Gemelli

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Terapia duplice vs triplice: luci e ombre

A. BORGHETTI

FIRENZE, 10.01.2023

Agenda

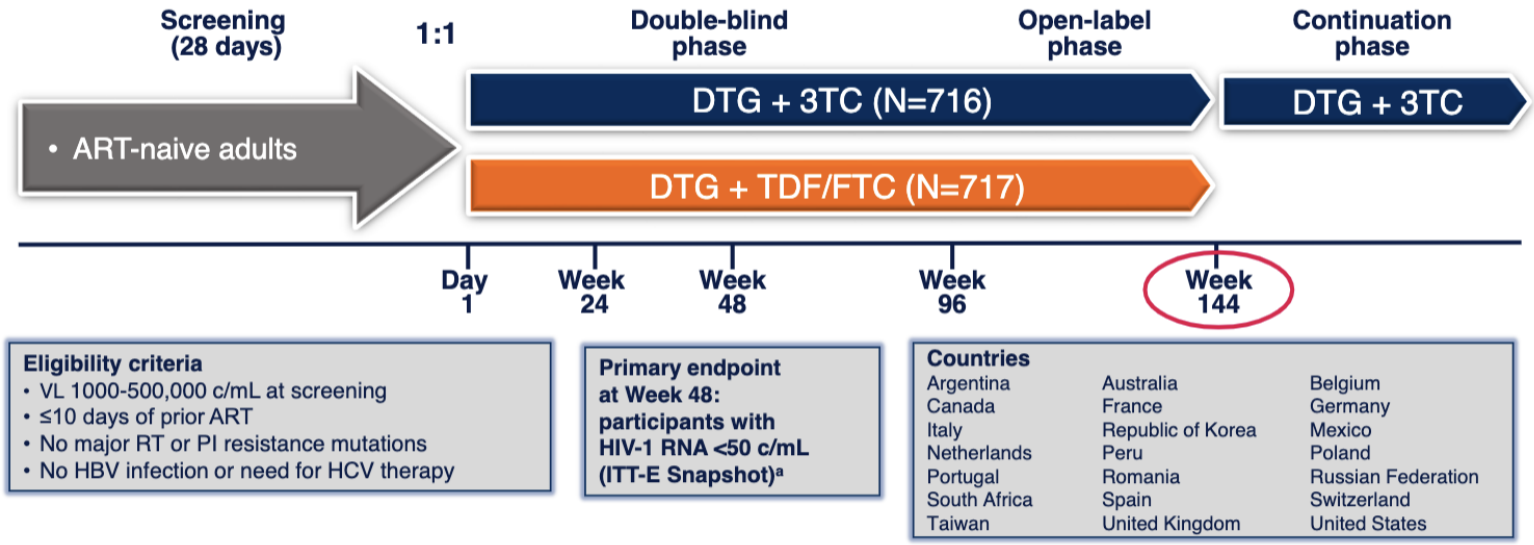
- Il paziente naive
- Il paziente virologicamente soppresso
- Conclusioni

Il paziente naive

Linee guida EACS 11.1

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)

GEMINI 1 e 2: disegno di studio



[a]–10% non-inferiority margin for individual studies.

Caratteristiche della popolazione

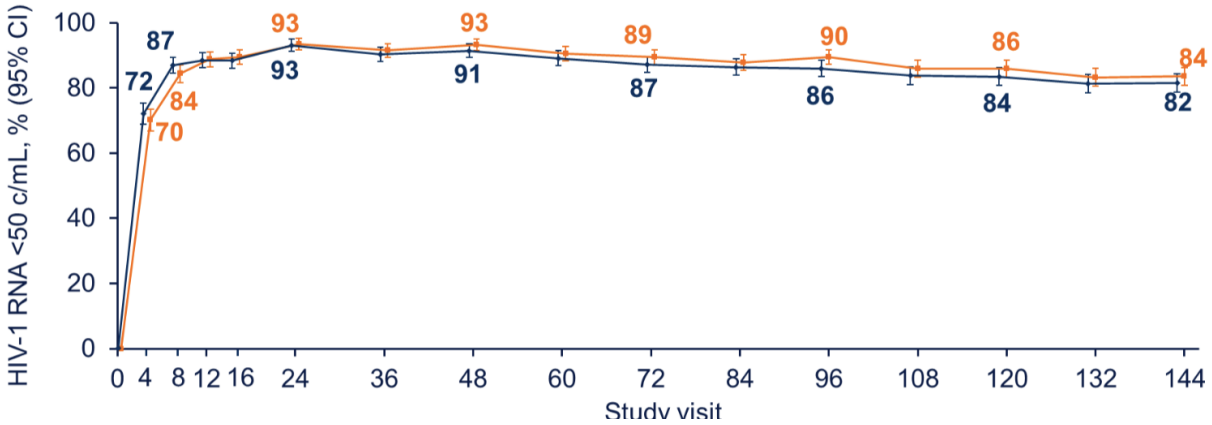
Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32 (18-72)	33 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	90 (13)	71 (10)
Asian	71 (10)	72 (10)
White	484 (68)	499 (70)
Other	71 (10)	75 (10)
HIV-1 RNA >100,000 c/mL, n (%)[a]	140 (20)	153 (21)
CD4+ cell count ≤200 cells/mm^3, n (%)	63 (9)	55 (8)

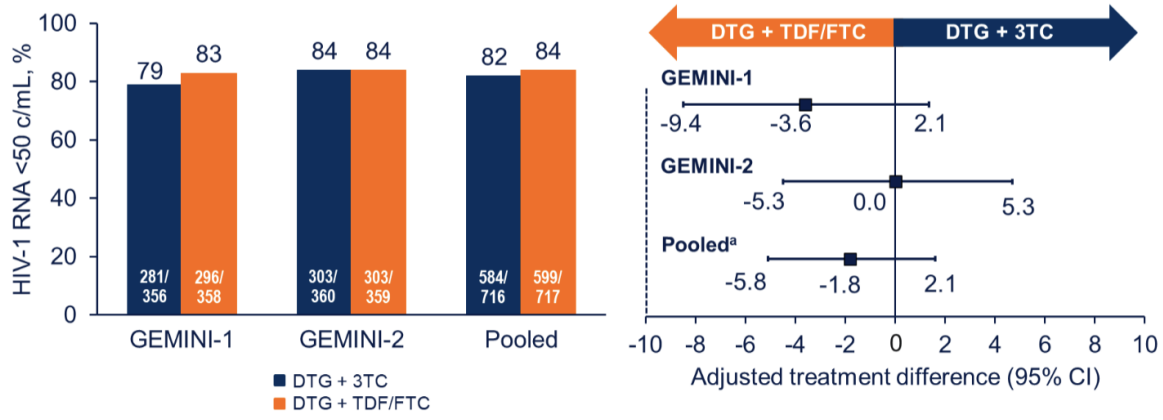
[a]2% of participants in each group had baseline HIV-1 RNA ≥500,000 c/mL and were included in the ITT-E analysis.

- 1433 participants in GEMINI-1 and GEMINI-2 were randomized and received ≥1 dose of study medication (DTG + 3TC, N=716; DTG + TDF/FTC, N=717)
- At baseline, 20% (n=293) of participants had HIV-1 RNA >100,000 c/mL and 8% (n=118) had CD4+ cell count ≤200 cells/mm^3

1. Cahn et al. *J Acquir Immune Defic Syndr*. 2020;83:310-318.

Risultati (1)





[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), baseline CD4+ cell count (≤200 vs >200 cells/mm³), and study (GEMINI-1 vs GEMINI-2).

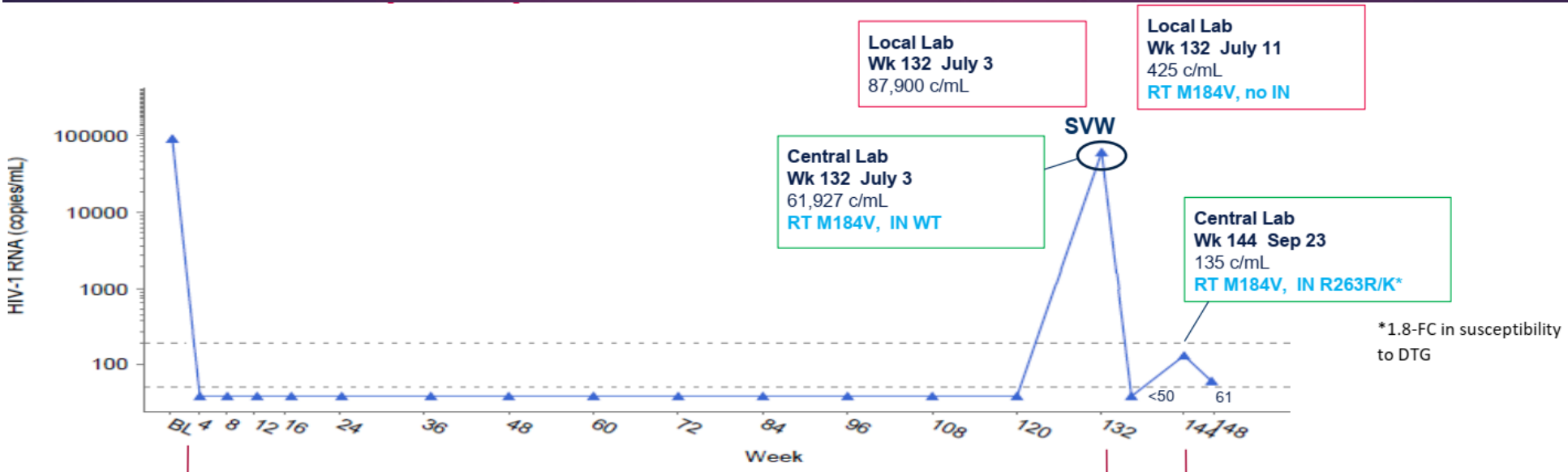
DTG + 3TC was non-inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL for GEMINI-1, GEMINI-2, and the pooled population at Week 144

Risultati (2)

- Across both studies, 12 participants (2%) in the DTG + 3TC group (1 since Week 96) and 9 participants (1%) in the DTG + TDF/FTC group (2 since Week 96) met protocol-defined CVW criteria through Week 144

- None of these participants had treatment-emergent INSTI or NRTI resistance mutations; 1 non-CVW participant with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG

Risultati (3)



Monogram testing:
No NRTI, NNRTI, INSTI mutations
PI: L10I, E35D, M36I, I62I/V, L89L/M

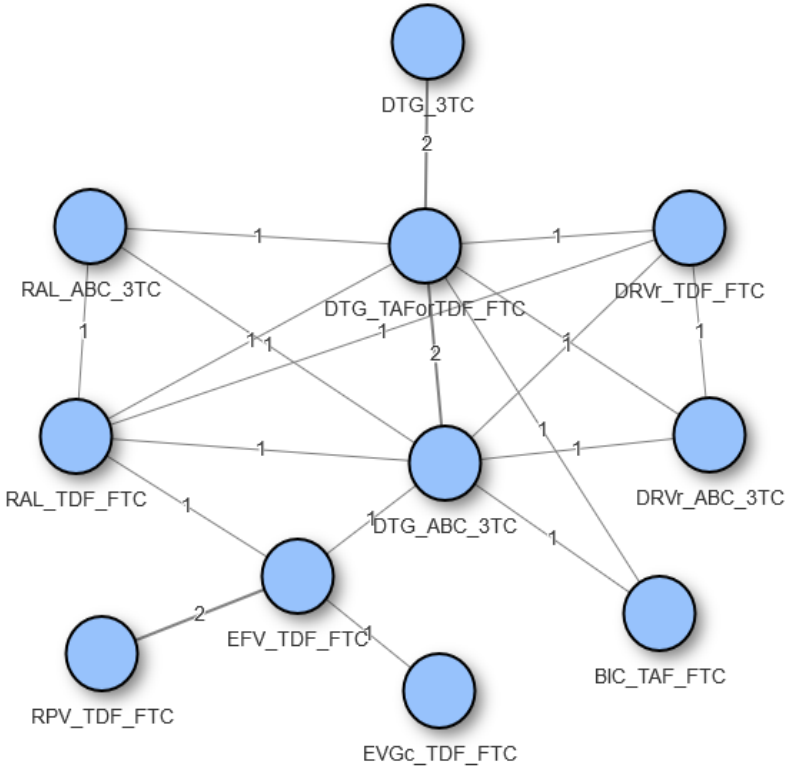
Monogram testing
M184V
No NNRTI, INSTI mutations
PI: L10I, E35D, M36I, I62V

