TERAPIA ANTIRETROVIRALE ORALE DUPLICE E TRIPLICE NEL PAZIENTE EXPERIENCED

Alberto Borghetti

Milano, 2 Maggio 2024

Outline

- Treatment guidelines: a comparison
- Open questions on switch strategies
  - 3-drug regimens
  - 2-drug regimens
- Conclusions

International guidelines: a comparison

	EACS 12.0 October 2023	DHHS February 2024	BHIVA 2023 interim update
Switch indications	To eliminate or improve adverse events, facilitate adequate treatment of comorbid conditions, and improve quality of life	Adverse events, drug–drug or drug–food interactions, pill burden, pregnancy, cost, or the desire to simplify a regimen may prompt regimen optimization.	Management of ARV drug toxicity or intolerance, more convenient dosing, to reduce pill burden, management of potential drug–drug interactions, individual preference and cost
Switch concerns	To sustain and not to jeopardize virological suppression	The fundamental principle of ARV regimen optimization is to maintain viral suppression without jeopardizing future treatment options.	Switching ART should not be at the cost of virological efficacy. Particular caution when switching from a high-genetic barrier to a low-genetic barrier regimen in the presence of known or suspected resistance (Grade 1B).
Three-drug regimens	In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy.	People with HIV who have no history of drug-resistance mutations or virologic failure can likely switch to any regimen that has been shown to be highly effective in ARV-naive patients (AI) In the setting of existing nucleoside reverse transcriptase inhibitor (NRTI) resistance, two NRTIs—TAF or TDF + plus FTC or 3TC should be included in the regimen with a fully active, high resistance barrier drug, such as DTG (BIII), bDRV (BIII), or BIC (CIII).	- BiC/FTC/TAF - DTG+FTC/TAF or FTC/TDF - DTG/3TC/ABC In addition, the following regimens are also acceptable: - TFV/FTC or ABC/3TC + DOR or RPV - TFV/FTC or ABC/3TC+EFV or NVP (not routinely) - TFV/FTC/EVG or RGV - TFV/FTC + bDRV or bATV or bLPV
Two-drug regimens	DTG+RPV XTC+DTG XTC+DRV/b	DTG+RPV DTG+3TC (FTC) bDRV+DTG	3TC/DTG DTG/RPV RGV+bDRV DTG+bDRV 3TC+bPI
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Open questions

- What is the best regimen in case of RAMs?
- What’s the role of time of viral suppression?
- How to use resistance test on HIV-DNA?
- What to do in case of HBcAg+ serostatus?
- What are the risk of jeopardising future treatment options in case of failure?

Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV

Paton NI et al. DOI: 10.1056/NEJMoa2101609

CLINICAL PROBLEM

For second-line treatment of HIV-1, the WHO recommends dolutegravir along with two nucleoside reverse-transcriptase inhibitors (NRTIs), usually zidovudine and lamivudine. Evidence of efficacy is limited when NRTI resistance is present, as is evidence for a switch from tenofovir in first-line treatment to zidovudine in second-line treatment. By contrast, good evidence supports use of a protease inhibitor (e.g., darunavir) with two NRTIs as second-line treatment even in patients with extensive NRTI cross-resistance.

CLINICAL TRIAL

Design: A multicenter, two-by-two factorial, randomized, open-label noninferiority trial was conducted to compare dolutegravir with darunavir and tenofovir with zidovudine in patients with HIV-1 viral load ≥1000 copies per milliliter despite at least 6 months of first-line treatment.

Intervention: 464 patients in sub-Saharan Africa were assigned to daily dolutegravir or ritonavir-boosted darunavir, along with either tenofovir plus lamivudine or zidovudine plus lamivudine. The WHO-recommended public health approach was used, including sparse viral load and safety monitoring and without baseline genotypic resistance testing to guide the selection of NRTIs. The primary outcome was viral suppression (<400 copies per milliliter) at 48 weeks.

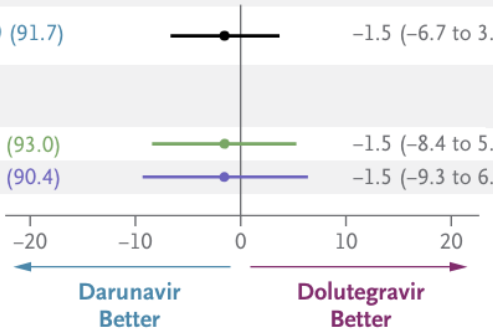
RESULTS

Efficacy: In suppressing viral load, dolutegravir was noninferior to darunavir and tenofovir was noninferior to zidovudine. Intermediate- or high-level resistance developed in four patients in the dolutegravir group.

Safety: No significant differences in safety outcomes occurred between the groups in either factorial comparison.

Subgroup Analysis of Viral Suppression in the Dolutegravir and Darunavir Groups

Subgroup	Dolutegravir	Darunavir	Difference in Percentage Points (95% CI)
	no. of patients/total no. (%)		
Intention-to-treat population	212/235 (90.2)	210/229 (91.7)	−1.5 (−6.7 to 3.7)
NRTI randomization group			
Tenofovir	108/118 (91.5)	107/115 (93.0)	−1.5 (−8.4 to 5.3)
Zidovudine	104/117 (88.9)	103/114 (90.4)	−1.5 (−9.3 to 6.4)



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Viral load at baseline			
<100,000 copies/ml	153/169 (90.5)	154/167 (92.2)	−1.7 (−7.7 to 4.3)
≥100,000 copies/ml	59/66 (89.4)	56/62 (90.3)	−0.9 (−11.4 to 9.5)
CD4+ cell count at baseline			
<200 cell/mm³	112/125 (89.6)	108/113 (95.6)	−6.0 (−12.5 to 0.6)
≥200 cell/mm³	100/110 (90.9)	102/116 (87.9)	3.0 (−5.0 to 11.0)
Sex			
Male	87/95 (91.6)	77/87 (88.5)	3.1 (−5.7 to 11.8)
Female	125/140 (89.3)	133/142 (93.8)	−4.4 (−10.9 to 2.1)
No. of predicted active NRTIs			
0	85/92 (92.4)	75/80 (93.8)	−1.3 (−8.9 to 6.2)
1	107/118 (90.7)	116/122 (95.1)	−4.4 (−10.9 to 2.1)
≥2	13/18 (72.2)	15/23 (65.2)	7.0 (−21.4 to 35.4)

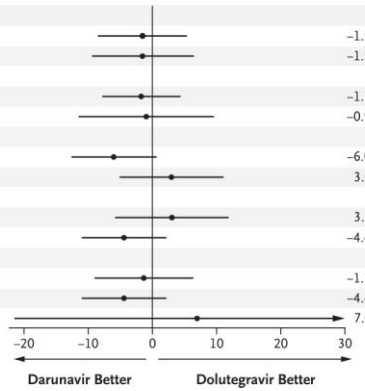


Figure 2. Subgroup Analysis of Viral Suppression in the Dolutegravir and Darunavir Groups.

Shown is the percentage of patients with a viral load of less than 400 copies per milliliter at week 48, according to randomly assigned treatment group and prespecified subgroups. The first subgroups shown are the other factorial randomization groups (i.e., the nucleoside reverse-transcriptase inhibitor [NRTI] treatment groups). The percentage of patients with viral suppression is based on the Food and Drug Administration (FDA) snapshot algorithm and includes all patients with data available for subgroup classification. The widths of the confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer treatment effects.

Summary of metabolic adverse events

Table S6 Body weight, body mass index, lipodystrophy and peripheral neuropathy*

Event category	Dolutegravir Group (N=235)	Darunavir Group (N=229)	Difference (95% CI) *Percentage points*	P	Tenofovir Group (N= 233)	Zidovudine Group (N= 231)	Difference (95% CI) *Percentage points*	P
Body weight change, mean(SD)	4.5 (8.7)	3.7 (9.0)	0.8 (-0.8 to 2.5)	0.325	4.3 (8.6)	4.0 (9.2)	0.3 (-1.4 to 2.0)	0.735
Male	3.1 (4.7)	1.9 (4.7)	1.2 (-0.2 to 2.6)	0.103	2.6 (5.2)	2.4 (4.2)	0.3 (-1.1 to 1.7)	0.681
Female	5.6 (10.7)	4.9 (10.8)	0.7 (-1.9 to 3.4)	0.594	5.4 (10.3)	5.1 (11.2)	0.3 (-2.3 to 3.1)	0.772
BMI change, mean (SD)	1.7 (3.2)	1.4 (3.2)	0.3 (-0.3 to 0.9)	0.262	1.6 (3.1)	1.5 (3.3)	0.1 (-0.5 to 0.7)	0.710
Male	1.1 (1.6)	0.6 (1.6)	0.4 (-0.1 to 0.9)	0.100	0.9 (1.8)	0.8 (1.5)	0.1 (-0.4 to 0.6)	0.727
Female	2.2 (3.9)	1.9 (3.8)	0.3 (-0.6 to 1.3)	0.496	2.1 (3.7)	2.0 (4.0)	0.1 (-0.8 to 1.1)	0.712
Incident BMI > 30, n (%)	13 (5.9)	12 (5.7)	0.2 (-4.0 to 4.7)	0.912	13 (6.0)	12 (5.5)	0.5 (-3.9 to 4.9)	0.818
Male	0	0	-	-	0	0	-	-
Female	13 (10.2)	12 (9.4)	0.8 (-6.1 to 7.8)	0.809	13 (10.5)	12 (9.2)	1.3 (-6.2 to 8.6)	0.737
Incident facial lipoatrophy, n(%)	1 (0.4)	3 (1.3)	-0.9 (-2.6 to 0.8)	0.305	1 (0.4)	3 (1.3)	-0.9 (-2.6 to 0.8)	0.313
Incident fat accumulation, n (%)	58 (25.1)	57(25.2)	-0.1 (-8.1 to 7.8)	0.978	56 (24.5)	59 (25.9)	-1.4 (-9.4 to 6.5)	0.726
Incident symptomatic peripheral neuropathy, n (%) †	1	0	-	-	1	0	-	-

* Assessments of body weight or BMI change performed during pregnancy were excluded (analysis of change performed with data from 220, 212, 215 and 217 patients in dolutegravir, darunavir, tenofovir and zidovudine groups respectively). The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I

Objective: We investigated the prevalence of preexisting M184V/I and associated risk factors among clinical trial participants with suppressed HIV and evaluated the impact of M184V/I on virologic response after switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

Design: Participant data were pooled from six clinical trials investigating the safety and efficacy of switching to B/F/TAF in virologically suppressed people with HIV.

Methods: Preexisting drug resistance was assessed by historical genotypes and/or baseline proviral DNA genotyping. Virologic outcomes were determined by last available on-treatment HIV-1 RNA. Stepwise selection identified potential risk factors for M184V/I in a multivariate logistic regression model.

Table 1. Overview of bictegravir/emtricitabine/tenofovir alafenamide switch studies in virologically suppressed people with HIV.

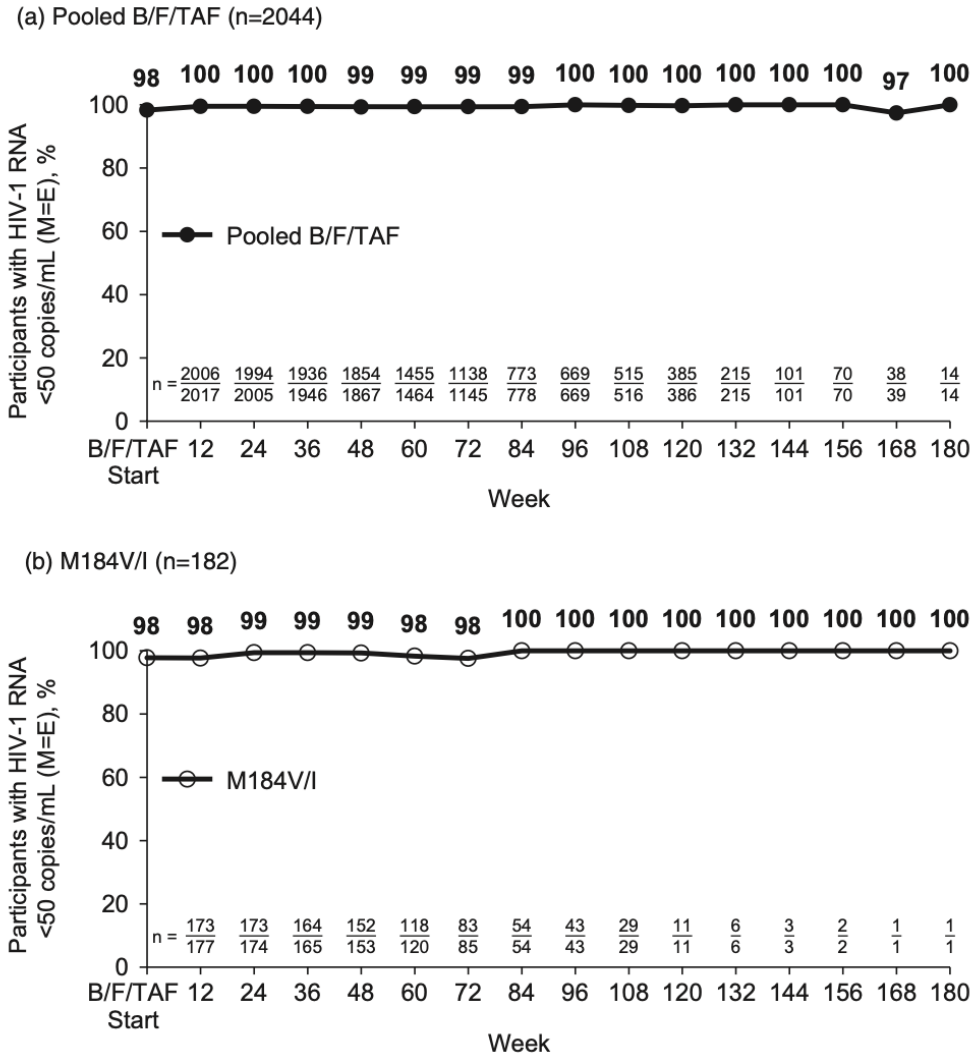
	All studies	Study 4030	Study 4580	Study 1844	Study 1878	Study 4449	Study 1474
Screening resistance criteria: M184V/I	–	Allowed	Allowed	Excluded	Excluded	Excluded	Excluded
Screening resistance criteria: bictegravir-associated	–	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Screening resistance criteria: TAF-associated	–	Allowed	Excluded	Excluded	Excluded	Excluded	Excluded
Baseline antiretroviral regimen[a]	–	DTG + either FTC/TDF or FTC/TAF	Any 3rd agent + 2 NRTIs	DTG/ABC/3TC (single or multiple tablets)	Boosted DRV or ATV + either FTC/TDF or ABC/3TC	EVG/COBI/ FTC/TAF or any 3rd agent + FTC/TDF	Any 3rd agent + 2 NRTIs
Trial design	–	Double-blind placebo-controlled randomized 1 : 1 switch to B/F/TAF or DTG + FTC/TAF	Open-label randomized 2 : 1 switch to B/F/TAF or stay on baseline regimen	Double-blind placebo-controlled randomized 1 : 1 switch to B/F/TAF or DTG/ABC/3TC	Open-label randomized 1 : 1 switch to B/F/TAF or stay on baseline regimen	Open-label single arm switch to B/F/TAF	Open-label single arm switch to B/F/TAF
Participants enrolled (*n*)	2386	565	495	563	577	86	100
Median age (criteria for study) (years)	48	51 (≥18)	49 (≥18)	46 (≥18)	48 (≥18)	69 (≥65)	12 (6-<18)
Median time since ART initiation (IQR) (years)	8.3 (4.3–15.4)	10.1 (4.4–18.7)	10.4 (5.9–17.3)	5.5 (2.7–10)	7.7 (4.1–14.0)	14.9 (6.9–19.3)	10.1 (7.4–11.4)
Participants switched to B/F/TAF (*n*)	2044	284	493[b]	547[b]	534[b]	86	100
Median B/F/TAF treatment duration (IQR) (weeks)	72 (51–102)	59 (53–63)	71 (48–72)	96 (49–119)	101 (72–120)	96 (95–96)	50 (30–52)
Participants included in LOCF analysis[c] (*n*)	2034	283	489	545	532	85	100
Timepoint for LOCF analysis	-	Week 48	Week 72/48[d]	End of study	End of study	Week 96	Week 48/24[e]
HIV-1 RNA <50 copies/ml at last visit by LOCF, % (*n*/*N*)	99% (2012/2034)	>99% (282/283)	99% (486/489)	98% (535/545)	99% (525/532)	100% (85/85)	99% (99/100)
Baseline PR/RT genotype available, % (*n*/*N*)	90% (1825/2034)	84% (237/283)	98% (468/489)	96% (522/545)	94% (498/532)	98% (83/85)	17% (17/100)
Baseline M184V/I, % (*n*/*N*)	10% (182/1825)	20% (47/237)	11% (50/468)	3% (17/522)	12% (62/498)	4% (3/83)	18% (3/17)
Baseline M184V/I + ≥1 other resistance substitution, % (*n*/*N*)	81% (147/182)	72% (34/47)	88% (44/50)	82% (14/17)	79% (49/62)	100% (3/3)	100% (3/3)
M184V/I HIV-1 RNA <50 copies/ml at last visit by LOCF, % (*n*/*N*)	98% (179/182)	100% (47/47)	100% (50/50)	100% (17/17)	95% (59/62)	100% (3/3)	100% (3/3)
Treatment emergent resistance to B/F/TAF (*n*)	0	0	0	0	0	0	0

