Clinical experience with Doravirine in dual-therapy versus triple-HAART: therapeutic efficacy and impact on metabolic profile

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Background

-Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial; Jean-Michel Molina et al., The Lancet 2020, https://doi.org/10.1016/S2352-3018(19)30336-4

-Changes in Metabolic Profile in PLWHIV Switching to Doravirine-Based Regimen; Iannone V. et al., Viruses 2023, https://doi.org/10.3390/v15051046;

-Doravirine: its role in HIV treatment; Alexander J et al., *Current Opinion in HIV and AIDS 2021, DOI:* 10.1097/COH.0000000000000709;

-Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain; Kai Juhani Kauppinen et al., AIDS 2022.

Data from San Paolo Doravirine Cohort

Objective

Our study aims to analyse EFFICACY and IMPACT ON METABOLIC PROFILE of doravirine-based regimens in a cohort of cART-experienced patients, comparing its use in dual-therapy vs triple-HAART NRTI-based.

Population

All cART-experienced patients starting a regimen containing doravirine at San Paolo Hospital, Milan, were included.

Outcomes

Virological failure (VF) = two subsequent HIV-RNA>50cp/ml or a single HIV-RNA>400cmL
Therapeutic failure (TF) = the first of two events: virological failure or therapy interruption fp/or any reason
Metabolic: the change in lipid profile and in the prevalence of patients with LDL below their CV-related target after switch

Statistical analysis

Demographic, HIV and comorbidities data were collected: metabolic syndrome was defined by at least three of the following: 1. waist circumference >102-88cm; 2. triglycerides≥150mg/dL; 3. HDL≤40-50mg/dL; 4. fasting glucose≥100mg/dL; 5. blood pressure ≥130/85mmHg (AHA/NHLBI definition).

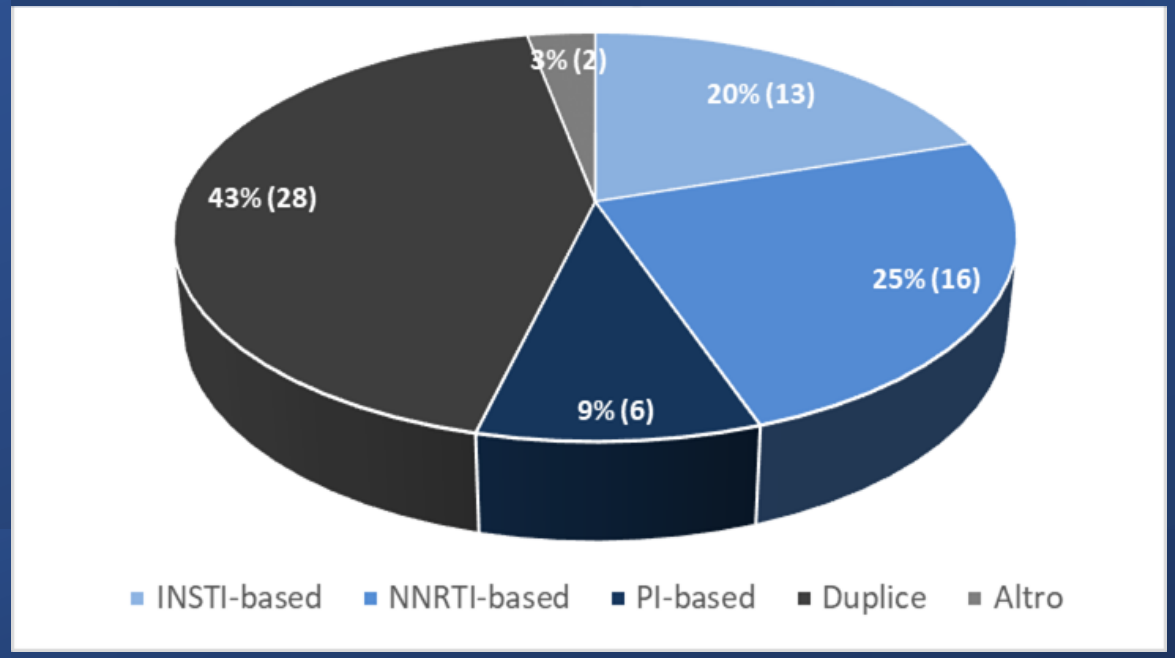
Lipids data (total cholesterol, HDL and LDL) were collected at switch (baseline) and after six months, change from baseline was analysed by Wilcoxon for paired test; p value<0.05 was considered significant.
CV risk SCORE and the individual target of LDL were calculated according to ESC/EAS Guidelines score for the management of dyslipidaemia.