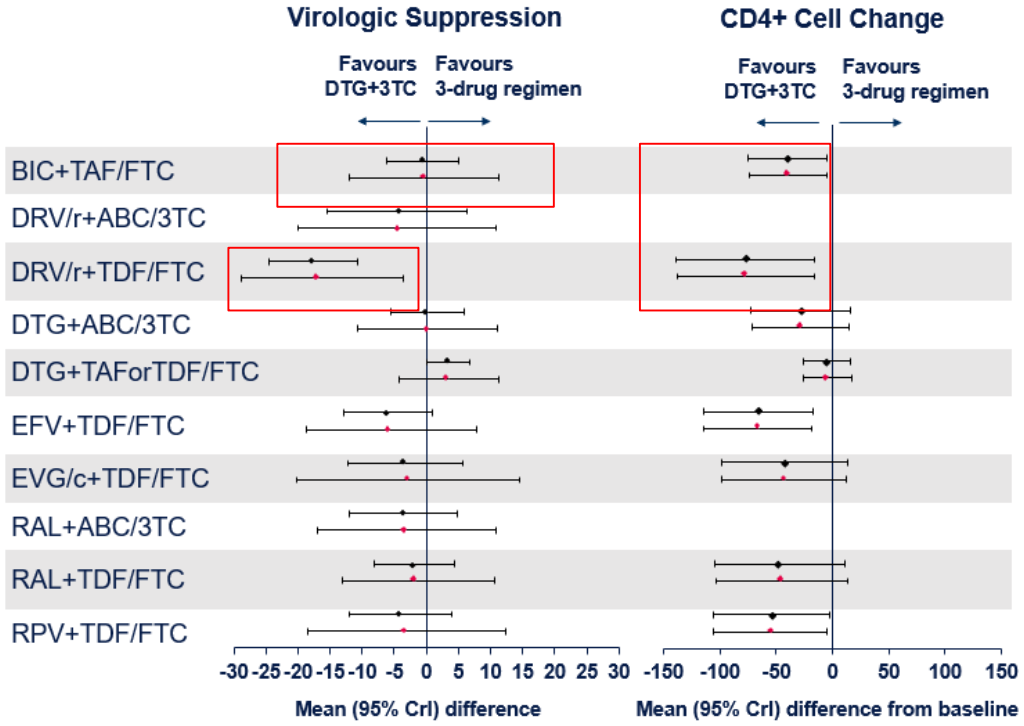
Monogram testing
M184V
K101K/E
R263R/K
PI: L10I, E35D, M36I, I62V

- Site reported that patient had not been adherent to ARV therapy
- Site reported also that participant had been taking a number of dietary supplements, and reported moderate (Grade 2) diarrhea prior to week 132.

- Participant with reported non-adherence
- Not a confirmed virological withdrawal (CVW)
- **M184V** at Week 132 (HIV-1 RNA 61,927 c/mL)
- **R263R/K** at Week 144 (HIV-1 RNA 135 c/mL)
- 1.8-fold change in susceptibility to DTG

COMPARATIVE EFFICACY AND SAFETY OF A COMBINATION THERAPY OF DOLUTEGRAVIR AND LAMIVUDINE VS 3-DRUG ANTIRETROVIRAL REGIMENS IN TREATMENT-NAIVE HIV-1 INFECTED PATIENTS AT 96 WEEKS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS





Katharina Nickel,[1] Nicholas J. Halfpenny,[2] Sonya J. Snedecor,[3] Yogesh Suresh Punekar[4]

Conclusions

- **Virologic suppression (VS)** achieved by DTG+3TC was superior to DRV/r+TDF/FTC and comparable to other 3DRs. The probability of DTG+3TC achieving better VS ranged from 2.5% with DTG+TAForTDF/FTC to 95.4% with EFV+TDF/FTC

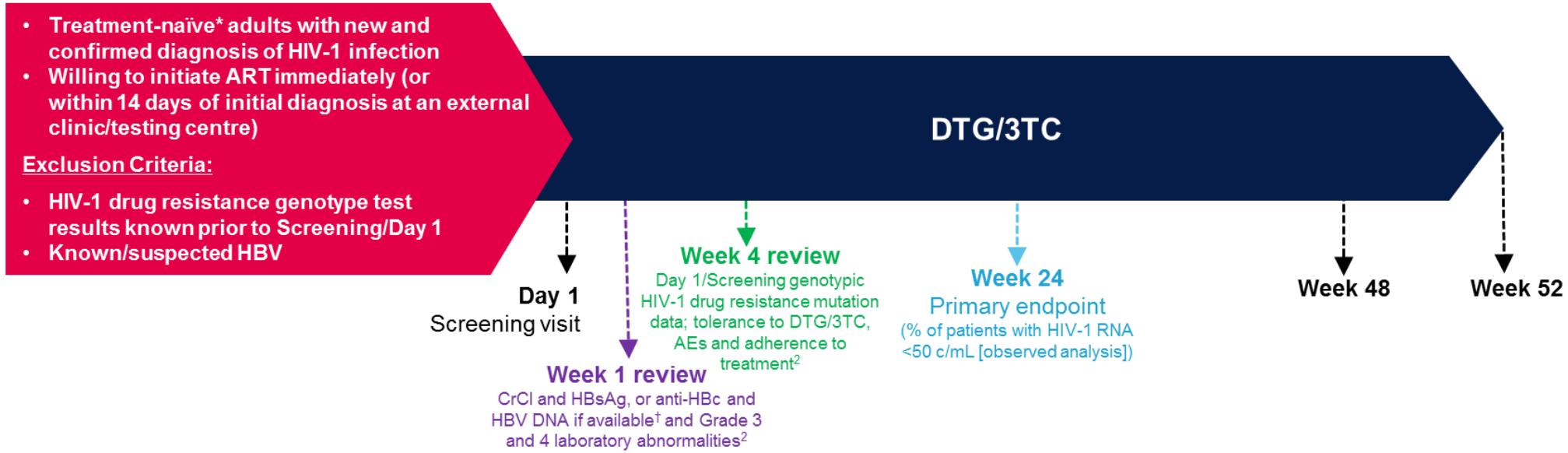
- Stratified by baseline viral load of >100,000 RNA copies/mL and ≤100,000 RNA copies/mL or CD4 >200 cells/µL and ≤200 cells/µL, DTG+3TC was broadly comparable to all the 3DRs also reporting those subgroup data with some significant differences

- **Mean CD4 cell changes** with DTG+3TC were statistically significantly higher from baseline when compared to BIC+TAF/FTC, DRV/r+TDF/FTC, EFV+TDF/FTC and RPV+TDF/FTC. DTG+3TC was otherwise comparable with all other regimens

Feasibility, efficacy, and safety of DTG/3TC as a first-line regimen in a test-and-treat setting for newly diagnosed PLWH: the STAT study

Phase IIIb, multicentre, open-label, single-arm study in the United States[1]

- **Objective:** to evaluate the feasibility, efficacy and safety of a rapid Test and Treat model of care using DTG/3TC as a first-line regimen over 48 weeks in patients with newly-diagnosed HIV-1 who are willing to start study treatment immediately, without waiting for screening laboratory results (N=128)
- **Primary endpoint:** the number of participants with plasma HIV-1 RNA <50 c/mL at Week 24 (observed analysis)

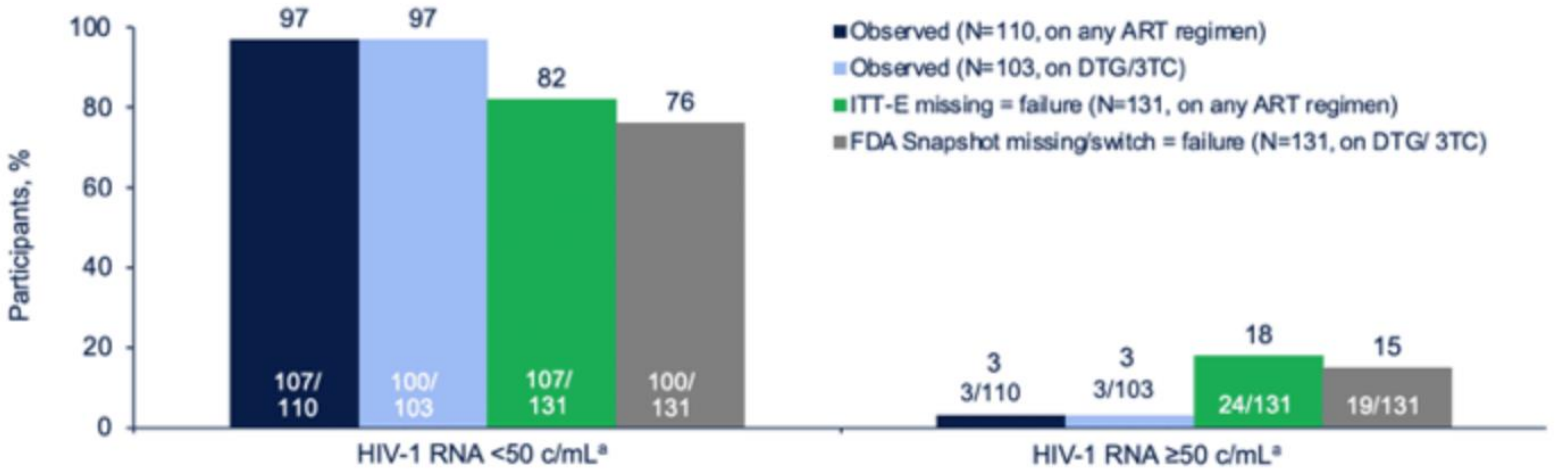


*Participants who received HIV PEP or PrEP are eligible if the last PEP/PrEP dose was >6 months from HIV diagnosis or there is documented HIV seronegativity ≥2 months after the last prophylactic dose and prior to the date of HIV diagnosis;[1] †If not available at Week 1, this should be reviewed at Week **4**

anti-HBc, HBV core antibody; **CrCl,** creatinine clearance; **HBsAg,** HBV surface antigen; **HBV,** hepatitis B virus; **PEP,** post-exposure prophylaxis; **PrEP,** pre-exposure prophylaxis

Rolle, ActHIV 2020

Summary of virologic outcomes at W48



[a]For Snapshot HIV-1 RNA <50 c/mL analysis, 103/131 participants were on DTG/3TC; for Snapshot HIV-1 RNA ≥50 c/mL analysis, 19/131 participants were on any ART regimen (12/131 participants had no virologic data at Week 48).