ART, antiretroviral therapy; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; IQR, interquartile range; PR/RT, protease/reverse transcriptase.
[a]Baseline antiretroviral regimens consisted of two nucleoside reverse transcriptase inhibitors (NRTIs), such as abacavir (ABC) and lamivudine (3TC) or emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), and a third agent, such as dolutegravir (DTG), darunavir (DVR), atazanavir (ATV) or elvitegravir boosted by cobicistat (EVG/COBI).
[b]Participants switched to B/F/TAF at baseline (4580: $n = 330$, 1844: $n = 282$, 1878: $n = 290$) or at weeks 24 (4580: $n = 163$) or 48 (1844: $n = 265$, 1878: $n = 244$).
[c]Virologic outcomes based on last available on-treatment postswitch HIV-1 RNA using last observation carried forward (LOCF) imputation were determined for participants who switched to B/F/TAF and had at least one postswitch on-treatment HIV-1 RNA measurement.
[d]Participants included in the LOCF analysis had outcomes determined at week 72 ($n = 327$ switched at baseline) or week 48 ($n = 162$ switched at week 24).
[e]Participants included in the LOCF analysis had outcomes determined at week 48 ($n = 75$) or week 24 ($n = 25$) based on duration of B/F/TAF treatment at time of analysis.

Outcomes

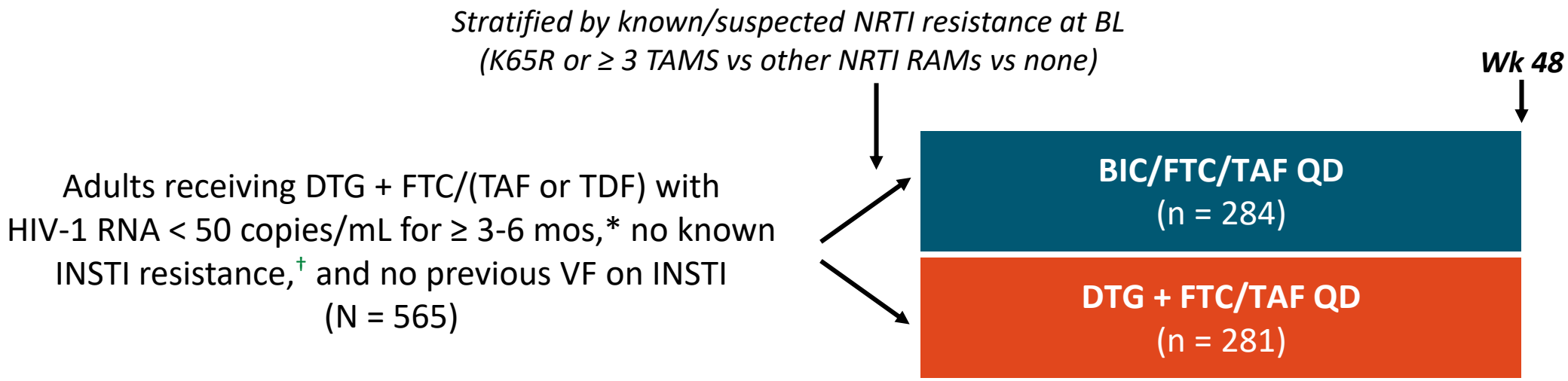
Table 2. Preexisting M184V/I and presence with other resistance substitutions in bictegravir/emtricitabine/tenofovir alafenamide-treated participants.

Category	Baseline genotype of participants with preexisting M184V/I	Pooled B/F/TAF ($n = 182$)
M184 substitutions	M184V only	88% (161)
	M184I only	6% (11)
	M184V and M184I mixture	5% (10)
Other resistance	M184V/I alone (no other resistance substitution)	19% (35)
	M184V/I + ≥1 other resistance substitution	81% (147)
Other NRTI-R	M184V/I + other NRTI-R[a]	47% (86)
	M184V/I + K65R/N	4% (8)
	M184V/I + ≥1 TAM[b]	40% (72)
	M184V/I + 1–2 TAMs	18% (33)
	M184V/I + ≥3 TAMs	21% (39)
	M184V/I + ≥3 TAMs including M41L and/or L210W	14% (26)
	M184V/I + K70E, L74I/V, Y115F, and/or Q151M[c]	15% (27)
NNRTI-R	M184V/I + NNRTI-R[d]	53% (97)
	M184V/I + K103N/S	37% (67)
	M184V/I + RPV-R[e]	27% (50)
	M184V/I + E138A/K/R[f]	7% (12)
PI-R	M184V/I + PI-R[g]	27% (50)
INSTI-R	M184V/I + primary INSTI-R[h]	2% (4)



Study 380-4030: Switch to B/F/T From DTG + FTC/(TAF or TDF)

- Randomized, double-blind, active-controlled phase III noninferiority trial



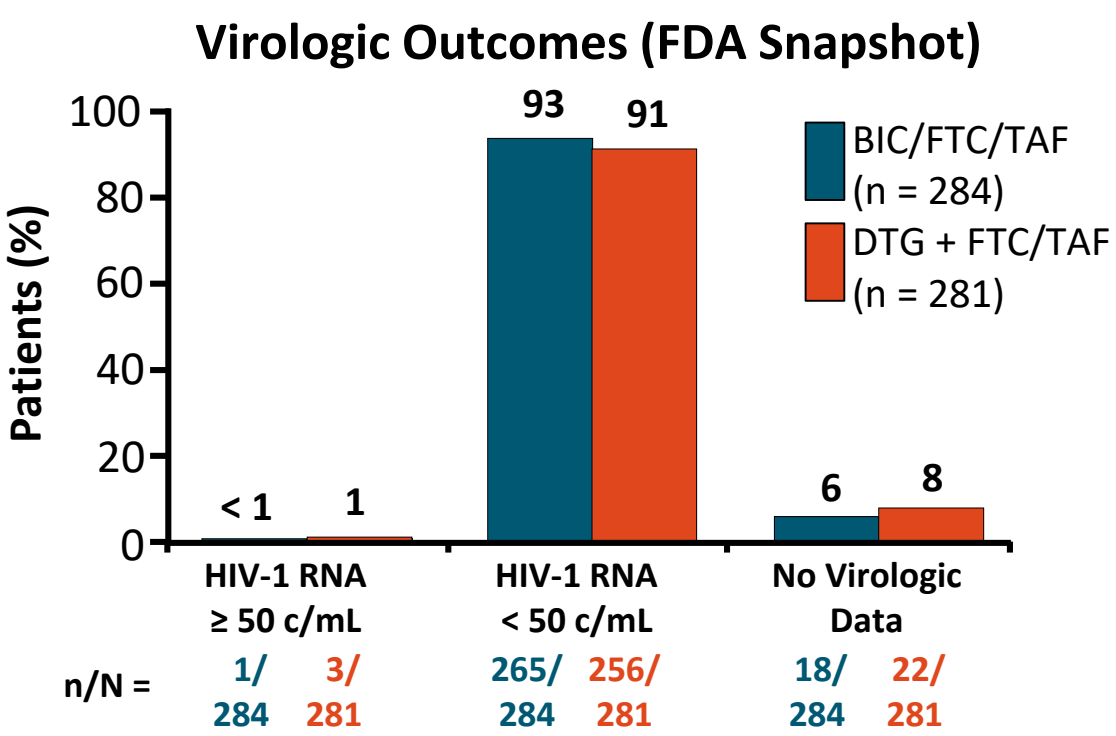
*3 mos if no known NRTI resistance mutations, 6 mos with known/suspected resistance.
†**Documented or suspected NRTI, NNRTI, or PI resistance permitted.**

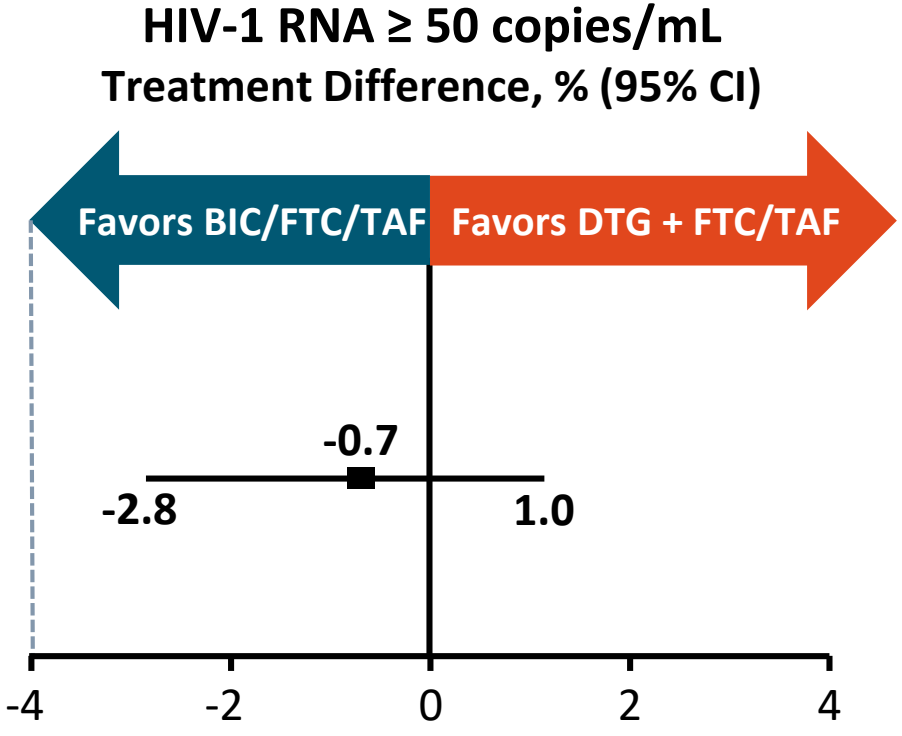
- Primary endpoint: HIV-1 RNA ≥ 50 c/mL at Wk 48 by FDA Snapshot algorithm
  - Noninferiority margin: 4%

Sax. Clin Infect Dis. 2020.

