Evaluation of dolutegravir-metformin drug-drug interactions in a clinical setting

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Background: Dolutegravir (DTG) is an organic cation transporter-2 and multidrug and toxin extrusion protein inhibitor. When metformin (MET) is coadministered with DTG in healthy volunteers, MET serum concentrations are significantly increased due to this transport inhibition. Limited data exist evaluating this interaction in HIV-infected patients.

Material/methods: This was a multicenter, retrospective case-series evaluating adult, HIV-infected patients between August 2013 and May 2015. Electronic medical records were used to identify eligible patients, those receiving concurrent DTG and MET, and to collect case-specific data. Laboratory parameters collected included serum creatinine (SCr), hemoglobin A1c (HgbA1c), plasma HIV RNA, CD4 count, and lactate. Adverse effects (AEs) were assessed using patient reported gastrointestinal intolerance and hypoglycemic symptoms. MET dose reduction or discontinuation was also recorded.

Results: Nineteen patients were identified as taking MET and DTG concurrently. All but one patient were on MET prior to DTG initiation, with twelve having received MET for at least six months prior to DTG (N=4 with unknown start dates). At DTG initiation, two patients had a preemptive MET dose reduction. Six patients were initiated on DTG with a MET dose greater than 1000 mg daily. Eleven patients had baseline and three to six month follow-up HgbA1c. Of those eleven patients, eight had stable or decreased values. Fifteen of the nineteen patients had an increase in SCr, with a median SCr increase of 0.35 mg/dL. Three patients reported gastrointestinal distress and three reported hypoglycemic symptoms. AEs resulted in MET dose reduction and subsequent discontinuation in two patients. There were no reported cases of lactic acidosis.

MET and DTG Regimens		

DTG total daily dose - N
    50 mg -10
    50 mg (FDC) - 8
    100 mg - 1
	MET total daily dose – N
	    500 mg - 2
	    1000 mg - 11
	    1500 mg - 1
	    1750 mg - 1
	    2000 mg - 4
		MET dose changes - N
		    No dose change - 14
		    Decreased dose - 3
		    Discontinued - 2

Laboratory Data			
Lab	**Baseline [Median;(IQR)]**	**3 months [Median;(IQR)]**	**6 months [Median;(IQR)]**
HgbA1c (%)	7.4 (6-8) (N=11)	6.7 (6.4-7.3) (N=9)	6.5 (6-8.2) (N=9)
CD4 count cells/mm^3 (%)	542 (26) [317-760;(16-37)]	493 (26) [289-777;(17-35)] (N=15)	492 (29) [419-842;(19-39)] (N=13)

	(N= 18)		
HIV RNA <20 cells/mm^3	10 (N=19)	11 (N=16)	11 (N=13)
SCr mg/dL	0.89 (0.78-1.23) (N=19)	1.13 (0.88-1.29) (N=16)	1.24 (0.95-1.33) (N=13)

DTG - dolutegravir; MET – metformin; FDC – fixed dose combination; IQR – interquartile range

Conclusions: In this small case series, diabetes control was maintained when MET was concurrently prescribed with DTG in HIV-infected patients. Although concurrent administration of DTG and MET required dose reduction and discontinuation in five recipients, HgbA1c appeared to improve over time. Additionally, providers concurrently prescribing DTG and MET may consider an empiric MET dose reduction to prevent intolerable ADRs.