- Most participants in the observed, ITT-E, and Snapshot analyses achieved HIV-RNA<50 cp/mL;
- ITT-E non suppression rates driven by non-virological factors (i.e., high withdrawal rate);
- 2 participants with confirmed virologic failure had no evidence of treatment-emergent resistance and both remained on DTG/3TC

Feasibility, efficacy, and safety of DTG/3TC as a first-line regimen in a test-and-treat setting for newly diagnosed PLWH: the STAT study (wk 48)

Reason for switch	Baseline plasma HIV-1 RNA, c/mL	Baseline CD4+ cell count, cells/mm^3	Visit window	Modified ART	Plasma HIV-1 RNA at Week 48, c/mL
BL HBV	108,597	60	Week 1	DTG/3TC + TAF	<40
BL HBV	129,665	98	Week 1	BIC/FTC/TAF	<40
BL HBV	37,290	101	Week 4	DTG + TAF/FTC	<40
BL HBV	256,879	<20[a]	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	NA[c]
Decision by participant or proxy	90,575	133	Week 4	BIC/FTC/TAF	NA[d]
BL HBV	13,170	327	Week 8	DTG/3TC + TAF	<40
BL M184V	18,752	456	Week 8	DTG/RPV	NA[e]
AE (rash)[f]	2,592,169	464	Week 12; Week 12	DRV/COBI/FTC/TAF; BIC/FTC/TAF	<40
Decision by participant or proxy	8091	308	Week 24	BIC/FTC/TAF	<40
Pregnancy	8406	1192	Week 24	RAL + TDF/FTC	327; <40
Participants who switched after Week 48 HIV-1 RNA assessment					
Lack of efficacy	123,644	41	Week 48	DTG + 3TC[g]	223; 182; 831
Non-adherence	27,294	423	Post–Week 48	Off treatment[h]	NA

Rolle, IDWeek 2021

Feasibility, efficacy, and safety of DTG/3TC as a first-line regimen in a test-and-treat setting for newly diagnosed PLWH: the STAT study

Class	Codon	Mutations	DTG + 3TC (N = 131)
Subjects with available genotypic data at Baseline			126
INSTI	E157	E157Q	9 (7%)
	L74	Any Mutation	5 (4%)
		L74I	4 (3%)
		L74L/M	1 (<1%)
	G193	Any Mutation	3 (2%)
		G193E	2 (2%)
		G193G/E	1 (<1%)
NNRTI	K103	Any Mutation	18 (14%)
		K103N	13 (10%)
		K103S	4 (3%)
		K103N/S	1 (<1%)
NRTI	M41	M41L	3 (2%)

Only codons with mutations reported by ≥3 subjects are presented

- Besides the individual with M184V TDR, other RAMs were detected in a proportion of subjects
- Many NNRTI failures occur with K103N/S plus M184V, thus **M184V could have been present as TDR but gone undetected** (no NGS data available at this time)

Rolle, Glasgow 2020

48 weeks efficacy and tolerability of DTG+3TC in adult HIV naïve patients. A multicenter real-life cohort

- Multicentre study, DTG+3TC as first line starting before Jan 31, 2020
- 135 patients were included, **treatment started without baseline GRT results in 71.9% of cases**
- Subsequently confirmed baseline resistance mutations in 17 patients (12.6%)

Table 1. Patients' baseline characteristics.

Baseline characteristics		Patients (N = 135)
Age (years) (median–IQR)		32 (27–39)
Gender, n (%)	Male	122 (90.4)
	Female	13 (9.6)
HIV transmission, n (%)	MSM	112 (83)
	MSW	20 (14.8)
	IDU	3 (2.2)
Country–region, n (%)	Spain	69 (51.1)
	Latinamerican	53 (39.3)
	Europe	6 (4.4)
	Others	7 (5.2)
CDC classification, n (%)	A	125 (92.6)
	B	7 (5.2)
	C	3 (2.2)
CD4+ cells/mm^3 (median–IQR)	Basal CD4+	469 (347–650)
	CD4 < 200	3 (2.2)
HIV-1 VL (c/mL), n (%)	≥ 100,000 copies/mL	23 (17)
	< 100,000 copies/mL	112 (83)
Hepatitis B co-infection, n (%)	HBsAg +	0
	Anti-HBc +	32 (23.7)
	Anti-HBs +	86 (63.7)
Hepatitis C co-infection (IgG HCV +), n (%)		7 (5.2)
HLAB*5701 positive, n (%)		11 (8.1)
Median time from diagnosis to start of treatment (weeks)		6 (IQR: 3–14)

Cabello, IAS 2021

Risultati

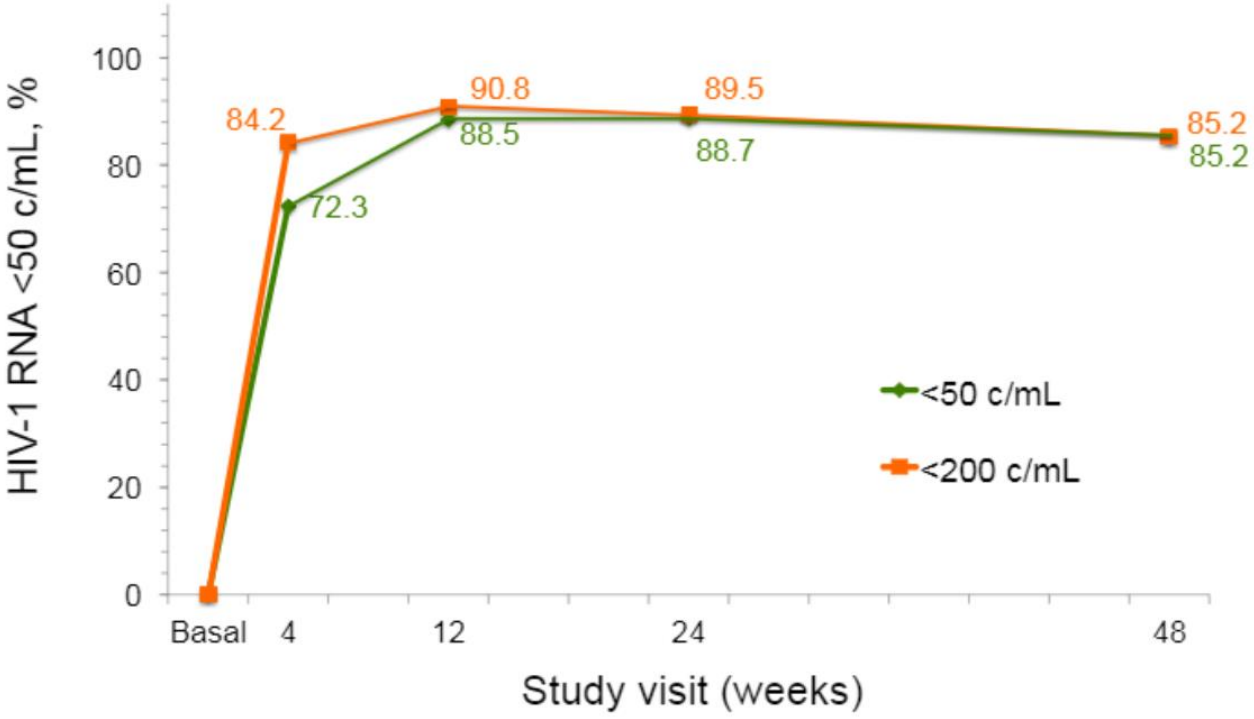


Table: Patients who discontinued treatment with DTG+3TC

Patient	Time to ART change (weeks)	Reason	Basal VL (c/mL)	w4	w12	w24	Final ART	Last VL (c/mL)
1	-	VF[a]	779	-	-	409	DTG/3TC	<50
2	1	M184V[b]	1,875	<50	-	-	DRV/c/TAF/FTC	<50
3	2	CNS AE	142	-	-	-	RPV+TDF/FTC	<50
4	6	M184V[c]	29,300	<50	-	-	DTG/RPV	<50
5	16	CNS AE	219	-	<50	-	DRV/c/TAF/FTC	LTFU
6	20	CNS AE	1,696	<50	<50	-	RPV/TAF/FTC	<50

ART: Antiretroviral treatment; VL: viral load; CNS AE: Central nervous system adverse event; VF: virological failure
[a]VF due to physician criteria (only one VL ≥ 200 c/mL but the patient stopped the treatment).
[b]The patient had plasma HIV-1 RNA 1,875 c/mL at baseline, switched to DRV/c/TAF/FTC on Day 8; <50 c/mL on Day 59.
[c]The patient had plasma HIV-1 RNA 29,300 c/mL at baseline, <50 c/mL on Day 43, switched to DTG+DRV/c on Day 43; switched to DTG/RPV afterwards.

DOLAVI study: real-world data of dolutegravir plus lamivudine in naive HIV-1-infected patients (week 48)

Table 1. General description of the population.

Variable	N = 88
Age (year), mean (±SD)	35.8 (±12.2)
Male, n (%)	77 (87.5)
Rapidly initiated DT, median (IQR)	0 (0–7)
Baseline HIV Viral Load, log_{10}, median (IQR)	4.49 (4–4.9)
Viral Load > 100,000 cop/mL, n (%)	17 (20)
Resistance mutations baseline, n (%)	3 (3.4)
K103 N	1 (33.3)
V106I, E138A	1 (33.3)
V108I	1 (33.3)
Baseline CD4, (Cell/uL), mean (±SD)	512.2 ± 250.3
CD4 < 200 cell/uL, n (%)	7 (8)
Baseline CD4/CD8 ratio, mean (±SD)	0.6 (±0.37)
CDC AIDS stage (A3, B3, C), n (%)	10 (11.4)
A1	42 (47.7)
A2	33 (37.5)
A3	8 (9.1)
B1	1 (1.1)
B2	2 (2.3)
C2	1 (1.1)
C3	1 (1.1)
Chronic hepatitis C cured, n (%)	3 (3.4)
Positive HVB surface and core antibodies, **n (%)**	1 (1.1)
Risk factor for HIV infection, n (%)	
Heterosexual	18 (20.5)
MSM	67 (76.1)
IVDU	3 (3.4)
Smoker, n (%)	47 (53.4)
Non-alcohol consumer, n (%)	62 (70.5)
Social drinker, n (%)	26 (29.5)
Weight, mean (±SD) (Kg)	72.3 (11.8)
BMI, mean (±SD), Kg/m^2	23.8 (3.9)
Waist, mean (±SD) (cm)	84.7 (12.7)
Underweight, n (%)	3 (3.5)
Normal weight, n (%)	53 (61.6)
Overweight, n (%)	25 (29.1)
Obese	5 (5.8)

- Open, single-arm, multicenter, non-randomized clinical trial in naives administered DTG+3TC QD as separate tablets
- 88 patients
  - CD4 512 cells/uL (8% had CD4 <200 cells/uL)
  - VL 30,902 cp/mL (20.0% VL >100,000 cp/mL)
  - **84.1% realized "test and treat"**
- At week 48, 86.3% (ITT) and 98.7% (PP) had VL <50 cp/mL
- 1 VF without emergent resistance
- Blips without VF in 5.2%

Hidalgo-Tenorio, Viruses 2022

Conclusioni

- La terapia a due farmaci con 3TC+DTG si è dimostrata non-inferiore alle DTG in associazione a 2NRTI;
- L'alta barriera di resistenza rende possibile l'utilizzo di dolutegravir in setting di rapid-ART;
- Servono studi dalla pratica clinica per definire la strategia ideale in pazienti più complessi

Il paziente virologicamente soppresso

Indicazioni allo switch terapeutico nel paziente con soppressione virologica

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

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen, see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions,** page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between Viral Hepatitis Drugs and ARVs
4. **Planned pregnancy or women wishing to conceive,** see Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

EACS Guidelines. Versione 10.1

Schemi di semplificazione

	EACS 11.1 (Oct 2022)	DHHS (Sep 2022)	Linee guida SIMIT (2017)
DTG + RPV	**Supported by large trials**	**AI**	**AI**
3TC + DTG	**Supported by large trials**	**AI**	BII
3TC + bATV	Supported by large trials	CI	**AI→switch da PI** BI→ switch da altre classi
3TC + bDRV	Supported by large trials	BI/BIII	**AI→switch da PI** BI→ switch da altre classi
RPV+CAB	**Supported by large trials**	**AI**	
3TC + bLPV	na	CI	na
DRV + RPV	Supported by small trials	na	CI
DTG + bDRV	Supported by small trials	CI	na
DRV + RAL	na	na	CI

Studi dalla pratica clinica

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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

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JOURNAL ARTICLE

Virological outcomes with dolutegravir plus either lamivudine or two NRTIs as switch strategies: a multi-cohort study

Get access

A Borghetti, M Alkhatib, A Dusina, L Duca, V Borghi, M Zazzi, S Di Giambenedetto

Journal of Antimicrobial Chemotherapy, Volume 77, Issue 3, March 2022, Pages 740–746,
https://doi.org/10.1093/jac/dkab429
Published: 28 November 2021 **Article history**

Dolutegravir-based dual maintenance regimens combined with lamivudine/emtricitabine or rilpivirine: risk of virological failure in a real-life setting

