9° WORKSHOP NAZIONALE CISAI

PREVENZIONE
E GESTIONE
DELLE CO-MORBIDITÀ
ASSOCIATE
ALL'INFEZIONE DA HIV

Dolutegravir-based antiretroviral regimens for HIV liver transplant patients in real life

Dario Cattaneo[1,2], Salvatore Sollima[3], Paola Meraviglia[3], Laura Milazzo[3], Davide Minisci[3], Marta Fusi[2], and Cristina Gervasoni[1,3]

[1]Gestione Ambulatoriale Politerapie (GAP) outpatient clinic, ASST Fatebenefratelli Sacco, Milano, Italy; [2]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco, Milan, Italy ; [3]Department of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy

FONDAZIONE ASIA
CISAI Coordinamento Italiano Studio Allergie e Infezione da HIV

BARI | 21-22 MARZO 2019
CENTRO CONGRESSI PALACE HOTEL BARI

Background

- ✓ Liver transplantation is now considered a safe procedure in selected HIV-infected patients with end-stage hepatic diseases thanks to the advent of potent antiretroviral therapies (ART)

- ✓ Potential concerns related to drug-drug interactions (DDIs) between immunosuppressive agents and ART have been overcome by the availability of booster-free, integrase inhibitor-based regimens

Background

Immunosuppressant	metabolism
Tacrolimus	CYP3A4, CYP3A5
Cyclosporine	CYP3A4, CYP3A5
Sirolimus	CYP3A4, CYP3A5
Everolimus	CYP3A4, CYP3A5
Micophenolate	UGT1A9, UGT2B7
Azathioprine	Thiopurine methyltransferase
Glucocorticoids	CYP3A4, CYP3A5

Antiretroviral	metabolism
Raltegravir	UGT1A1
Elvitegravir/cobicistat	CYP3A4, CYP3A5
Dolutegravir	UGT1A1 (90%), CYP3A (10%)
Bictegravir	UGT1A1 (50%), CYP3A (50%)

Background

- ✓ Dolutegravir may represent an attractive option for HIV-infected liver transplant recipients because of minimal dependence to CYP3A-mediated metabolism, high potency and high genetic barrier, as well as for longer half-life compared with raltegravir, allowing once daily administration* and reduced pill burden

- ✓ However, only a few, scanty data are available on the use of dolutegravir in real life transplant settings, involving exclusively case reports of kidney transplant recipients

*the QD formulation of raltegravir is not available yet in all countries

Objective of the study

- ✓ In the present study, we sought to investigate the usefulness of dolutegravir-based maintenance antiretroviral therapies in HIV-infected liver transplant patients regularly followed in the ASST Fatebenefratelli Sacco University Hospital

Methods

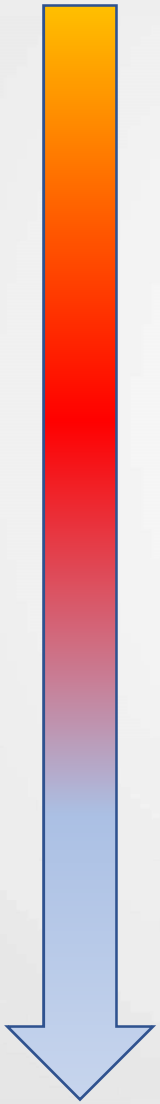
- ✓ The database of our Infective Diseases Clinics (with 2300 HIV-infected patients on active follow-up) was investigated in search for HIV, liver transplant recipients on:
  - Calcineurin inhibitor-based immunosuppression;
  - Treated with dolutegravir for at least one month;
  - At least one year of follow-up after dolutegravir introduction/withdrawal;
  - Available data on therapeutic drug monitoring of immunosuppressive trough concentrations

Demographic characteristics

Demographics	Data
HIV-positive, Liver Tx	9 (8 men, 1 woman)
Mean age	57 ± 3 years
Reasons for liver Tx	- Hepatocellular carcinoma (n=2) - Hepatitis C (n=5) - HBV/δ related cirrhosis (n=2)
Time to Tx (last F.U)	5.8 ± 3.2 years
Immunosuppressive therapy	- Tacrolimus (n=4) - Cyclosporine (n=5) - Everolimus (n=2)
Antiretroviral therapy	- TDF/FTC/raltegravir (n=5) - TDF/FTC/dolutegravir (n=1) - TDF/FTC/fosamprenavir (n=1) - ABC/3TC/raltegravir (n=1) - Raltegravir/darunavir/r (n=1)