Study 380-4030: Virologic Outcomes at Wk 48

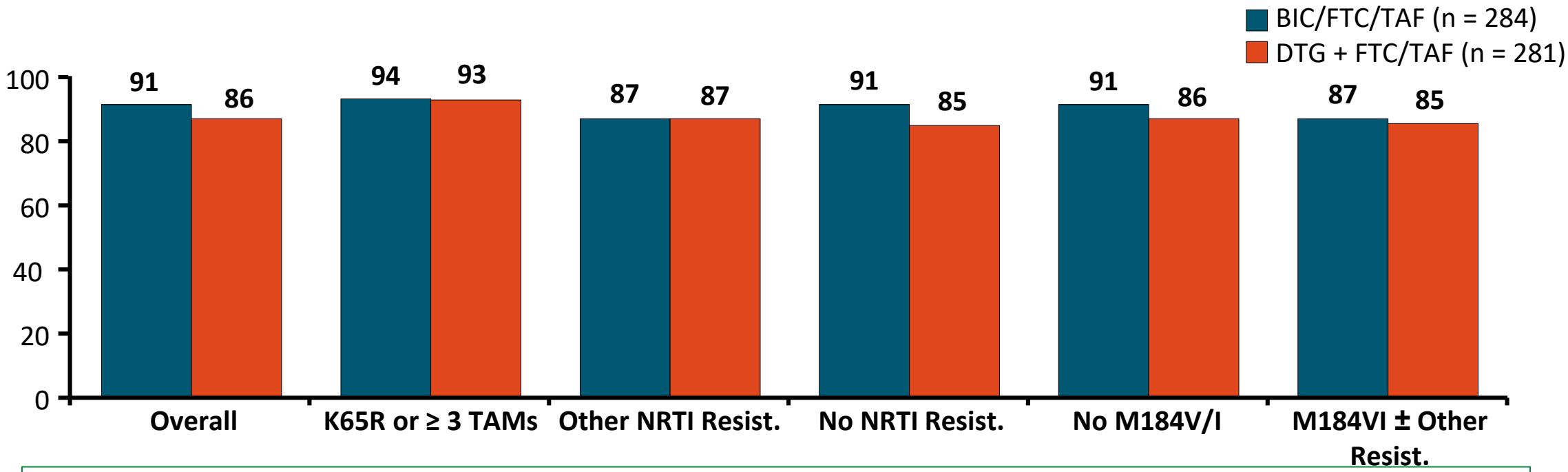
- Patients with viral suppression on stable triple DTG-based ART switched to BIC/FTC/TAF or continued DTG-based ART; documented or suspected NRTI, NNRTI, or PI resistance permitted
  - Preexisting NRTI resistance: 25% in BIC/FTC/TAF arm and 24% in DTG-based ART arm





Study 380-4030: Viral Suppression After Switch From DTG to BIC by Baseline NRTI Resistance

- HIV-1 RNA ≥ 50 c/mL not observed in any patient with preexisting NRTI resistance



Data suggest switching 1 high-resistance barrier drug for another may be effective in patients with viral suppression, even in the setting of underlying resistance

Effectiveness of BIC/FTC/TAF as switch strategy in virologically suppressed: real world data from a monocentric cohort

ICAR Italian Conference on AIDS and Antiviral Research
From prevention to cure: ready for new challenges

BARI 14-16 GIUGNO 2023
UNIVERSITÁ DEGLI STUDI ALDO MORO
Presidenza del Congresso:
F. Ceccherini Silberstein, M. Formisano,
S. Lo Caputo, A. Saracino

- Retrospective monocentric cohort study

- **Inclusion criteria**
  - switching to TAF/FTC/BIC after reaching virological suppression (HIV-RNA < 50 cp/mL)
  - period 2018-2022
- **Exclusion criteria**
  - patients with no follow-up visits

- **Primary endpoints**:

  1) Time to virological failure (VF, i.e. 2 consecutive HIV-RNA ≥ 50 cp/mL or a single HIV-RNA ≥ 200 cp/mL) and treatment discontinuation (TD) for any reason, estimated by Kaplan-Meier;

  2) Predictors of VF and TD estimated by multivariable Cox regression with stepwise backward selection of covariates

- **Secondary endpoints**:

  1) Changes in CD4 count, CD4-to-CD8 ratio, creatinine, metabolic profile from baseline up to 36 months (analysis of variance for repeated measures)

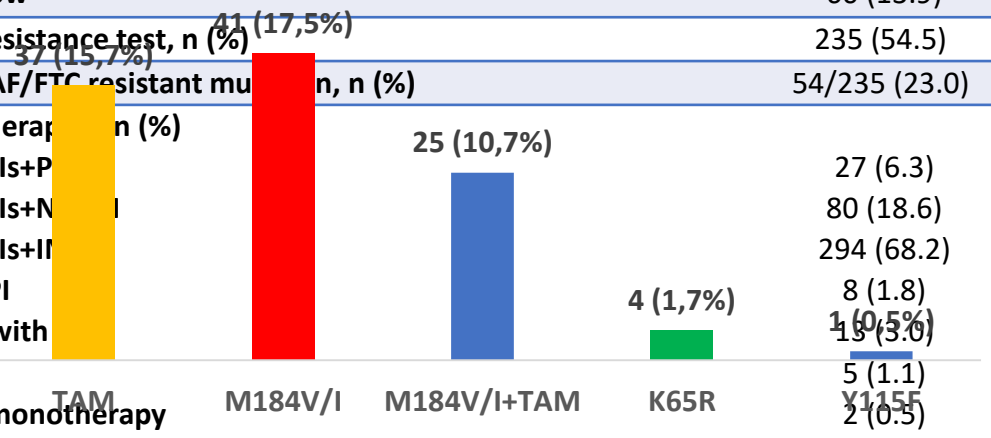
  2) Predictors of variation in both CD4 and CD4-to-CD8 at 12 months were analyzed through linear regression.

Patient's characteristics at baseline

VARIABLES	N = 431
Age (years), median (IQR)	55 (46-61)
Ethnicity, n (%)	
Caucasian	366 (84.9)
Non-Caucasian	65 (15.1)
Male gender, n (%)	295 (68.5)
Risk factor for HIV, n (%)	
Heterosexual	191 (44.3)
MSM	176 (40.8)
IDU	57 (13.3)
Other/Unknown	7 (1.6)
Anti-HCV antibodies positive, n (%)	66 (15.3)
HbsAg positive, n (%)	16 (3.7)
HIV viral subtype, n (%)	
B	176 (40.8)
Non-B	40 (9.3)
Unknown	215 (49.9)
Time since HIV diagnosis (years), median (IQR)	18 (8-27)
Time of cumulative exposure to ARVs (years), median (IQR)	14 (7-23)
Time of viral suppression (years), median (IQR)	6 (3-12)
Previous AIDS-defined event, n (%)	148 (34.3)
At least one previous failure, n (%)	224 (52.0)
Previous failure with a INI-based regimen, n (%)	18 (4.2)
CD4/CD8 ratio, median (IQR)	0.7 (0.5-1.0)
CD4+ count (cell/µL), median (IQR)	615 (450-820)

VARIABLES	N = 431
HIV-RNA (copies/mL), n (%)	
TND	329 (76.3)
1-29	87 (20.2)
30-49	15 (3.5)
Nadir CD4 cell/µL, n (%)	
< 200	239 (55.5)
200-349	99 (23.0)
350-499	51 (11.8)
≥ 500	42 (9.7)
Zenith HIV-RNA (cp/mL), n (%)	
< 100,000	167 (38.8)
100,000-499,999	157 (36.4)
≥ 500,000	47 (10.9)
unknow	60 (13.9)
HIV drug resistance test, n (%)	235 (54.5)
Previous TAF/FTC resistant mu n, n (%)	54/235 (23.0)
Previous therap n (%)	
2 NRTIs+P	27 (6.3)
2 NRTIs+N I	80 (18.6)
2 NRTIs+I	294 (68.2)
3TC+PI	8 (1.8)
Dual with	13 (3.0)
PI+INI	5 (1.1)
PI in monotherapy	2 (0.5)
other	2 (0.5)
Reason for switch, n (%)	
pro-active	356 (82.6)
toxicity	26 (6.0)
drug-drug interactions	3 (0.7)
non compliance	3 (0.7)
unknown	43 (10.0)

Drug resistance-associated mutations at historical genotype (N=235)



Results: time to virological failure

16 VF occurred during 22 months of median follow-up time (2.0 per 100 patients-years follow-up)

Figure 1. Estimated probability of VF

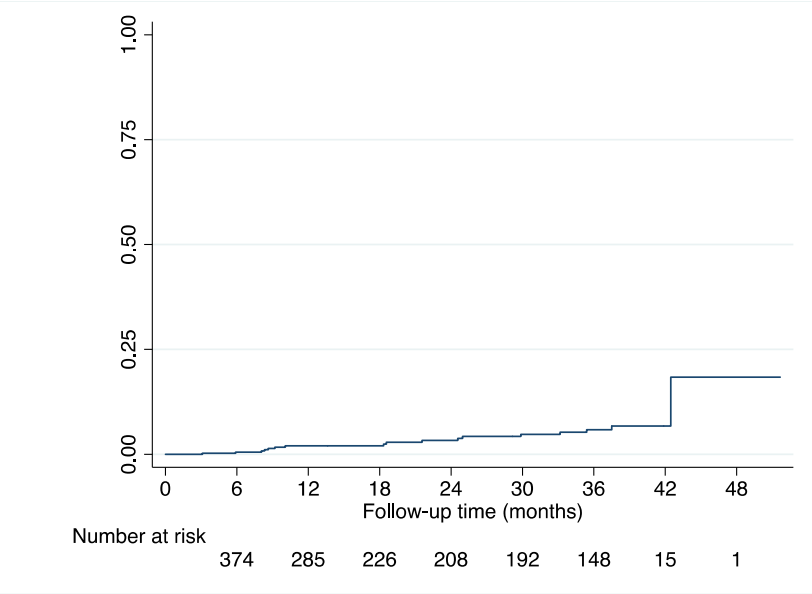


Table 1. Probabilities of VF at 1, 2 and 3 years

Follow-up time	Estimated probabilities of VF
1 Year	2.0% (95% CI 1.0%-4.2%)
2 Years	2.9% (95% CI 1.5%-5.6%)
3 Years	5.5% (95% CI 3.2%-9.2%)

Caucasian ethnicity (versus others, aHR 0.32, 95% CI 0.11-0.94; p= 0.039) and a history of **previous VF** (versus none, aHR 10.06, 95% CI 1.32-76.56; p = 0.026) independently **predicted VF.**

Details of virological failures

Age	Sex	Ethnicity	Pre-switch therapy	Archived DRMs	Viremia (cp/mL) at VF	Good adherence reported	Time to virological suppression (months)
43	M	Unknown	FTC/TAF/EVG/c	n.a.	213	no	6
52	F	Sub-saharan africa	FTC/TAF+RAL	Wild-type	1.634	yes	HIV-RNA in progress
59	M	Caucasian	FTC/TAF/RPV	n.a.	10.000.001	no	10
53	F	Caucasian	FTC/TAF/EVG/c	n.a.	18.359	no	1
45	M	Caucasian	FTC/TAF/EVG/c	n.a.	210	no	18
53	M	Caucasian	FTC/TAF+DTG	n.a.	58; 225.891	no	Treatment discontinued
76	F	Caucasian	3TC/ABC/DTG	**K65R,K70N,M184V**	778	yes	1
62	M	Caucasian	FTC/TAF+RAL	Wild-type	63; 116	no	18
45	F	South-American	DRV/c + TDF	Wild-type	505	no	Treatment discontinued
35	M	South-American	FTC/TAF+RAL	n.a.	424.283	no	5
54	M	Caucasian	FTC/TAF/EVG/c	Wild-type	15.676	yes	HIV-RNA in progress
44	F	Unknown	FTC/TAF/EVG/c	n.a.	21.718	no	1
50	F	Caucasian	ABC/3TC+ATZ/r	Wild-type	109; 98	no	15
54	F	Caucasian	FTC/TAF+DTG	n.a.	1.340.468	no	Treatment discontinued
35	M	Caucasian	FTC/TAF/EVG/c	Wild-type	1.639	unknown	18
55	M	Caucasian	FTC/TAF+DTG	Wild-type	1.407	yes	6

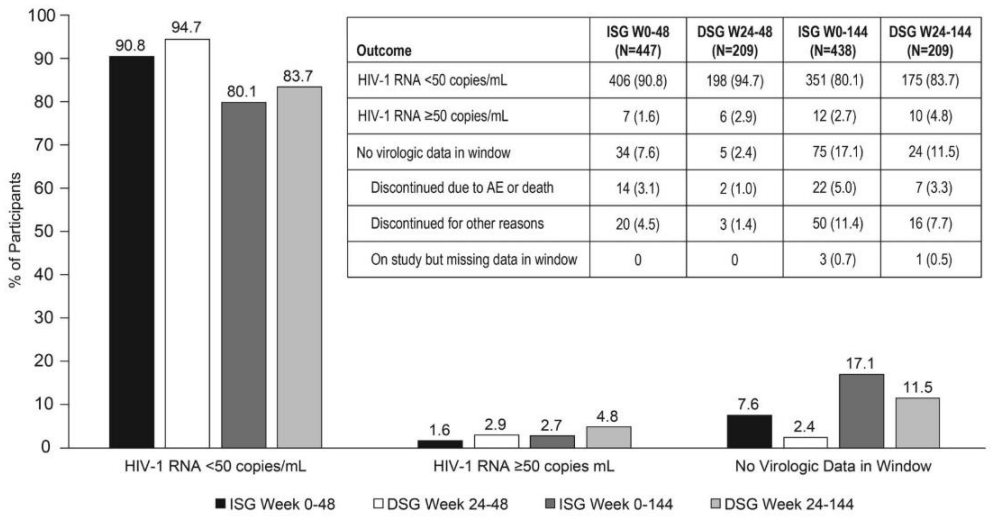
Doravirine

Virologically Suppressed Populations

Participants in the DRIVE-SHIFT trial who were stable for ≥6 months with 2 NRTIs plus a boosted PI, boosted elvitegravir, or an NNRTI were switched to DOR/3 TC/TDF at day 1 or week 24.[19] Overall, 4% (n = 24/656) of participants entered the trial with RT K103N, Y181C, and/or G190A substitutions.[19] Seven participants met the criteria for PDVF: 6 in the immediate-switch group and 1 in the baseline group (after switching to DOR/3 TC/TDF) (Table 2). None of these participants had RT K103N, Y181C, or G190A substitutions at baseline. Two DOR-treated participants in the immediate-switch group had samples that met the threshold criteria for resistance testing (Table 3). No genotypic or phenotypic resistance to DOR, 3 TC, or TDF was identified among participants in the immediate-switch group. The participant in the baseline group who received ritonavir-boosted darunavir, FTC, and TDF displayed an RT M184M/I substitution. Viral drug resistance testing was also performed in 1 participant in the immediate-switch group who discontinued for reasons other than PDVF; no genotypic or phenotypic resistance was observed. Among the 24 participants with baseline NNRTI resistance-associated mutations, 96% (n = 23/24) had HIV-1 RNA <50 copies/mL at week 48: 91% (n = 10/11) in the immediate-switch group (1 participant with HIV-1 RNA <50 copies/mL discontinued on day 29 because of protocol deviation) and 100% (n = 13/13) in the baseline group.[19]