Colin Deschanvres[1]*, Jacques Reynes[2,3], Isabelle Lamaury[4], David Rey[5], Romain Palich[6], Firouzé Bani-Sadr[7], Olivier Robineau[8], Claudine Duvivier[9], Laurent Hocqueloux[10], Lise Cuzin[11,12], Veronique Joly[13], Francois Raffi[1], André Cabie[12] and Clotilde Allavena[1] on behalf of the Dat'AIDS Study Group†

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

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Short Communication

Real world efficacy of dolutegravir plus lamivudine in people living with HIV with undetectable viral load after previous failures

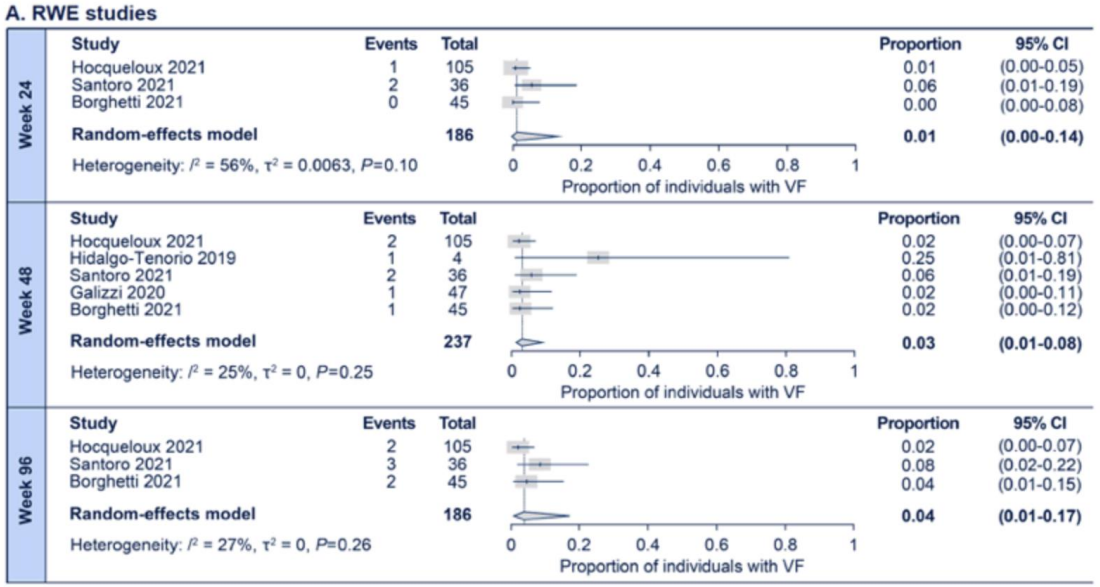
Roberta Gagliardini[a,*], Patrizia Lorenzini[a], Alessandro Cozzi-Lepri[b], Alessandro Tavelli[c], Vanni Borghi[d], Laura Galli[e], Gianmarco Tagliaferri[f], Franco Maggiolo[g], Cristina Mussini[d], Antonella Castagna[e,h], Antonella d'Arminio Monforte[f], Andrea Antinori[a]

Effectiveness of Dolutegravir + Lamivudine in Real-world Studies in People With HIV-1 With M184V/I Mutations: A Systematic Review and Meta-analysis

Glasgow; October 23-26, 2022

Study (cohort)	Proportion with pre-switch M184V/I	M184V/I identification method	VF time point, week	VF outcomes, n/N (%)	VF definition
RWE studies					
Hocqueloux 2021 (Dat'AIDS)[5]	105/695 (15.11%)	RNA and proviral DNA genotypes (pooling both)	24 48 96	1/105 (0.95) 2/105 (1.90) 2/105 (1.90)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
Santoro 2021 (LAMRES)[6]	36/533 (6.75%)	RNA and proviral DNA genotypes	24 48 96	2/36 (5.56) 2/36 (5.56) 3/36 (8.33)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
Borghetti 2021 (ODOACRE)[7,8]	48/669 (7.17%)[a]	Historical genotypes; does not specify RNA or proviral DNA	24 48 96	0/45 1/45 (2.22) 2/45 (4.44)	1 VL ≥1000 c/mL or 2 consecutive VL ≥50 c/mL
Galizzi 2020 (NR)[9]	47/174 (27.01%)[b]	Either RNA or proviral DNA genotypes at baseline (before switch)	24 48 96	— 1/47 (2.13) —	2 consecutive confirmed VL >50 c/mL or 1 VL >50 c/mL followed by ART modification or 1 VL >1000 c/mL
Hidalgo-Tenorio 2019 (DOLAMA)[10]	4/178 (2.25%)	Baseline RNA genotype	24 48 96	— 1/4 (25.00) —	2 consecutive VL >50 c/mL
RCTs					
ART PRO[11]	17/41 (41.46%)	Proviral DNA genotype	24 48 96	0/17 0/17 0/17	VL ≥50 c/mL
SOLAR 3D[12]	50/100 (50.00%)	Historical genotypes; does not specify RNA or proviral DNA	24 48 96	— 1/50 (2.00) —	VL ≥50 c/mL
TANGO[2]	4/322 (1.24%)	Proviral DNA genotype	24 48 96	0/4[c] 0/4 —	VL ≥50 c/mL
DOLULAM[13]	17/27 (62.96%)	RNA and proviral DNA genotypes	24 48 96	0/17 0/17 0/17	VL >50 c/mL
SALSA[3]	5/192 (2.60%)	Proviral DNA genotype	24 48 96	— 1/5 (20.00)[d] —	VL ≥40 c/mL

NR, not reported. [a]Cohort reference reporting the proportion with VF for individuals with M184V/I was used for analysis (n=45 individuals with M184V/I).[8] [b]Assumption: n=60 PWH with M184V/I were reported out of N=220 total PWH with available pre-switch genotype resistance data across 2 groups but not reported for DTG + 3TC specifically. Table n with M184V/I was calculated according to the proportion of PWH in the DTG + 3TC (n=174) vs other group (n=46). [c]Assumption: Week 24 was not reported, but reports described no VF to Week 48. [d]Assumption: VFs and discontinuations were not directly reported; study reported n (%) with VL <40 c/mL and TND, and here VF is assumed to be VL ≥40 c/mL.



- Overall low prevalence of M184V/I and of virological failure
- No reported cases of INSTIstreatmet-emergent mutations

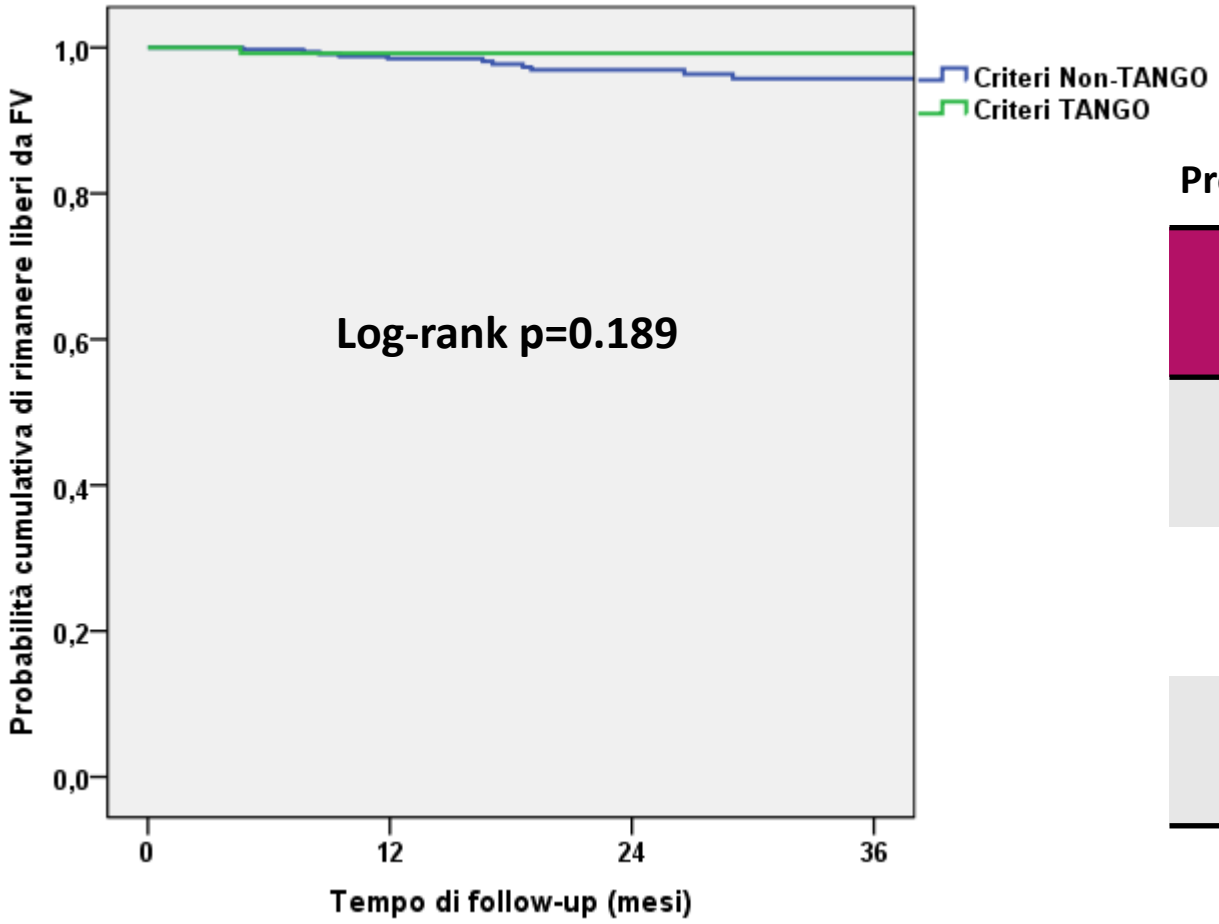
Shall we dance? Extending TANGO'S Results to Clinical Practice

- **Obiettivo**: confrontare l'efficacia di una terapia di mantenimento con 3TC+DTG in una popolazione selezionata di pazienti (secondo i criteri TANGO) vs una popolazione "non selezionata"

- **Metodi**
  - Popolazione ODOACRE;
  - Gruppo studio (almeno un criterio di esclusione TANGO): mutazioni a NRTI o InSTI, CDC C, insufficienza epatica, coinfezione epatite B, una viremia≧50 copie/ml negli ultimi 6 mesi, due viremie≧50 copie/mL o una singola≧200 copie/mL fra i 6 e i 12 mesi prima dello screening; storia di switch terapeutico per fallimento virologico;
  - Gruppo controllo: pazienti con tutti i criteri di arruolamento in TANGO;
  - Outcome: Differenza nel tempo al fallimento virologico (2 viremie consecutive≧50 copie/mL o una singola≧1000 copie/ml).