Tx: transplantation, F.U.: follow-up: TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; ABC: abacavir; 3TC: lamivudine; r: ritonavir

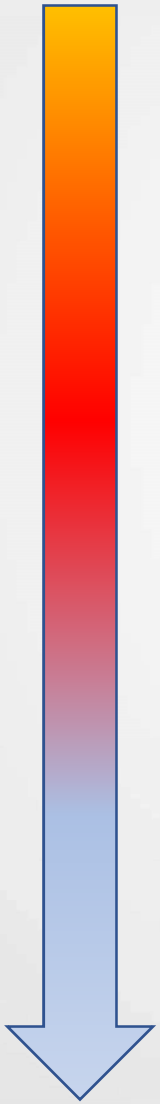
Time-course of ARV therapy



Time 0: **Liver Tx (n=9)**

- TDF/FTC/raltegravir (n=5)
- TDF/FTC/dolutegravir (n=1)
- TDF/FTC/fosamprenavir (n=1)
- ABC/3TC/raltegravir (n=1)
- Raltegravir/darunavir/r (n=1)

Time-course of ARV therapy



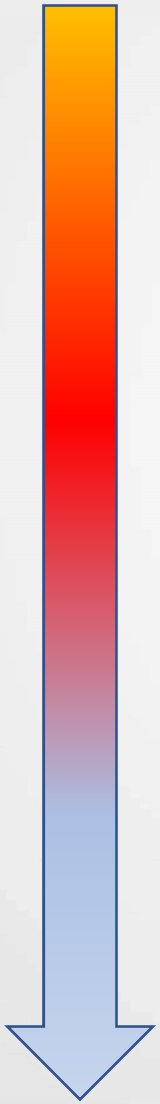
Time 0: **Liver Tx (n=9)**

- TDF/FTC/raltegravir (n=5)
- TDF/FTC/dolutegravir (n=1)
- TDF/FTC/fosamprenavir (n=1)
- ABC/3TC/raltegravir (n=1)
- Raltegravir/darunavir/r (n=1)

Simplification: **4.6 ± 3.5 years**

- TAF/FTC/dolutegravir (n=6)
- TDF/FTC/dolutegravir (n=1)
- Darunavir/cobi/dolutegravir (n=1)
- ABC/3TC/dolutegravir (n=1)

Time-course of ARV therapy



Time 0: **Liver Tx (n=9)**

- TDF/FTC/raltegravir (n=5)
- TDF/FTC/dolutegravir (n=1)
- TDF/FTC/fosamprenavir (n=1)
- ABC/3TC/raltegravir (n=1)
- Raltegravir/darunavir/r (n=1)

Simplification: **4.6 ± 3.5 years**

- TAF/FTC/dolutegravir (n=6)
- TDF/FTC/dolutegravir (n=1)
- Darunavir/cobi/dolutegravir (n=1)
- ABC/3TC/dolutegravir (n=1)