TABLE 2. Resistance Analysis Summary of Participants With PDVF at Week 96*

Trial (N)†	PDVF‡ Status	Nonresponder, n (%)	Rebounder, n (%)	Participants With PDVF Who Failed Because of DOR Phenotypic Resistance, n (%)
P007 (N = 108)	Confirmed HIV-1 RNA ≥40 and ≤200 copies/mL	12 (11.1)	1 (0.9)	0
	Confirmed HIV-1 RNA >200 copies/mL	4 (3.7)	2 (1.9)	
	Total	16 (14.8)	3 (2.8)	
DRIVE-BEYOND (N = 10)	Confirmed HIV-1 RNA ≥50 and ≤200 copies/mL	0	1 (10.0)	0
	Confirmed HIV-1 RNA >200 copies/mL	0	0	
	Total	0	1 (10.0)	
P011 (N = 31)§	Confirmed HIV-1 RNA ≥50 and ≤200 copies/mL	1 (3.2)	5 (16.1)	0
	Confirmed HIV-1 RNA >200 copies/mL	0	0	
	Total	1 (3.2)	5 (16.1)	
DRIVE-FORWARD (N = 383)	Confirmed HIV-1 RNA ≥50 and ≤200 copies/mL	0	19 (5.0)	1 (0.3)‖
	Confirmed HIV-1 RNA >200 copies/mL	3 (0.8)	12 (3.1)	
	Total	3 (0.8)	31 (8.1)	
DRIVE-AHEAD (N = 364)	Confirmed HIV-1 RNA ≥50 and ≤200 copies/mL	0	18 (4.9)	6 (1.6)
	Confirmed HIV-1 RNA >200 copies/mL	6 (1.6)	10 (2.7)	
	Total	6 (1.6)	28 (7.7)	
DRIVE-SHIFT (N = 656)	Confirmed HIV-1 RNA ≥50 and ≤200 copies/mL	NA	5 (0.8)	0
	Confirmed HIV-1 RNA >200 copies/mL	NA	2 (0.3)	
	Total	NA	7 (1.1)	



Outcome	ISG W0-48 (N=447)	DSG W24-48 (N=209)	ISG W0-144 (N=438)	DSG W24-144 (N=209)
HIV-1 RNA <50 copies/mL	406 (90.8)	198 (94.7)	351 (80.1)	175 (83.7)
HIV-1 RNA ≥50 copies/mL	7 (1.6)	6 (2.9)	12 (2.7)	10 (4.8)
No virologic data in window	34 (7.6)	5 (2.4)	75 (17.1)	24 (11.5)
Discontinued due to AE or death	14 (3.1)	2 (1.0)	22 (5.0)	7 (3.3)
Discontinued for other reasons	20 (4.5)	3 (1.4)	50 (11.4)	16 (7.7)
On study but missing data in window	0	0	3 (0.7)	1 (0.5)

No viral resistance to doravirine was identified.

ACCEPTED MANUSCRIPT

NRTI resistance mutations predict virological failure in HIV-positive patients during lamivudine plus dolutegravir maintenance therapy in clinical practice

Alberto Borghetti ✉, Andrea Giacomelli, Vanni Borghi, Arturo Ciccullo, Alex Dusina, Massimiliano Fabbiani, Stefano Rusconi, Maurizio Zazzi, Cristina Mussini, Simona Di Giambenedetto ✉

Open Forum Infectious Diseases, ofab103, https://doi.org/10.1093/ofid/ofab103

- **Objective**: investigating the impact of past NRTI resistance on 3TC/DTG, the combination of M184V/I plus at least one TAM significantly increased the risk of VF.
- **Methods**: An observational cohort from 3 large University hospitals of patients starting 3TC-DTG;
  - **Inclusion criteria**: suppressed viral load (HIV-RNA<50 copies/mL) at the time of switch (baseline), no evidence of HBV chronic infection. No other eligibility criterium (such as lack of previous VF, a minimum time of continuous virological suppression before switch, availability of pretreatment genotype with no documented RAMs)
  - **Statistical analysis**: Predictors of time to VF (defined as the first of 2 consecutive HIV-RNA>50 copies/mL or a single HIVRNA≥200 copies/mL) were identified through a multivariable Cox regression model with a stepwise selection of covariates (covariates associated with the outcome at a p-value>0.05 were excluded).

Caratteristiche della popolazione (baseline)

Variables	All population (n=669)	Presence of RAMs at historical genotype (n=75)	Absence of RAMs at historical genotype (n=263)	p-value
Age (years)	52 (45-59)	54 (51-59)	49 (40-56)	**<0.001**
Male gender	474 (70.9)	53 (70.7)	195 (74.1)	0.548
Caucasian ethnicity	611 (91.3)	69 (92.0)	242 (92.0)	0.997
Risk factor for HIV:				**<0.001**
- Heterosexual	286 (42.8)	28 (37.3)	113 (43.0)	
- MSM	270 (40.3)	24 (32.0)	128 (48.6)	
- IDUs	95 (14.2)	20 (26.7)	17 (6.5)	
- Other	18 (2.7)	3 (4.0)	5 (1.9)	
Anti-HCV serostatus	127 (19.0)	20 (26.7)	29 (11.0)	**0.001**
Zenith HIV-RNA:				0.843
-≤10^5 cp/mL	344 (51.4)	39 (52.0)	133 (50.6)	
->10^5 and ≤5 x 10^5 cp/mL	193 (28.9)	26 (34.7)	85 (32.3)	
- ≥ 5 x 10^5 cp/mL	92 (13.8)	10 (13.3)	44 (16.7)	
- Unknown	40 (6.0)	0 (0.0)	1 (0.4)	
Nadir CD4 ≤200 cells/µL	291 (45.8)	42 (56.8)	94 (36.0)	**0.001**
CDC stage C (n=426)	121 (28.4)	17 (22.7)	33 (12.6)	**0.011**
Time since HIV diagnosis (years)*	15 (8-22)	24 (19-28)	9 (5-14)	**<0.001**
Time of cumulative exposure to ARVs*	12 (6-19)	20 (18-22)	7 (4-11)	**<0.001**
Time of viral suppression (years)*	8 (4-11)	8 (4-12)	5 (3-8)	**<0.001**
HIV-RNA at last genotype (cp/mL)*	21,450 (3,300-88,118)	3,733 (431-15,220)	35,383 (6,759-126,465)	**<0.001**
Detectable baseline HIV-RNA**	218 (32.6)	26 (34.7)	99 (37.6)	0.638
ARV therapy before switch:				**0.013**
- 2NRTIs+3rd drug	410 (61.3)	34 (45.3)	166 (63.1)	
- Two-drug regimen	231 (34.5)	35 (46.7)	88 (33.5)	
- Other combinations	28 (4.2)	6 (8.0)	9 (3.4)	
Reasons for switch to 3TC+DTG:				0.783
- proactive switch	243 (36.3)	26 (34.7)	93 (35.4)	
- toxicity	214 (32.0)	24 (32.0)	93 (35.4)	
- other/unknown	212 (31.7)	25 (33.3)	77 (29.2)	

Variables	All population (n=669)	Presence of RAMs at historical genotype (n=75)	Absence of RAMs at historical genotype (n=263)	p-value
HIV viral subtype:	n=316	n=68	n=247	0.085
- B	262 (82.9)	63 (92.7)	198 (80.3)	
- A	7 (2.2)	0	7 (2.8)	
- C	9 (2.9)	0	9 (3.6)	
- CRF	23 (7.3)	1 (1.5)	22 (8.9)	
- F	11 (3.4)	3 (4.4)	8 (3.2)	
- Other	2 (1.3)	1 (1.5)	3 (1.2)	
NRTIs-RAMs:				
TAMs			na	na
- M41L	31 (9.2)	31 (9.2)		
- D67N	22 (6.5)	22 (6.5)		
- K70R	20 (5.9)	20 (5.9)		
- L210W	14 (4.1)	14 (4.1)		
- T215YF	30 (8.9)	30 (8.9)		
- K219QE	20 (5.9)	20 (5.9)		
Non-TAMs				
- M184V/I	48 (14.2)	48 (14.2)		
- K65R/E/N	4 (1.2)	4 (1.2)		
- K70E	1 (0.3)	1 (0.3)		
- L74V	4 (1.2)	4 (1.2)		
- Y115F	1 (0.3)	1 (0.3)		
Other NRTIs-RAMs				
- T69Ins	0 (0)	0 (0)		
- A62V	4 (1.2)	4 (1.2)		
- V75I	1 (0.3)	1 (0.3)		
- F77L	1 (0.3)	1 (0.3)		
- F116Y	1 (0.3)	1 (0.3)		
- Q151M	1 (0.3)	1 (0.3)		
Previous failure with a INI-based regimen	14 (2.1)	2 (2.7)	9 (3.4)	0.745
Previous failure with a 3TC/FTC-based regimen	287 (42.9)	62 (82.7)	74 (28.1)	**<0.001**

Predictors of virological failure

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)	0.046		
M184V/I with TAMs (presence vs absence)					**4.63 (1.19-17.94)**	**0.027**
Previous failure on an INI-based regimen (at least one vs none)	5.84 (1.28-26.64)	0.025	6.41 (1.36-30.18)	0.019	5.51 (1.15-26.50)	0.033
Time of virological suppression (>2 years vs ≤2)	0.29 (0.10-0.86)	0.023	0.27 (0.09-0.80)	0.018	0.23 (0.08-0.74)	0.013

Notes: all Cox models were built after a stepwise selection of the following covariates (variables associated with the outcome at a p-value>0.05 were excluded at each step): age, ethnicity, risk factor for HIV infection, detectable HIV-RNA at baseline, nadir CD4 and zenith HIV-RNA, viral subtype and HIV-RNA at last GRT, time of viral suppression at baseline and previous VF with an integrase inhibitor (INI)-containing regimen. The variables representing RAMs were different according to the 5 models: *in model 1 we used "presence of any NRTI-RAM versus none", *in model 2 "presence of at least one TAM versus none", *in model 4 "presence of M184V/I without TAMs versus all other combinations of RAMs or no RAMs": as none of these variables was associated with VF, they were not included in their respective Cox models. **Model 3 included the "presence of M184V/I versus absence of M184V/I". ***Model 5 included "presence of M184V/I plus at least one TAM versus all other combinations of RAMs or no RAMs".

Open Forum Infectious Diseases

MAJOR ARTICLE

Efficacy of Lamivudine Plus Dolutegravir vs Dolutegravir-Based 3-Drug Regimens in People With HIV Who Are Virologically Suppressed

Alberto Borghetti,[1] Arturo Ciccullo,[2] Francesca Lombardi,[3] Diana Giannarelli,[4] Rosa Anna Passerotto,[3] Francesco Lamanna,[3] Antonella Carcagni,[4] Damiano Farinacci,[1] Alex Dusina,[1] Gianmaria Baldin,[1] Maurizio Zazzi,[5] and Simona Di Giambenedetto[1,3]

Component	Target trial	Emulated trial using real-world data
Design	Multicentre open-label two-parallel arm superiority randomised trial.	Historic cohort study within the Antiviral Response Cohort Analysis (ARCA) database
Aim	Estimate the effect of starting DT within a pre-specified period of virological suppression (6 months, 1, 2 and 3 years) versus switching to another TT on the hazard of virological failure (2 consecutive HIV-RNA≥50 cps/ml or one HIV-RNA≥200 cp/mL)	Same
Eligibility	PLWH on a triple therapy (TT) with 2 NRTIs plus a PI or a NNRTI, reaching HIV-RNA<50 cps/mL; Switching to dolutegravir plus 2 NRTIs (TT group) or to lamivudine plus dolutegravir (DT group) between December 2014 and June 2020	Same
Exclusions	Positive HBsAg-serostatus; Previous treatment with dolutegravir; Absence of at least one previous genotypic resistance test on HIV-RNA.	Same
Treatment strategies	1. Triple therapy (TT) with 2NRTI+anchor drug 2. Dual therapy (DT) with lamivudine+dolutegravir	Same
Treatment assignment	Patients are randomly assigned to either strategy	Patients are non-randomly assigned to a treatment strategy. **Randomisation is emulated via cloning of patients in both arms.**
Outcome	Hazard ratio of VF with the DT versus the TT	Same
Follow up	Follow up starts at the moment of the first HIV-RNA<50 cps/mL during a TT	Follow up starts at the moment of the first HIV-RNA<50 cps/mL during a TT, which does not correspond to the moment of treatment assignment
Censoring	Loss to follow up, death, switch to another therapy or the last available HIV-RNA	Loss to follow up, death, switch to another therapy or the last available HIV-RNA
Adjustment variables	Gender, age, ethnicity, risk factor for HIV, CDC stage C, zenith HIV-RNA, nadir CD4 count, number of previous virological failures, HCV-positive serostatus, HIV viral-subtype, **resistance-associated mutation at historical genotype**	Same
Causal contrast	Per protocol	Per protocol: we do not know what the intention to treat was from the data; In each arm of the emulated trial, **patients who deviate from the protocol are censored at their time of deviation**

Characteristics of study population

Variables	Triple therapy arm (n=422)	Dual therapy arm (n=204)	p-value
Age, median (IQR)	45 (44-46)	44 (42-45)	0.299
Male sex, n (%)	297 (70.4)	160 (78.4)	**0.033**
Risk factor for HIV infection (%):			**<0.001**
- **Heterosexual**	176 (41.7)	88 (43.1)	
- **MSM**	140 (33.2)	90 (44.1)	
- **PWID**	64 (15.1)	23 (11.3)	
- **Other/unknown**	42 (10.0)	3 (1.5)	
Caucasian ethnicity, n (%)	333 (78.9)	159 (77.9)	0.965
Years since HIV diagnosis, median (IQR)	5 (1-13)	3 (1-9)	**0.002**
Years of antiretrovirals exposure, median (IQR)	2 (1-10)	1 (0-5)	**<0.001**
Zenith HIV-RNA (log_{10} copies/mL), median (IQR)	4.57 (4.44-4.70)	4.73 (4.58-4.88)	0.136
Nadir CD4 count (cells/µL), median (IQR)	217 (200-234)	267 (246-289)	**0.001**
Previous virological failure (at least one), n (%)	47 (11.1)	22 (10.8)	0.895
CDC stage C, n (%)	53 (12.6)	14 (6.7)	**0.031**
Anti-HCV positive serostatus, n (%)	74 (17.5)	21 (10.3)	**0.018**
RAMs to study drugs at historical genotype (at least one), n (%)	87 (20.6)	18 (8.8)	**<0.001**
M184V/I mutation	52 (12.3)	8 (3.9)	**0.001**
B viral subtype, n (%)	346 (82.0)	156 (76.5)	**0.010**

Abbreviation: MSM: Men who have sex with men; PWID: People Who Inject Drugs (PWID); RAMs Resistance-associated mutations.

