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Dolutegravir and Doravirine in Combination: When Standard Antiretroviral Regimens are Unacceptable

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Abstract

Background

A drug-drug interaction study between dolutegravir and doravirine in healthy volunteers found no evidence of untoward interaction. Whilst we hypothesize that the combination would be safe and effective, there is no supportive clinical data. We aimed to assess the rationale for use of dolutegravir and doravirine in combination and clinical outcomes among persons with HIV infection (PWH) receiving care at the Washington DC VAMC.

Methods

A quality improvement initiative utilized the clinical case registry to identify all PWH receiving both dolutegravir and doravirine. We conducted chart review to examine (a) the reasons for switch from other ART to dolutegravir and doravirine, and comorbidities, HIV resistance mutations or drug interactions precluding the use of standard ART, (b) adverse events or side effects and (c) achievement of virologic suppression.

Results

A case registry search revealed 21 individuals receiving combination dolutegravir doravirine from 2018–2020 (Table 1 and Figure 1). Side effects were not noted except one patient developed mild diarrhea that improved with continuation of therapy. Four patients were hospitalized during the follow-up period for reasons unrelated to the medications. One patient who was admitted to the ICU with shock and multi-organ failure was switched on admission but died four days later and therefore was not included in the analysis of viral outcome (Table 2). One patient had cardiac arrest following missed dialysis, hyperkalemia and rectal hemorrhage from metastatic rectal cancer.

Conclusion

In an era of abundant ART options, we identified a subset of older PWH whose treatment options are defined by extensive comorbidities, viral resistance, and medication interactions or toxicities. Doravirine is attractive for this population as it can be used in renal impairment, moderate hepatic impairment, is unaffected by timing of meals, and (unlike rilpivirine) has no interaction with proton pump inhibitors. Dolutegravir is included in NRTI-sparing regimens that HHS guidelines suggest should be considered in older PWH, especially with CKD. We found that dolutegravir with doravirine is well tolerated, and achieves virologic suppression in the majority of PWH, indicating this combination is useful when other ART options cannot be used.

Introduction

- Doravirine is an FDA-approved non-nucleoside reverse transcriptase inhibitor used for treatment of HIV [1]
- Doravirine can be used safely in those with renal impairment and moderate hepatic impairment [2]
- Pharmacokinetic studies show bioavailability of doravirine is not affected by timing of dosing in relation to meals [3]
- Unlike rilpivirine, doravirine has no significant drug-drug interactions with proton pump inhibitors [2]
- A pharmacokinetic study in healthy volunteers found no significant drug-drug interactions between dolutegravir and doravirine but there are no clinical studies to support this ART combination [4]

Adverse Events

- Two deaths occurred during the follow-up period, but these were not related to ART.
- One patient had a total of 7 hospitalizations for reasons unrelated to ART (fluid overload, NSTEMI, bleeding complications related to line placement and Wernicke's encephalopathy) and one further patient was admitted for a subcapsular hematoma.
- No drug discontinuations related to adverse events or side effects occurred, one patient developed self-limiting diarrhea.

Results

Table 1: Patient Demographics

Mean Age (Range)	
	61.8 years (50-74)
Gender	
	Male: 90.5% (19/21)
	Female: 9.5% (2/21)
Race	
	African-American: 95.2% (20/21)
	Caucasian: 4.8% (1/21)
Comorbidities	
	Hypertension 61.0% (13/21)
	Coronary artery disease: 19.0% (4/21)
	Diabetes Mellitus, Type 2: 19.0% (4/21)
	Chronic Kidney Disease: 28.6% (6/21)
	Cancer: 14.3% (3/21)
	Active Hepatitis B: 9.5% (2/21)
	Hepatitis C: 33% (7/21)
	Cirrhosis: 23.8% (5/21)
	Peptic Ulcer Disease: 19.0% (4/21)
	Lower GI Bleed: 14.3% (3/21)
	Seizure disorder: 14.3% (3/21)
	Peripheral Neuropathy or Radiculopathy: 28.6% (6/21)
	Dementia or Cognitive Impairment: 19.0% (4/21)
	Psychiatric Disorders: 47.6% (10/21)
Antiretroviral Therapy Regimen	
	Dolutegravir/Doravirine alone: 66.7% (14/21)
	Dolutegravir/Doravirine + Lamivudine: 14.3% (3/21)
	Dolutegravir/Doravirine + Emtricitabine: 4.8% (1/21)
	Dolutegravir/Doravirine + Tenofovir: 4.8% (1/21)
	Dolutegravir/Doravirine + Cobicistat-boosted Darunavir: 4.8% (1/21)
	Dolutegravir/Doravirine + Emtricitabine/Tenofovir: 4.8% (1/21)
Mean Duration of Follow-Up (Range)	
	10 months (3-17)