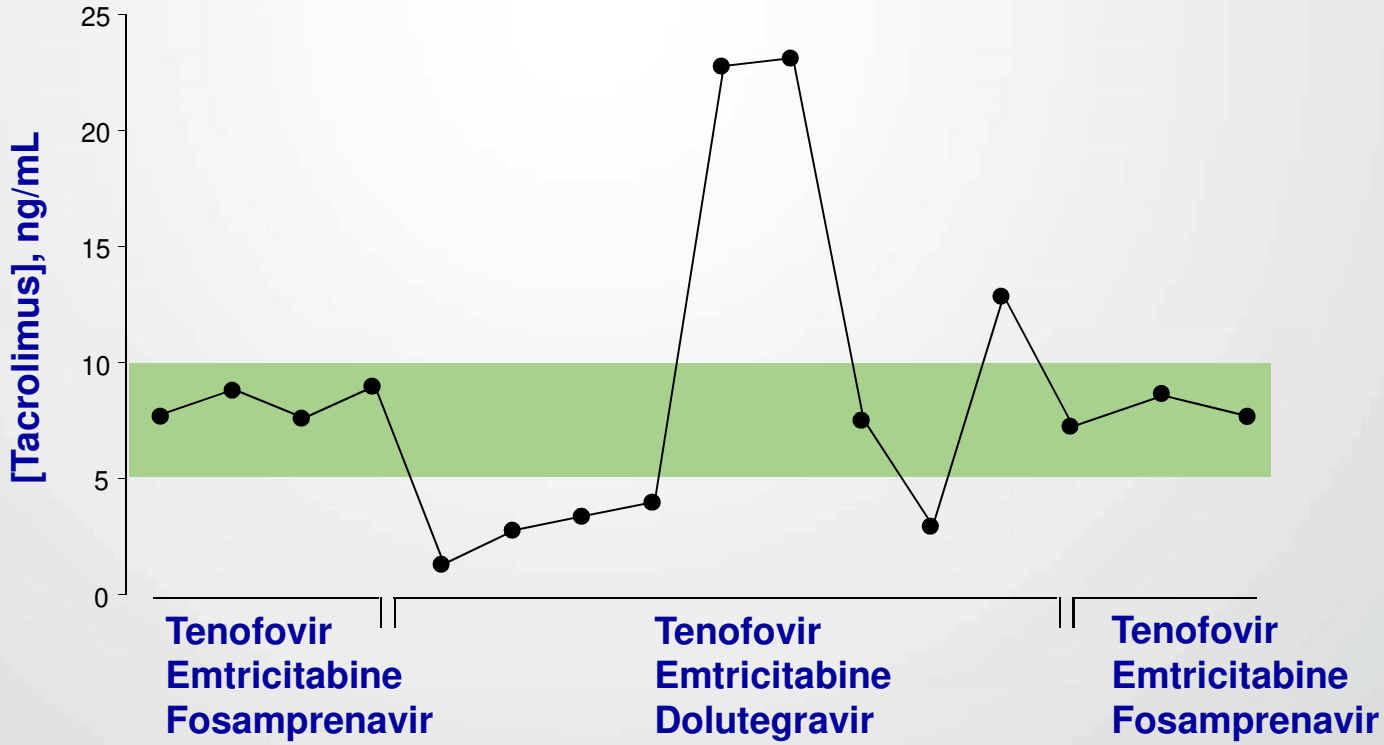
Last follow-up: **5.8 ± 3.2 years**

- TAF/FTC/dolutegravir (n=5)
- TDF/FTC/fosamprenavir (n=1)
- TAF/FTC/raltegravir (n=2)
- ABC/3TC/raltegravir (n=1)

4 out of the 9 patients returned to previous ART

Patient 1

	Before switch to dolutegravir	During the switch to dolutegravir
Serum AST (IU/L)	38	78 (+105%)
Serum ALT (IU/L)	19	100 (+426%)



Dolutegravir: Clinical and Laboratory Safety in Integrase Inhibitor–Naive Patients

Table 4. Summary of grade 2 to 4 post-baseline–emergent liver chemistry toxicities for individuals coinfected with HBV and/or HCV