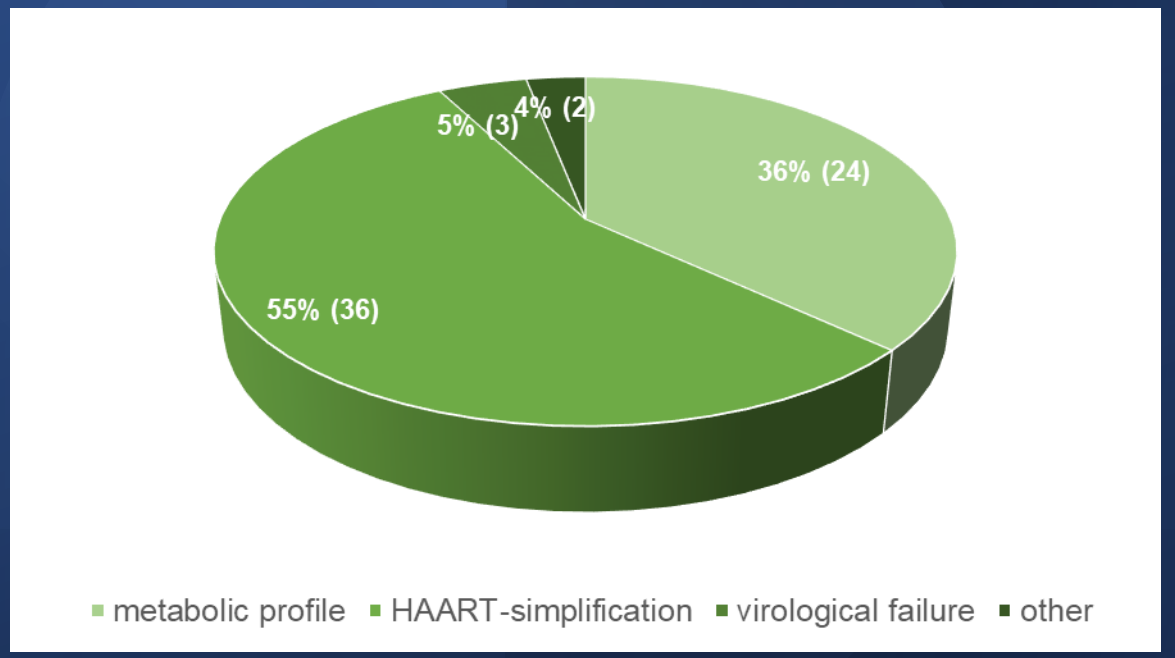
Virological failure and therapeutic failure were evaluated by Kaplan-Meier curves.

Demographic characteristics of Doravirine cohort (18 Delstrigo; 8 TAF/FTC/DOR; 39 Dual-Therapy)

