Effects of Tenofovir/Emtricitabine on Endogenous Deoxyribonucleotide Pools In Vivo

Poster # 526

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ABSTRACT

BACKGROUND: The potential effects of nucleoside analogs on endogenous deoxyribonucleotides (dNTP) in vivo have not been fully elucidated. The goal of this study was to characterize and quantify the effects of tenofovir-disoproxil fumarate (TDF)/emtricitabine (FTC) therapy on endogenous dNTP pools in HIV-negative and HIV-positive adults.

METHODS: Participants were enrolled in a pharmacokinetic study of daily TDF/FTC therapy. Peripheral blood mononuclear cells (PBMC) were collected at baseline (pre-drug), and days 1, 3, 7, 20, and 30 during dosing. HIV-negative adults had visits on days 5, 15, and 30 of drug washout, while HIV-positive adults continued therapy through day 60. The 8 hours post dose samples were used from all on-drug study visits. PBMC were isolated, counted, lysed, and endogenous dNTP including dCTP, dGTP, TTP, and dATP were quantified with validated LC-MS/MS methodology. Comparisons were made with paired t-tests.

RESULTS: 279 PBMC samples were analyzed from 40 participants (21 HIV-negative and 19 HIV-positive); 13 female and 27 male, median age 31 years. 34 subjects completed all study visits, two HIV negative and four HIV-positive subjects stopped early. dNTP were generally (not statistically) higher at baseline in HIV-negative vs HIV-positive participants, with median values of 834 vs 780 (dCTP), 303 vs 244 (dGTP), 475 vs 386 (TTP), and 153 vs 152 (dATP) fmol/10^6 cells. Compared with baseline values, HIV-negative subjects had a reduction of 26% for dCTP (p=0.003), 30% for dGTP (p=0.001), 53% for TTP (p<0.001), and 21% for dATP (p=0.06) by day 3; while corresponding values for HIV-positive subjects were 17% for dCTP (p=0.20), 12% for dGTP (p=0.36), 34% for TTP (p=0.01), and an increase of 9% for dATP (p=0.99). dNTP generally remained below baseline until drug discontinuation. After 5 days of washout in the HIV-negative participants, dNTP had essentially returned to baseline values with differences of -6% for dCTP (p=0.33), -14% for dGTP (p=0.16), -1% for TTP (p=0.87), and -11% for dATP (p=0.07).

CONCLUSIONS: Endogenous dNTP pools in PBMCs decreased during TDF/FTC therapy, with greater reductions among HIV-negative subjects. These dNTP changes may indicate direct perturbation (eg drug interference with dNTP regulation pathways) and/or indirect perturbation (eg drug-induced reduction of immune activation, in turn reducing dNTP). The effects of lower dNTP on cellular function and antiviral effect should be evaluated in future studies.

BACKGROUND

- Deoxyribonucleoside triphosphates (dNTPs) are important for cell proliferation, immune modulation, and antiviral response.
- Tenofovir monophosphate inhibits purine nucleoside phosphorylase (PNP) which may raise dNTP, but the effects of TFV/FTC on dNTP has not been fully elucidated in vivo.

OBJECTIVE

To evaluate the effects of TDF/FTC therapy on cellular dNTP pools in PBMC of HIV-negative and positive individuals.

METHODS

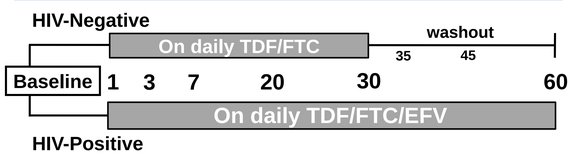


Figure 1. Clinical study design. Baseline samples obtained prior to treatment initiation. HIV-negative individuals had 30 days of TDF/FTC treatment, then 30 days of washout. HIV-positive subjects had 60 days of daily TDF/FTC/EFV(Efavirenz) therapy. PBMC samples were taken at 8 hours post dose from visits at day 1, 3, 7, 20, 30, and 60, while HIV negative group had two additional visits at day 35 and 45 during washout period.

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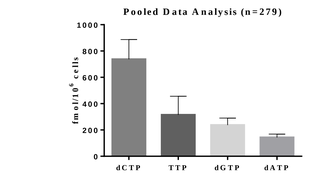
RESULTS

Demographics

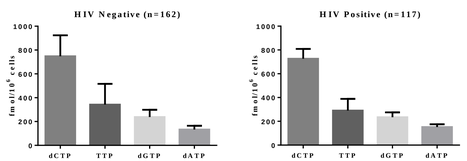
Characteristic	Number
HIV Status	
Negative	21
Positive	19
Gender	
Female	13
Male	27
Race	
White	19
Black	16
Hispanic	5
Median eGFR (range) mL/min/1.73 m^2	93.3 (66.0-130.8)
Median Age (range) years	31 (20-52)
Median BMI (range) kg/m^2	26.6 (19.9-37.7)
Participants / Withdrawals	40 / 6

Table 1. Demographic characteristics of the study population.