Figure 1: Reasons for Switching to Dolutegravir with Doravirine

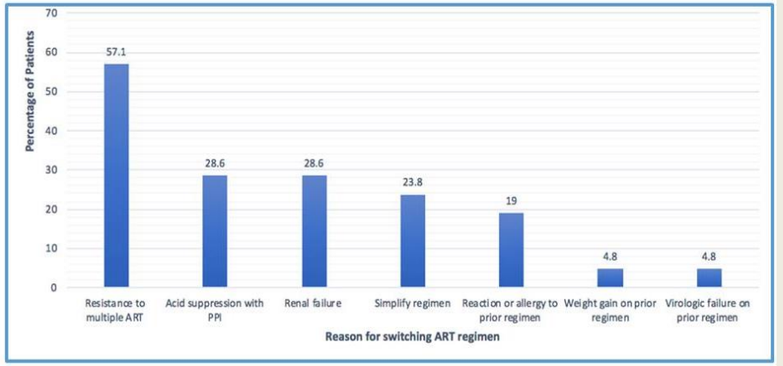

Table 2: Virologic Control Before and After Switching to Dolutegravir with Doravirine

	Virologic control in 12 months prior to switch (all patients)	Virologic control post-switch (>12 months follow-up)	Virologic control post-switch (all patients)
Undetectable VL (<50), % (n)	61.9% (13)	55.6% (5)	70% (14)
VL 50 to 200, % (n)	14.3% (3)	22.2% (2)	10% (2)
VL>200, % (n)	14.3% (3)	22.2% (2)	15% (3)*
No VL data, % (n)	9.5% (2)	-	5% (1)
Mean CD4	513	561	560
CD4 <200	14.3% (3)	22.2% (2)	15% (3)
No CD4 data	9.5% (2)	-	15% (3)
Total number of persons included	21	9	20

*One with preexisting V106A mutation

Table 3: Virologic Control Before and After Switching: Subgroup Analysis of Those Who Received Dolutegravir with Doravirine Alone

	Virologic control in 12 months prior to switch	Virologic control post-switch
Undetectable VL (<50), % (n)	71.4% (10)	71.4% (10)
VL 50 to 200, % (n)	14.3% (2)	14.3% (2)
VL>200, % (n)	14.3% (2)	14.3% (2)*
Mean CD4	681.5	681.0
CD4 <200	0% (0)	0% (0)
No CD4 data	0% (0)	7.1% (1)
Total number of persons included	14	14

*One patient with preexisting V106A mutation overlooked at time of switching, one patient had viral load of 230 on this regimen and emtricitabine was added after 7 months.

Summary

What does this study show? The combination of dolutegravir with doravirine (with or without additional ART drugs) appeared to be safe and well tolerated in a small group of patients in our clinic, and achieved virologic suppression in most cases.

What are the limitations of our study? This was a single center quality improvement study of patients within our own clinic setting, therefore the findings may not be generalizable to other clinic populations.

What further research needs to be undertaken? We suggest that additional prospective studies be undertaken to examine the utility of dolutegravir with doravirine as a possible two-drug NRTI-sparing ART regimen

References

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