A Retrospective Study To Evaluate The Safety And Efficacy Of A Neucleoside-Sparing Regimen Of Darunavir, Ritonavir AND Dolutegravir

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A Retrospective Study To Evaluate The Safety and Efficacy Of A Neucleoside-Sparing Regimen Of Darunavir, Ritonavir And Dolutegravir

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Background

Aging with HIV infection is a relatively new phenomenon and investigators are only beginning to understand its implications for clinical care and for our understanding of aging more generally. Several sequelae of aging with HIV have been identified, including increased cardiovascular risk, bone loss, and renal dysfunction. Various antiretrovirals have been implicated in contributing to or exacerbating these conditions, most specifically the nucleoside reverse transcriptase inhibitors (NRTI) class. Despite the approval of various new pharmaceutical compounds over the last few years, the NRTI class remains limited in safe therapeutic options. The most commonly used NRTI, tenofovir, has been implicated in numerous studies causing and/or contributing to renal disorders in persons with HIV [1,2,3]. In addition, data from the D:A:D study has shown in increased risk of cardiovascular disease (CVD) among patients receiving treatment for HIV and that certain medications appear to be associated with that risk, including the NRTI abacavir [4]. HIV therapy is life-long and providers have opted to use nucleoside-sparing regimens to minimize these toxic effects. The purpose of this study is to determine the real-world efficacy and safety of a nucleoside-sparing regimen of darunavir 800 mg, ritonavir 100 mg, and dolutegravir 50 mg by mouth once daily. While not well studied, this two-drug regimen was chosen for its lack of drug-drug interactions [5], predictable pharmacokinetic profile [6] and exceptional tolerability [7,8,9].

Methods

We conducted a retrospective chart review of approximately 400 HIV+ patients receiving treatment at SIHF Healthcare, an urban diverse FQHC to identify those who were receiving a NRTI-sparing regimen of DRV and DTG. Subjects were included if they were ≥ 18 years of age, receiving DRV/r QD + DTG QD for ≥ 24 weeks, and had laboratory data through 48 weeks of follow up. Subjects were excluded if they received a regimen of darunavir/ritonavir in combination with dolutegravir for <24 weeks duration, if they received darunavir/ritonavir + DTG + NRTI's, missed more than five doses over two weeks prior to study visit or if there was missing laboratory data for ≥2 or more study time points. The primary endpoints evaluated were the percent of patients with an RNA <50 copies/mL at 48 weeks after initiation of the once daily two-drug regimen, as well as, the change in serum creatinine from baseline to 48 weeks. Main secondary endpoints included changes from baseline in CD4+ cell counts, incidence and severity of adverse events and, analysis of RNA and serum creatinine at time points 24, 36 and 48 weeks.

The percent of patients with an RNA <50 copies/mL at each time point was analyzed using McNemar's test following the guidelines of the Snapshot algorithm. Missing RNA data was considered a treatment failure. Change in mean serum creatinine from baseline was analyzed using Wilcoxon signed rank test.

Change in mean CD4+ cell counts from baseline was analyzed using a paired t-test. All analyses used a p-value of less than or equal to 0.05 as significant. Statistical analyses were performed using R software, version 3.4.3.

Results

The Mean age of the cohort was 51 yrs and had an average of 12.5 years of HIV seropositivity. Table 1. The cohort had a mean baseline CD4+ of 485 with an RNA of 20K copies. Table 2. Of note, 55% of study subjects had a viral load of > 50 copies at baseline. 95% of study subjects at week 48 met the primary endpoint of < 50 copies/mL (P-value 0.002), 95%CI [2.24, NA]. Figure 1. The lone failure was due to missing data. Also, there were no significant differences in serum creatinine from baseline to 48 weeks (p = 0.5753). Figure 2. However, at week 24, one study subject did not have data (serum creatinine) in window. There were no significant changes in CD4+ cell count from baseline at time points 24, 36 or 48 weeks. Figure 3.

Table 1

Descriptive Stats - Demographics

	N	%
Gender		
Female	8	40%
Male	12	60%
Race		
Black	15	75%
White	5	25%

Age in years	
Mean (SE)	51.05 (0.96)
Median	53.00
Range	37.00 – 61.00
std	8.20
HIV in years	
Mean (SE)	12.54 (0.98)
Median	9.50
Range	0.25 – 32.00
std	8.79
Weight in Pounds	
Mean (SE)	160.30 (4.04)
Median	157.00
Range	106.00 – 244.0
std	33.77

Table 2

Descriptive Stats – CD4 and Viral Load

Viral Load	Baseline	Week 24	Week 36	Week 48
N	20	19	14	19
Missing=Failure	0	1	6	1
Mean (SE)	20458 (12389.4)	10232 (9559.583)	33.57 (12.82)	22.63 (1.50)
Median	95.0	20	20.00	20.00
Range	20.0 – 207720.0	20 -1820101	20.00 – 200	20.00 – 40.00
SD	55407.07	41669.26	47.98	6.53

