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Efficacy and Safety of Efavirenz (EFV), Lamivudine (3TC), Didanosine EC (ddI EC), as a Once-Daily Regimen for Treatment-Naïve HIV Patients: 48-Week Results from the DART I Trial

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Background

It is thought that once-daily regimens are preferred over those taken more than once a day. The Daily Antiretroviral Therapy (DART I) trial is a Phase IV, 96-week, open-label, single-arm, prospective multi-center trial assessing the efficacy, safety, and tolerability of a three-pill, once-daily regimen containing once-daily EFV (600 mg), 3TC (300 mg) and ddI EC (400 mg [250 mg if weight <60 kg]) in treatment-naïve HIV subjects. The primary endpoint was to evaluate the proportion of subjects with plasma HIV-RNA <400 copies/mL at 48 weeks. Secondary objectives include safety, tolerability, and adherence to the regimen. Issues such as potency, tolerability, and simplicity may result in levels of adherence to therapy that improves therapeutic success. The efficacy and safety at 48 weeks of this simplified daily regimen are presented in this poster.

Methods

Important inclusion criteria for the study were:

- Treatment-naïve subjects with HIV RNA viral load (VL) ≥1000 copies/mL (Roche Amplicor HIV-1 assay)
- CD4 ≥100 cells/mm³ obtained within 14 days prior to start of therapy
- age ≥18 years
- weight ≥40 kg

Exclusion criteria were:

- evidence of hypersensitivity to any study agent
- hepatitis
- pancreatitis
- failure to fall within acceptable laboratory and clinical parameters as set forth in the protocol
- subjects who were pregnant

The proportion of subjects with VL <400 and <50 copies/mL at all timepoints up to 48 weeks were determined on an intent-to-treat (ITT) basis with non-completer = failure analysis (NC=F), as well as on an observed basis. The VL decrease in those who had a baseline VL ≥100,000 copies/mL was determined. Changes from baseline (BL) in the HIV RNA and CD4 levels were calculated at each timepoint. All adverse events were tracked and summarized.

Results

Sixty-five subjects were enrolled in this study. Table 1 shows the demographics, BL HIV RNA, and CD4 cell count levels. Of a total of 12 discontinuations prior to Week 48, 3 subjects (5%) discontinued due to adverse events and 9 (14%) due to the reasons listed in Table 2. No discontinuations were due to lack of efficacy. A high proportion of subjects were virally suppressed at both the <400 copies/mL (82% ITT and 100% observed) and <50 copies/mL (80% ITT and 98% observed) levels at Week 48, as shown in Figures 1 and 2. The significant mean changes from BL in VL and CD4 levels for both the ITT and observed analyses are illustrated in Figures 3 and 4. There were no serious adverse events over the 48 weeks of the study. All Grade 2-4 treatment-related adverse events that occurred with a frequency ≥2% are shown in Table 3. Three subjects experienced Grade 3-4 lipase increases; none were associated with clinical pancreatitis. There were two cases of Grade 1 (mild) peripheral neuropathy. In the 28 subjects with a BL VL of ≥100,000 copies/mL, there was a VL decrease of >2 $\log_{10}$ copies/mL at Week 2, with a 3.7 $\log_{10}$ copies/mL decrease at Week 48, as seen in Figure 5. When stratified by viral load, subjects with a BL VL >100,000 copies/mL demonstrated a high proportion of virologic suppression at Week 48, as seen in Figures 6 and 7. Median percent increases from BL for total cholesterol (TC), HDL cholesterol, LDL cholesterol, and triglycerides were 23, 32, 19, and 27%, respectively; the median BL values were 156, 39, 97, and 102 mg/dL respectively. The median TC:HDL Ratio decreased from a BL of 4.17 to 3.75 (p>0.05).

