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A Multicenter Registry in HIV/HCV Co-infected Patients Initiating Ledipasvir/Sofosbuvir

Stefan Mauss[1], Cody Chastain[2], Kristen Marks[3], Lance Okeke[4], Kimberly Workowski[5], Lawrence Park[4,6,7], Christopher Woods[4,6,7], Kenneth Sherman[8], Gregory Robbins[9], Juergen Rockstroh[10], Susanna Naggie[4,11]

[1]Center for HIV and Hepatogastroenterology, Dusseldorf, Germany; [2]Vanderbilt University School of Medicine, Nashville, TN, United States; [3]Weill Cornell Medicine, New York City, New York, United States; [4]Duke University School of Medicine, Durham, NC, United States; [5]Emory University School of Medicine, Atlanta, Georgia, United States; [6]Duke Global Health Institute, Durham, NC, United States; [7]Durham Veterans Affairs Medical Center, Durham, NC, United States; [8]University of Cincinnati College of Medicine, Cincinnati, OH, United States; [9]Massachustes General Hospital, Boston, MA, United States; [10]University of Bonn, Bonn, Germany; [11]Duke Clinical Research Institute, Durham, NC, United States

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Background

- Direct acting antiviral (DAA) therapies for the treatment of chronic HCV infection offer excellent sustained virologic response (SVR) rates, regardless of HIV infection.[1]
- Drug interactions with antiretrovirals (ARVs) remain a complicating factor when treating HIV/HCV co-infected patients with DAA.[2,3]
- Ledipasvir is an inhibitor of P-gp and BCRP intestinal efflux transporters, resulting in increased exposure to tenofovir when dosed concomitantly with tenofovir disoproxil fumarate (TDF)-containing regimens.[3] There is potential for further increased exposure when TDF is part of a pharmacologically boosted ARV regimen; which were not allowed in the phase III study of ledipasvir/sofosbuvir in patients with HIV infection.[1]
- Clinicians have approached this drug interaction differently, with some switching the ARV regimen and some continuing while monitoring renal function.
- Switches in ARV regimens due to drug interactions with DAA may put patients at risk of HIV treatment failure and has been reported to increase DAA failure[4].

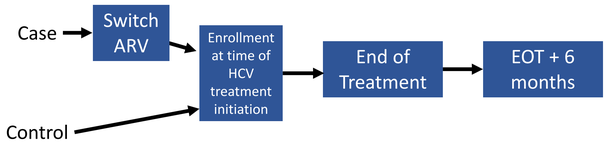
Objectives

- Primary objective: Assess the proportion of patients who are free of HIV treatment failure during the study period
- Secondary objectives:
  - Assess the proportion of patients who are free of HIV virologic failure during the study period
  - Assess the predictors of HIV treatment and virologic failure
  - Assess rates of (1) nephrotoxicity, (2) sustained virologic response (SVR12), and HIV-associated non-AIDS related conditions (HANA)

Study Design/Population

- Multicenter (N=9), three-year, observational clinical registry
- Study population: patients with HIV/HCV co-infection treated with ledipasvir/sofosbuvir (8-24 weeks)
- Enrollment: retrospective and prospective
- Case:control ratio 1:1. Case defined as patients with switch in ARV regimen prior to HCV therapy. Control defined as patients without switch in ARV regimen.
- Study visits: baseline, end of therapy, end of therapy + 24 weeks

Study Design/Schematic



- Inclusion
  - ≥18 years of age and capacity to sign consent
  - HIV/HCV co-infection
  - On stable ARV regimen consisting of at least two active ARV for 12 weeks prior to switch (case) or start of DAA therapy (control)
  - Evidence of HIV RNA <50 copies/mL prior to switch (case) or prior to start of DAA therapy (control)
  - Received/initiating ledipasvir/sofosbuvir regimen
- Exclusion
  - Failure of ARV regimen in prior 6 months
  - AIDS defining illness in prior 6 months
  - Active Co-morbidity that in opinion of investigator might confound the results of the study

Statistical Analysis

- Primary Endpoint: Composite HIV treatment failure
  - Virologic failure, discontinuation/switch of ARV regimen, lost to follow-up, progression to AIDS or death
- Secondary Endpoints
  - HIV virologic failure: HIV RNA >50 copies/mL confirmed at 2 different time points >1 week apart
  - Nephrotoxicity outcomes: any of the following (1) confirmed change from baseline creatinine of ≥ 0.4 mg/dL OR (2) confirmed decrease in creatinine clearance (calculated by the Cockcroft-Gault equation) <50 mL/min OR (3) confirmed incident proteinuria (> 1+ protein on urinalysis)
  - Rates of sustained virologic response: SVR12 and SVR24 defined as HCV RNA <LLOD at 12 weeks and 24 weeks after the end of treatment
- Simple proportions will be presented with a 95% confidence interval. Proportions for two groups will be compared using Chi-square and/or Fisher's exact text with p<0.05