Incidence of virological failure by unadjusted Kaplan-Meier estimation

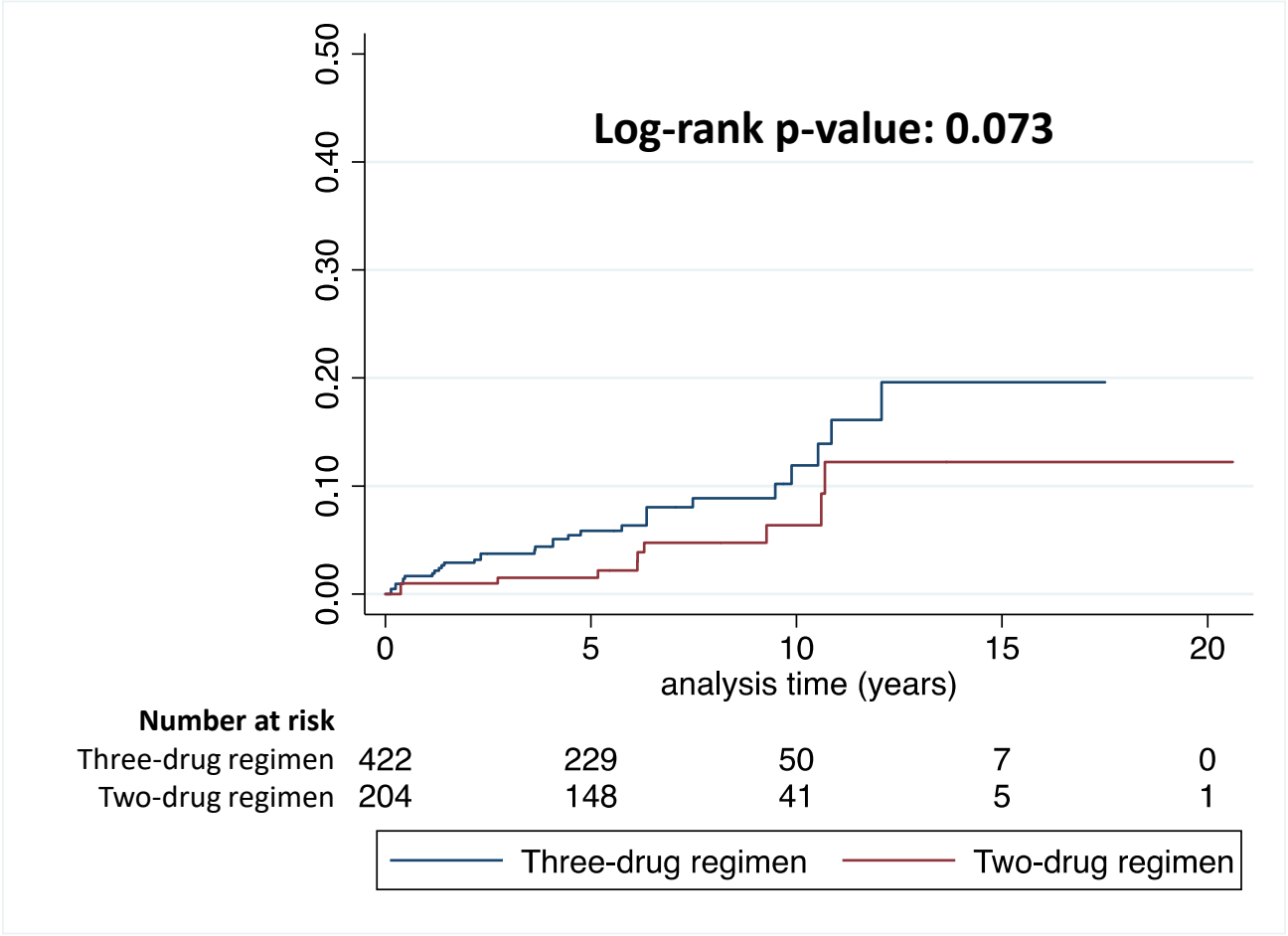


Table 1. Estimated probability of VF during time according to treatment group

Time of follow-up	DT	TT
1 year	1.0% (0.3%-3.4%)	1.7% (1.0%-3.5%)
2 years	1.0% (0.3%-3.4%)	2.9% (1.7%-5.1%)
3 years	1.5% (0.5%-4.6%)	3.7% (2.3%-6.1%)

Incidence of virological failure by IPCW-Kaplan-Meier estimation

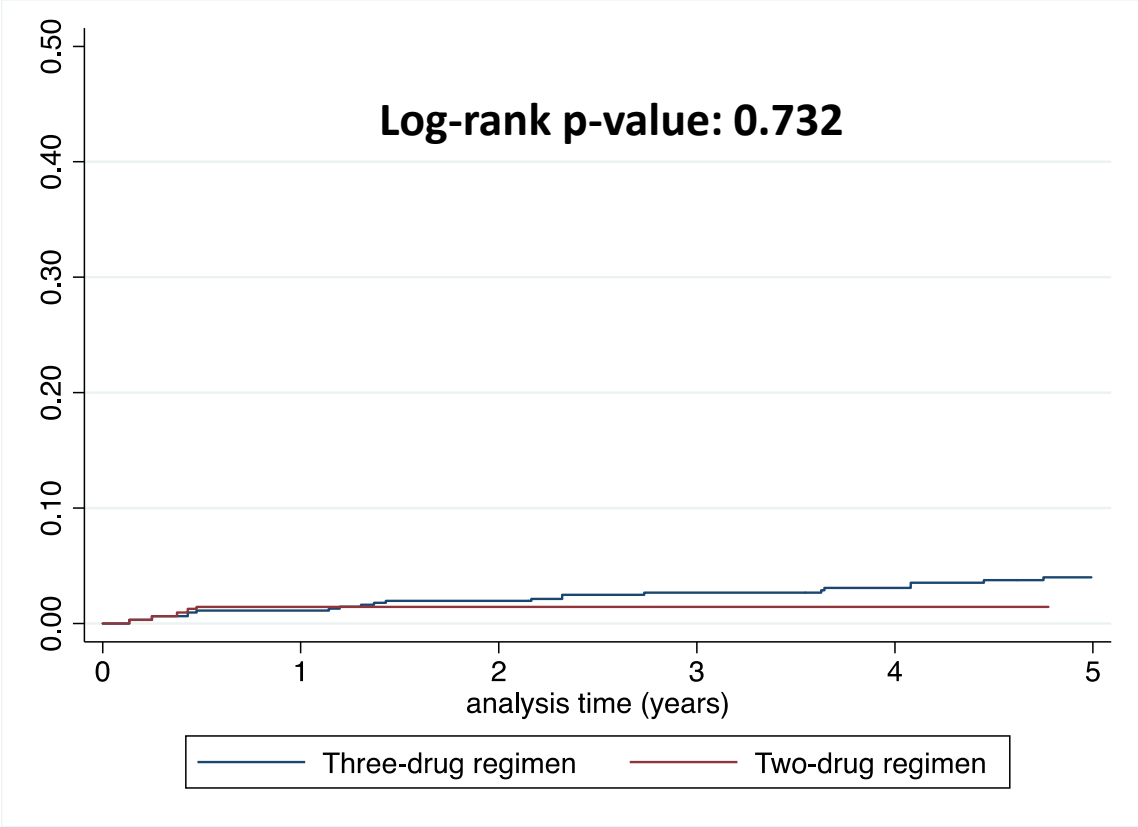


Table 2. Estimated probability of VF during time according to treatment group

Time of follow-up	DT	TT
1 year	1.5%	1.1%
2 years	1.5%	2.0%
3 years	1.5%	2.7%

IPW Cox regression analysis: 6 months grace period

Table 3. IPCW-adjusted Cox regression exploring the role of RAMs (at least one versus none) to the backbone on the risk of VF, with TT and no RAMs being the reference category in model A and TT with RAMs the reference category in model B.

	Model A		Model B	
Variable	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
TT no mutations	Ref	Ref	0.74 (0.35-1.56)	0.428
TT at least one RAM	1.35 (0.64-2.85)	0.428	Ref	Ref
DT no mutations	0.88 (0.29-2.61)	0.812	0.65 (0.17-2.53)	0.533
DT at least one RAM	**3.55 (1.08-11.68)**	**0.037**	2.63 (0.62-11.16)	0.190

Table 4. IPCW-adjusted Cox regression exploring the role of RAMs to the backbone (stratified as: TAMs with no M184V/I, M184V/I and no TAMs, TAMs plus M184V/I, other mutations to NRTIs) on the risk of VF. In model A, TT with no RAMs is the reference category, in model B TT and M184V/I no TAMs is the reference category.

	Model A		Model B	
Variable	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
TT no RAMs	Ref	Ref	0.41 (0.14-1.18)	0.099
TT and TAMs, no M184V/I	1.40 (0.49-4.02)	0.533	0.57 (0.14-2.27)	0.425
TT and M184V/I, no TAMs	2.46 (0.84-7.15)	0.099	Ref	Ref
TT with TAMs and M184V/I	na	na	na	na
TT and other RAMs	6.30 (1.46-27.09)	0.013	2.56 (0.47-14.08)	0.279
DT no RAMs	0.89 (0.30-2.64)	0.826	0.36 (0.07-1.76)	0.207
DT and TAMs, no M184V/I	**4.78 (1.03-22.14)**	**0.046**	1.94 (0.29-13.24)	0.497
DT and M184V/I, no TAMs	**7.53 (1.63-34.73)**	**0.010**	3.06 (0.45-20.84)	0.252
DT with TAMs and M184V/I	na	na	na	na
DT and other RAMs	na	na	na	na

IPW Cox regression analysis: 6 months grace period

Table 3. IPCW-adjusted Cox regression exploring the role of RAMs (at least one versus none) to the backbone on the risk of VF, with TT and no RAMs being the reference category in model A and TT with RAMs the reference category in model B.

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DT at least one RAM	**3.55 (1.08-11.68)**	**0.037**	2.63 (0.62-11.16)	0.190

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TT and other RAMs	6.30 (1.46-27.09)	0.013	2.56 (0.47-14.08)	0.279
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DT and M184V/I, no TAMs	**7.53 (1.63-34.73)**	**0.010**	3.06 (0.45-20.84)	0.252
DT with TAMs and M184V/I	na	na	na	na
DT and other RAMs	na	na	na	na

Journal of Global Antimicrobial Resistance 28 (2022) 274–281

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

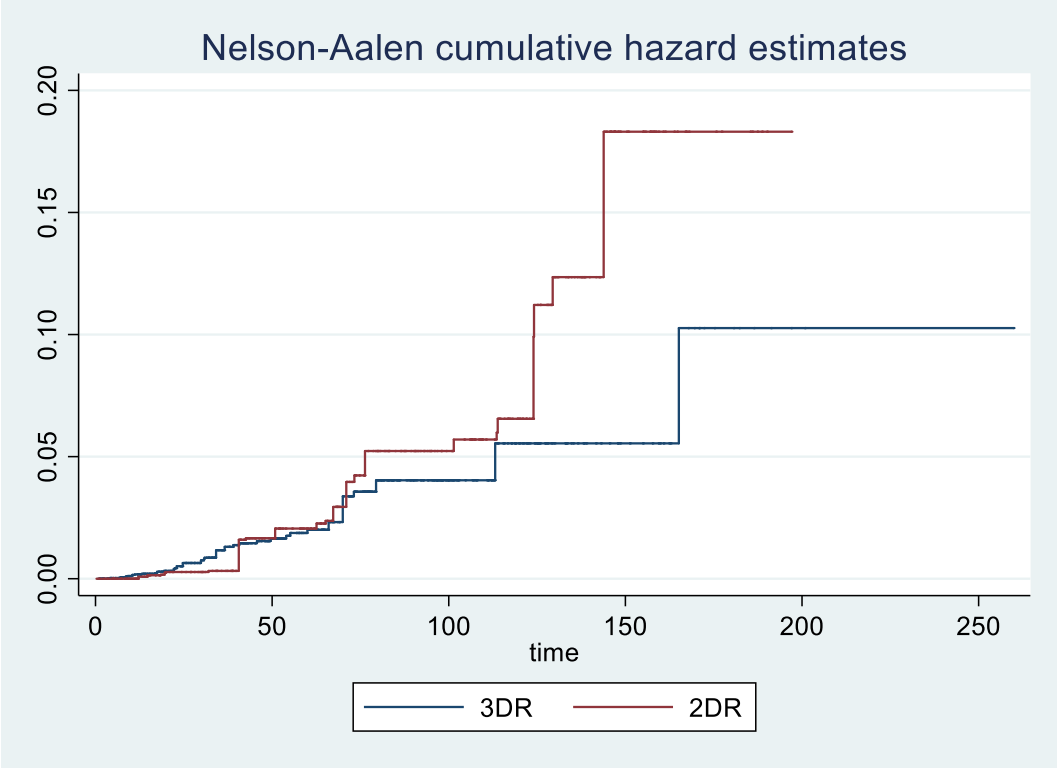
journal homepage: www.elsevier.com/locate/jgar

Impact of resistance mutations on efficacy of dolutegravir plus rilpivirine or plus lamivudine as maintenance regimens: a cohort study

Roberta Gagliardini[a], Michela Baccini[b], Sara Modica[c,d], Francesca Montagnani[d,e], Giacomo Zanelli[d,e], Alberto Borghetti[f], Emanuela Dreassi[b], Francesca Lombardi[f], Monica Pecorari[g], Vanni Borghi[h], Annapaola Callegaro[i], Valeria Micheli[j], Marco Annovazzi Lodi[k], Barbara Rossetti[e,*], Maurizio Zazzi[d], on behalf of the ARCA cohort

- **Objective**: to evaluate the impact of resistance mutations on efficacy of dolutegravir-based 2-drug regimens (2DR).
- **Methods**: retrospective study from the ARCA cohort
  - Endpoints: treatment failure, virological failure and treatment discontinuation
  - Inclusion criteria: virologically suppressed HIV-1 infected patients switching to dolutegravir+lamivudine or +rilpivirine, or to a dolutegravir-based 3-drug regimen (3DR), with pre-baseline genotype
  - Statistical methods: The average causal effect of the treatment (ATE) was estimated on all outcomes by a PS matching approach. A univariate Cox regression model was fitted on the matched sample to estimate ATE in the form of marginal hazard ratio of 3DR vs. 2DR

Results



Nelson-Aalen cumulative hazard estimates for virological failure, by treatment group, calculated on the matched data set.