CD4 Count	Baseline	Week 24	Week 36	Week 48
N	20	20	14	20
Missing=Failure	0	0	6	0
Mean (SE)	485.1 (67.0)	453.9 (67.22)	428.1 (67.95)	455.7 (64.98)
Median	458.5	379.5	376.0	428.5
Range	24.0 – 1011.0	93.0 – 1145.0	112.0 – 877.0	70.0 – 1142.0
SD	299.41	300.64	254.24	290.56

Figure 1

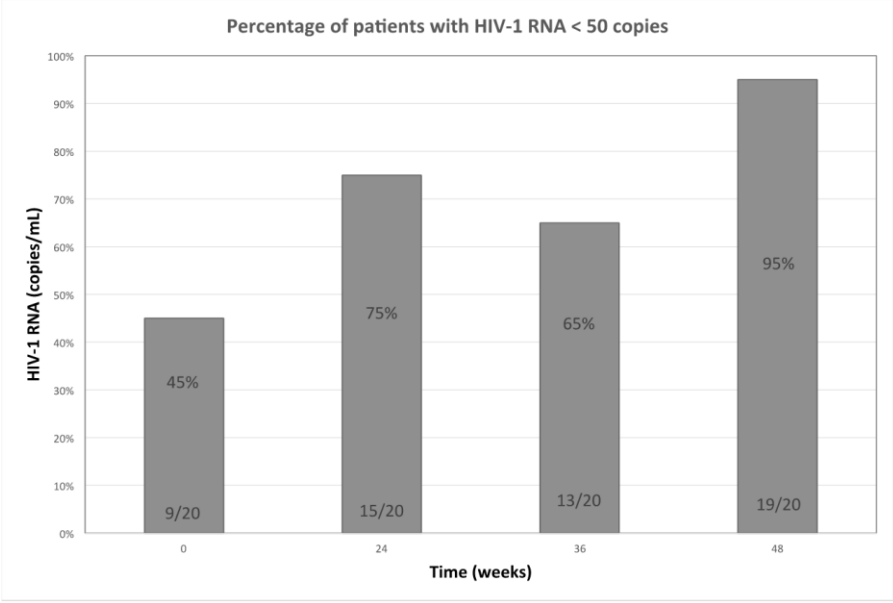


Figure 2

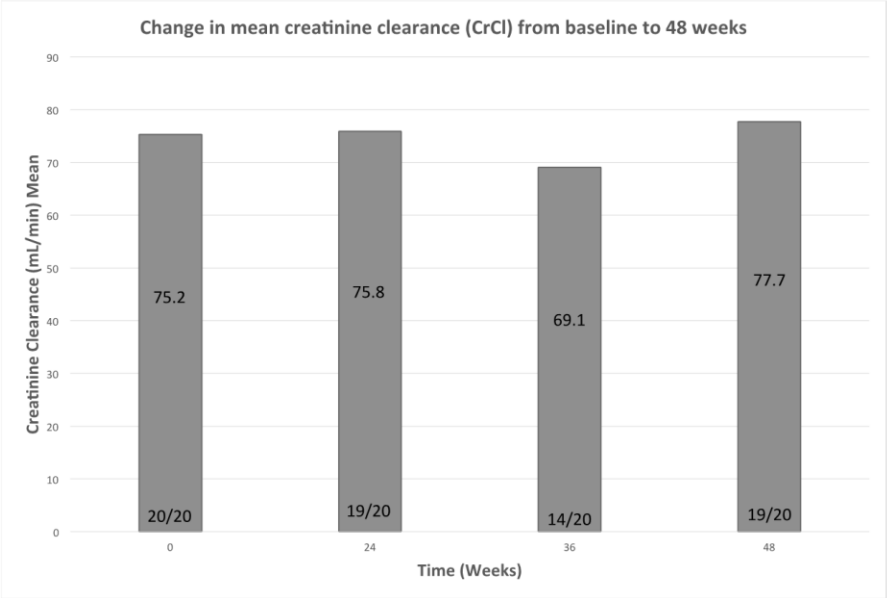
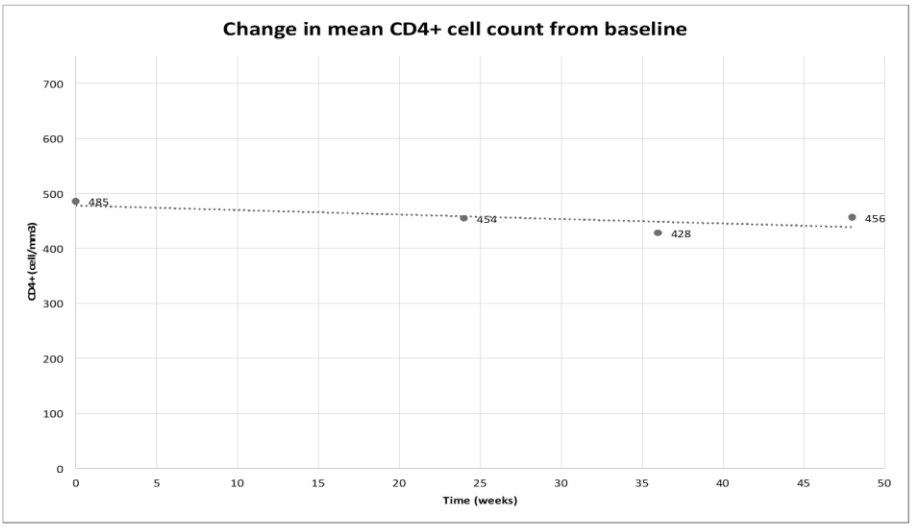