Table 1: Baseline Characteristics

		ddI EC QD 3TC QD + EFV QD (N=65)
Demography	Mean Age, (years)	38
	Male	86%
	White	55%
	Black	31%
	Other	14%
Clinical	Mean HIV RNA ($\log_{10}$ copies/mL)	4.80
	≥100,000 copies/mL	43%
	Mean CD4 Counts (cells/mm³)	311

Table 2: Patient Disposition at Week 48

	ddI EC QD 3TC QD + EFV QD
ITT Population	65
Total Discontinuations, n (%)	12 (18%)
Reasons for Discontinuation	
Adverse Event	3 (5%)
Withdrew Consent	3 (5%)
Lost to Follow-up	1 (2%)
Protocol Violation	1 (2%)
Other	4 (6%)

*Adverse events included: hypertriglyceridemia (Grade 1); lipase increase (Grade 2); lipase increase (Grade 4)

Figure 1: Virologic Response HIV RNA <400 copies/mL: Baseline to Week 48

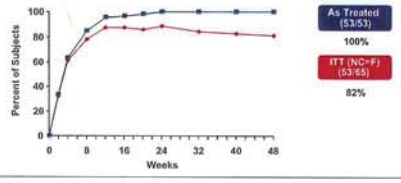


Figure 2: Virologic Response HIV RNA <50 copies/mL: Baseline to Week 48

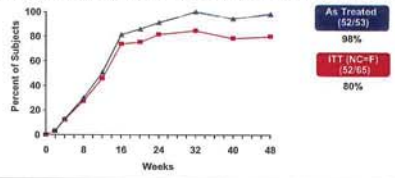


Figure 3: Baseline to Week 48 Mean Change in HIV RNA Level

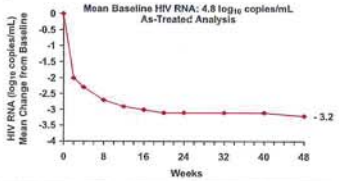


Figure 4: Baseline to Week 48 CD4 Cell Mean Change

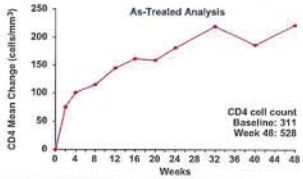


Table 3: All Grade 2-4 Treatment-Related Adverse Events (≥2%)

Grade 2-4 at Week 48	ddI EC + 3TC + EFV n=65
Fatigue	6 (9%)
Dizziness	5 (8%)
Abnormal Dreams	3 (5%)
Diarrhea	3 (5%)
Lipase Increased	3 (5%)
Disturbance in Attention	2 (3%)
Feeling Abnormal	2 (3%)
Insomnia	2 (3%)
Libido Decreased	2 (3%)
Mood Swings	2 (3%)

Figure 5: Mean Change in HIV RNA Level for Subjects ≥100,000 $\log_{10}$ copies/mL at Baseline

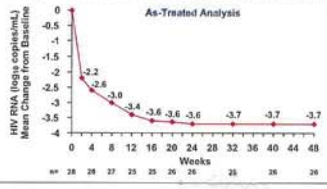


Figure 6: Virologic Response HIV RNA in Subjects <100,000 $\log_{10}$ copies/mL at Baseline (N=37)

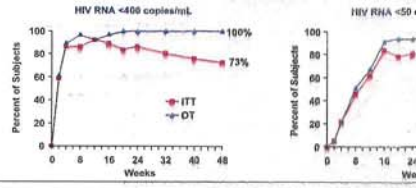
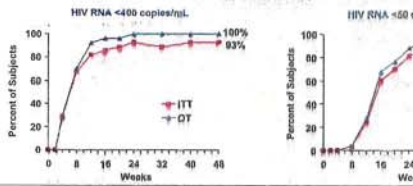


Figure 7: Virologic Response HIV RNA in Subjects ≥100,000 $\log_{10}$ copies/mL at Baseline (N=28)



Conclusions

- EFV, 3TC and ddI EC administered once daily to treatment-naïve HIV subjects was safe and efficacious at 48 weeks resulting in:
  - 100% viral supression in the as-treated group and 82% in the ITT group at the plasma HIV-RNA <400 copies/mL level
  - 98% (as-treated) and 80% (ITT) of subjects with plasma HIV-RNA <50 copies/mL
  - rapid and sustained virologic response in HIV RNA in subjects with baseline viral loads ≥100,000 copies/mL
  - significant reductions in viral load (a mean decrease of 3.2 $\log_{10}$ copies/mL) and significant increases in CD4 cell counts (a mean increase of 217 cells/mm³)
  - no serious adverse events and very few treatment related adverse events occurred in this study
  - There were no cases of treatment-related clinical peripheral neuropathy
- This EFV, 3TC and ddI EC regimen was well tolerated and resulted in few treatment-limiting adverse events, providing a simple, convenient, once-daily option for HIV patients.