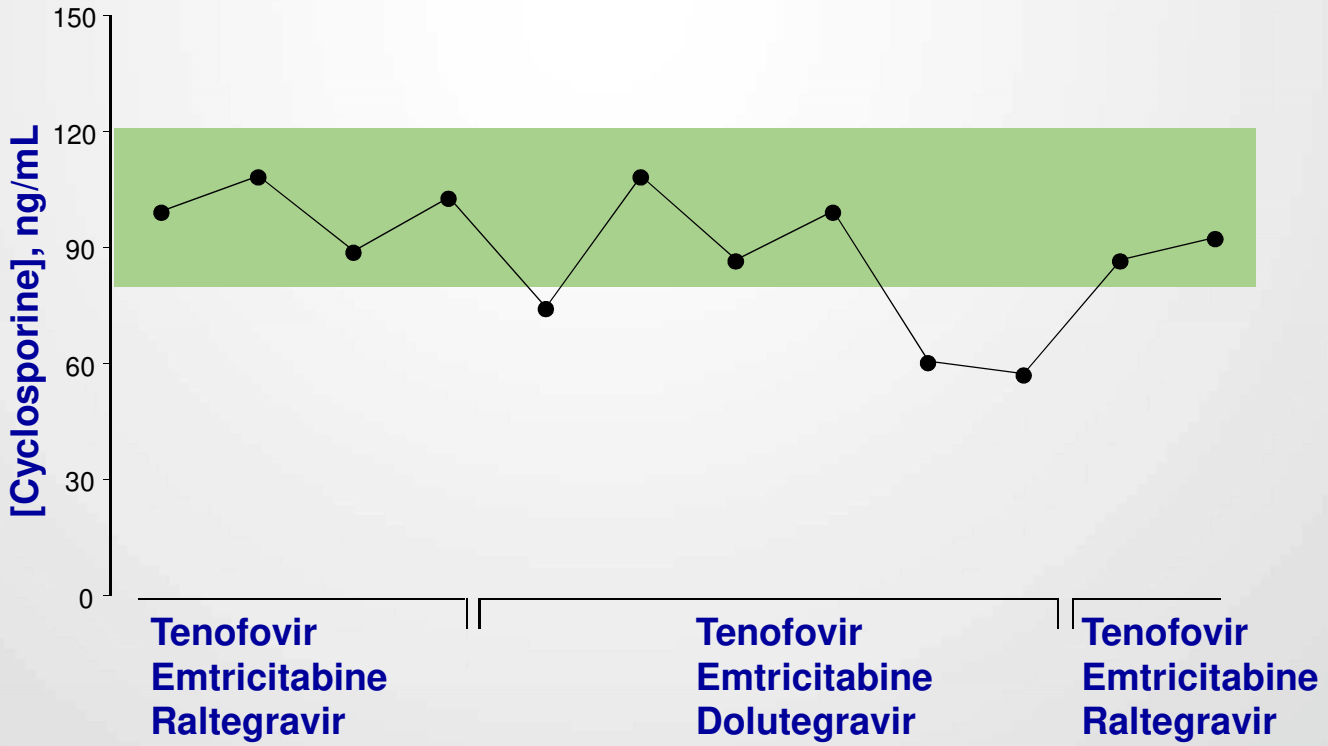
	HBV and/or HCV coinfected				No HBV and/or HCV coinfection			
	DTG	RAL	EFV/TDF/FTC	DRV/r	DTG	RAL	EFV/TDF/FTC	DRV/r
ART naive								
n	116	43	30	20	1100	363	385	222
ALT, *n* (%)	18 (16)	10 (23)	7 (23)	2 (10)	37 (3)	14 (4)	17 (4)	4 (2)
AST, *n* (%)	16 (14)	6 (14)	6 (20)	2 (10)	50 (5)	18 (5)	18 (5)	7 (3)
Bilirubin, *n* (%)	3 (3)	1 (2)	0	0	20 (2)	9 (2)	2 (<1)	1 (<1)
ART experienced (INI naive)								
n	50	65	NA	NA	289	272	NA	NA
ALT, *n* (%)	11 (22)	5 (8)	NA	NA	10 (3)	9 (3)	NA	NA
AST, *n* (%)	10 (20)	12 (18)	NA	NA	8 (3)	8 (3)	NA	NA
Bilirubin, *n* (%)	6 (12)	8 (12)	NA	NA	35 (12)	27 (10)	NA	NA

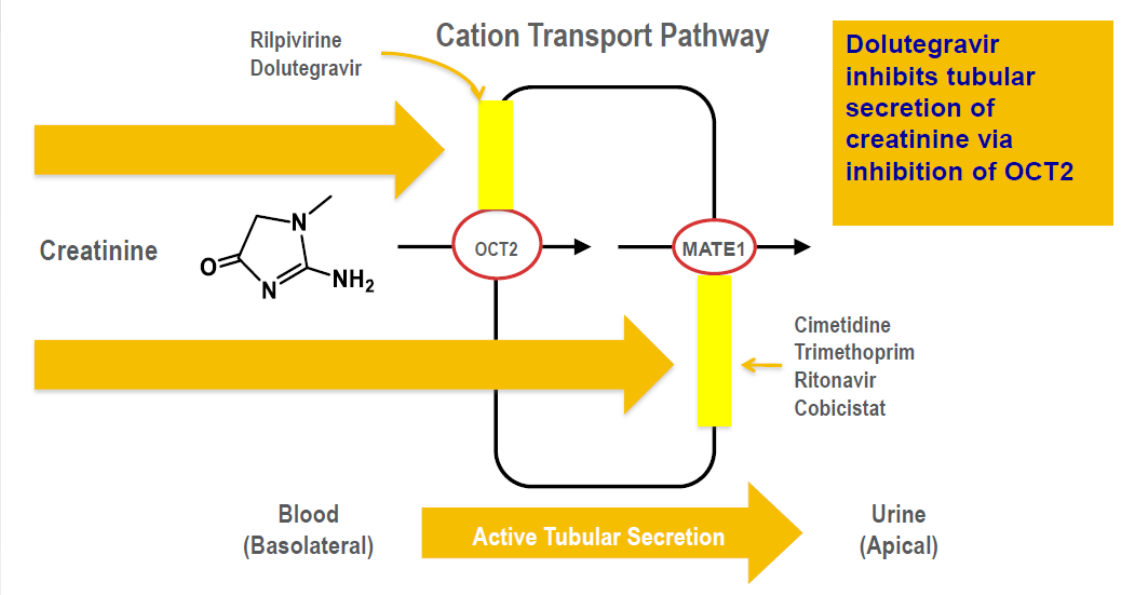
Note: ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; DRV/r = darunavir + ritonavir; HBV = hepatitis B virus; HCV = hepatitis C virus; INI = integrase inhibitor; RAL = raltegravir; TDF = tenofovir.