Figure 3



Adverse Events

As per the study protocol, an adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product.

Of note, there was no treatment-emergent resistance detected or virological failures in any of the subjects. Common side effects reported by patients were insomnia (30%), diarrhea (20%) and headache (15%). There were no adverse events that led to discontinuation of the study regimen. Table 3.

Table 3 [10]

Patient ID	**Adverse Event**	**Severity**	**Relationship to Study Product**	**Action Taken**	**Suspected study drug: DRV/r or DTG**
#2	Diarrhea	Grade 1	Possible	None	DRV/r
#4	Insomnia	Grade 1	Possible	None	DTG
#6	Insomnia	Grade 1	Possible	None	DTG
#7	Headache, Diarrhea	Grade 1	Possible	None	Both
#8	Headache, Diarrhea	Grade 1	Possible	None	Both
#9	Insomnia	Grade 1	Possible	None	DTG
#10	Insomnia	Grade 1	Possible	None	DTG
#14	Insomnia	Grade 1	Possible	None	DTG
#15	Insomnia	Grade 1	Possible	None	DTG
#20	Headache, Diarrhea	Grade 1	Possible	None	Both

Adverse Drug Reaction

As per study protocol, an adverse drug reaction (ADR) is defined as a response to a medicinal product that is noxious and unintended.

Of note, no adverse drug reactions were reported during this study.

Serious Adverse Event

As per study protocol, this is defined as any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product or is otherwise medically important.

Of note, no serious adverse events were reported during this study.

Finally, no female subject (40% or 8/20 subjects) became pregnant during the 48 weeks of the study.

Discussion

The results show that after 48 week of darunavir 800 mg, ritonavir 100 mg and dolutegravir 50mg by mouth once daily, patients were able to maintain virologic suppression and there were no discontinuations due to adverse events.

Clinically, this regimen may be beneficial for patients who experience side effects with other antiretroviral therapy or for those who struggle with adherence issues as this is a once daily regimen. However, there are several limitations to this research. Due to the small sample size and data selection from a single center, it is difficult to extrapolate the results to the general HIV population. Additionally, using snapshot analysis to evaluate efficacy can be flawed as it may not reflect the true response characteristics over the whole treatment phase.

Toxicities associated with antiretroviral compounds are drug-class specific. A commonly used NtRTI was tenofovir disoproxil fumarate (TDF). This compound is known to affect renal function and bone mineral density (BMD). In 2016, the Food And Drug Administration (FDA) approved a TDF pro-drug, tenofovir alafenamide [11]. Switching to this compound was associated with statistically significant efficacy and safety advantages over TDF [12].

The NEAT study (NEAT001/ANRS143) found that the regimen of raltegravir in combination with darunavir/ritonavir was about equal to a triple drug regimen of tenofovir/emtricitabine in combination with darunavir/ritonavir in terms of efficacy and safety in treatment naïve patients [13]. However, subjects with CD4 counts below 200 cells/µL and viral loads above 100,000 copies/mL did not do as well

A second study was SWORD-1/SWORD-2 which evaluated the N(t)RTI sparing, dual-drug regimen of once-daily dolutegravir plus rilpivirine vs. current antiretroviral regimen (CAR). The authors found that at week 48, the regimen of dolutegravir plus rilpivirine was non-inferior to CAR and showed a safety profile consistent with its components, supporting the use of this two-drug regimen to maintain HIV suppression [14].

Conclusion

In this study the combination of darunavir/ritonavir in combination with dolutegravir yielded high rates of virologic suppression. While some patients experienced adverse events known to be associated with darunavir or dolutegravir, all adverse events were low grade and did not require discontinuation of treatment or alteration in dose

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