	All (65)	Dual-therapy (39)	Triple-HAART (26)	P
Age, median (IQR)	55 (51-60)	59 (55-62)	50 (45-55)	<0.0001
Female, n (%)	26 (40)	21 (58)	5 (19)	0.005
AIDS, n (%)	17 (27)	11 (31)	6 (23)	0.5
ART years, median (IQR)	15 (10-22)	17.5 (13-23)	13 (10-18)	0.05
Previous virological failure with mutations, n (%)	19 (29)	15 (38)	4 (15)	0.04
CD4+ at switch, cell/ul median (IQR)	680 (471-845)	714 (460-1001)	672 (502-740)	0.4
Undetectable VL at switch, n (%)	56 (86)	33 (85)	23 (88)	0.6
BMI≥30, n (%)	15 (24)	10 (26)	5 (22)	0.7
Diabetes, n (%)	10 (15)	6 (15)	4 (15)	0.9
Hypertension, n (%)	27 (42)	17 (45)	10 (38)	0.5
Metabolic-Syndrome, n (%)	23 (36)	16 (43)	7 (26)	0.18

Previous HAART regimens and reasons for switch



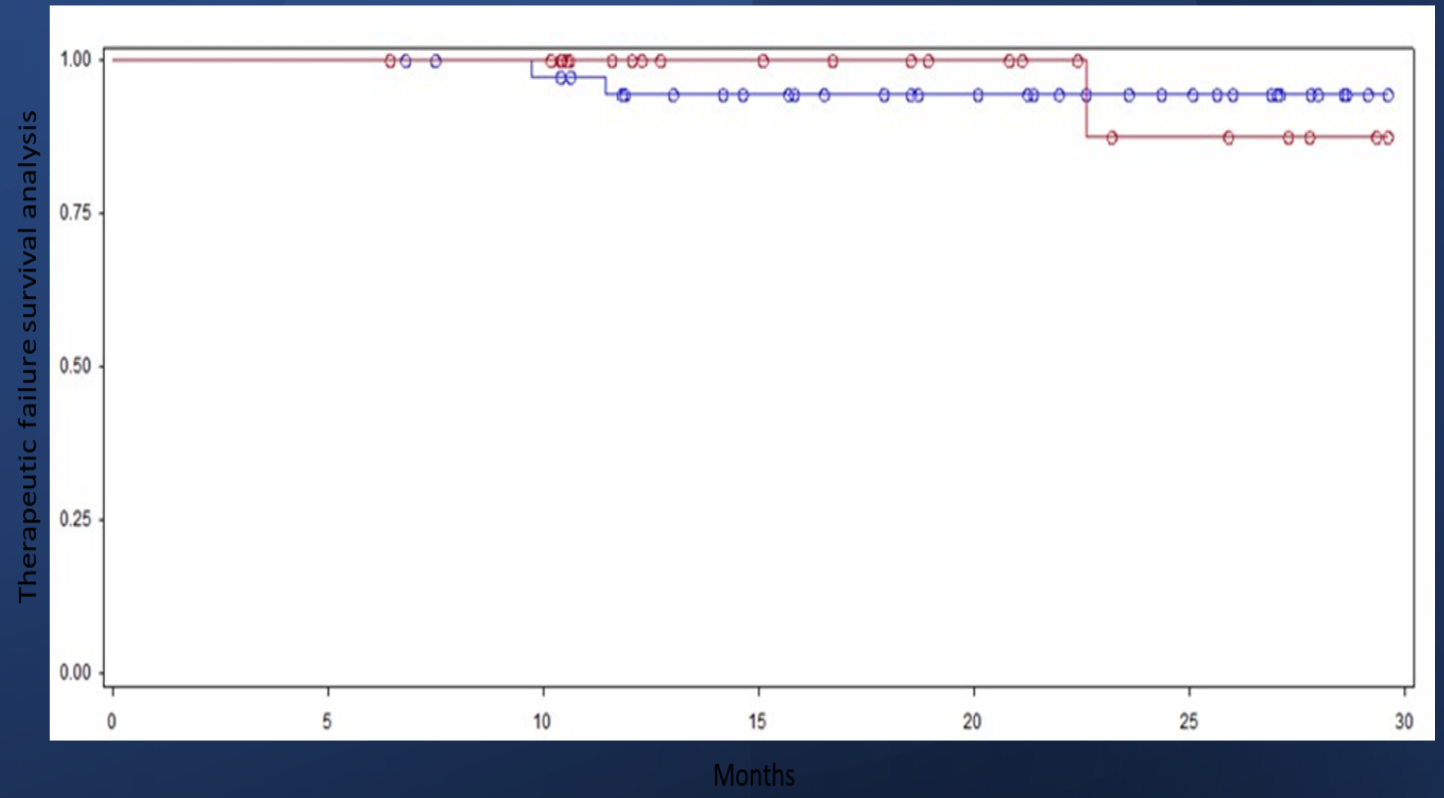


Treatment failure (TF)