Table 1. Estimated cumulative incidences at 48 and 72 weeks and 90% confidence intervals (CI) by treatment group, calculated on the matched sample.

Outcome	Treatment	48 Weeks			72 Weeks		
		Cumulative incidence	90% CI		Cumulative incidence	90% CI	
Treatment failure	3DR	24.5%	22.2%	27.0%	37.1%	34.3%	40.0%
	2DR	15.8%	13.9%	17.9%	23.1%	20.8%	25.7%
Virological Failure	3DR	4.7%	3.5%	5.8%	6.5%	5.1%	8.0%
	2DR	4.2%	3.1%	5.3%	7.4%	5.8%	9.0%
Treatment Discontinuation	3DR	19.9%	17.7%	22.1%	30.5%	27.8%	33.2%
	2DR	11.6%	9.9%	13.3%	15.7%	13.6%	17.8%

Table 2. Estimated hazard ratios of 2DR vs 3DR and 90% confidence intervals (CI) from the Cox regression models on the matching sample.

Outcome	Patients Group	HR	90% CI	
Treatment failure	All patients	0.54	0.48	0.60
	Not resistant	0.48	0.42	0.55
	At least LLR	0.78	0.62	0.99
Virological Failure	All patients	1.02	0.78	1.34
	Not resistant	0.64	0.45	0.89
	At least LLR	3.96	2.10	7.46
Treatment Discontinuation	All patients	0.45	0.40	0.51
	Not resistant	0.45	0.39	0.53
	At least LLR	0.46	0.35	0.60

Emergent resistance is not a major concern with bPI or DTG plus 3TC switch therapy

Trial	N	Regimens	Outcome
OLE	127 123	LPV + 2NRTI LPV + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs***
ATLAS-M	133 133	ATV + 2NRTI ATV + 3TC	Non inferiority/superiority of 2DR **No emergent resistance to study drugs**
SALT	143 143	ATV + 2NRTI ATV + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs**
DUAL GESIDA	123 126	DRV + 2NRTI DRV + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs**
ASPIRE	45 45	Current 3DR DTG + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs**
TANGO	372 379	TAF based 3DR DTG + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs**
SALSA	247 246	3DR DTG + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs**
DOLAM	134 131	3DR DTG + 3TC	Non inferiority of 2DR **No emergent resistance to study drugs****

*One subject with K103N and M184V at failure later found to be present also at baseline together with Y181C

**One subject with emerging K70E, K219E, G190R, and M230I

Virologic Outcomes of Lamivudine/Dolutegravir in Virologically suppressed persons with expected or confirmed resistance to Lamivudine (VOLVER clinical trial-GESIDA 11820)

Purpose

We investigated the efficacy of dolutegravir/lamivudine (DTG/3TC) as a maintenance treatment for people with HIV (PWH) and previous lamivudine (3TC) resistance, not detected in proviral DNA Sanger genotyping.

Methods

Open-label, single arm, multicentric clinical trial of a switch to DTG/3TC. NCT04880785.

Key inclusion criteria

- Virologically suppressed PWH
- Past 3TC resistance: confirmed by genotypic testing or suspected based on prior virological failure while receiving emtricitabine or lamivudine
- No prior integrase resistance or virological failure under integrase inhibitors (INSTI)
- CD4+ >200 cells/mm3
- Sanger proviral DNA sequencing at screening without 3TC resistance mutations

Virologic withdrawal criteria:

- Confirmed Virologic Withdrawal (CVW): A viral load (VL) ≥ 50 copies/mL followed by a VL≥ 200 copies/mL in re-test 2-4 weeks apart.
- Precautionary Virologic Withdrawal (PVW): Three consecutive VL 50-200 copies/mL (each VL separated 2-4 weeks).

Primary endpoint: proportion of participants with HIV-1 RNA viral load (VL) ≥50 copies/mL at 48 weeks in the intention-to-treat-exposed (ITT-e) population using the US Food and Drug Administration (FDA) snapshot algorithm.

Participant disposition

Participants screened (n=167)

Participants excluded (n=46)

- M184V/I in Sanger proviral DNA (n=35)
- Other reasons (n=11)
  - 2 unmet CD4+/VL criteria
  - 1 liver function tests
  - 3 consent withdrawal
  - 3 lost to follow-up
  - 1 decision of investigator
  - 1 non amplification proviral DNA

Participants enrolled (n=121)*

**All participants received at least one dose of DTG/3TC*

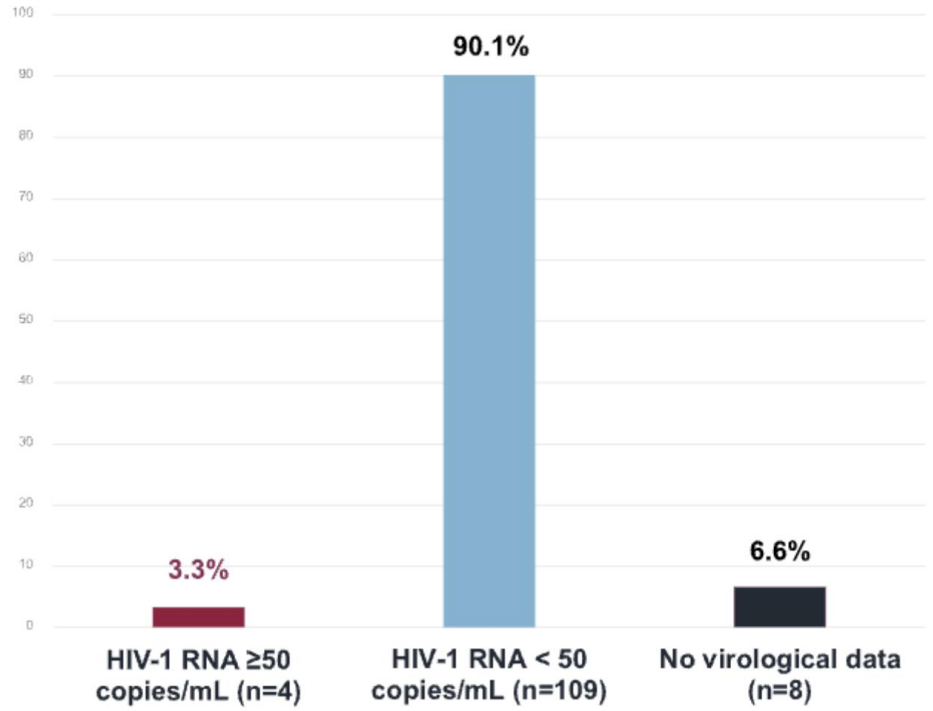
Participants withdrawn from study (n=12)

- 1 Confirmed Virologic Withdrawal ***(CVW)***
- 1 Precautionary Virologic Withdrawal ***(PVW)***
- 1 Protocol deviation
- 2 Lost to Follow-Up
- 2 investigator criteria
- 4 adverse events (AE)
- 1 consent withdrawal

Participants through w48 (n=109)

Results

	All (n=121)
HIV-1 RNA < 50 copies/mL	**109 (90.1%)**
HIV-1 RNA ≥50 copies/mL	**4 (3.3%)**
HIV-1 RNA ≥50 copies/mL in W48 window	0 (0)
Discontinuation due to Lack of Efficacy	2 (1.65%)
Discontinuation for other reasons and Last VL ≥50 copies/mL	2 (1.65%) *
No virologic data at week 48	**8 (6.6%)**
Discontinuation Due to an Adverse Event (AE)	3 (2.48%)
Discontinuation for other reasons and Last VL<50 copies/mL	5 (4.13%) **



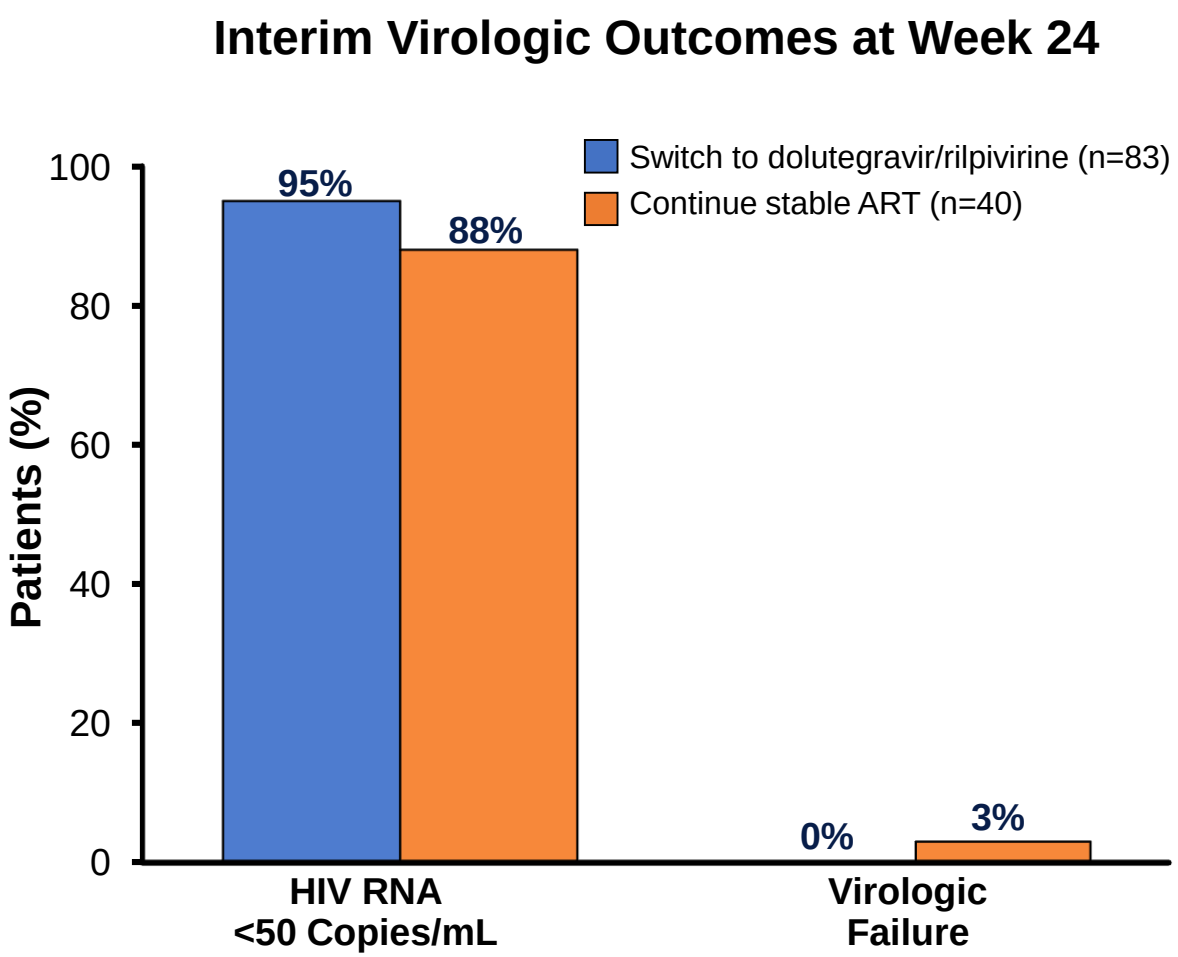
***Discontinuation for other reasons and Last VL ≥50 copies/mL:**
- 1 Lost to follow-up
- 1 adverse event and VL at study withdrawal 90 copies/mL

****Discontinuation for other reasons and Last VL<50 copies/mL:**
- 1 Lost to follow-up
- 1 protocol deviation (M184V in proviral DNA at screening)
- 2 investigator criteria (1 lung cancer, 1 M184V detected in plasma population genotyping at transient rebound, suppressed while still on DTG/3TC not fulfilling criteria for PVW/CVW but switched to DTG+DRV/c)
- 1 consent withdrawal

After excluding lamivudine mutations in proviral DNA by population sequencing, **DTG/3TC effectively maintained virological suppression in persons with HIV and prior history of 3TC resistance.**

No treatment-emergent resistance was observed.