Pooled Data



	dCTP	TTP	dGTP	dATP
25% Percentile	604.5	219.5	199.7	115.9
Median	737.4	315.0	237.1	142.6
75% Percentile	887.3	456.1	290.1	169.1



dCTP	TTP	dGTP	dATP		dCTP	TTP	dGTP	dATP
605.6	220.8	197.7	111.3	25% Percentile	586.7	202.2	202.1	135.5
748.2	342.5	237.7	133.2	Median	725.9	290.1	234.5	152.4
923.5	516.6	298.5	164.8	75% Percentile	808.5	388.6	275.7	175.1

Figure 2. & Table 2. Histograms of all dNTP pool levels and tables of medians and interquartile ranges.

HIV Negative

HIV Positive

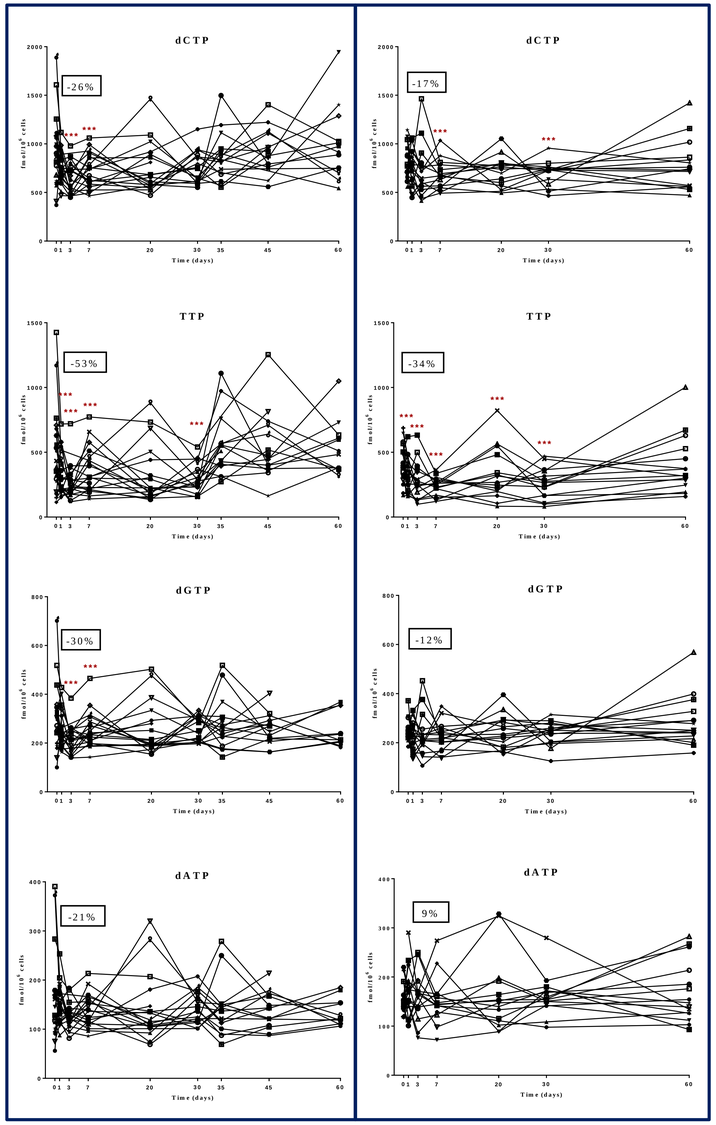


Figure 3. Spaghetti plots of dNTP pool change in HIV-negative and positive adults. Asterisks (***) indicates statistically significant (p<0.05) decrease compared with baseline values. Boxed values are the percentage change of medians at day 3 compare with baseline values.

Medians

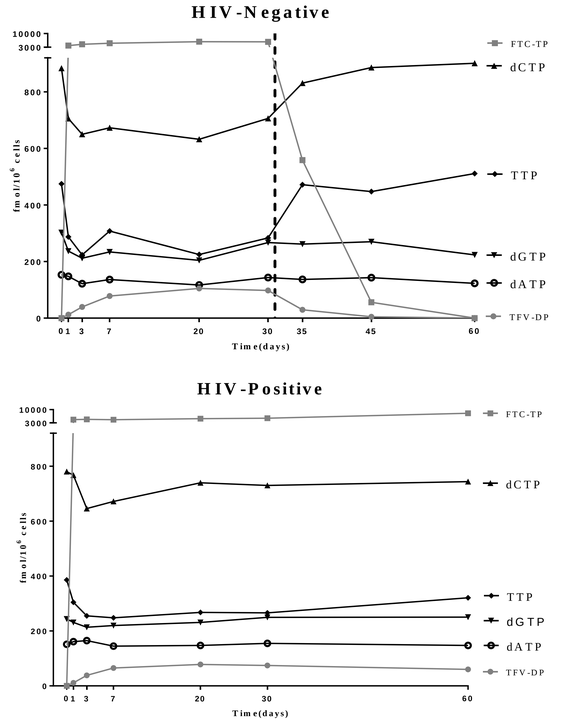


Figure 4. Medians of dNTPs and TFV-DP/FTC-TP in HIV-negative (upper panel) and positive (lower panel) subjects.

CONCLUSIONS & DISCUSSION

Short-term daily TDF/FTC therapy was associated with decreased endogenous dNTP pool levels. Thymidine triphosphate concentrations were consistently decreased. dNTP levels had greater reductions in HIV-negative subjects, but returned to baseline during the washout in these subjects.

The clinical significance of reduced cellular dNTP levels and the mechanisms of these reductions should be further investigated in future studies.

Acknowledgments and References

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