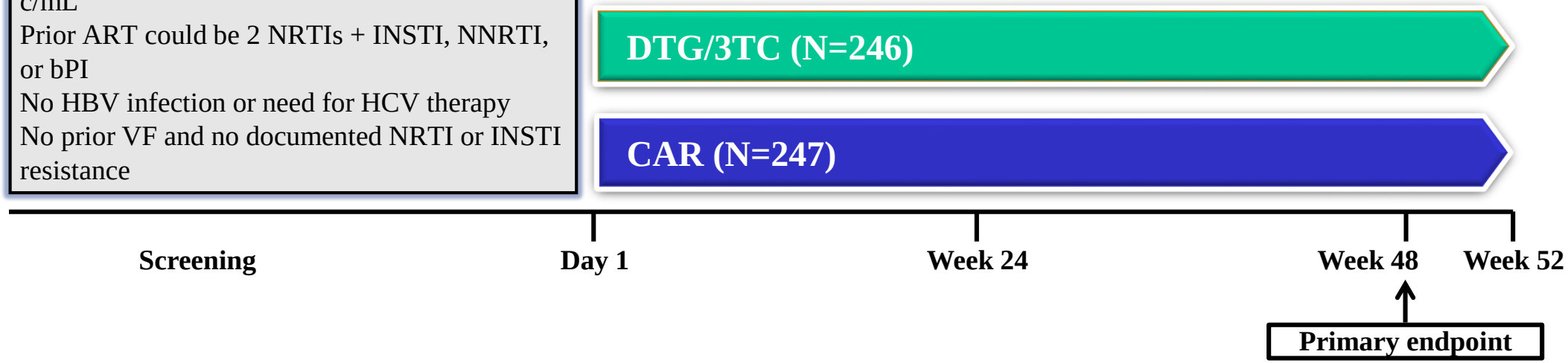
[a]The other participant withdrew from the study due to physician decision and had no virologic data at Week 48. [b]Non-suppression at Week 48 driven by study withdrawals (eg, withdrawn consent, lost to follow-up; n=6) and ART modifications (n=10); 3 participants had data in window and HIV-1 RNA ≥50 c/mL (all in the >100,000 to ≤500,000 c/mL VL category).

Rolle et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Poster P056.

SALSA Phase 3 Study Design

Eligibility criteria
≥2 documented HIV-1 RNA measurements <50 c/mL
Prior ART could be 2 NRTIs + INSTI, NNRTI, or bPI
No HBV infection or need for HCV therapy
No prior VF and no documented NRTI or INSTI resistance

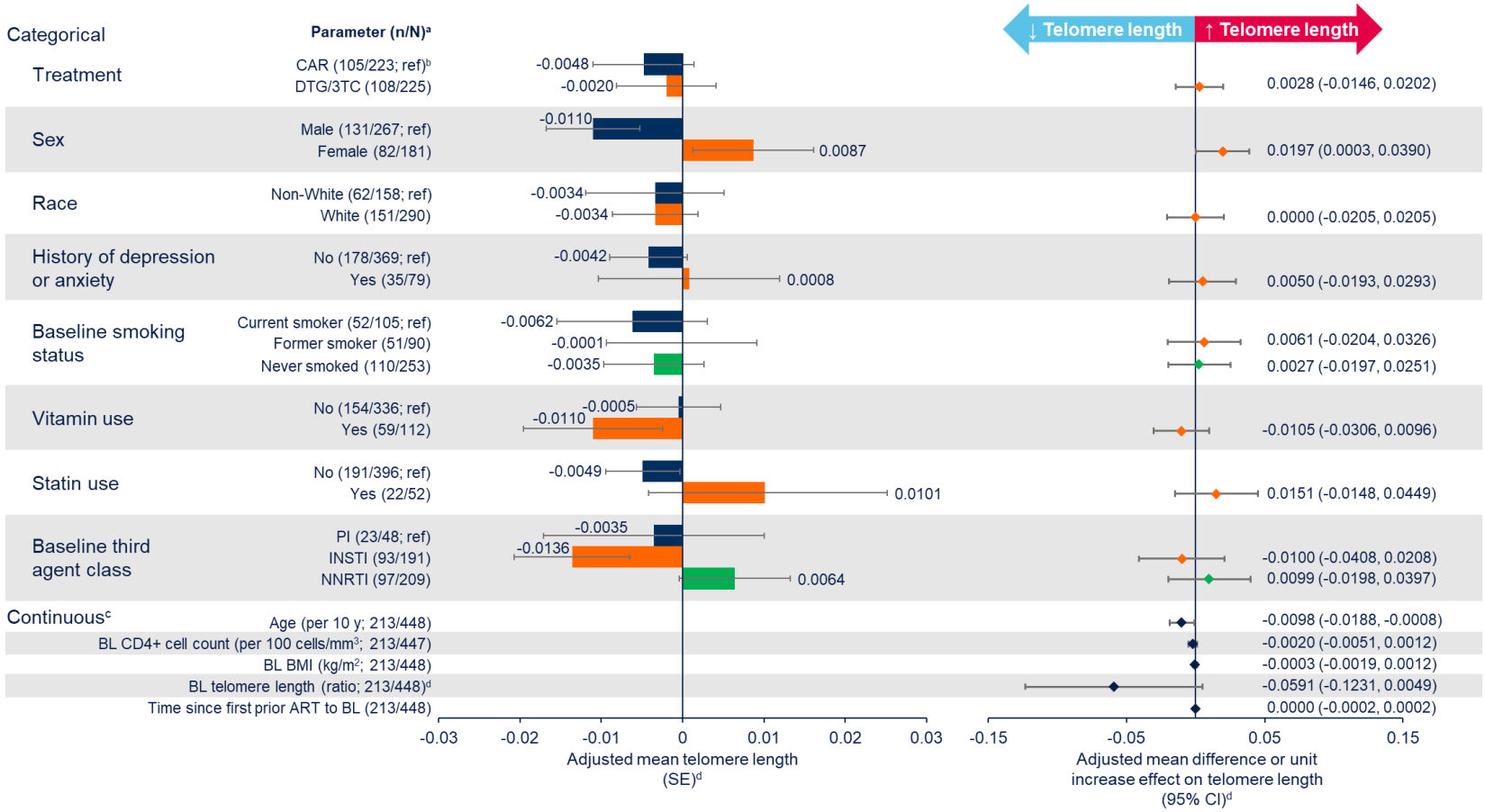
Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study



Underwood et al. CROI 2023; Virtual and Seattle, WA. Poster 694.

Forest Plot View of Telomere Length Change From Baseline (CFB) at Week 48 by Covariate and Treatment Group

- Adjusted mean CFB in TL in the DTG/3TC and CAR groups were similar, −0.0020 vs −0.0048, respectively (treatment difference, 0.0028; 95% CI, −0.0146, 0.0202; *P*=0.751)
- Baseline factors associated with TL included age and sex (women had longer TL)
- TL decreased with increasing age and trended toward shorter length at Week 48 with baseline TL



BL, baseline; Ref, reference. [a]N represents the number of participants with non-missing baseline covariate data, and n represents the number of participants with at least one telomere length data at either baseline or Week 48. [b]Reference for adjusted mean difference. [c]Reported as increase (>0) or decrease (<0) in adjusted mean change in telomere length. [d]Telomere length is measured as a ratio of telomere to single-copy gene.

Underwood et al. CROI 2023; Virtual and Seattle, WA. Poster 694.

Blood Telomere Length Gain in PLWH Switching to DTG+3TC vs Continuing Triple Therapy

693

Francesca Lombardi [1], Alessia Sanfilippo[2], Massimiliano Fabbiani[3],Alberto Borghetti[1], Arturo Ciccullo[4], Iolanda Mozzetta[1] , Erica Tamburrini[1], Simona Di Giambenedetto[1,2] .
[1] Fondazione Policlinico Universitario A. Gemelli IRCCS , UOC Malattie Infettive, Roma. [2]Università Cattolica del Sacro Cuore, Roma, Italia. [3] Azienda Ospedaliero-Universitaria Senese, Siena, Italia. [4]Ospedale San Salvatore, L'Aquila, Italia.

Dynamics of BTL 48 weeks after switching to dual therapy

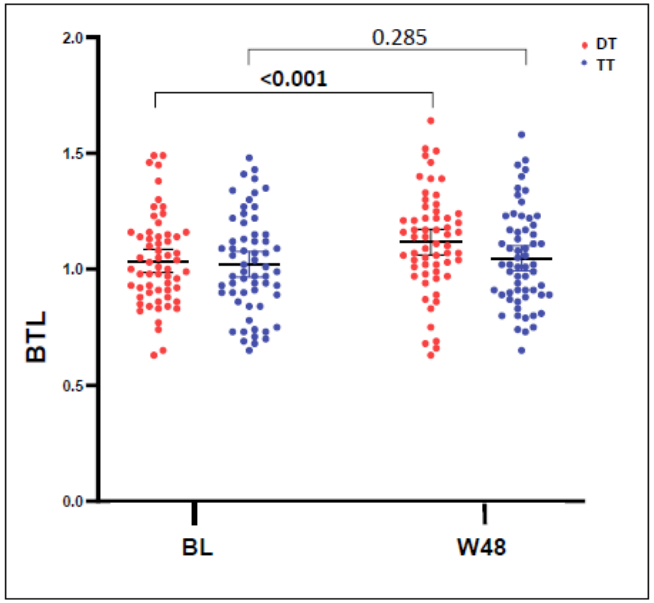


Figure 4. Dynamics of BTL at the two different time-points according to the study groups. Dot plot represents the distribution of BTL. Central horizontal bars represent the mean values and error bars represent the 95% CIs

- An overall increase in the mean (95%CI) BTL was observed from BL to W48, from 1.03 (0.99-1.06) to 1.08 (1.04-1.12) [+0.05 (0.02-0.08) (p=0.001)].
- **A marked mean BTL gain was observed in the DT group from 1.03 (0.98-1.08) to 1.12 (1.06-1.17) [+0.08 (0.04-0.12), p<0.001].**
- In the TT group the gain was not statistically significant from 1.02 (0.96-1.07) to 1.05 (0.99-1.12) [+0.03 (-0.02-0.072), p=0.285].
- In a sub-analysis perfomed in the DT group (n=60) we observed a significant mean BTL gain 48 weeks after stopping either FTC/TDF-TAF or ABC
- **FTC/TDF-TAF group (n=35) from 1.04 (0.97-1.11) to 1.11 (1.03-1.19) [+0.07 (0.01-0.13), p=0.020]**
- **ABC group (n=25) from 1.04 (0.96-1.11) to 1.13 (1.05-1.21) [+0.10 (0.04-0.16), p=0.002].**