WISARD Trial: Impact of Archived K103N in Patients Switched to Oral Dolutegravir/Rilpivirine as Maintenance Therapy→ dato a 48 settimane



- Open-label (7 countries) treatment-experienced patients on stable ART
  - Archived **K103N**
  - No history of previous treatment failure
- Randomized groups
  - Switch to dolutegravir/rilpivirine (n=83)
  - Continue stable ART (n=40)
- Interim results at week 24
  - Virologic suppression was maintained in patients with archived K103N who were switched to dolutegravir/rilpivirine
  - No virologic failures in the dolutegravir/rilpivirine arm

Moyle, IAS 2021

HIV genotypes in the SWORD 1 & 2 studies confirmed virological withdrawals through week 148

Week of failure	Previous regimen	Viral loads, copies/mL[c]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[d])	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[b,e]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	NNRTI: none INSTI V151V/I	————
Week 76[b]	ATV, ABC/3TC	79; 162; 217	NNRTI: V108I INSTI: L74I	No result (sample failed testing)	————
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[e]	RPV/TDF/FTC	147; 289, 503	Samples not collected	NNRTI: K103N**, V179I♦ INSTI: none	RPV, 5.24 DTG, 1.6
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	————
Week 112	RAL/TDF/FTC	118, 230, 324	NNRTI: none INSTI: E157Q, G193E, T97T/A	NNRTI: M230M/L INSTI: E157Q, G193E	RPV, 2 DTG, 1.47
Week 112	DRV,RTV/TDF/FTC	W112: 127, 148 W124: 307, 219	Test not performed	Test not performed due to low VL	————
Week 136[b]	EFV/TDF/FTC	4,294, 7247	No result (sample failed testing)	NNRTI: E138A, L100L/I INSTI: sample failed testing	RPV, 4.14

11/990 (1.1%) confirmed virological withdrawals through week 148

3 cases (0.3%) of documented emergent resistance to RPV

van Wyk, BHIVA 2019

HIV genotypes in the SWORD 1 & 2 studies confirmed virological withdrawals through week 148

Week of failure	Previous regimen	Viral loads, copies/mL[c]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[d])	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[b,e]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	NNRTI: none INSTI V151V/I	————
Week 76[b]	ATV, ABC/3TC	79; 162; 217	NNRTI: V108I INSTI: L74I	No result (sample failed testing)	————
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[e]	RPV/TDF/FTC	147; 289, 503	Samples not collected	NNRTI: K103N**, V179I♦ INSTI: none	RPV, 5.24 DTG, 1.6 ■
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	————
Week 112	RAL/TDF/FTC	118, 230, 324	NNRTI: none INSTI: E157Q, G193E, T97T/A	NNRTI: M230M/L INSTI: E157Q, G193E	RPV, 2 DTG, 1.47 ■
Week 112	DRV,RTV/TDF/FTC	W112: 127, 148 W124: 307, 219	Test not performed	Test not performed due to low VL	————
Week 136[b]	EFV/TDF/FTC	4,294, 7247	No result (sample failed testing)	NNRTI: E138A, L100L/I INSTI: sample failed testing	RPV, 4.14

11/990 (1.1%) confirmed virological withdrawals through week 148

No cases of documented emergent resistance to DTG

van Wyk, BHIVA 2019

Switch to DTG/RPV and risk of virological failure in a real-life setting (Dat'AIDS cohort)

					Resistance mutations			
					historical genotype		genotype at VF	
n	Second regimen	Time to VF	History of VF	Plasma HIV RNA at VF (copies/mL)	NRTI or NNRTI	INSTI	NRTI or NNRTI	INSTI
1	rilpivirine	W75	NNRTI	68, 133	K103H/N/S/T	none	K103H/N/S/T	none
2	rilpivirine	W6	no	531	none	none	E138K	none
3	rilpivirine	W32	no	142, 189[a]	none	none	K101E, E138K	N155H
4	rilpivirine	W86	no	474	not available	none	E138A	none
5	rilpivirine	W34	no	52 310	E138K	none	E138A, L100I	L74I[c]
6	rilpivirine	W5	no	109, 109	K103H/N/S/T	none	K103H/N/S/T	none

INSTI, integrase strand transfer inhibitor; VF, virological failure; xTC, lamivudine or emtricitabine.
[a]Plasma HIV RNA at discontinuation of dolutegravir-based maintenance dual therapy was 787 copies/mL.
[b]All plasma HIV RNA values following virological failure were ≤50 copies/mL.
[c]L74I alone does not confer genotypic resistance to dolutegravir.

- 799 PLWH on dolutegravir/rilpivirine with a median follow-up of 20 months (IQR = 11–31)
- VF occurred in 3.8% (n = 30), 17 had a genotype at failure and 6 harboured DRM (two emerging RAMs)
- The only predictive factor of VF on DTG/RPV was the history of failure on an NNRTI-based regimen (aHR = 2.97, 95% CI = 1.28–6.93)

Deschanvres, CID 2022

HIV-1 drug resistance in people on dolutegravir-based antiretroviral therapy: a collaborative cohort analysis

Tom Loosli, Stefanie Hossmann, Suzanne M Ingle, Hajra Okhai, Katharina Kusejko, Johannes Mouton, Pantxika Bellecave, Ard van Sighem, Melanie Stecher, Antonella d'Arminio Monforte, M John Gill, Caroline A Sabin, Gary Maartens, Huldrych F Günthard, Jonathan A C Sterne, Richard Lessells, Matthias Egger*, Roger D Kouyos**

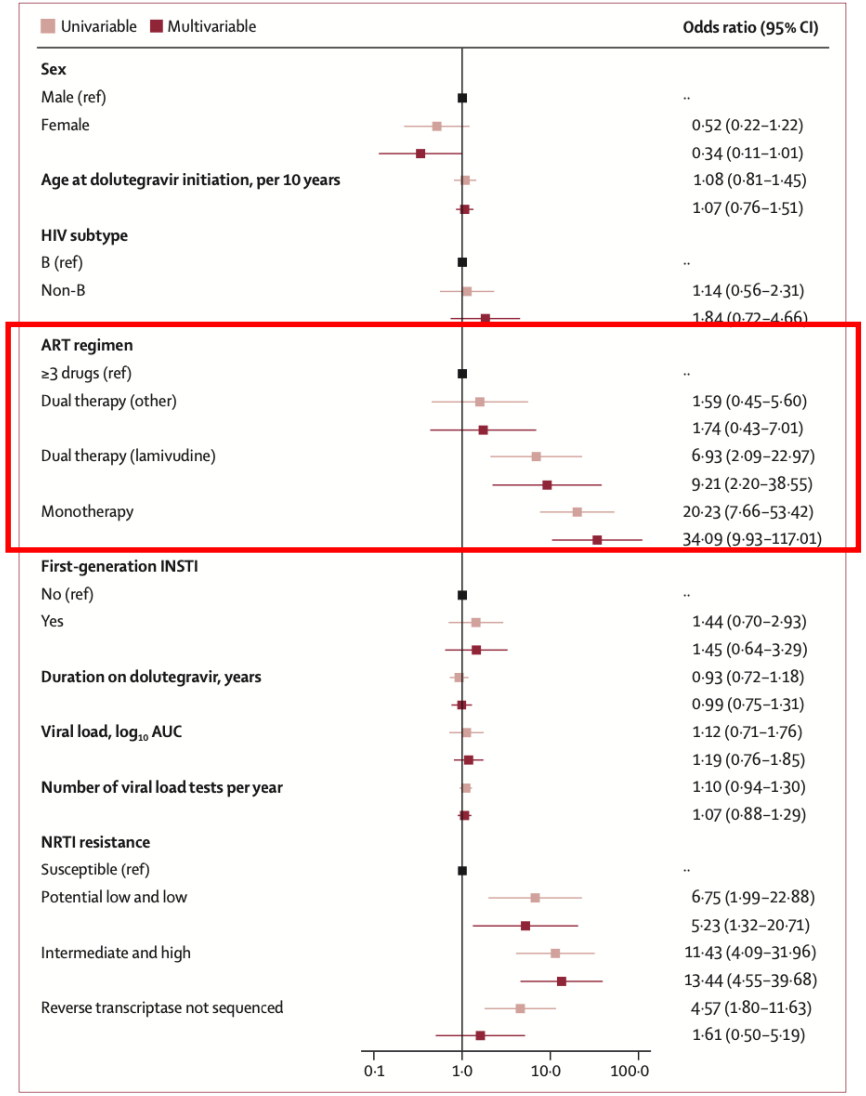
Summary

Background The widespread use of the integrase strand transfer inhibitor (INSTI) dolutegravir in first-line and second-line antiretroviral therapy (ART) might facilitate emerging resistance. The DTG RESIST study combined data from HIV cohorts to examine patterns of drug resistance mutations (DRMs) and identify risk factors for dolutegravir resistance.

Methods We included cohorts with INSTI resistance data from two collaborations (ART Cohort Collaboration, International epidemiology Databases to Evaluate AIDS in Southern Africa), and the UK Collaborative HIV Cohort. Eight cohorts from Canada, France, Germany, Italy, the Netherlands, Switzerland, South Africa, and the UK contributed data on individuals who were viraemic on dolutegravir-based ART and underwent genotypic resistance testing. Individuals with unknown dolutegravir initiation date were excluded. Resistance levels were categorised using the Stanford algorithm. We identified risk factors for resistance using mixed-effects ordinal logistic regression models.

Findings We included 599 people with genotypic resistance testing on dolutegravir-based ART between May 22, 2013, and Dec 20, 2021. Most had HIV-1 subtype B (n=351, 59%), a third had been exposed to first-generation INSTIs (n=193, 32%), 70 (12%) were on dolutegravir dual therapy, and 18 (3%) were on dolutegravir monotherapy. INSTI DRMs were detected in 86 (14%) individuals; 20 (3%) had more than one mutation. Most (n=563, 94%) were susceptible to dolutegravir, seven (1%) had potential low, six (1%) low, 17 (3%) intermediate, and six (1%) high-level dolutegravir resistance. The risk of dolutegravir resistance was higher on dolutegravir monotherapy (adjusted odds ratio [aOR] 34·1, 95% CI 9·93–117) and dolutegravir plus lamivudine dual therapy (aOR 9·21, 2·20–38·6) compared with combination ART, and in the presence of potential low or low (aOR 5·23, 1·32–20·7) or intermediate or high-level (aOR 13·4, 4·55–39·7) nucleoside reverse transcriptase inhibitor (NRTI) resistance.

Interpretation Among people with viraemia on dolutegravir-based ART, INSTI DRMs and dolutegravir resistance were rare. NRTI resistance substantially increased the risk of dolutegravir resistance, which is of concern, notably in resource-limited settings. Monitoring is important to prevent resistance at the individual and population level and ensure the long-term sustainability of ART.



Unlocking Antiretroviral Treatment Potential: use of doravirine in PLHIV with past NNRTI resistance associated mutations

Patient	Past NNRTI RAM	Genotype interpretation to DOR	DOR containing regimen*	Cumulative GSS (past RNA/DNA genotypes)
3	K103R+Y181C +G190A	I	DOR + DTG	1,5
4	K101E+K103N +Y181C+G190A	I	DOR + DTG	1,5
5	L100I+E138A +Y181C+G190A	I	DOR + RAL	1,5
8	K101E+G190A	I	DOR + RAL	1,5
13	K103N+Y181C +H221Y+M230L	R	DOR + DTG	1
14	L100I+K103N	R	DOR + DTG	1
15	Y188L	R	DOR + DTG	1
16	L100I+K103N	R	DOR + DTG	1
21	Y181C+G190A +H221Y	R	DOR + DTG	1

- Real life efficacy of switch to DOR in 87 virologically suppressed (VS) PLHIV with past NNRTI RAMs in RNA/DNA genotype (Paris)
  - 23 with **intermediate** or **high-level** R to DOR
    - 9 switched to **2DR DOR/INSTI**

- **All maintained VS at W48**

Abdi, EACS 2023

Open Forum Infectious Diseases

MAJOR ARTICLE

A Randomized Trial of Dolutegravir Plus Darunavir/Cobicistat as a Switch Strategy in HIV-1-Infected Patients With Resistance to at Least 2 Antiretroviral Classes

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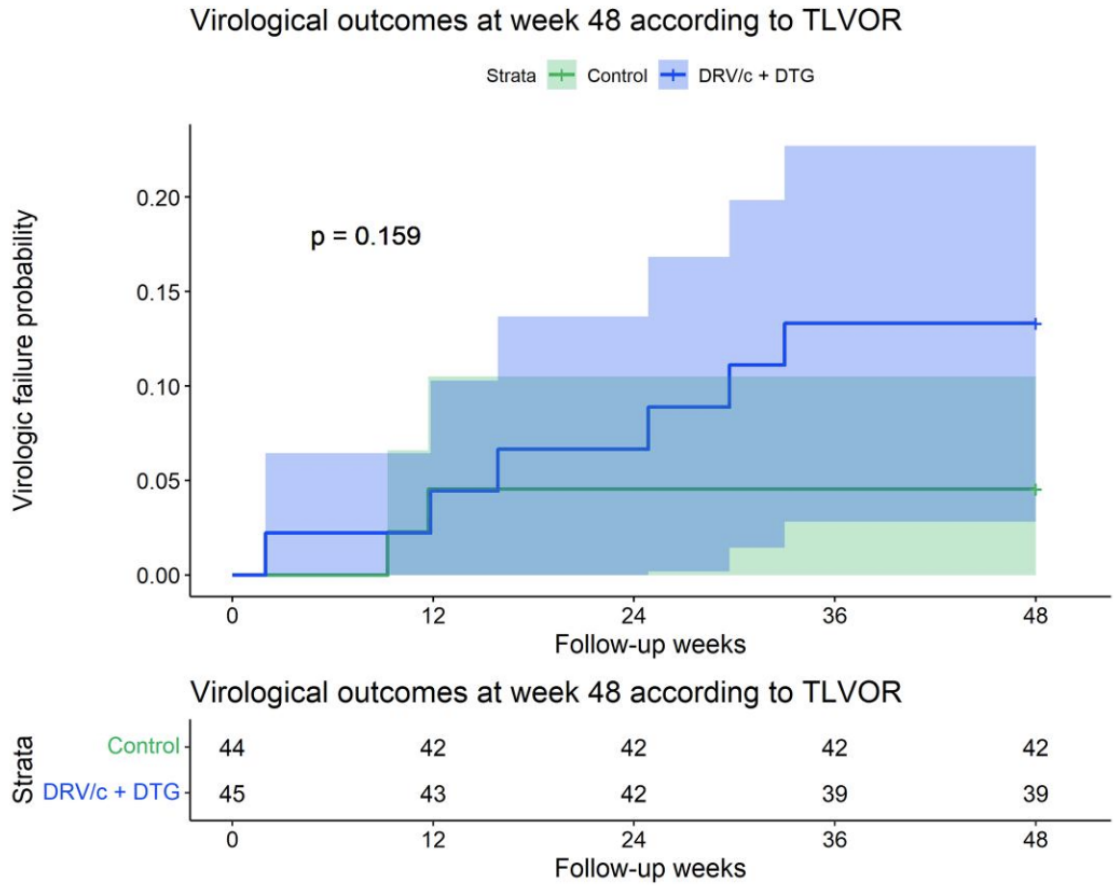
Background. Suppressed patients with drug-resistant HIV-1 require effective and simple antiretroviral therapy to maintain treatment adherence and viral suppression.

Methods. This randomized, open-label, noninferiority, multicenter pilot study involved HIV-infected adults who met the following criteria: confirmed HIV-1 RNA <50 copies/mL for ≥6 months preceding the study randomization, treatment with at least 3 antiretroviral drugs, and a history of drug resistance mutations against at least 2 antiretroviral classes but remaining fully susceptible to darunavir (DRV) and integrase inhibitors. Participants were randomized 1:1 to switch to dolutegravir (DTG; 50 mg once per day) plus DRV boosted with cobicistat (DRV/c; 800/150 mg once per day; 2D group) or continue with their baseline regimen (standard-of-care [SOC] group). The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at week 48 relative to time to loss of virologic response, with a noninferiority margin set at −12.5%. Virologic failure was defined as confirmed HIV-1 RNA ≥50 copies/mL or a single determination of HIV-1 RNA >50 copies/mL followed by antiretroviral therapy discontinuation.