Variabili	Gruppo TANGO n=145	Gruppo Non-TANGO n=412	P value
Età (anni), Mediana (IQR)	49 (40-55)	53 (47-58)	**<0.001**
Sesso maschile	111 (76.6)	281 (68.2)	**0.058**
Caucasici	128 (88.3)	389 (94.4)	**0.023**
Fattore di rischio per HIV:			**<0.001**
- Eterosessuale	56 (38.6)	169 (41.0)	
- MSM	37 (25.5)	108 (26.2)	
- IDU	15 (10.4)	86 (20.9)	
- Altro/ignoto	37 (25.5)	49 (11.9)	
CDC Stadio C	20 (13.8)	62 (15.0)	0.854
Anti HCV positivi	25 (17.2)	101 (24.5)	0.076
Zenith HIV-RNA (log_{10} copie/mL), mediana (IQR)	4.95 (4.45-5.35)	4.89 (4.37-5.43)	0.780
Nadir CD4+ cell count (cells/mm^3), mediana (IQR)	278 (140-395)	212 (93-309)	**0.001**
Sottotipo HIV non-B	5 (3.4)	13 (3.2)	0.875
Anni dalla diagnosi di HIV, mediana (IQR)	9 (5-17)	18 (10-24)	**<0.001**
Anni di esposizione cumulativa a ARV, mediana (IQR)	7 (3-12)	13 (8-19)	**<0.001**
Mesi di soppressione virologica, mediana (IQR)	61.5 (31.5-103.1)	95.4 (51.5-126.9)	**<0.001**
Conta CD4+ basale (cell/mm^3), mediana (IQR)	692 (453-912)	660 (500-876)	0.826
Fallimento virologico precedente	/	223 (54.1)	NA
Precedente regime ARV:			**<0.001**
- 2NRTI + bPI	22 (15.2)	55 (13.3)	
- 2NRTI + NNRTI	87 (60.0)	55 (13.3)	
- 2NRTI + INI	32 (22.0)	57 (13.8)	
- Dual/Monoterapia	4 (2.8)	220 (53.4)	
- Altro	0 (0)	25 (6.2)	
Mutazione M184V all'ultimo GRT	/	45 (10.9)	NA
Motivo di switch a DTG+3TC:			**<0.001**
- Semplificazione/switch proattivo	49 (33.8)	106 (25.7)	
- Dislipidemia	5 (3.4)	87 (21.1)	
- Tossicità GI	13 (9.0)	31 (7.5)	
- Tossicità renale	13 (9.0)	18 (4.4)	
- Osteopenia/osteoporosi	20 (13.8)	7 (1.7)	
- Altra tossicità	10 (6.8)	10 (2.4)	
- Interazioni farmacologiche	6 (4.1)	30 (7.3)	
- Altro/ignoto	29 (20.1)	123 (29.9)	

Soppressione virologica nel tempo



Probabilità di soppressione virologica a 24, 48, 96 settimane

	Gruppo TANGO	Gruppo Non-TANGO
24 settimane	99.2% (97.7-100.0)	98.5% (97.2-99.8)
48 settimane	99.2% (97.7-100.0)	96.9% (94.9-98.9)
96 settimane	99.2% (97.7-100.0)	95.7% (93.2-98.3)

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)
  - 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:				na
TAMs			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**

Predittori di fallimento virologico

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”.

Virological outcomes with dolutegravir plus either lamivudine or two NRTIs as switch strategies: a multi-cohort study

- **Objectives** To compare the efficacy of dolutegravir plus lamivudine-dual therapy (DT) with that of dolutegravir plus 2 nucleoside reverse transcriptase inhibitors (NRTIs)-triple therapy (TT) as switch strategies.

- **Methods** A multi-center retrospective study from the ARCA database;
  - Inclusion criteria: HIV-positive, HBsAg-negative patients with viral suppression (HIV-RNA $\leq$50 copies/mL), switching to DT or TT;
  - The effect of DT versus TT on virological failure (VF, defined as two consecutive HIV-RNA >50 copies/mL or one HIV-RNA $\geq$200 copies/mL) was evaluated by multivariate Cox regression models, overall and after stratifying for the presence of NRTI resistance-associated mutations (RAMs).

Caratteristiche della popolazione alla baseline

Variable	TDF(TAF)/3TC(FTC) n= 118	ABC/3TC n= 306	3TC/DTG n= 204	p-value
Age (years)*	50 (45-54)	50 (42-56)	49 (40-56)	0.984
Male gender	85 (72.0)	214 (69.9)	160 (78.4)	0.102
Risk factor for HIV:				**<0.001**
- **Heterosexual**	49 (41.5)	127 (41.5)	88 (43.1)	
- **MSM**	38 (32.2)	102 (33.3)	90 (44.1)	
- **IDUs**	25 (21.2)	41 (13.4)	23 (11.3)	
- **Other/unknown**	6 (5.1)	36 (11.8)	3 (1.5)	
Anti-HCV seropositive status	22 (18.6)	53 (17.3)	21 (10.3)	**0.052**
CDC stage C	20 (17.0)	33 (10.8)	14 (6.9)	**0.018**
Nadir<=200 cell/μL	64 (54.2)	154 (50.3)	77 (37.8)	**0.003**
Zenith HIV-RNA>500,000 cp/mL	16 (13.6)	37 (12.1)	22 (10.8)	0.756
Time since HIV diagnosis (years)*	10 (4-20)	10 (6-17)	9 (5-15)	0.303
Cumulative exposure to antiretrovirals (years)	9 (3-17)	8 (4-14)	7 (4-11)	0.237
Antiretroviral therapy before switch:				**<0.001**
- **2NRTI+PI**	84 (71.2)	184 (60.1)	85 (41.7)	
- **2NRTI+NNRTI**	34 (28.8)	122 (39.9)	119 (58.3)	
Reason for switch:				**<0.001**
- **Proactive switch**	32 (27.1)	128 (41.8)	75 (36.8)	
- **Toxicity**	21 (17.8)	61 (19.9)	61 (29.9)	
- **DDIs**	3 (2.5)	7 (2.3)	13 (6.4)	
- **Low adherence**	12 (10.2)	6 (2.0)	0 (0.0)	
- **Other/unknown**	50 (42.4)	104 (34.0)	55 (27.0)	
Previous virological failure	10 (8.5)	37 (12.1)	22 (10.8)	0.562
Years of virological suppression*	3 (1-5)	4 (2-6)	4 (3-8)	**<0.001**
Baseline CD4 count <=400 cells/μL	34 (28.8)	58 (19.0)	27 (13.2)	**0.003**
CD4/CD8 < 0.8	59 (50.0)	126 (41.2)	58 (28.4)	**0.001**
B subtype	95 (80.5)	253 (82.7)	156 (76.5)	0.106
M184V/I at historical genotype	20 (17.0)	32 (10.5)	8 (3.9)	**<0.001**
Number of active NRTI (according to GSS):				**<0.001**
- **Fully-active backbone**	93 (78.8)	253 (82.7)	192 (94.1)	
- **At least potential low-level RAM to one NRTI in the regimen**	25 (21.2)	53 (17.3)	12 (5.9)	

Effetto totale della dual therapy sul fallimento virologico

Variable	HR (95% CI)	p-value	aHR (95% CI)	p-value
Dual therapy (versus triple)	0.50 (0.24-1.03)	0.061	0.58 (0.25-1.34)	0.200
Age:				
- < 40 years old	Ref		Ref	
- 40-<50	0.94 (0.48-1.87)	0.867	0.35 (0.14-0.86)	**0.023**
- ≥50	1.02 (0.42-2.52)	0.961	1.30 (0.47-3.61)	0.612
CDC stage C (versus others)	2.91 (1.42-5.94)	**0.003**	4.06 (1.55-10.64)	**0.004**
Cumulative exposure to antiretrovirals (years):				
- ≤3	Ref		Ref	
- >3-7	1.30 (0.39-4.30)	0.673	5.61 (1.37-23.03)	**0.017**
- >7-14	1.64 (0.52-5.16)	0.396	15.81 (3.74-66.93)	**<0.001**
- >14	3.15 (1.07-9.31)	**0.038**	35.82 (6.99-183.71)	**<0.001**
Reason for switch:				
- Proactive switch	Ref		Ref	
- Toxicity	1.21 (0.51-2.87)	0.667	0.94 (0.35-2.57)	0.907
- DDIs	3.16 (0.89-11.21)	0.075	3.30 (0.70-15.71)	0.133
- Low adherence	7.84 (2.94-20.96)	**<0.001**	5.10 (1.55-16.76)	**0.007**
- Other/unknown	1.28 (0.56-2.91)	0.558	1.68 (0.69-4.06)	0.251
Duration of virological suppression:				
≥4	Ref		Ref	
2-<4	0.98 (0.39-2.42)	0.959	1.27 (0.44-3.64)	0.654
≤2	2.65 (1.34-5.24)	**0.005**	5.33 (2.08-13.66)	**0.001**
CD4-to-CD8 ratio <0.8 (versus ≥0.8)	2.88 (1.32-6.25)	**0.008**	2.85 (1.18-6.86)	**0.020**
Nadir CD4 count ≤200 cells/ mm³ (versus >200 cells/mm³)	0.99 (0.53-1.84)	0.975	0.22 (0.09-0.53)	**0.001**
Zenith HIV-RNA (copies/mL):				
<100,000	Ref		Ref	
100,000-<500,000	1.54 (0.77-3.09)	0.220	1.97 (0.90-4.31)	0.091
≥500,000	2.00 (0.89-4.48)	0.094	3.74 (1.49-9.35)	**0.005**
Time since last genotypic resistance test (per 1 year more)	0.94 (0.86-1.01)	0.099	0.90 (0.82-0.98)	**0.015**

Note: the model was also adjusted for resistance mutations (at least one mutation conferring resistance to one NRTI in the backbone versus none), gender, risk factor for HIV infection, anti-HCV positive serostatus, previous therapy and viral subtype. **Abbreviations**: DDIs, drug-drug interactions. Numbers in bold represent statistically significant associations (at a p-value≤ 0.05).

Effetto del backbone in presenza o assenza di M184V/I

Table 4. HRs for VF according to type of backbone and presence versus absence of M184V/I

ART	Model 1, aHR (95% CI)	*P*	Model 2, aHR (95% CI)	*P*	Model 3, aHR (95% CI)	*P*	Model 4, aHR (95% CI)	*P*
Tenofovir/emtricitabine (M184V/I absent)	reference		**26.44 (2.35–297.15)**	**0.008**	1.82 (0.69-4.80)	0.229	**6.52 (1.09–38.82)**	**0.040**
Tenofovir/emtricitabine (M184V/I present)	**0.04 (0.00–0.43)**	**0.008**	reference		**0.09 (0.01–0.83)**	**0.036**	0.25 (0.02–3.82)	0.316
Abacavir/lamivudine (M184V/I absent)	0.55 (0.21–1.46)	0.229	**14.56 (1.20–176.80)**	**0.036**	reference		3.59 (0.58–22.20)	0.169
Abacavir/lamivudine (M184V/I present)	**0.15 (0.03–0.92)**	**0.040**	4.06 (0.26–62.85)	0.316	0.28 (0.05–1.72)	0.169	reference	
Lamivudine (M184V/I absent)	**0.24 (0.07–0.78)**	**0.018**	6.27 (0.47–84.28)	0.166	0.43 (0.18–1.05)	0.064	1.55 (0.21-11.25)	0.667
Lamivudine (M184V/I present)	5.20 (0.41–66.66)	0.205	**137.50 (4.24–4464.06)**	**0.006**	9.44 (0.79–112.40)	0.076	**33.88 (1.75–656.47)**	**0.020**

Each model was also adjusted for age, gender, risk factor for HIV infection, anti-HCV positive serostatus, CDC stage, cumulative exposure to antiretrovirals, previous therapy, reason for switch, duration of viral suppression at baseline, nadir CD4 count, zenith HIV-RNA, baseline CD4-to-CD8 ratio, viral subtype and time since last genotypic resistance test. Since HRs for covariates were similar to those reported in Table 2, results are not repeated in Table 4.
Numbers in bold represent statistically significant associations (at a *P* value ≤0.05).

Note: each model was also adjusted for age, gender, risk factor for HIV infection, anti-HCV positive serostatus, CDC stage, cumulative exposure to antiretrovirals, previous therapy, reason for switch, duration of viral suppression at baseline, nadir CD4 count, zenith HIV-RNA, baseline CD4-to-CD8 ratio, viral subtype and time since last genotypic resistance test. Since hazard ratios for covariates were similar to those reported in table 2, results were not repeated in table 3. Numbers in bold represent statistically significant associations (at a p-value≤ 0.05).