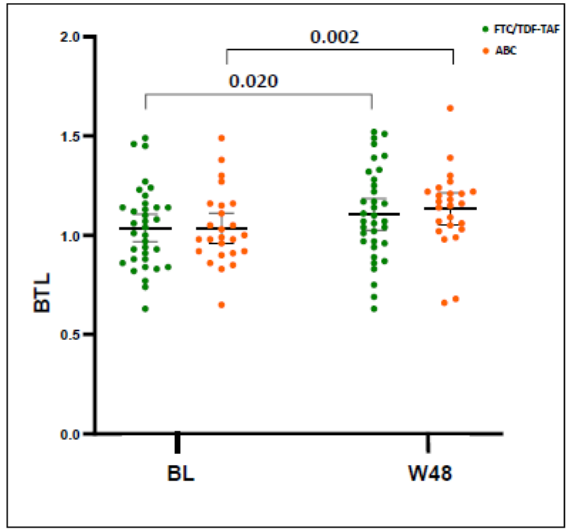
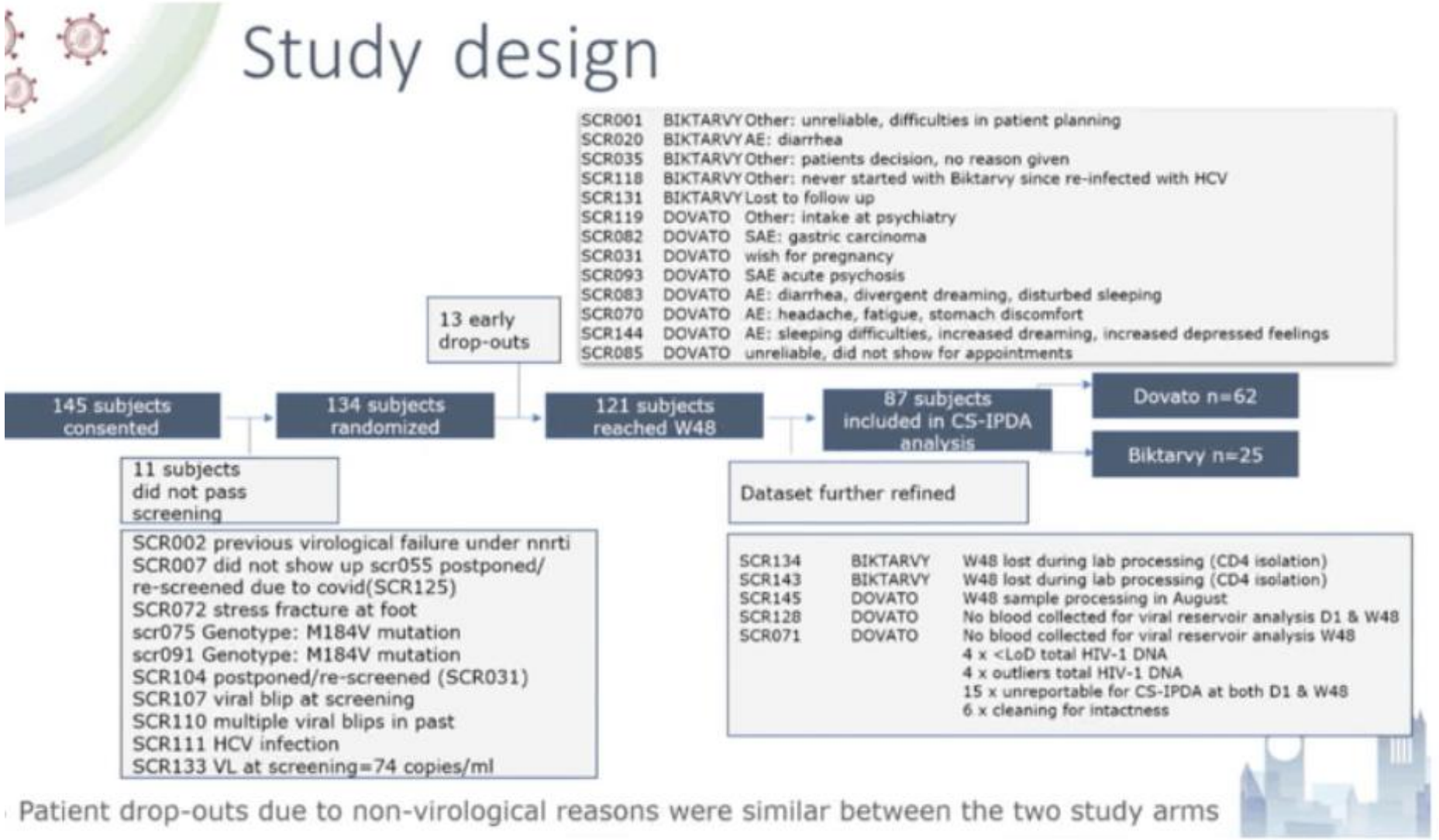


Figure 5. Dynamics of BTL at the two different time-points according to the subgroups (FTC/TDF-TAF and ABC). Dot plot represents the distribution of BTL. Central horizontal bars represent the mean values and error bars represent the 95% CIs

Impact of switch to 3TC/DTG on total and intact DNA (RUMBA study)

Linos Vandekerckhove et al. HIV Glasgow 2022

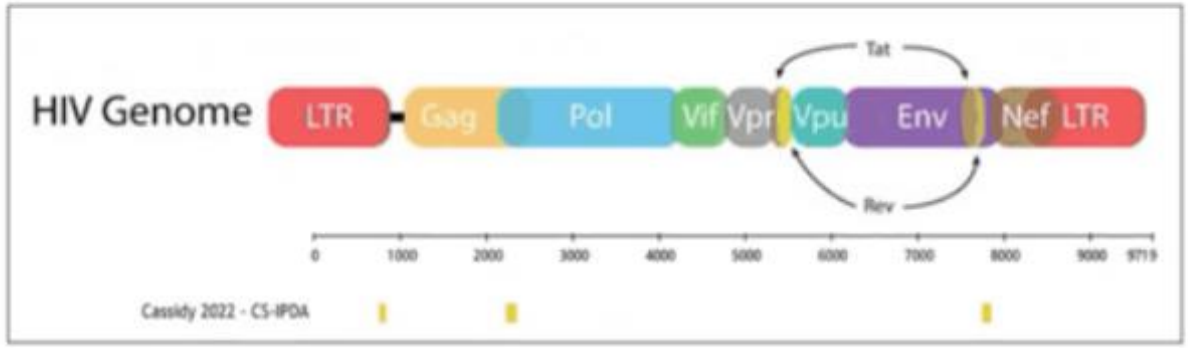


Impact of switch to 3TC/DTG on total and intact DNA (RUMBA study)

Linos Vandekerckhove et al. HIV Glasgow 2022

Methods

- Blood collection at D1 and W48 -> PBMC -> CD4 -> DNA
- Multiplex digital PCR assay: total HIV-1 DNA assay + Cross-Subtype IPDA



- Normalization based on cell input: *RPP30*
- Data analysis ddpcrRquant algorithm

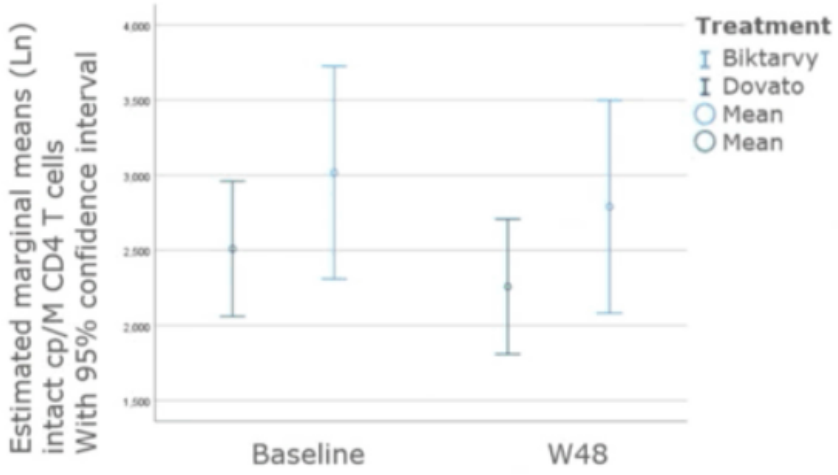
Cassidy NA, Fish CS, Levy CN *et al*. HIV reservoir quantification using cross-subtype multiplex ddPCR. Iscience. 2022 Jan 21;25(1):103615.