The probability of TF at 12 months was 3.5% (IC 95% 0%-8.3%):
-two patients interrupted for adverse events (intolerance and allergy) and one patient for viral blip.

No virological failure occurred.

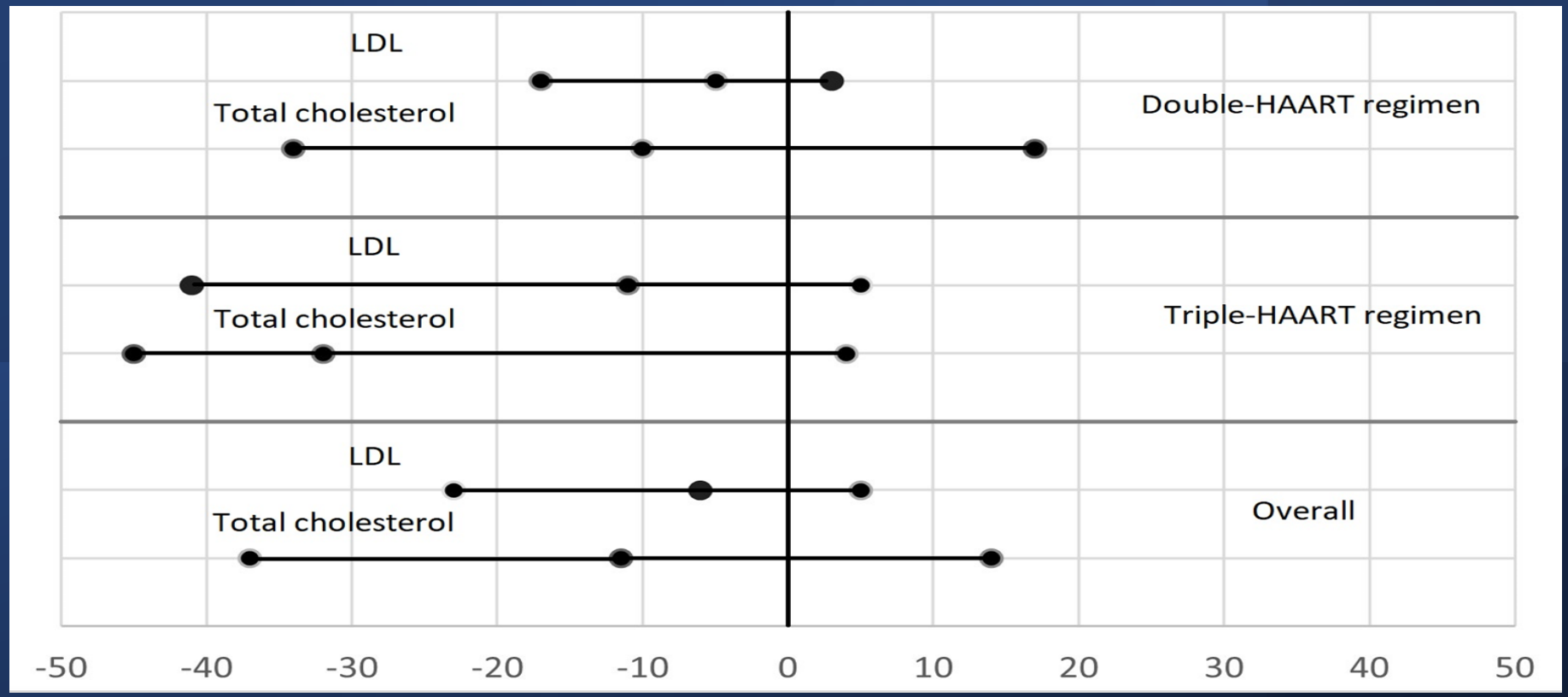
There was no difference in the risk of TF according to the type of regimen: dual vs triple-HAART