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

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

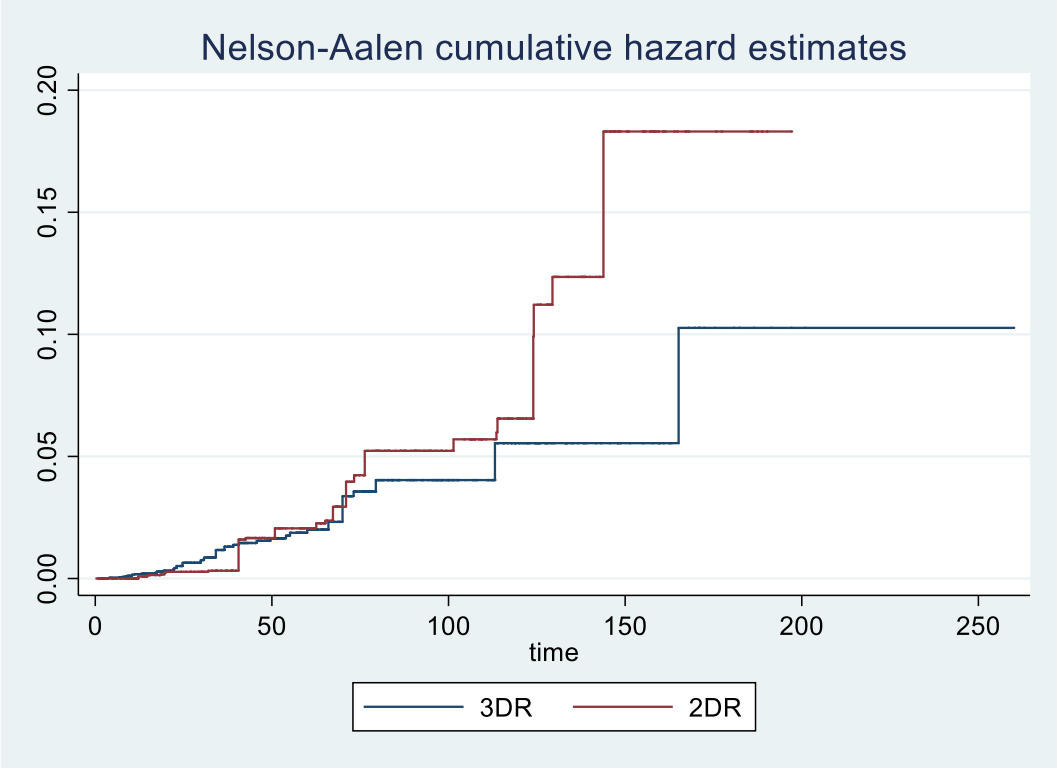
journal homepage: www.elsevier.com/locate/jgar

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

Risultati principali (1)



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.

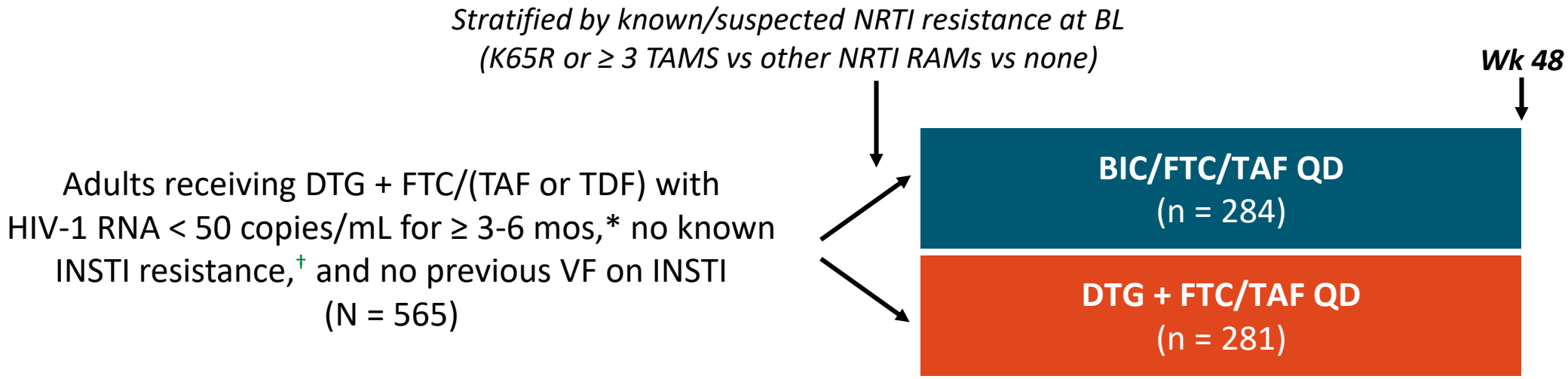
Outcome	Treatment	48 Weeks			72 Weeks		
		Cumulative incidence	90% CI		Cumulative incidence	90% CI	
Treatment failure	3DR	24.5%	22.2%	27.0%	37.1%	34.3%	40.0%
	2DR	15.8%	13.9%	17.9%	23.1%	20.8%	25.7%
Virological Failure	3DR	4.7%	3.5%	5.8%	6.5%	5.1%	8.0%
	2DR	4.2%	3.1%	5.3%	7.4%	5.8%	9.0%
Treatment Discontinuation	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

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

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



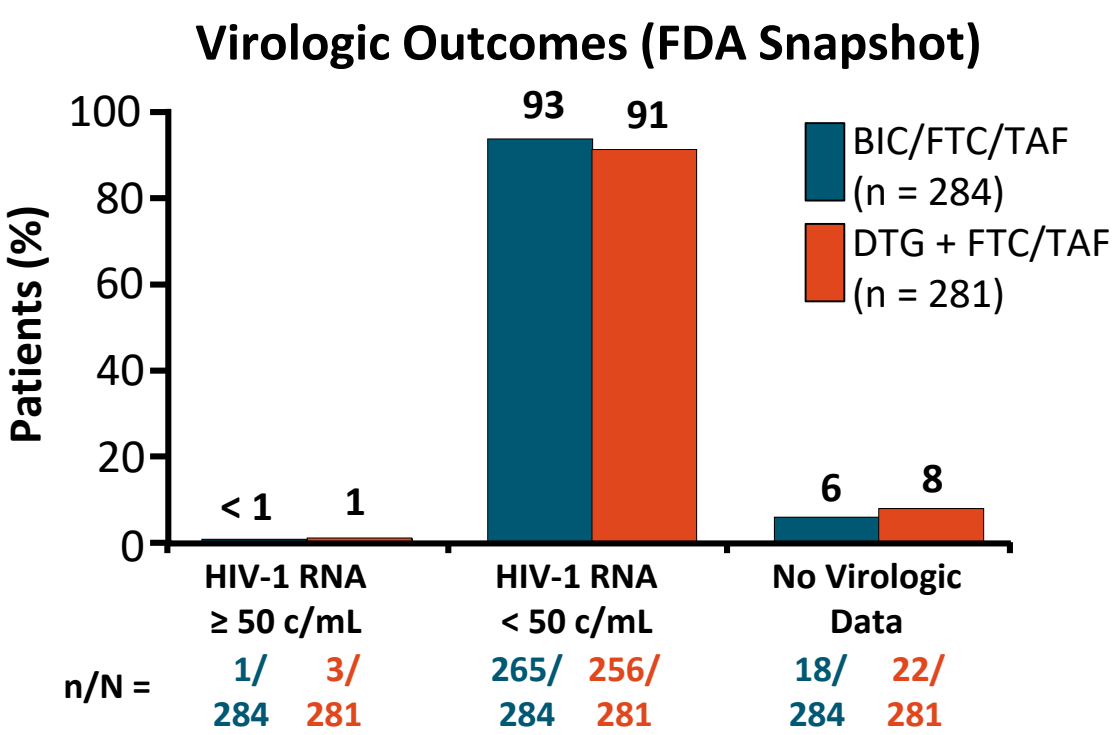
*3 mos if no known NRTI resistance mutations, 6 mos with known/suspected resistance.
†**Documented or suspected NRTI, NNRTI, or PI resistance permitted.**

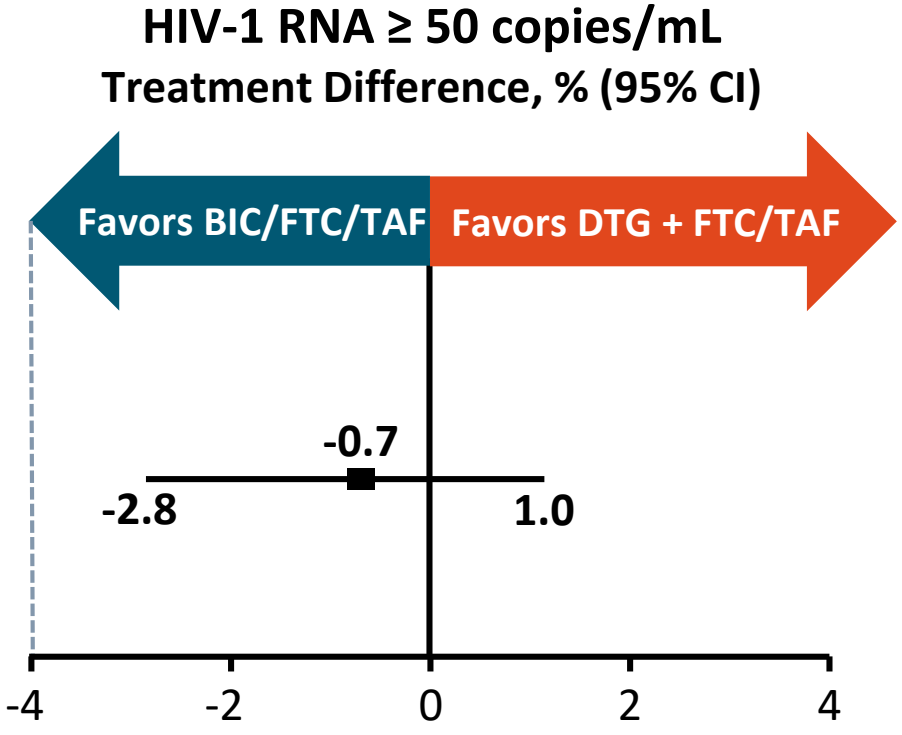
- Primary endpoint: HIV-1 RNA ≥ 50 c/mL at Wk 48 by FDA Snapshot algorithm
  - Noninferiority margin: 4%

Sax. Clin Infect Dis. 2020;[Epub].

Study 380-4030: Virologic Outcomes at Wk 48

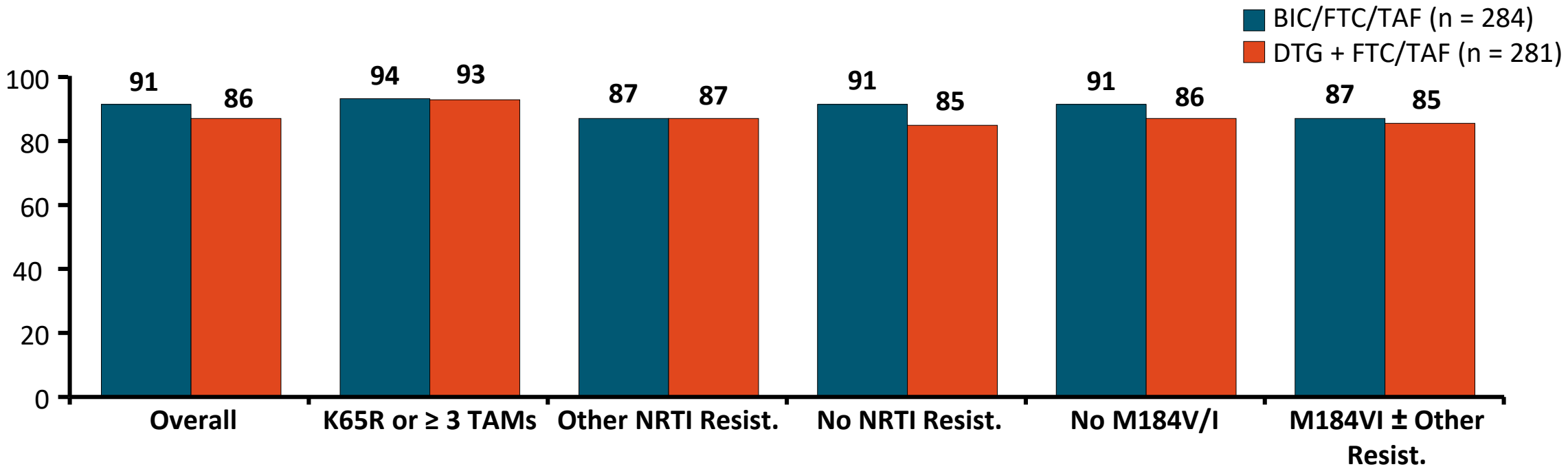
- Patients with viral suppression on stable triple DTG-based ART switched to BIC/FTC/TAF or continued DTG-based ART; documented or suspected NRTI, NNRTI, or PI resistance permitted
  - Preexisting NRTI resistance: 25% in BIC/FTC/TAF arm and 24% in DTG-based ART arm