Results. Forty-five participants were assigned to the 2D group and 44 to the SOC group. Time to loss of virologic response showed no difference in the proportion maintaining HIV-1 RNA <50 copies/mL at week 48: 39 of 45 (86.7%; 95% CI, 73.21%–94.95%) in the 2D group vs 42 of 44 (95.4%; 95% CI, 84.53%–99.44%) in the SOC group (log-rank $P = .159$) with an estimated difference of −8.7 (95% CI, −22.72 to 5.14). Only 2 (4.5%) in the SOC group experienced virologic failure, and 3 participants from the 2D group experienced adverse events leading to treatment discontinuation.

Conclusions. In suppressed patients with at least 2 resistant antiretroviral classes, noninferiority could not be demonstrated by fully active DRV/c plus DTG. Nevertheless, there were no unexpected adverse events or virologic failure. DRV/c plus DTG may be considered a once-daily therapy option only for well-selected patients.



Hepatitis B Reactivation in PLWH With Anti-Core Antibody After Switch to an Anti-HBV Sparing Regimen

Giulia Morsica[1], Riccardo Lolatto[1], Sara Diotallevi[1], Valentina Svicher[2], Costanza Bertoni[1,3], Alessia Siribelli[1,3], Hamid Hasson[1], Sabrina Bagaglio[1], **Tommaso Clemente[1,3]**, Arianna Forniti[4], Romina Salpini[2], Caterina Uberti Foppa[1,3], Antonella Castagna[1,3], Nicola Gianotti[1]

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RESULTS

- Overall, 34 PLWH with antiHBc and HBsAb and 7 with isolated antiHBc switched to an antiHBVsr (Table 1).
- Median follow-up after switch to antiHBVsr: 8.91 months [(IQR 6.78 - 24.14); in PLWH with HBsAb 8.96 months (IQR 6.78 - 24.14); in PLWH with isolated antiHBc 6.97 months (IQR 5.56 - 43.22); p=0.742].
- No reactivations in PLWH with antiHBc and HBsAb.

Table 1. Characteristics of PLWH with antiHBc at switch to antiHBVsr according to the presence or absence of anti-HBsAg

BL Characteristics	Overall (n=41)	antiHBc positive (n=7)	antiHBc HBsAb positive (n=34)	p
Age (years)	55.1 (50.2 - 62.2)	57.8 (43.2 - 70.2)	54.4 (50.2 - 61.5)	0.690
Male sex	41 (100%)	7 (100%)	34 (100%)	-
Years of HIV infection	15.4 (9.5 - 20.4)	15.5 (10.1 - 26.4)	15.3 (8.9 - 19.7)	0.533
HIV-RNA <50 copies/mL 50-200 copies/mL	 40 (97.6%) 1 (2.4%)*	 7 (100%) 0 (0%)	 33 (96.8%) 1 (3.2%)*	0.661
CD4⁺ cells count (cells/mm³)	607 (460 - 772)	693 (485 - 867)	603 (459 - 772)	0.726
AntiHBVsr DTG/RPV CAB/RPVLA	 15 (36.6%) 26 (63.4%)	 3 (42.9%) 4 (57.1%)	 12 (35.3%) 22 (64.7%)	0.693
HBV-DNA <10 IU/mL (available in 26 PLWH)	26 (100%)	5 (100%)	21 (100%)	-
ALT levels (IU/L)	27.5 (21 - 32)	28 (20 - 32)	27 (21 - 39)	0.763

*One participant had HIV-RNA >50, <200 copies/mL before switching to DTG/RPV

Of 7 PLWH with **isolated antiHBc**, 1 (14.3%) experienced **HBV reactivation** 3 months after switching to **CAB/RPVLA**

Figure 2. Trend of transaminases in the participant with HBV reactivation

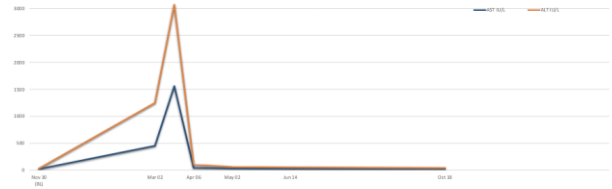
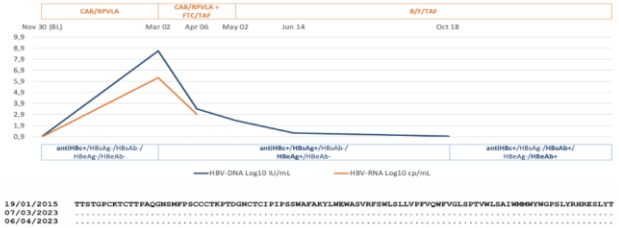


Figure 3. Trend of HBV-DNA, -RNA and serology in the participant with HBV reactivation. Alignment of the partial HBsAg before any ART and during HBV reactivation in the bottom



- In this individual (Figure 2 and Figure 3) we observed:
  - HBV-RNA positive at baseline (8 copies/mL) and very low levels of HBV-DNA (6 copies/mL) by ddPCR assay
  - Overt HBV infection assessed by HBsAg and hepatitis B e antigen (HBeAg) seroreversion and highly increased HBV-DNA
  - HBV genotype A2, with sequence identical to that obtained prior to any ART
  - Progressive decrease in HBV-DNA and normalization of transaminases after receiving emtricitabine/tenofovir alafenamide (FTC)/TAF.

viruses

MDPI

Article

Role of HBcAb Positivity in Increase of HIV-RNA Detectability after Switching to a Two-Drug Regimen Lamivudine-Based (2DR-3TC-Based) Treatment: Months 48 Results of a Multicenter Italian Cohort

Vincenzo Malagnino [1,2,*], Romina Salpini [3], Elisabetta Teti [1], Mirko Compagno [1,2], Ludovica Ferrari [1], Tiziana Mulas [1], Valentina Svicher [4], Marta Zordan [1], Monica Basso [5], Giuliana Battagin [6], Sandro Panese [7], Maria Cristina Rossi [8], Renzo Scaggiante [9], Daniela Zago [5], Marco Iannetta [1,2], Saverio Giuseppe Parisi [5], Massimo Andreoni [1,2] and Loredana Sarmati [1,2]

	HBcAb+ (*n* = 51)	HBcAb− (*n* = 109)	*p*-Value
Sex ratio M/F, %F	39/12 (23.5%)	87/22 (20.2%)	0.62
Age, years, median (IQR)	47 (37–55)	40 (31–50)	**0.0014**
Calendar year of HIV diagnosis, median (IQR)	2007 (2000–2012)	2010 (2006–2017)	**0.039**
Nadir CD4+, cell/mmc, median (IQR)	222 (69–335)	266 (158–445)	**0.023**
History of HIV viral rebound, *n* (%)	10 (19.6%)	12 (11%)	0.12
cART pre-switch, *n* (%):			0.33
2NRTI + PI	16 (31.4%)	33 (30.3%)	
2NRTI + NNRTI	15 (29.4%)	36 (33%)	
2NRTI + INI	13 (25.5%)	34 (31.2%)	
Other	7 (13.7%)	6 (5.5%)	
cART TAF/TDF-containing pre-switch, *n* (%):	44 (86.3%)	97 (88.9%)	0.83
CD4+ at 2DR switch, cell/mmc, median (IQR)	683 (547–944)	680 (545–926)	0.91
HCVAb+ serology, *n* (%)	8 (15.7%)	11 (10.1%)	0.22
HIV RNA 24 months pre-2DR switch, *n* (%):			0.41
Undetectable	33 (64.7%)	67 (61.4%)	
<20 cp/mL Target detected	16 (31.3%)	29 (26.6%)	
Detectable >20 cp/mL	2 (4%)	13 (12%)	
HIV RNA 12 months pre-2DR switch, *n* (%):			0.40
Undetectable	38 (74.5%)	89 (81.6%)	
<20 cp/mL Target detected	6 (11.7%)	10 (9.2%)	
Detectable >20 cp/mL	7 (13.8%)	10 (9.2%)	
HIV RNA at 2DR switch, *n* (%):			0.87
Undetectable, *n* (%)	34 (66.8%)	83 (76.2%)	
<20 cp/mL Target detected	14 (27.5%)	20 (18.3%)	
Detectable >20 cp/mL	3 (5.9%)	6 (5.5%)	
Persistently TND pre-switch, *n* (%)	15 (29.4%)	43 (39.4%)	0.29
2DR strategy:			0.74
3TC + PI	11 (21.6%)	26 (23.9%)	
3TC + DTG	40 (78.4%)	83 (76.1%)	
HIV RNA 24 months post-2DR switch, *n* (%):			**<0.0001**
Undetectable	33 (64.7%)	79 (87.8%)	
<20 cp/mL Target detected	17 (33.3%)	6 (6.7%)	
Detectable >20 cp/mL	1 (2%)	5 (5.5%)	
HIV RNA 36 months post-2DR switch, *n* (%) *:			**0.011**
Undetectable	32 (62.7%)	66 (86.8%)	
<20 cp/mL Target detected	15 (29.4%)	6 (7.9%)	
Detectable >20 cp/mL	4 (7.9%)	4 (5.3%)	
HIV RNA 48 months post-2DR switch, *n* (%) **:			**0.021**
Undetectable	16 (57.2%)	56 (86.1%)	
<20 cp/mL Target detected	8 (28.6%)	5 (7.7%)	
Detectable >20 cp/mL	4 (14.2%)	4 (6.2%)	
Persistently TND during 48 months after switch, *n* (%) ***	1 (3.5%)	33 (50.7%)	**<0.0001**

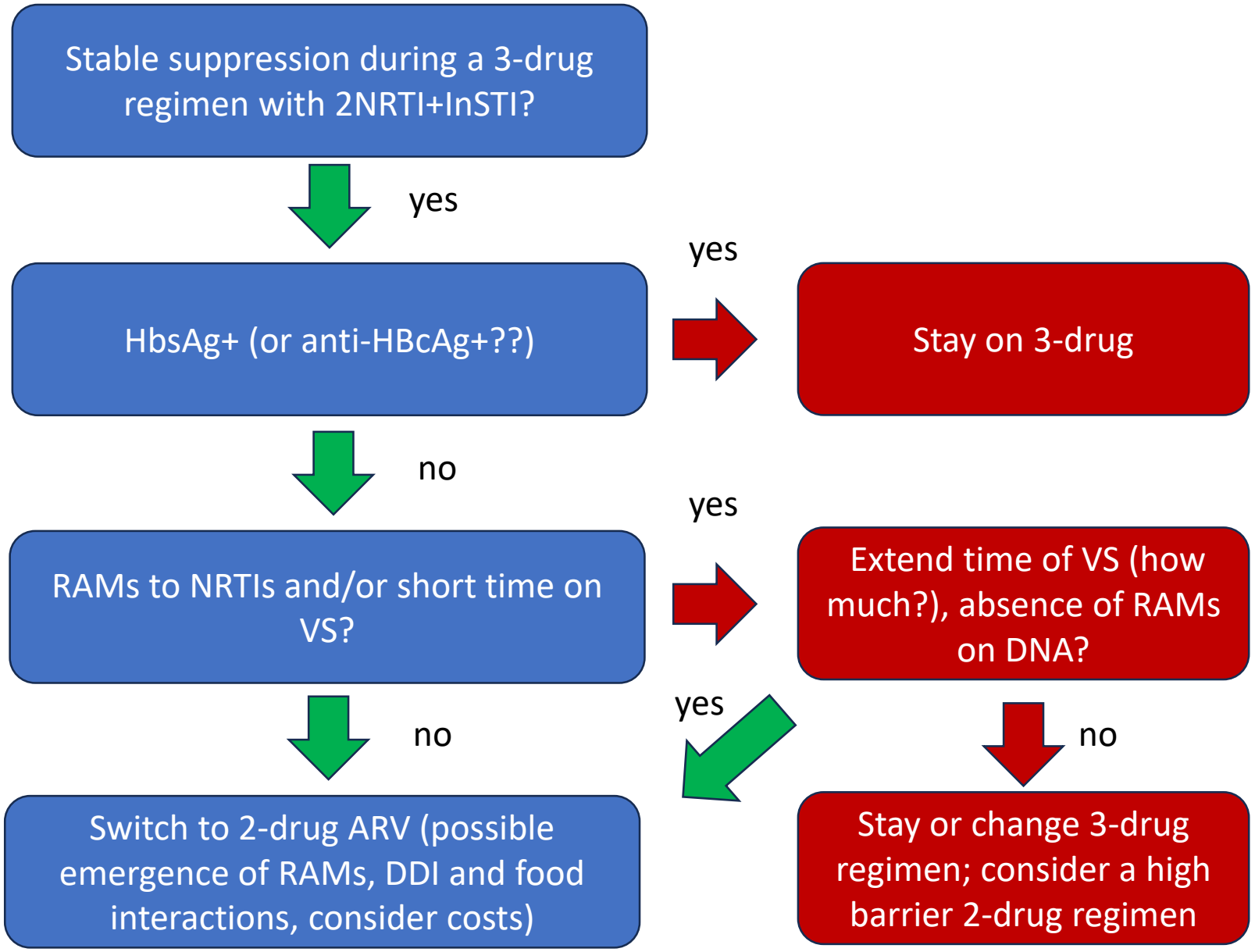
*: Data available for 141 pts; **: Data available for 127 pts; ***: data available for 93 pts.

All patients maintained virological suppression at the different observation times (6, 12, 24, 36, and 48 months after the switch), although with different levels of low-level viremia

Table 3. Univariate and Multivariate analysis for estimated factors with predictive impact on Detected HIV-RNA during the entire follow-up 48 months after the 2DR-3TC-containing switch.

	Univariable		*Multivariable*	
	OR (95% CI)	***p*-Value**	**OR (95%)**	***p*-Value**
Age,	1.01 (0.94–1.04)	0.39	0.97 (0.96–1.03)	0.85
Calendar year of HIV infection	1.10 (0.98–1.19)	0.76	0.95 (0.89–1.02)	0.17
Nadir CD4+ cell count, >250/mm^3	1 (0.99–1.12)	0.23	0.97 (0.63–1.51)	0.61
Previous HIV VF	3.04 (1.05–13.16)	0.028	2.00 (0.40–6.32)	0.39
HbcAb-positivity	9.32 (4.04–22.48)	0.003	7.46 (2.35–14.77)	**0.004**

Conclusions: is it time to consider a new switch algorithm?



Thanks for the attention!