Dual-therapy= blue line
Triple-therapy_red line

Change in lipid profile after 6 months

Overall population [Δ total-col= -11.5mg/dL (IQR+14; -37) p=0.006; Δ LDL-col= -6mg/dL (IQR+5; -23) p=0.02]
Triple-HAART [Δ total-col= -32mg/dL (IQR+4; -45) p=0.04; Δ LDL-col= -11mg/Dl (IQR+5; -41) p=0.05]
Dual-regimen [Δ total-col= -10mg/dL (IQR+17; -34) p=0.08; Δ LDL-col= -5mg/Dl (IQR+3; -17) p=0.2]

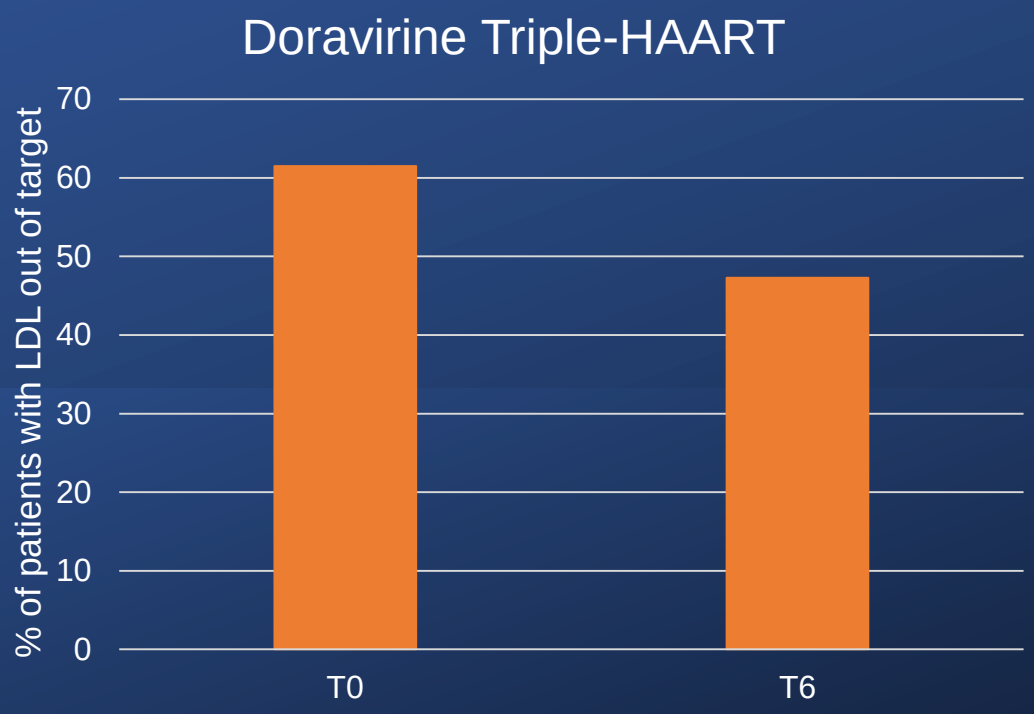


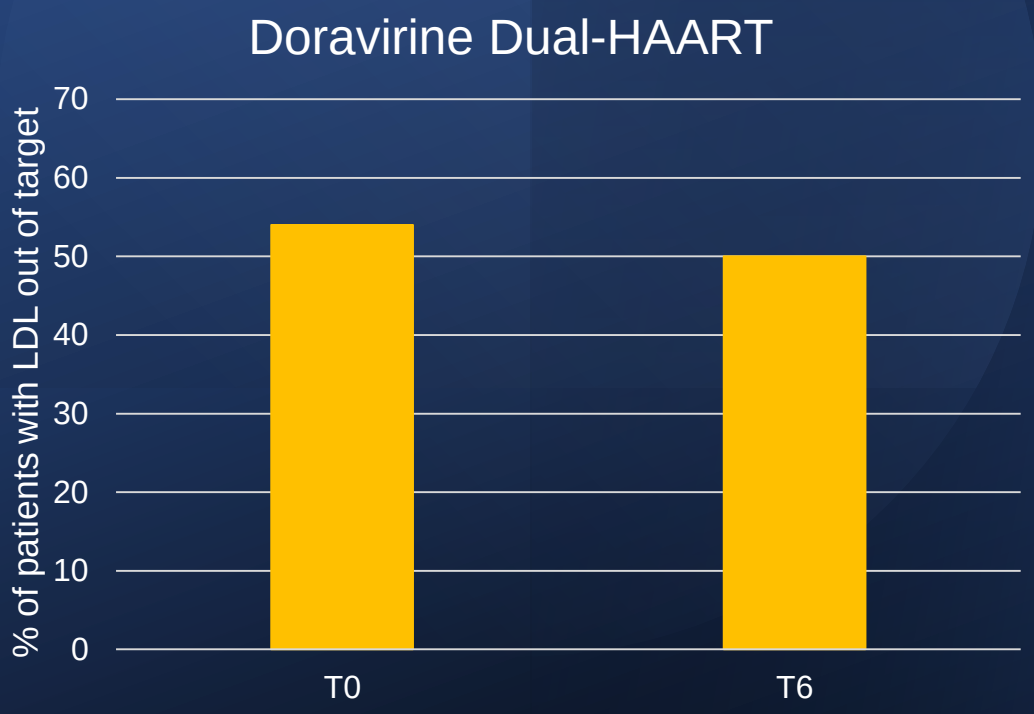
Change in lipid profile: impact on clinical outcome

-For each patient the CV risk score has been estimated by ESC/EACS Guidelines

-According to the CV risk category a different target of LDL has been defined

-The prevalence of patients with «LDL OUT-OF-TAGET» has been estimated at T0 and T6 after switch to DORAVIRINE





Future directions

Going on with data collection of the «DORAVIRINE cohort»: collect data on all patients switching to a DORAVIRINE based-regimens in order to monitor:

-Virological and therapeutic efficacy

-Metabolic changes (lipids, body weight, antropometric measures and HOMA-IR)

Delstrigo in switch-strategy in PLWH with high CV risk