HIV Clin Trials 2014;15(5):199–208

Patient 2

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	0.8	1.8 (+125%)





…and/or…

ELSEVIER

Nephrotoxicity of Calcineurin Inhibitors

D. Abramowicz, K. M. Wissing, and N. Broeders

Transplantation Proceedings, 32 (Suppl 1A), 3S–5S (2000)

Patient 3

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	1.1	1.7 (+55%)

Patient 4

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	1.3	1.6 (+23%)
GI disturbances**	none	Nausea/vomiting

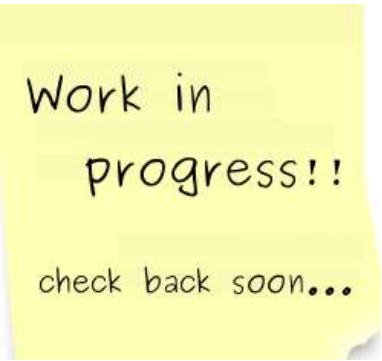
** episodes of nausea/vomiting can be ascribed either to dolutegravir, cobicistat or calcineurin inhibitors…

Gestione
Ambulatoriale
Politerapie

Dott.ssa Cristina Gervasoni
Dott. Dario Cattaneo
& collaboratori

Mercoledi 13 Marzo 2019

- ✓ Paziente maschio (Vo.Si. 26/03/1961)
- ✓ Trapianto di fegato per cirrosi: 2014
- ✓ TARV al trapianto: raltegravir + atazanavir/r
- ✓ Semplificazione: introdotto dolutegravir, tolto ritonavir
- ✓ Aumento creatinina sierica….
- ✓……



Conclusions

- ✓ We have shown here that half of the LTx patients were switched back from dolutegravir-based to their previous antiretroviral regimens. However, not all safety concerns can be univocally ascribed to dolutegravir
- ✓ Significant fluctuation in the tacrolimus and cyclosporine concentrations were observed in some patients immediately after the switch to dolutegravir related to unknown mechanisms
- ✓ The management of HIV-infected liver transplant recipients in clinical practice is still a complex task…

DDIs between INIs and CNIs

- ✓ Dolutegravir and raltegravir have low propensity to cause DDIs given their neutral effects on metabolic enzymes, however…

J Antimicrob Chemother 2016; **71**: 1341–1345
doi:10.1093/jac/dkv466 Advance Access publication 10 January 2016

Journal of Antimicrobial Chemotherapy

Reduced raltegravir clearance in HIV-infected liver transplant recipients: an unexpected interaction with immunosuppressive therapy?

Dario Cattaneo[1], Massimo Puoti[2], Salvatore Sollima[3], Cristina Moioli[2], Caterina Uberti Foppa[4], Sara Baldelli[1], Emilio Clementi[5,6] and Cristina Gervasoni[3]*

Unanticipated effects of INIs on ABC transport proteins that play important roles in the disposition of CNI?

Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid

Annagloria Palazzo*, Mattia Trunfio, Veronica Pirriatore, Maurizio Milesi, Amedeo De Nicolò, Chiara Alcantarini, Antonio D'Avolio, Stefano Bonora, Giovanni Di Perri and Andrea Calcagno

J Antimicrob Chemother 2018; **73**: 826–827

9° WORKSHOP NAZIONALE CISAI

PREVENZIONE
E GESTIONE
DELLE CO-MORBIDITÀ
ASSOCIATE
ALL'INFEZIONE DA HIV

FONDAZIONE ASIA

CISAI
Coordinamento Italiano Studio Allergie e Infezione da HIV

BARI | 21-22 MARZO 2019
CENTRO CONGRESSI PALACE HOTEL BARI

"..people from the lab…"

Sara Baldelli
Igor Bonini
Simone Castoldi
Valeria Cozzi
Cristina Montrasio
Stefania Cheli
Marta Fusi
Emilio Clementi

"…and those from GAP.."

Cristina Gervasoni
Noemi Astuti
Tiziana Formenti
Bianca Ghisi
Andrea Giacomelli
Paola Meraviglia
Davide Minisci
Chiara Resnati

Thank you all!