Impact of switch to 3TC/DTG on total and intact DNA (RUMBA study)

Linos Vandekerckhove et al. HIV Glasgow 2022

Results intact copies

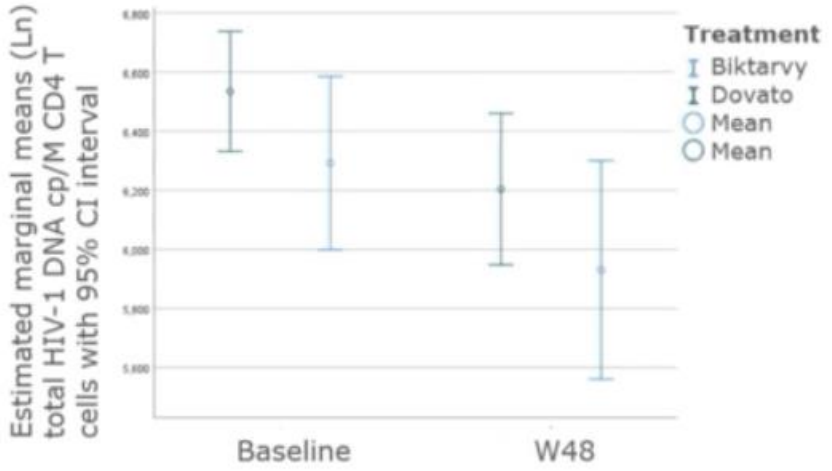
- Mixed model analysis on natural log (Ln) transformed intact copies
- Dovato n=62, Biktarvy n=25 on each timepoint



- At W48, the number of intact cp/M CD4 in the Dovato group is not significantly different from the Biktarvy group (p=0,231)
- The estimated mean difference in intact cp between baseline and W48 between the groups is not significantly different

Results total HIV-1 DNA

- Mixed model analysis on natural log (Ln) transformed total HIV-1 DNA copies (unadjusted)
- Dovato n=73, Biktarvy n=35 on each timepoint



- At W48, the number of total HIV-1 DNA cp/M CD4 in the Dovato group is not significantly different from the Biktarvy group (p=0,465)
- The estimated mean difference in total HIV-1 DNA cp between baseline and W48 between the groups is not significantly different

RUMBA: Impact of Switching to DTG/3TC vs BIC/FTC/TAF (Secondary Endpoint)

- **Study design:** Open-label, randomized, controlled, longitudinal, clinical trial evaluating metabolic outcomes (weight, BMI, waist circumference, lipids, Fibroscan, insulin resistance, DXA scans) in 134 suppressed PLWH switched to DTG/3TC vs switching to or remaining on BIC/FTC/TAF
- 130 PLWH were included in the ITT-E analysis: 67.8% were switched to DTG/3TC from BIC/FTC/TAF
- Results demonstrated statistically significantly different estimated mean differences over time between the groups with regard to **ALT, HDL cholesterol, lean trunk mass, and fat percentage**
- Data will continue to be followed out to 144 weeks

Baseline data for both groups

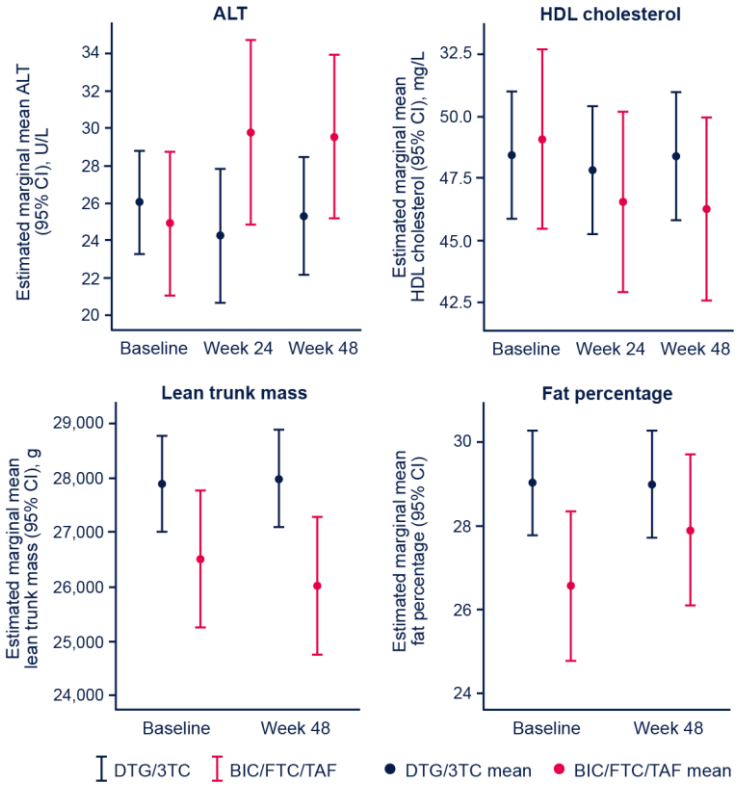
	N	DTG/3TC	BIC/FTC/TAF	*P* value
ART regimen at BL, n (%)	130			0.072
DTG/ABC/3TC		27 (31)	22 (51)	
BIC/FTC/TAF		59 (68)	21 (49)	
DTG + FTC/TAF		1 (1)	0 (0)	
Months on ART, median (IQR)	123	97 (87.5-112.5)	72 (68.1-98.7)	0.128
Months on 2nd-generation INSTI, median (IQR)	125	42 (35.9-46.0)	51 (39.0-51.4)	0.491
CD4 nadir, median (IQR), cells/mm^3	121	324 (293-383)	269 (247-378)	0.510
Weight, mean (SD), kg	130	81.2 (12.4)	75.3 (13.0)	**0.013**
Waist, mean (SD), cm	128	95.4 (11.8)	89.2 (11.2)	**0.006**
BMI, median (IQR), kg/m^2	130	25.9 (23.4-28.4)	24.8 (21.8-26.1)	**0.024**

Significantly different estimated mean differences over time (baseline – Week 48) between the groups

	DTG/3TC	BIC/FTC/TAF	*P* value
ALT, U/L	-0.73	+4.6	**0.035**
HDL cholesterol, mg/L	-0.07	-2.80	**0.044**
Lean trunk mass, gram	+105.77	-489.37	**0.027**
Fat percentage	-0.04	+1.33	**0.003**

Other estimated mean differences over time (baseline – Week 48) between the groups

	DTG/3TC	BIC/FTC/TAF	*P* value
Weight, kg	+0.256	+0.18	0.918
Waist, cm	-0.02	+1.02	0.204
BMI, kg/m^2	+0.07	+0.04	0.919
Cholesterol, mg/dL	-2.52	-9.30	0.287
LDL cholesterol, mg/dL	-1.82	-7.56	0.311
Triglycerides, mg/dL	-3.79	-21.15	0.198
HOMA-IR	-0.166	-0.43	0.347



Degroote et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Poster P150.

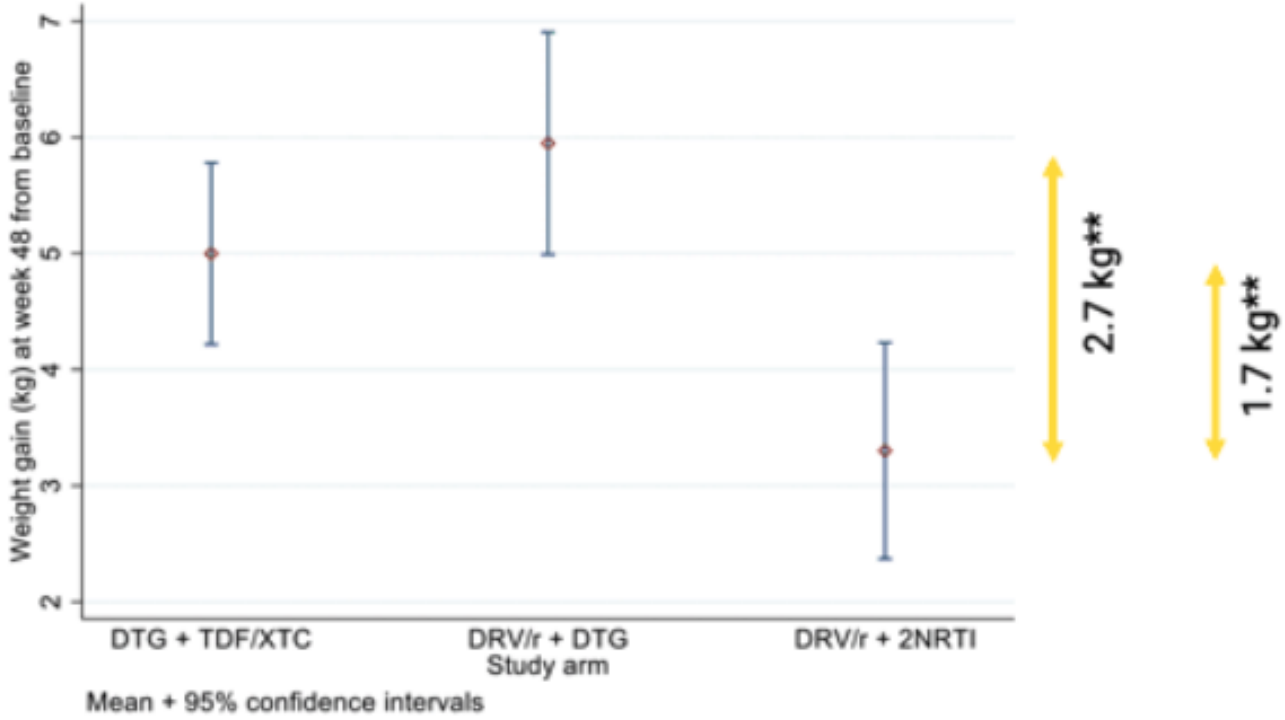
RUMBA Adjusted Metabolic Outcomes at 48 Weeks

- **Study design:** Randomized (2:1), open-label, controlled trial of adults switching to DTG/3TC (n=87) compared with switching to (or staying on) BIC/FTC/TAF (n=43)
- **Aim:** To evaluate the effects of switch from 2nd-generation INSTI-based triple ART to DTG/3TC 2DR on metabolic health
- **Results:** After adjusting for baseline BMI, statistically significant changes were observed favoring DTG/3TC in ALT, HDL-C, lean trunk mass, trunk fat mass, and fat percentage at Week 48
  - No significant differences in other lipid parameters (TG, LDL-C, TC), glucose, insulin, HOMA-IR, or liver fibrosis

	DTG/3TC	BIC/FTC/TAF	*P* value
ALT, U/L	−0.73	+4.55	0.040
HDL-C, mg/L	−0.043	−2.84	0.043
Lean trunk mass, g	+112	−474	0.032
Trunk fat mass, g	+41	+719	0.043
Fat percentage	−0.04	+1.32	0.003

Degroote et al. CROI 2023; Virtual and Seattle, WA. Poster 672.