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

Ruolo dei Long-acting

A COMBINATION OF VIRAL AND PARTICIPANT FACTORS INFLUENCE VIROLOGIC OUTCOME TO LONG-ACTING CABOTEGRAVIR + RILPIVIRINE: MULTIVARIABLE AND BASELINE FACTOR ANALYSES ACROSS ATLAS, FLAIR AND ATLAS-2M PHASE 3 STUDIES

- David A. Margolis[1], Jonathan M. Schapiro[2], Carlo Federico Perno[3], Daniel R. Kuritzkes[4], Romina Quercia[5], Parul Patel[1], Joseph W. Polli[1], Amy Cutrell[1], David Dorey[6], Yongwei Wang[7], Sterling Wu[8], Veerle van Eygen[9], Herta Crauwels[9], Susan L. Ford[10], Mark Baker[11], Christine Talarico[1], Marty St. Clair[1], Jerry Jeffrey[1], C. Thomas White[1], Simon Vanveggel[9], Rodica Van Solingen-Ristea[9], Kati Vandermeulen[9], William R. Spreen[1], Jan van Lunzen[12]

Multivariable Analysis: Four Factors Were Associated With an Increased Odds Ratio of CVF, Three Are Baseline Factors

Parameter	Final Model OR (95% CI), p-value*
RPV RAM(s) at baseline†	37.24 (8.44–>99), p<0.001
Log_2 of *post hoc* Week 8 RPV trough concentration	4.17 (1.59–11.11), p=0.004
Baseline HIV-1 subtype A6/A1	6.59 (1.82–25.26), p=0.005
BMI (kg/m^2) at baseline	1.13 (1.03–1.25), p=0.014
Pre-specified INSTI mutation (excluding L74I non-M mixture) at baseline‡	0.11 (0.01–0.83), p=0.029
Log_2 of *post hoc* Week 8 CAB trough concentration	Not significant
Female at birth	Not significant
Q8W regimen	Not significant
L74I (non-M mixture) INSTI polymorphism at baseline	Not significant
NNRTI RAM(s) (excluding RPV RAMs) at baseline‡	Not significant

*Odds ratios (ORs), 95% penalised profile CIs and penalised likelihood ratio p-values are provided. Covariates with p<0.05 in the final backwards elimination model are presented. CAB and RPV PK parameters were log_2-transformed; therefore, the corresponding ORs are per halving of each variable.
†Identified per the IAS–USA 2019 list of mutations.[1]
‡Identified per the IAS–USA list of mutations associated with resistance to bictegravir, CAB, dolutegravir, elvitegravir or raltegravir[1] and observed mutations during *in vitro* passage of dolutegravir or seen in a previous dolutegravir study (NCT01328041) in INSTI-experienced subjects.
BMI, body mass index (kg/m^2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; Q8W, every 8 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

1. Wensing AM, et al. *Top Antivir Med.* 2019;27(3):111–121.

Multivariable Analysis: A Combination of Baseline RPV RAMs*, Subtype A6/A1 or BMI ≥30 Modestly Increased the Risk of Virologic Failure

Factor	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
No baseline factors	3/732 (0.41)	694/732 (95)
Any one baseline factor	1/272 (0.37)	261/272 (96)
Two or more baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1039 (1.3) [0.67–2.13]	980/1039 (94) [92.74–95.65]

- Sensitivity and specificity of at least two baseline factors is optimal

	PPV	NPV	Sensitivity	Specificity
Two or more factors	26%	99.6%	69%	97.5%
Any one factor	<1%	98%	8%	74%

*Identified per the IAS–USA 2019 list of mutations.[1]
BMI, body mass index (kg/m2); CAB, cabotegravir; CI, confidence interval; CVF, confirmed virologic failure; LA, long-acting; NPV, negative predictive values; PPV, positive predictive values; RAM, resistance-associated mutation; RPV, rilpivirine.
1. Wensing AM, et al. *Top Antivir Med.* 2019;27(3):111–121.

Clinical Infectious Diseases

MAJOR ARTICLE

First Demonstration Project of Long-Acting Injectable Antiretroviral Therapy for Persons With and Without Detectable Human Immunodeficiency Virus (HIV) Viremia in an Urban HIV Clinic

Katerina A. Christopoulos,[1] Janet Grochowski,[1] Francis Mayorga-Munoz,[1] Matthew D. Hickey,[1] Elizabeth Imbert,[1] John D. Szumowski,[1] Samantha Dilworth,[2] Jon Oskarsson,[1] Mary Shiels,[1] Diane Havlir,[1] and Monica Gandhi[1]

[1]Division of HIV, ID, and Global Medicine, University of California–San Francisco, San Francisco, California, USA; and [2]Division of Prevention Science, University of California–San Francisco, San Francisco, California, USA

Characteristics of 39 Patients Initiating Long-Acting Injectable Cabotegravir and Rilpivirine With at Least 2 Follow-up Injections

Characteristic	N (%)
Age, median (IQR, range), years	46 (39–55, 31–68)
Gender	
Cis-gender man	35 (89.7)
Cis-gender woman	3 (7.7)
Transgender woman	1 (2.6)
Race/Ethnicity	
Black	8 (20.5)
Hispanic	10 (25.6)
White	15 (38.5)
Multiracial/Other	6 (15.4)
Housing	
Stable	23 (59.0)
Unstable	13 (33.3)
Homeless	3 (7.7)
Insurance	
Medicare	25 (64.1)
Medicaid	13 (33.3)
Healthy San Francisco (uninsured)	1 (2.6)
Current stimulant use	20 (54.1)
Antiretroviral regimen at referral	
TAF/FTC/BIC	15 (38.5)
TAF/FTC/DRV-c	12 (30.8)
ABC/3TC/DTG	4 (10.3)
Other DTG-containing regimen[a]	4 (10.3)
TDF/3TC/DOR	2 (5.1)
ELV-c containing regimen[b]	2 (5.1)
HIV VL ≥30 copies RNA/mL at time of referral	18 (46.2)
HIV VL ≥30 copies RNA/mL proximal to first injection	15 (38.0)
Log_{10} HIV VL of those with ≥30 copies RNA/mL at first injection, mean (standard deviation)	4.67 (1.16)
CD4 cell count/mm^{3c}, median (IQR)	
Those with VL ≥30 copies/mL	99 (51–299)
Those with VL <30 copies/mL	732 (364–883)
Attended a primary care visit in each 6-month period of the year prior to first injection	
Those with VL ≥30 copies/mL[d]	14 (93.3)
Those with VL <30 copies/mL	20 (83.3)

Risultati

- Between June 2021 and April 2022, 51 patient initiated LAI-ART, with 39 receiving at least 2 follow-up injections by database closure (median age, 46 years; 90% cisgender men, 61% non-White, 41% marginally housed, 54% currently using stimulants). Of 24 patients who initiated injections with viral suppression (median CD4 cell count, 706 cells/mm3), 100% (95% confidence interval [CI], 86%–100%) maintained viral suppression. Of 15 patients who initiated injections with detectable viremia (median CD4 cell count, 99 cells/mm3; mean log10 viral load, 4.67; standard deviation, 1.16), 12 (80%; 95% CI, 55%–93%) achieved viral suppression, and the other 3 had a 2-log viral load decline by a median of 22 days.

- In summary, in this small demonstration project, we found that patients with detectable viremia due to challenges adhering to oral ART can be successfully started on CAB/RPV-LA. Our data show early success in suppressing this group of patients on CAB/RPV-LA and in keeping patients with viral suppression suppressed. A longer period of follow-up and a larger cohort, along with other demonstration projects to examine the use of CAB/RPV-LA in hard-to-reach populations and qualitative assessments of acceptability, are needed.

Received: 18 March 2022 | Accepted: 12 July 2022
DOI: 10.1111/hiv.13370

ORIGINAL ARTICLE

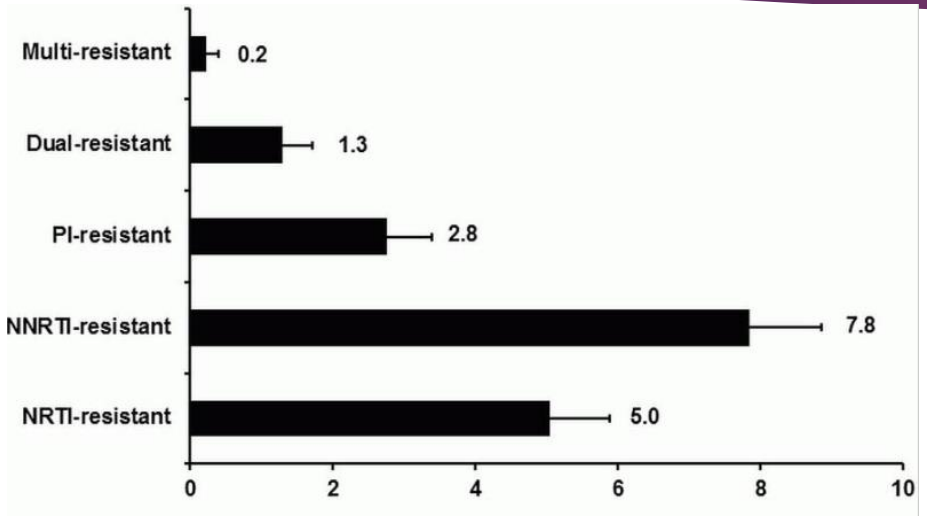
Compassionate use of long-acting cabotegravir plus rilpivirine for people living with HIV-1 in need of parenteral antiretroviral therapy

Ronald D'Amico[1] | Santiago Cenoz Gomis[2] | Riya Moodley[3] | Rodica Van Solingen-Ristea[4] | Bryan Baugh[5] | Erika Van Landuyt[4] | Veerle Van Eygen[4] | Sherene Min[1] | Amy Cutrell[1] | Caroline Foster[6] | Daniella Chilton[7] | Sabine D. Allard[8] | Annemiek Ruiter[3]

Through July 2020, 35 people living with HIV-1 had data available. The most frequent reason for compassionate use request was chronic nonadherence due to psychological conditions (n = 15). **Of 35 people living with HIV-1, 28 had detectable viremia (median viral load 60 300 copies/mL) and seven were virologically suppressed at programme entry**; *16/28 and 6/7 achieved or maintained virological suppression at data cutoff, respectively.* ***Seven people living with HIV-1 discontinued for incomplete virological response****, six with detectable viremia at initiation; six and four had new reverse transcriptase and integrase mutations at discontinuation, respectively.* **Six nonfatal serious adverse events were reported, two considered possibly treatment related**. Four deaths were reported; none were treatment related. One individual reported two pregnancies and continued LA dosing.