Baseline Characteristics

Characteristics	Overall N=281	ARV Switch N=110	Control N=171
Age (y), mean (SD)*	54 (9.2)	56 (8.5)	53 (9.6)
Male, n (%)*	234 (83)	83 (76)	151 (88)
Black, n (%)*	119 (43)	54 (50)	65 (38)
CD4, median (IQR)	594 (427,804)	554 (427,818)	640 (427,803)
HCV Genotype 1, n (%)	266 (95)	102 (93)	164 (96)
Cirrhosis, n (%)	53 (19)	21 (20)	32 (19)
Antiretrovirals, n (%)			
Boosted-PI*	92 (33)	54 (49)	38 (22)
NNRTI	98 (35)	33 (30)	65 (38)
INSTI*	128 (46)	39 (36)	89 (52)
TDF*	188 (67)	88 (80)	100 (58)
Boosted-TDF*	54 (19)	44 (40)	10 (6)
TAF	15 (5)	3 (3)	12 (7)
Creatinine Clearance (mL/min), mean (SD)	95 (48)	95 (38)	96 (53)
Length of DAA therapy, n (%)			
8 weeks	33 (12)	6 (6)	27 (17)
12 weeks	235 (88)	102 (94)	133 (83)
On PPI, n (%)	38 (14)	13 (12)	26 (15)

*P<0.05 for ART switch vs Control

Outcomes

Characteristics : n (%)	Overall N=281	ARV Switch N=110	Control N=171	p-value
HIV Treatment Failure	17 (6)	7 (6)	10 (5)	1.00
HIV viral failure	3 (1)	2 (2)	1 (1)	0.56
ARV switch or d/c	14 (5)	5 (4)	9 (5)	1.00
Development of:				
AIDS	0 (0)	0 (0)	0 (0)	--
Death	0 (0)	0 (0)	0 (0)	--
Nephrotoxicity	72 (26)	25 (23)	47 (28)	0.40
Incident proteinuria	38 (14)	13 (12)	25 (15)	0.29
Creatinine rise ≥ 0.4 mg/dL	18 (6)	9 (8)	9 (9)	0.33
Creatinine Clearance <50 mL/min	26 (9)	8 (7)	18 (10)	0.41
Incidence of HANA	9 (3)	4 (4)	5 (3)	0.74
SVR12 (N=242)*	239 (99)	94 (99)	145 (99)	1.00

*14% without HCV RNA available after DAA therapy

Outcomes

	Nephrotox N=72	No Nephrotox N=209	p-value
Baseline renal function			
Proteinuria, n (%)	38 (53)	0 (0)	< 0.01
Creatinine (mg/dL), mean (SD)	1.08 (0.36)	1.07 (0.87)	0.29
Creatinine Clearance (mL/min), mean (SD)	90 (38)	95 (34)	0.048
TDF-based regimen, n (%)	51 (71)	137 (66)	0.47
Boosted-TDF regimen, n (%)	14 (19)	40 (19)	1.00

Predictors of HIV Tx Failure

Predictors, n (%)	Failure N=17	No Failure N=264	p-value
ARV Resistance mutations			
NRTI	2 (12)	35 (13)	1.00
NNRTI	1 (6)	22 (8)	1.00
Protease inhibitors	2 (12)	11 (4)	0.18
Previous non-baseline ART exposure			
Any	8 (47)	165 (62)	0.21
NNRTI	5 (29)	84 (32)	1.00
Integrase inhibitors	2 (12)	40 (15)	1.00

Conclusions

- Patients who had their ARVs switched prior to DAA therapy did not experience more HIV treatment failure than controls. Switches were more common in patients on PI or TDF.
- HIV virologic failure was rare. HIV treatment failure was primarily due to ARV switches made while on DAA therapy. One switch occurred in a patient meeting nephrotoxicity criteria.
- Nephrotoxicity criteria were met in 72 (26%) of patients. These events were independent of ARV switch and were not associated with TDF or boosted-protease containing regimens.
- Nephrotoxicity was more common in patients with lower baseline creatinine clearance or baseline proteinuria, although it was not associated with discontinuation of ARV or DAA therapy.
- HCV treatment response was excellent in this real-world cohort of patients with HIV/HCV co-infection, and independent of ARV switch.

[1]Naggie et al. NEJM 2015; 373:705-13, [2]Martinello et al. OFID 2016; 18:3(2):ofw105, [3]Gilead Sciences. Harvoni [package insert] 2014. Foster City, CA, Gilead Sciences, Inc., [4]Falade-Nwulia et al. Hepatology 2017; 66:1402-1412.

Funding: Investigator Initiated Grant from Gilead Sciences