Mean weight (kg) change at week 48 (Stage 2 only)



Mean weight gain was greater in both DTG+DRV/r 2.7kg (p<0.001) and DTG+TDF/XTC 1.7kg (p=0.006) arms compared to DRV/r +2NRTI

UNSW Kirby Institute

UNSW SYDNEY

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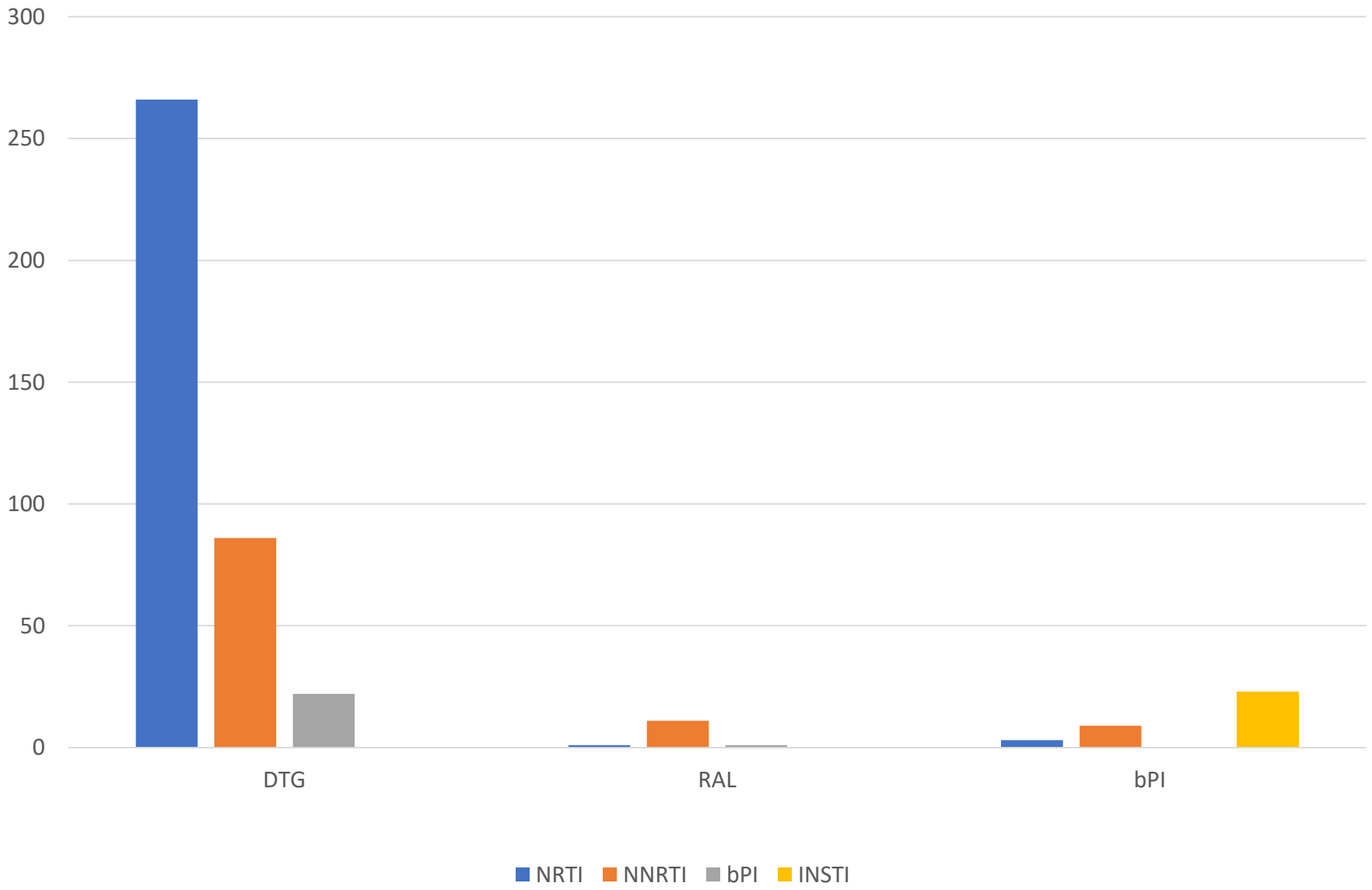
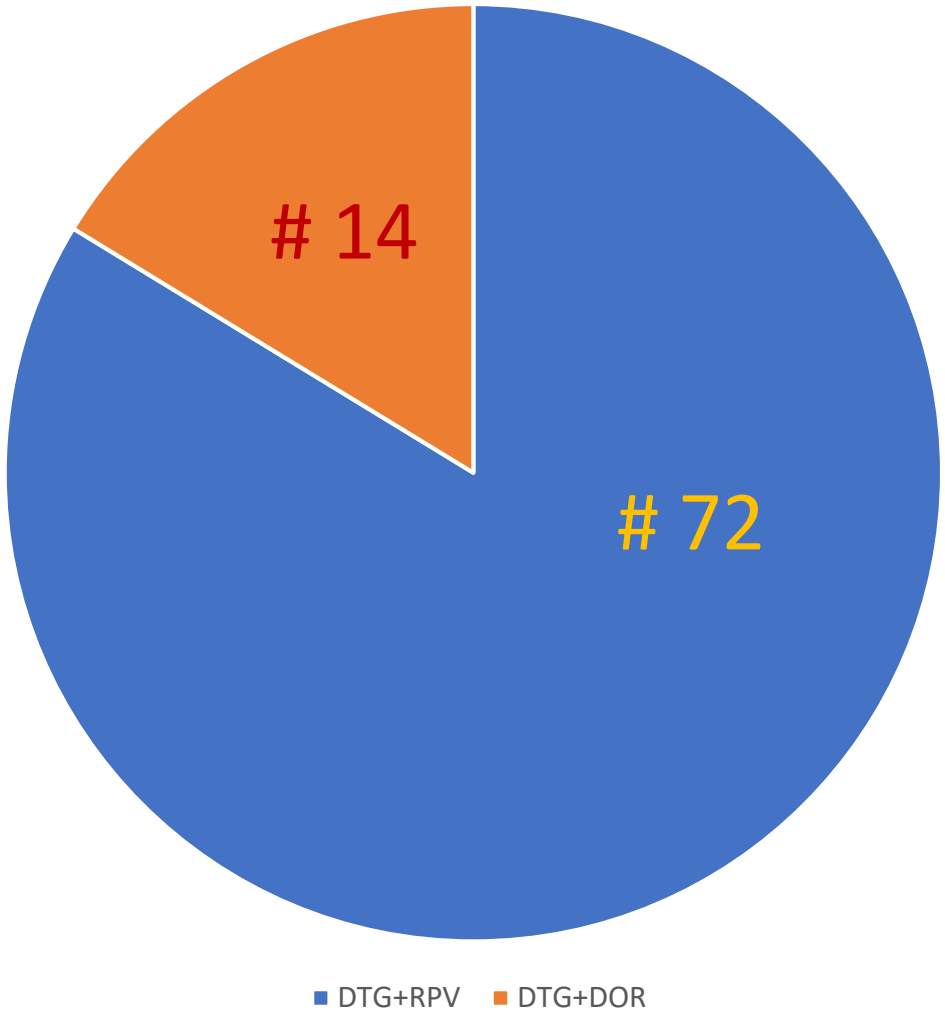
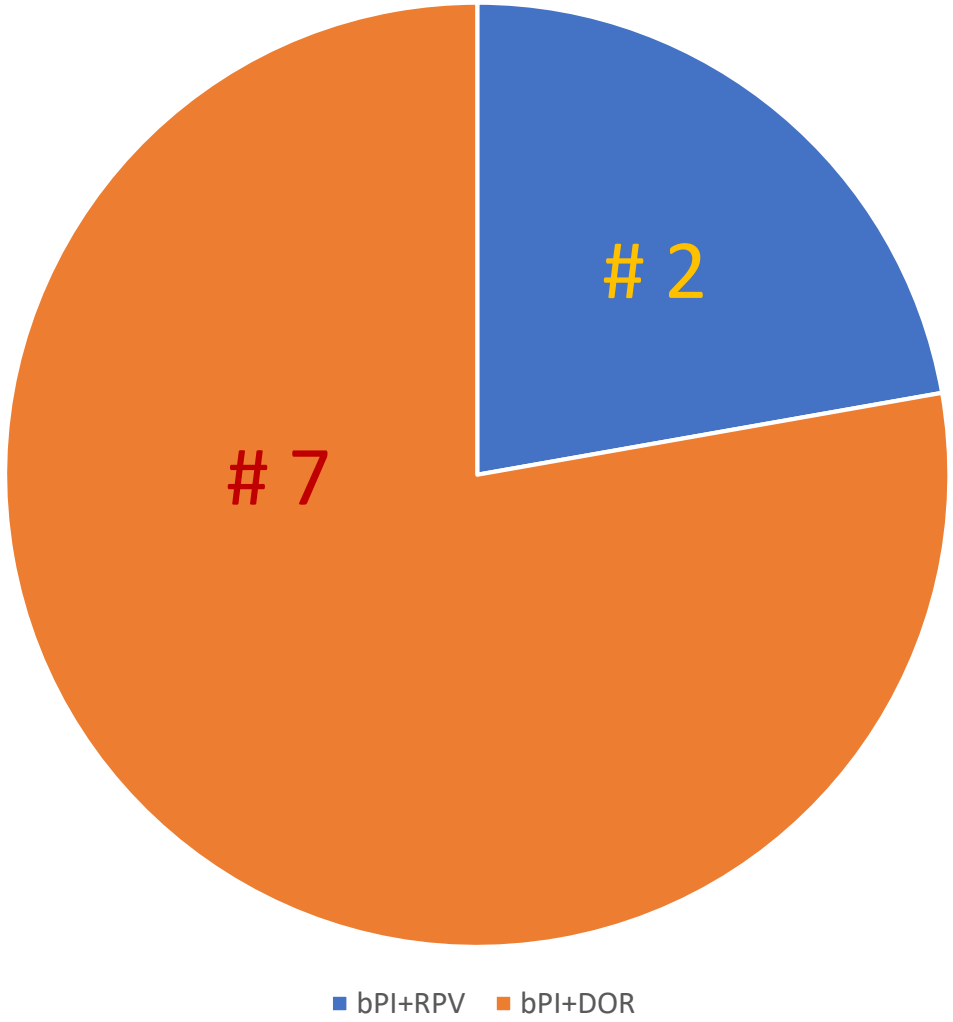
CROI 2023, Abs 198

Dual therapy (I.D. Unit, Legnano)



Dual therapy DTG-NNRTI





Dual therapy bPI-NNRTI

Simplification and Drug Res (2DR)

Dolutegravir (DTG) and Lamivudine (3TC) for Maintenance of HIV Viral Suppression in Adults With and Without Historical Resistance to Lamivudine: 48-Week Results of a Pilot Clinical Trial (ART-PRO)