Clinical Proposal of a Prospective Observational Study

Population

-Inclusion criteria: experienced patients virologically suppressed + one of the following:
- metabolic syndrome
- high-moderate cardiovascular risk and LDL>=130mg/dL

-Exclusion criteria:
- eGFR<70ml/min with proteinuria >400mg/24h
- osteopenia/osteoporosis

Outcomes

-Virological and therapeutic efficacy

-Metabolic:
- lipid changes after 6-12-24 months
- prevalence of patients with LDL out-of-CV-target after 6-12-24 months
- Change in body weight and antropometric measures after 12-24 months
- Change in HOMA-IR after 12-24 months

-Bone and kidney toxicities:
- eGFR after 6-12-24 months; proteinuria after 12 and 24 months
- DEXA after 24 months

	T0	T6	T12	T24
CD4	X	X	X	X
HIV-RNA	X	X	X	X
Creatininemia	X	X	X	X
Esame urine	X	X	X	X
Proteinuria 24h	X		X	X
DEXA	X			X
Profilo lipidico	X	X	X	X
Glicemia	X	X	X	X
Insulinemia	X		X	X
Circonferenza addominale	X	X	X	X
Peso corporeo	X	X	X	X
Pressione arteriosa	X	X	X	X

Critical issues

-The need of larger cohorts to investigate efficacy and metabolic benefits of DORAVIRINE in real life cohort

-Collaborations with other Centers or Cohorts (CISAI – DODO Cohort)