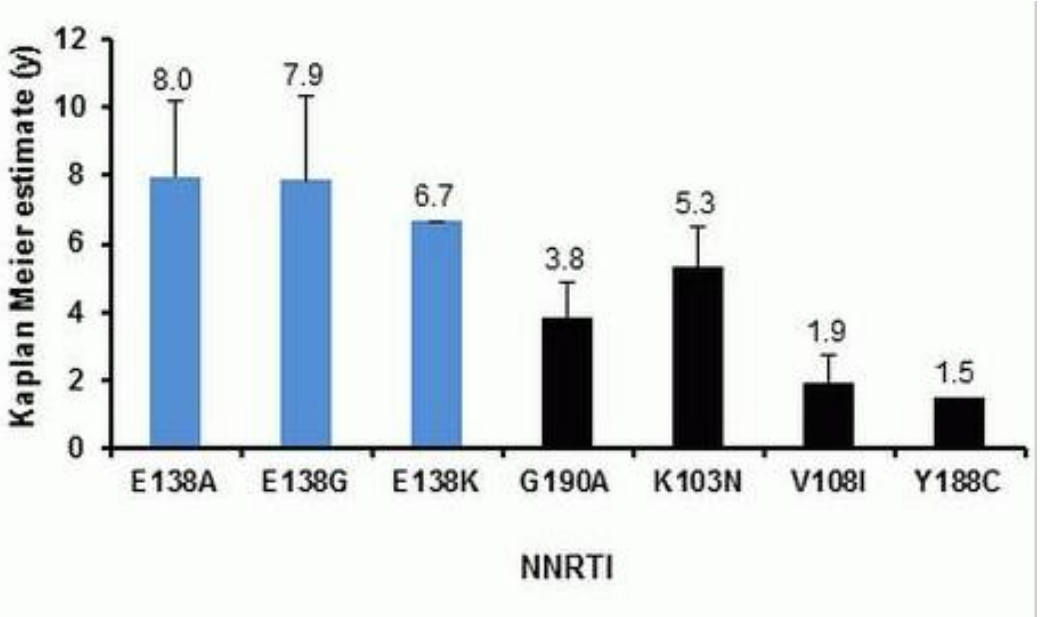
Characteristic	N = 35
Female at birth	20 (57)
Perinatally infected	11 (31)
Age, y	36 (20–67)
Body mass index, kg/m^2	21 (16–38)
Current AIDS diagnosis	23 (66)
No. of regimens before compassionate use	4 (1–10)
HIV-1 RNA ≥50 copies/mL	28 (80)
≥50 to 10 000	9
>10 000 to 50 000	4
>50 000 to 100 000	4
>100 000	11
CD4+ cell count, cells/mm^3	100 (3–918)
Initiation of injections without oral lead-in	12 (34)
Primary reason for compassionate use request, n	
Psychological[a]	15
Physical challenges[b]	8
Malabsorption	6
Dysphagia	3
Limited cognitive skills	3

Resistenze trasmesse a NNRTI



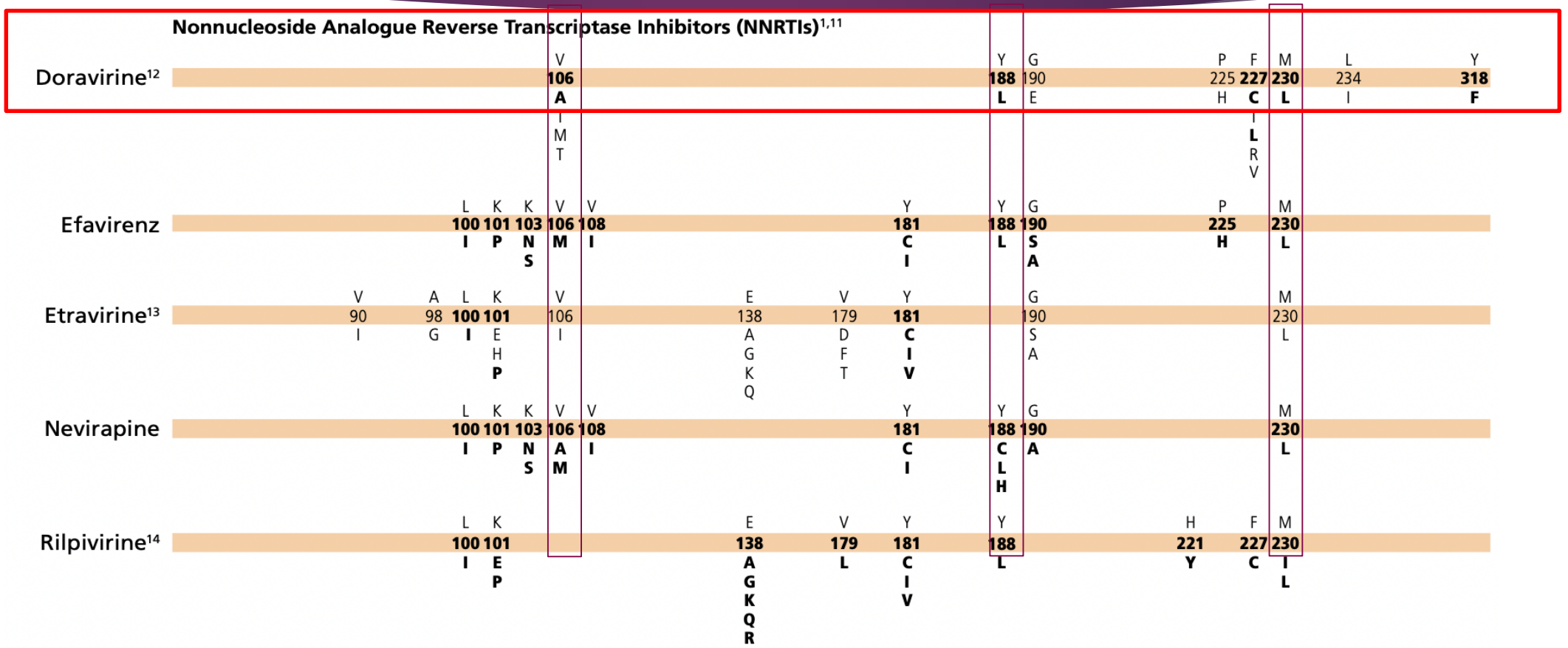
Prevalenza complessiva di TDRM dal 1996 al 2017

Persistenza di TDRM agli NNRTI nella coorte tedesca



Machnowska et al., 2019

Doravirina e mutazioni di resistenza



Resistance mutation list, IAS 2022

Impact of HIV-1 Resistance-Associated Mutations on Susceptibility to Doravirine: Analysis of Real-World Clinical Isolates

Ernest Asante-Appiah,[a] Johnny Lai,[b] Hong Wan,[a] Dongmei Yang,[b] Elizabeth Anne Martin,[a] Peter Sklar,[a] Daria Hazuda,[a] Christos J. Petropoulos,[b] Charles Walworth,[b] Jay A. Grobler[a]

Prevalence and DOR Susceptibility of Patient Samples Bearing Common NNRTI RAMs

Samples Bearing NNRTI Substitution*	Prevalence, n (%)†	DOR Median Fold-Shift‡	Interquartile Range
K103N	580, (14.3%)	1.25	0.81–2.42
V106I	218, (5.4%)	1.28	0.75–2.69
Y181C	214, (5.3%)	2.23	1.19–4.56
V108I	126, (3.1%)	2.15	1.29–5.46
K101E	123, (3.0%)	1.46	0.98–2.34
G190A	99, (2.4%)	1.82	0.96–4.07
E138K	56, (1.4%)	1.64	0.86–2.37
K103N + Y181C	53, (1.3%)	3.06	1.2–5.1

*NNRTI substitutions present in >50 isolates were evaluated
†Prevalence of isolates with substitution(s) (n) irrespective of presence of any NNRTI substitutions in total of clinical isolates (N = 4070)
‡Median fold-chain relative to wild-type with a fold-shift set to 1
DOR, doravirine; NNRTI, non-nucleotide reverse transcriptase inhibitor

Distribution of DOR Median Fold-Shifts Relative to Number of NNRTI RAMs In Patient Samples

NNRTI RAMs in Sample	Median Fold-Shift	Interquartile Range	Number of Samples, n	Prevalence, n/N (%), (N = 4070)	P-value‡
1	0.9	0.61–1.31	953	23.41	0.07
2	1.27	0.76–2.41	398	9.78	<0.0001
3	2.27	1.21–7.67	219	5.38	<0.0001
4	3.03	1.37–13.24	108	2.65	<0.0001
≥5	5.57	2.44–33.64	59	1.45	<0.0001

‡p-value from the Man-Whitney U to test whether a randomly selected fold-shift from a group of X number of RAMs is greater than or less than a randomly selected fold-shift from the group with any RAMs except X.
NNRTI, non-nucleotide reverse transcriptase inhibitor; RAM, resistance-associated mutation

TABLE 5 Proportion of NNRTI-resistant clinical isolates that are susceptible to other NNRTIs

	Percentage of resistant samples susceptible to other NNRTIs, %				
NNRTI	Doravirine-resistant[a]	Efavirenz-resistant	Etravirine-resistant	Nevirapine-resistant	Rilpivirine-resistant
Doravirine-susceptible[a]		62.2	44.7	65.8	45.0
Efavirenz-susceptible	17.1		31.0	18.7	28.1
Etravirine-susceptible	45.2	68.8		65.0	24.4
Nevirapine-susceptible	9.3	1.6	6.0		8.7
Rilpivirine-susceptible	31.9	59.4	5.6	57.4	

[a]A doravirine cutoff 3-fold was used for this comparison.
NNRTI, nonnucleoside reverse transcriptase inhibitor.

Observational Study

Medicine®

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Real life use of dolutegravir doravirine dual regimen in experienced elderly PLWH with multiple comorbidities and on polypharmacy

A retrospective analysis

Maria Mazzitelli, MD[a,b,*], Lolita Sasset, MD[a], Davide Leoni, MD[a], Cristina Putaggio, MD[a], Anna Maria Cattelan, MD[a]

Study design	Retrospective, observational, single-center cohort study in Italy
Subjects included	Patients aged >50 years with multimorbidity and polypharmacy who were treated with DOR + DTG and followed up for 3 months (N=18)
Assessments	Virological failure (3 months), metabolic parameters, renal function

Patient Characteristics

Variable	N=18
Mean age, years ± SD	61.3 ± 7.6
Male, n (%) Female, n (%)	13 (72.2) 5 (27.8)
Mean length of HIV disease, years ± SD	23 ± 8.5
Previous experience of AIDS events, n (%)	9 (50)
Risk factors for HIV infection, n (%) IDU Unprotected sex with men	 8 (44.4) 6 (33.3)
Severe polypharmacy, n (%)	5 (27.8)

Variable	N=18
Most frequent comorbidities,* n (%) Dyslipidemia Hypertension Depression	 16 (88.8) 14 (77.7) 7 (38.9)
Reason for switch,† n (%) DDI‡ Simplification Toxicity High CV and metabolic risk Virological failure	 8 (50) 11 (69) 4 (25) 13 (72.2) 2 (13)
Regimen before switch, n (%) INSTI + 2NRTI or NRTI NNRTI + NRTI PI-containing regimen	 4 (22) 2 (11) 12 (67)

Results

Parameter	Before switch	After switch	P-value
Undetectable HIV RNA, n (%)	15 (88.2)	17 (100)	-
Mean $CD4^+$ cell count, cell/mm^3 ± SD	607 ± 240	629 ± 232	0.37
Mean cholesterol, mmol/L ± SD	5.1 ± 3.3	4.8 ± 1.4	0.1
Mean HDL, mmol/L ± SD	1.5 ± 0.7	1.1 ± 0.4	0.75
Mean LDL, mmol/L ± SD	3.1 ± 1.0	2.9 ± 1.1	0.49
Mean TGs, mmol/L ± SD	1.41 ± 0.7	1.5 ± 0.7	0.2
Mean body weight, kg ± SD	75.2 ± 11.6	73.1 ± 11.6	<0.01
Mean waist circumference, cm ± SD	98.1 ± 0	95.9 ± 9.8	<0.01
Mean BMI, kg/m^2 ± SD	25.4 ± 3.2	24.7 ± 3.3	<0.01
Creatinine level, µmol/L ± SD	86.1 ± 22	90.7 ± 23.4	0.04
Mean eGFR, mL/min ± SD	79.4 ± 21	75.2 ± 20.9	0.03

- There were significant reductions in BMI, body weight, and waist circumference after switching to DOR + DTG compared with pre-switch measurements
- A significant increase in serum creatinine (p=0.04) and a significant decrease in eGFR (p=0.03) were also observed
- There was no significant change in $CD4^+$ T cell count after switching to DOR + DTG
- Lipid and fasting glucose values did not change significantly from baseline

Conclusioni

- Nel paziente con esperienze di trattamento non esiste il concetto di "One size fits all";
- Il raggiungimento e mantenimento del successo virologico, nonostante le terapie innovative, continua a dipendere dai dati viro-immunologici e dalla storia clinica del paziente;
- La selezione del paziente in base a queste caratteristiche, nonché a caratteristiche difficilmente valutabili retrospettivamente (es. aderenza) rimane un fattore cruciale per determinare la terapia migliore per il singolo paziente.

Grazie per l'attenzione!