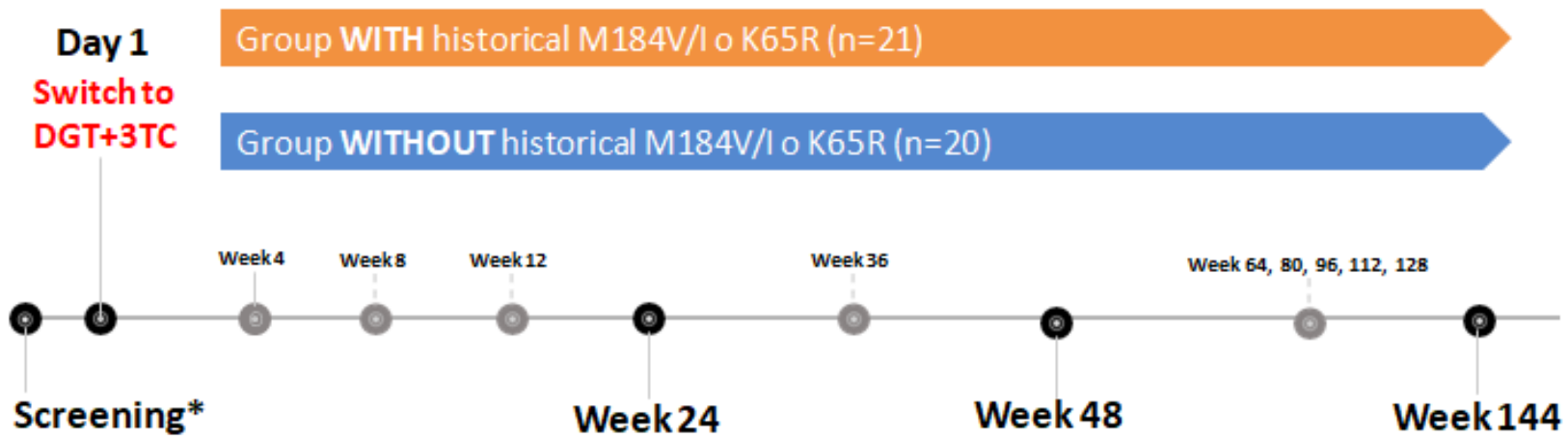
Pilot, single--arm, phase IIa, open label clinical trial conducted at 2 sites in Madrid (Spain)

Inclusion

- CD4> 350 cel/µL and VL < 50 copies/mL for 12 months (1 blip allowed)
- Stable ART for 3 months
- FTC or 3TC in past/present treatment
- INSTI naive

Exclusion

- M184V/I or K65R in baseline proviral DNA Sanger genotype
- HBAgS +
- Pregnant/women wishing to conceive

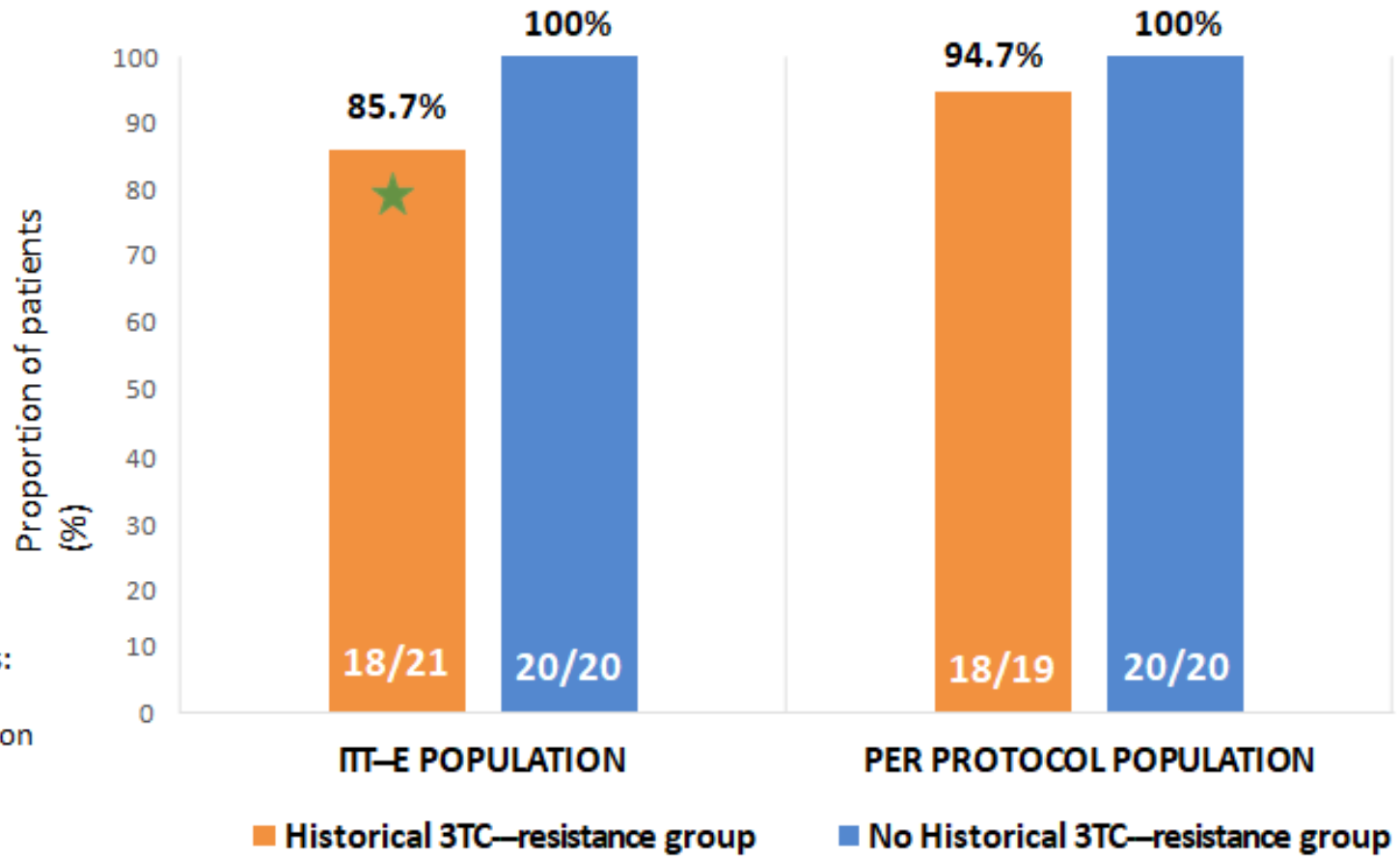


*GEN---PRO: e--poster PE13/2

R De Miguel Buckley et al. ART--PRO #PS7/5. 17th European AIDS Conference (Basel, 2019)

Dolutegravir (DTG) and Lamivudine (3TC) for Maintenance of HIV Viral Suppression in Adults With and Without Historical Resistance to Lamivudine: 48-Week Results of a Pilot Clinical Trial (ART-PRO)

At week 48, 92.7% (38/41) of participants maintained HIV—RNA VL < 50 copies/mL



★ Discontinuations:
1 AE
2 protocol violation

Per protocol population: 2 patients excluded from analysis

Transient viral rebound in 10 cases (4 with and 6 without historical 3TC resistance), 63-1943 copies/ml, all returned to undetectable VL with same DTG/3TC therapy

R De Miguel Buckley et al. ART–PRO #PS7/5. 17th European AIDS Conference (Basel, 2019)

Dolutegravir (DTG) and Lamivudine (3TC) for Maintenance of HIV Viral Suppression in Adults With and Without Historical Resistance to Lamivudine: 48-Week Results of a Pilot Clinical Trial (ART-PRO)

	All participants (n=41)	Historical resistance to lamivudine (n=21)	No historical lamivudine resistance (n=20)	*p* value
M184V (Proviral DNA Sanger genotype)*	2 (4·9)	2 (9·5)	0 (0)	0·488
M184V/I detected by NGS in proviral DNA, n (%)				
>20%	8 (19·5)	7 (33)	1 (5)	0·046
>10%	13 (31·7)	11 (52·4)	2 (10)	0·007
>5%	17 (45·5)	14 (66·7)	3 (15)	0·002
>1%	27 (65·9)	20 (95·2)	7 (35)	<0·01
K65R/E/N detected by NGS in proviral DNA, n (%)†				
>20%	1 (2·4)	1 (4·8)	0 (0)	1
>10%	2 (4·9)	2 (9·5)	0 (0)	0·488
>5%	2 (4·9)	2 (9·5)	0 (0)	0·488
>1%	3 (7·3)	3 (14·3)	0 (0)	0·233

* Protocol violation

>1% M184I/V detected in HIV-1 DNA in almost all patients with historical 3TC resistance and one third of those without historical 3TC resistance

R De Miguel Buckley et al., EBioMed 2020

OFID 2022 paper

Open Forum Infectious Diseases

BRIEF REPORT

Long-term Evaluation of Residual Viremia in a Clinical Trial of Dolutegravir Plus Lamivudine as Maintenance Treatment for Participants With and Without Prior Lamivudine Resistance

Rosa De Miguel Buckley,[1,2,a] David Rial-Crestelo,[2,3,a] Rocío Montejano,[1,2] Adriana Pinto,[3] María Jimenez-Gonzalez,[1,2] Maria Lagarde,[2,3,4] Andrés Esteban-Cantos,[1,2] Paula Aranguren-Rivas,[3] Julen Cadiñanos,[1,2] Otilia Bisbal,[2,3] Juan Miguel Castro,[1] Mireia Santacreu-Guerrero,[3] Laura Bermejo-Plaza,[3] Victoria Moreno,[1] Asunción Hernando,[2,3] Luz Martín-Carbonero,[1,2] Rafael Rubio,[2,3,4] Rafael Delgado,[4,5] José Ramón Arribas,[1,2,6,b] and Federico Pulido,[2,3,4,b] for the Antiretroviral Treatment Guided by Proviral Genotype (ART-PRO) Study Group

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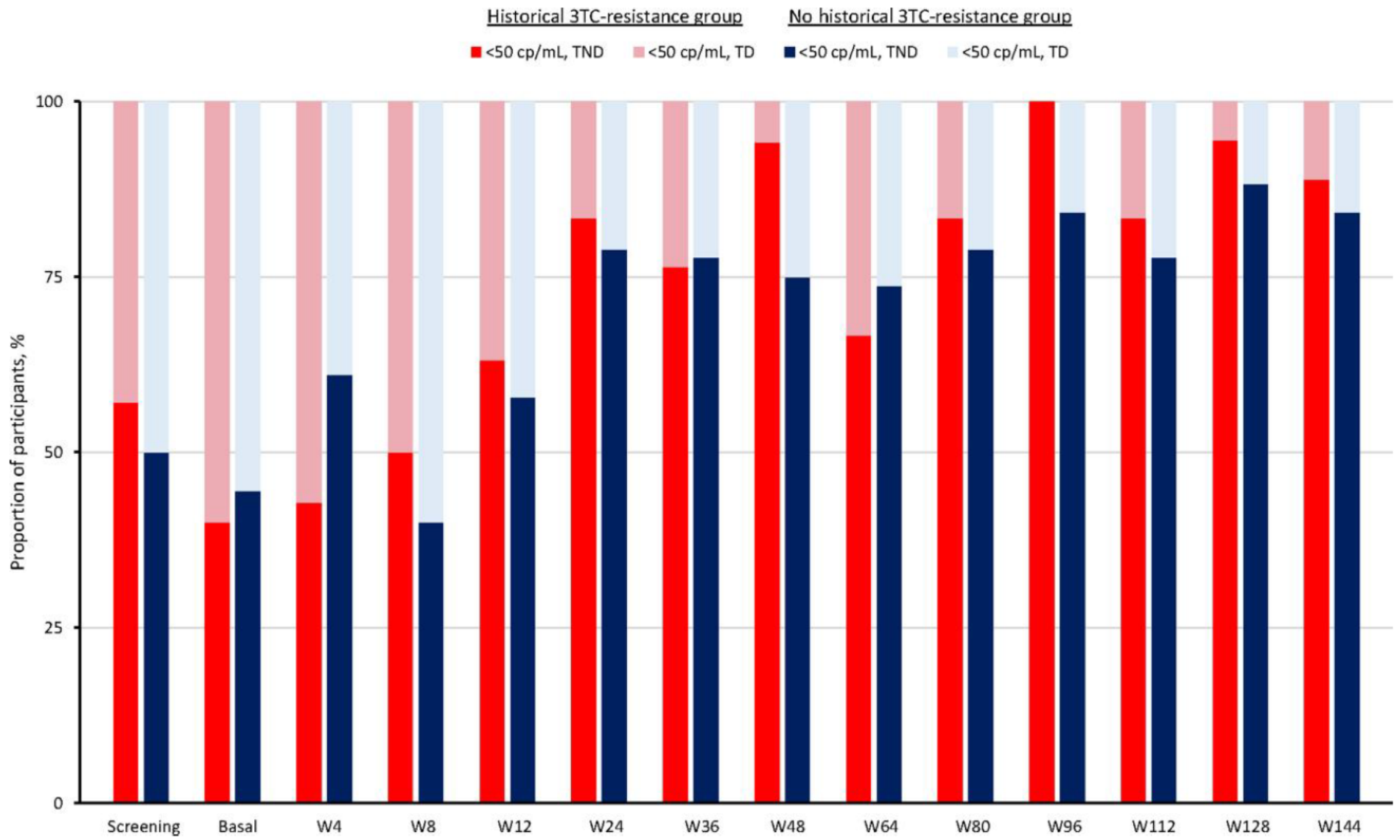
FDA Snapshot at Week 144, ITT–e Population

Outcome	All Participants (N = 41)	Historical Resistance to Lamivudine (n = 21)	No Historical Resistance to Lamivudine (n = 20)	*P* Value
HIV-1 RNA <50 copies/mL	37 (90.2)	18 (85.7)	19 (95)	.61
HIV-1 RNA ≥50 copies/mL	0 (0)	0 (0)	0 (0)	
HIV-1 RNA ≥50 copies/mL in week 144 window	0 (0)	0 (0)	0 (0)	
Discontinuation study drug due to lack of efficacy	0 (0)	0 (0)	0 (0)	
Discontinuation study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL	0 (0)	0 (0)	0 (0)	
No virologic data at week 144	4 (9.8)	3 (14.3)	1 (5)	.61
Discontinuation study drug due to AE	1 (2.4)	1 (4.8)	0 (0)	
Discontinuation study drug due to other reasons and last available HIV-1 RNA <50 copies/mL	3 (7.3)	2 (9.5)	1 (5)	

Proportion of participants with HIV RNA <50 copies/mL, TND and <50 copies/mL, target detected



Caveat

- NGS analysis on DNA (no cut-off was used in general analysis; in any case, it was only reported in the *post hoc* analysis)
- Sample size
- Absent info on the previous regimen (bPI-based? NNRTI-based?)
- INSTI-naive: a scenario that would be unlikely in the future
- POC trial, still to be confirmed by fully powered studies, *e.g.* VOLVER

Switch and Drug Res (if M184V/I is known or the picture is not reassuring)

BRAAVE 2020: Switch to B/F/TAF in Black American Adults, W72

Study Design

- Phase 3b, randomized, open-label, multicenter

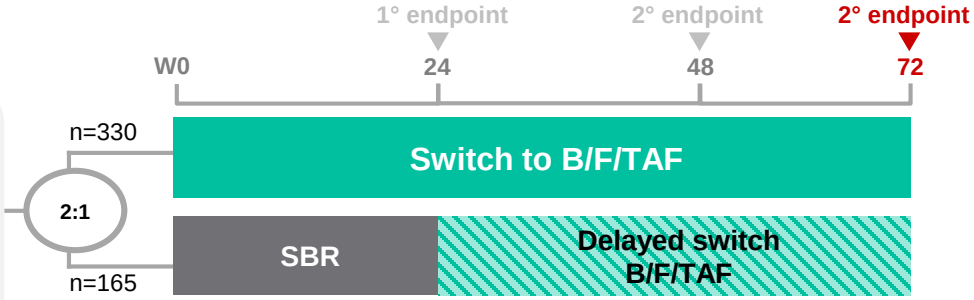
Outcome

Assess the efficacy of B/F/TAF in virologically suppressed Black Americans with preexisting resistance, viral blips, and suboptimal adherence

Baseline-W72

HIV suppressed Black American adults on 2 NRTIs + third agent*

- Self-described as Black American, or mixed race, including Black
- Suppressed ≥6 months
- $eGFR_{CG}$ ≥50 mL/min



ARV resistance criteria at baseline

Included
- NRTI-R
  - M184V/I
  - 1–2 TAMs
  - Other substitutions
- NNRTI-R
- PI-R

Excluded
- NRTI-R
  - K65R/N/R
  - T69 insertions
  - ≥3 TAMs
- Primary INSTI-R

Endpoints

Primary
- HIV-1 RNA ≥50 copies/mL at W24 by FDA Snapshot analysis

Secondary
- HIV-1 RNA <50 copies/mL at W24 by FDA Snapshot analysis
- Change from baseline in CD4 count at W24
- Efficacy/safety through W48/W72

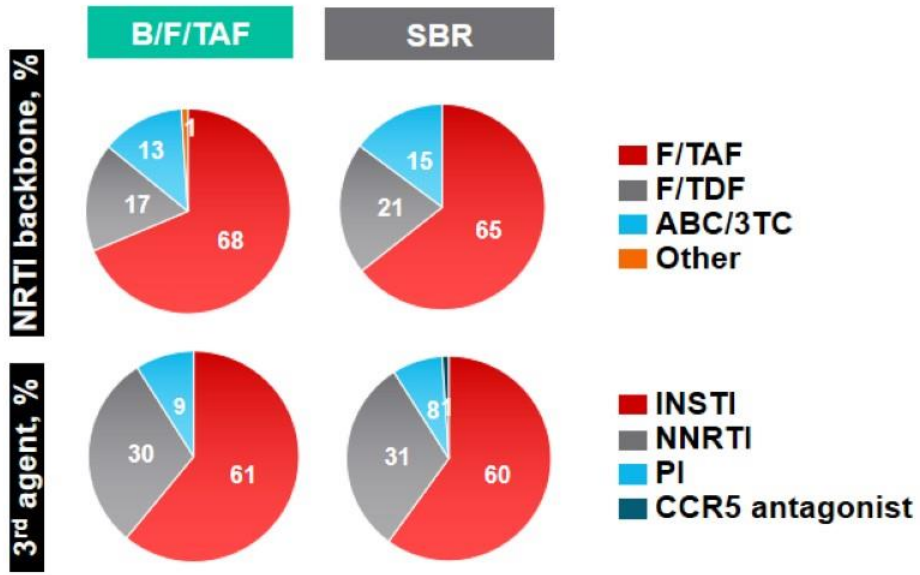
*Third agent: INSTI (except BIC), NNRTI (except etravirine), PI, or maraviroc
$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; SBR, stay on baseline regimen; TAM, thymidine-associated mutation

Andreatta K, et al. IDWeek 2021, Poster #629

Baseline Characteristics and Regimens

Baseline Characteristics*	B/F/TAF n=330	SBR n=165
Age, years	49 (18–79)	49 (19–70)
Sex at birth, % female	31	33
Gender identity, % transgender	2	4
Hispanic/Latinx ethnicity, %	5	3
CD4 count, cells/µl	747 (570, 922)	758 (494, 969)
$eGFR_{CG}$, mL/min	110 (88, 132)	107 (86, 132)
Weight, kg	88 (79, 103)	89 (76, 104)
Body mass index, kg/m^2	29.2 (25.9, 34.0)	29.3 (25.7, 34.3)
HBV coinfection, %	5	2

*Median (Q1, Q3), except for age median (range)



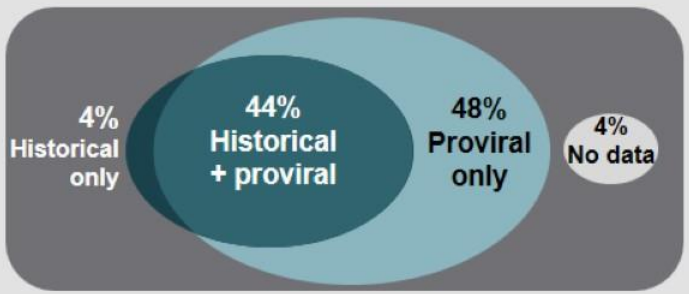
SBR, Stay on Baseline Regimen

Hagins D, et al. IDWeek 2020. Poster #1046

Baseline Resistance

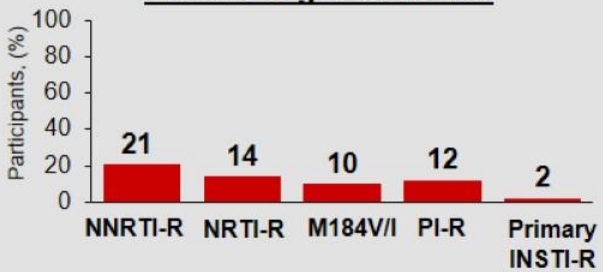
Baseline Resistance Data Sources

- Baseline historical genotype
  - PI/RT: 48% of participants
  - IN: 10-11% of participants
- Baseline proviral genotype*
  - 92% of participants



* Drug resistance detected in proviral DNA can help predict virologic rebound in PLWH,[3] but proviral genotyping assays have sampling limitations due to small blood volumes and low frequency of circulating latently infected CD4 cells

Preexisting Resistance



- 10% (51/495) of participants had M184V/I, most of which was previously undocumented (45/51)

	B/F/TAF	SBR
Resistance†	**34%**	**35%**
1-class resistance	22%	22%
2-class resistance	9%	8%
3-class resistance	2%	5%

Preexisting resistance was frequent among virologically suppressed Black adults

IN, integrase. RT, reverse transcriptase. SBR, Stay on Baseline Regimen. R, resistance
†Greater than 1 resistance substitution per ARV class

1. Hagins D, et al. IDWeek 2020. Poster #1046
2. Andreatta K, et al. IDWeek 2020. Oral 109
3. Armenia D, et al. J Clin Virol 2018;104:61-64

Pre-existing Resistance in RT, PR, and IN

Participants, % (n)	B/F/TAF n=330	SBR n=165
NRTI-R	**13 (44)**	**16 (26)**
K65R	1 (2)	1 (2)
M184V/I	9 (31)	12 (20)
Any TAM	6 (20)	10 (16)
1–2 TAMs	5 (18)	5 (8)
≥3 TAMs	1 (2)	5 (8)
Other (K70E, L74I/V, Y115F, Q151M)	2 (7)	3 (5)
NNRTI-R	**21 (70)**	**19 (32)**
K103N/S	10 (33)	12 (20)
Rilpivirine associated*	9 (29)	8 (13)
PI-R	**11 (36)**	**16 (26)**
Atazanavir or darunavir associated†	2 (6)	3 (5)

Participants, % (n)	B/F/TAF n=330	SBR n=165
Primary INSTI-R	**2 (8)**	**2 (3)**
T66A	0	1 (1)
E92G	1 (2)	1 (1)
Y143C/H	1 (3)	1 (1)
Q148H/K/R	1 (3)	0
Secondary INSTI-R	**45 (149)**	**48 (80)**
M50I	21 (69)	23 (38)
T97A	3 (10)	1 (1)
S119P/R/T	21 (70)	20 (33)
E157K/Q	8 (26)	10 (16)

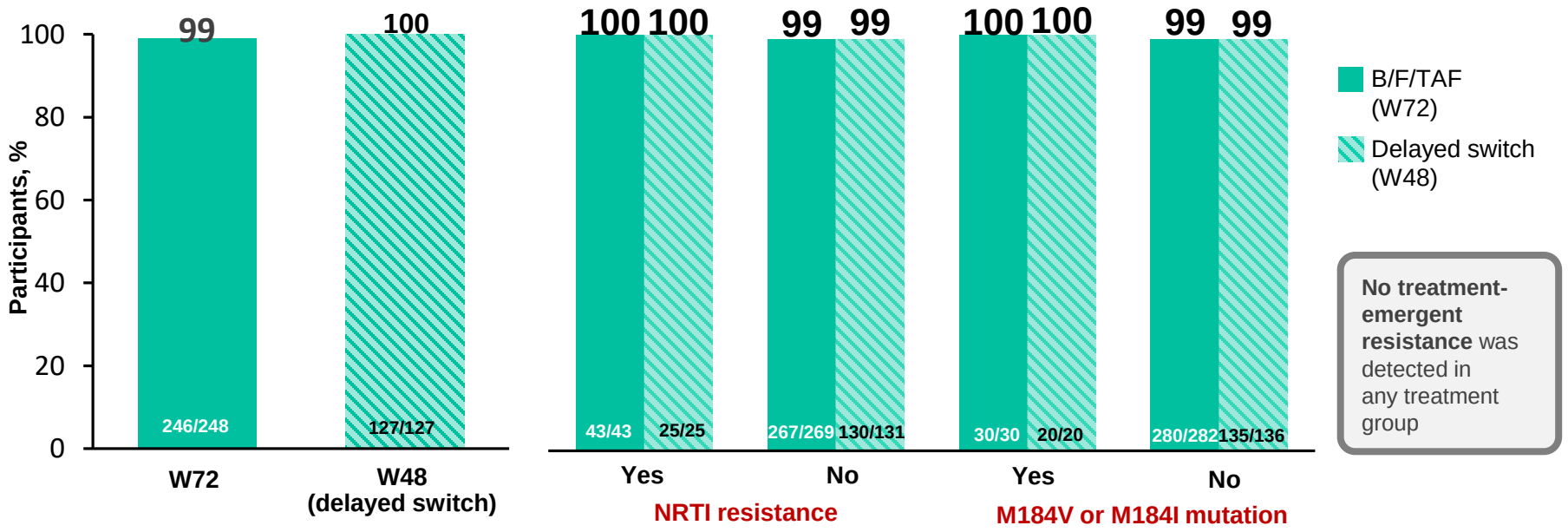
- All participants with preexisting resistance detected post-randomization continued on study and were included in efficacy analyses

Preexisting resistance was frequent among virologically suppressed Black adults

*L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L in RT
†I47V, I50L/V, I54M/L, L76V, I84V, and N88S in PR.
Andreatta K, et al. IDWeek 2020. Oral 109

BRAAVE 2020: Switch to B/F/TAF in Black American Adults, W72 (End of Study)

HIV-1 RNA <50 c/mL at W72 (M=E, Full Analysis Set)



Virologic suppression was maintained in Black American adults on B/F/TAF despite pre-existing NRTI resistance, including M184V/I

Full Analysis Set: Denominator for percentage is number of participants in B/F/TAF with non-missing HIV-1 RNA value at each visit

Kumar P, et al. vIAS 2021, PEB161

Study Design[1]

Objectives

- To determine the prevalence of preexisting M184V/I among 2034 virologically suppressed participants in 6 clinical trials
  - Studies 4030 and 4580 allowed M184V/I at screening (n=772)
  - Studies 1844, 1878, 4449, and 1474 which M184V/I excluded at screening (n=1262)
- To evaluate the impact of preexisting M184V/I on virologic outcomes after switching to B/F/TAF

Resistance Analysis

- Baseline: historical HIV-1 genotype reports were collected if available and HIV-1 proviral DNA genotype testing was performed on baseline samples
  - Participants with preexisting resistance detected after enrollment continued on study and were included in all analyses
- Post-baseline: participants with HIV RNA ≥200 copies/mL at confirmed virologic failure, Week 48, or last visit on study drugs had HIV-1 RNA genotype and phenotype testing performed

HIV-1 Drug Resistance Substitutions (based on IAS-USA)[2]

NRTI-R	K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R)
NNRTI-R	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L
	RPV-R: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L
PI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
INSTI-R	T66I/A/K, E92Q/G, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

1. Andreatta K, et al. HIV Drug Therapy 2020. Glasgow. P123
2. Wensing AM, et al. Top Antivir Med 2017;24:132-41

Baseline Resistance-Associated Substitutions

Baseline Genotype, % (n or n/N)	Pooled B/F/TAF n=2034
PR/RT data available (historical and/or proviral)	**90 (1825)**
NRTI-R	**16 (288/1825)**
M184V/I	**10 (182)**
V only substitution	**9 (161)**
I only substitution	**1 (11)**
V and I substitutions	**1 (10)**
K65R/E/N	1 (18)
Any TAM	9 (167)
NNRTI-R	**22 (397/1825)**
RPV-R	9 (170)
K103N/S	11 (205)
PI-R	**11 (201/1825)**
IN data available (historical and/or proviral)	**85 (1731)**
INSTI-R	**2 (30/1731)**

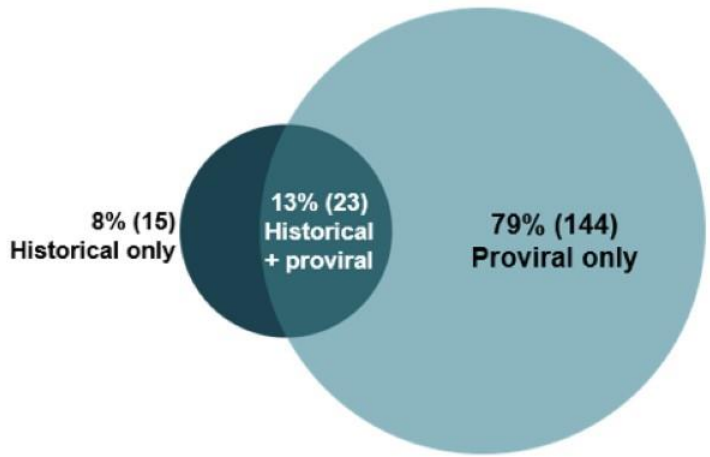
M184V/I alone	19% (35/182)
M184V/I + NNRTI-R	53% (97/182)
M184V/I + other NRTI-R	47% (86/182)
M184V/I + TAMs	39% (71/182)
M184V/I + PI-R	27% (50/182)
M184V/I + INSTI-R	2% (4/182)

- M184V/I was frequently detected with other resistance substitutions
- Participants with preexisting M184V/I were older, more often from the USA, Black race, with baseline CD4 cell counts <500 cells/µL vs participants without M184V/I

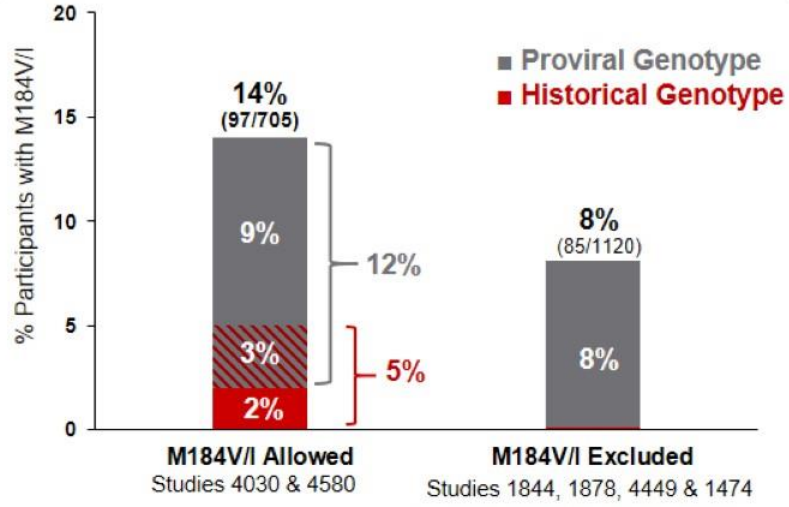
M184V/I was detected in 10% of participants with M184V being the most common substitution

Andreatta K, et al. HIV Drug Therapy 2020. Glasgow. P123

M184V/I Detection



Overall M184V/I was detected in 10% of participants, most of which was previously undocumented

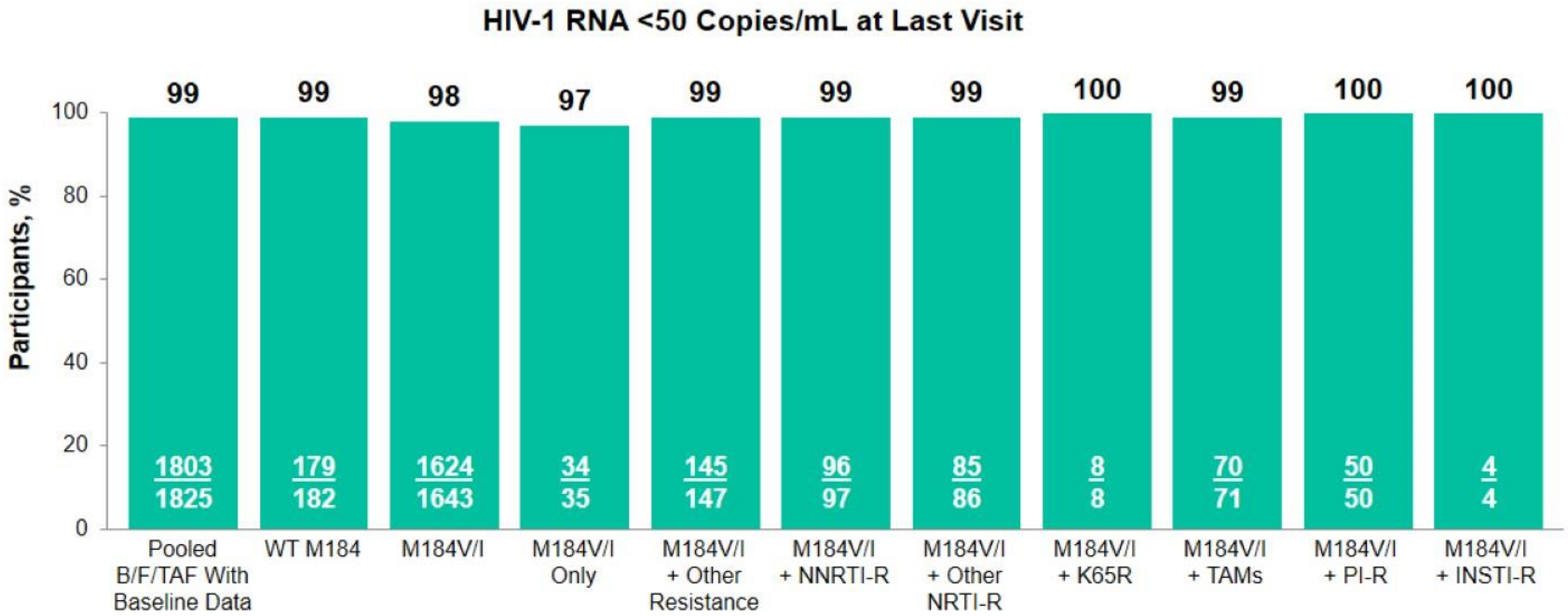


Undocumented M184V/I observed in 8-9% of participants. This may affect regimen selection in real world setting

Andreatta K, et al. HIV Drug Therapy 2020. Glasgow. P123

‡

Virologic Suppression by Preexisting M184V/I: Pooled B/F/TAF Group



B/F/TAF is an effective and durable treatment for virologically suppressed PLWH, including those with known or undocumented M184V/I at baseline

Andreatta K, et al. HIV Drug Therapy 2020. Glasgow. P123

Open Forum Infectious Diseases

BRIEF REPORT

Nucleoside Reverse-Transcriptase Inhibitor Resistance Mutations Predict Virological Failure in Human Immunodeficiency Virus-Positive Patients During Lamivudine Plus Dolutegravir Maintenance Therapy in Clinical Practice

Alberto Borghetti,[1] Andrea Giacomelli,[2,3] Vanni Borghi,[4] Arturo Ciccullo,[5] Alex Dusina,[5] Massimiliano Fabbiani,[6] Stefano Rusconi,[2,3] Maurizio Zazzi,[7] Cristina Mussini,[4] and Simona Di Giambenedetto[1,5]

An observational cohort from 3 large University hospitals of patients starting 3TC-DTG, with suppressed viral load (HIV-RNA >50 copies/mL) at the time of switch (baseline) and with no evidence of hepatitis B virus chronic infection.

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Table 2. Predictors of Virological Failures According to Different Cox Regression Models

Exposure Variable	Models 1, 2, 4* aHR (95% CI)	*P* Value	Model 3** aHR (95% CI)	*P* Value	Model 5*** aHR (95% CI)	*P* Value
M184V/I (presence vs absence)			3.31 (1.02–10.74)	.046		
M184V/I with TAMs (presence vs absence)					4.63 (1.19–17.94)	.027
Previous failure on an INI-based regimen (at least 1 vs none)	5.84 (1.28–26.64)	.025	6.41 (1.36–30.18)	.019	5.51 (1.15–26.50)	.033
Time of virological suppression (>2 years vs ≤2)	0.29 (0.10–0.86)	.023	0.27 (0.09–0.80)	.018	0.23 (0.08–0.74)	.013

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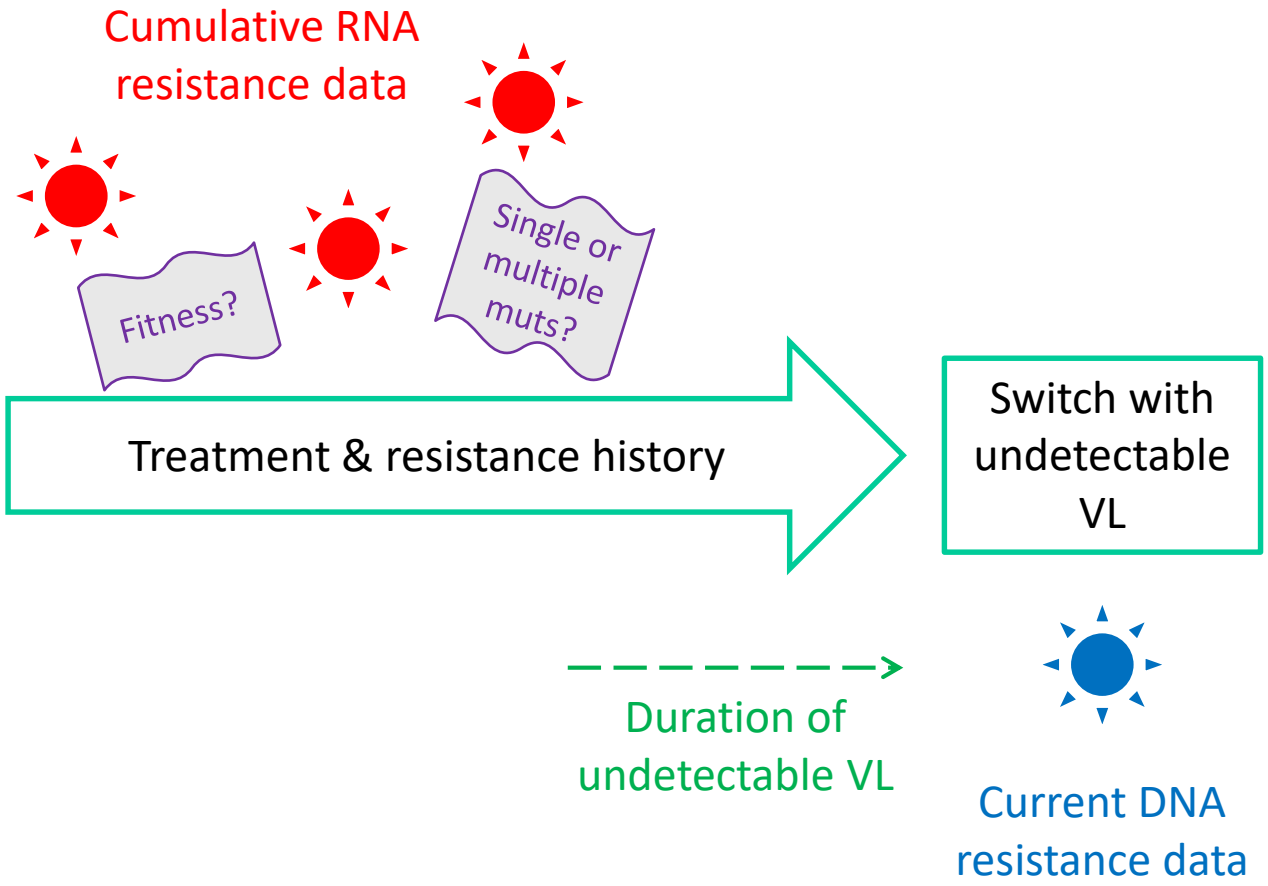
Impact of drug resistance…on HIV Tx



- **RNA resistance** is the reference data but must be integrated with VF data
- **DNA resistance** can be useful but also misleading
  - Non-functional provirus
  - Dilution over time
- **Duration of undetectable VL** makes ALL old mutations less important
- **Not all mutations are the same**
  - Lower fitness, less impact (M184V vs. NNRTI RAMs)
  - Single mutation less important than multiple mutations

Courtesy of Maurizio Zazzi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