THE FOTO STUDY

48 week Results to assess durability of the strategy of taking Efavirenz, Tenofovir and Emtricitabine Five-days-On, Two-days-Off each week in virologically suppressed patients

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Background

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- Antiretroviral treatment interruption strategies that result in virologic rebound have negative clinical consequences
- Nevertheless, daily adherence to antiretroviral therapy remains a challenge for some patients
- We completed a pilot trial[1] demonstrating that a two-day interruption on some antivirals maintains virologic suppression
  - Patients on different antiretroviral regimens with ongoing virologic suppression on daily therapy changed to a schedule of Five consecutive days On treatment followed by Two days Off ("FOTO")
  - Up to 48 weeks, virologic suppression was maintained in all ten subjects on efavirenz plus NRTIs
  - Interpretation: The FOTO treatment schedule success is in part due to the prolonged half-lives of efavirenz and companion NRTIs

(1) Cohen CJ et al *HIV Clin Trials* 2007 Jan-Feb 8: 19-23

Hypotheses

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- A multidrug regimen comprised of antiretroviral agents with long half-lives will maintain virologic suppression despite regular brief treatment interruptions
  - The absence of virologic rebound will avoid negative clinical consequences of viremia
- Brief treatment interruption will positively address aspects of "pill-fatigue" and costs associated with daily treatment, and may address long-term toxicity issues

Methods-1

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- **Subjects**: HIV-1 positive adults (age ≥18) on efavirenz (EFV), tenofovir (TDF) and emtricitabine (FTC) with HIV RNA < 50 c/mL
- **Study Design:** n=60 in six centers
  - **Randomized, non-blinded controlled design**
  - **n=30 randomized to take EFV/TDF/FTC for 5 consecutive days each week (typically Monday through Friday) followed by 2 days off medication each week for 48 weeks (Five On Two Off; FOTO)**
  - **n=30 randomized to remain on daily EFV/TDF/FTC for 24 weeks (DAILY) and then allowed to cross-over to FOTO (if VL was < 50 c/ml at week 24)**
- **Primary Objective:** To compare virologic control at week 24
- **Sample size**: n=60 has 80% power (one-sided testing) to reject inferiority – defined as a ≥15% lower rate of maintaining virologic suppression on FOTO vs. DAILY

Methods-2

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- **Secondary Objectives:**
  - To evaluate change in CD4 counts in both arms
  - To evaluate quality of life (QOL) in both arms
  - To evaluate antiretroviral toxicity in both arms
  - To evaluate adherence in both arms
- **PK Substudy**: A subset of subjects participated in a pharmacologic study of plasma EFV levels
- **Definition of Virologic Failure:** HIV RNA level > 400 which was confirmed on repeat measurement.
- **Definition of Blip**: Isolated HIV RNA measurement between 50 and 500.

Methods-3

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- **Inclusion Criteria**
  - **CD4 count ≥ 200 for ≥ 90 days**
  - **HIV RNA <75 for at least 90 days; < 50 at screening**
  - **Treatment with EFV/TDF/FTC for ≥ 90 days as Atripla® or EFV/Truvada®**
  - **No active hepatitis B infection**
- **Measures**
  - **HIV viral load: Roche Amplicor® ultrasensitive RT-PCR assay**
  - **Adherence: self report of missed and extra doses; pill counts**
  - **Safety: clinical and lab adverse events (ACTG toxicity grading scale)**
  - **QOL: Validated Likert scale for treatment preferences 4 weeks after starting FOTO**
- **Schedule of Visits**
  - **Baseline, week 4, week 12 and then every 12 weeks until study completion**
  - **DAILY subjects also came at week 28 for the four-week FOTO assessment**
  - **Week 4 and 24 visits were always after the two-day interruption period; other visits were often similarly scheduled**

Results: Disposition

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- **Baseline characteristics were similar in the two groups**
  - 83% male; Mean age 44 years
  - 70% White, 22% African-American, 8% other race
  - Mean CD4 670
- **Disposition of n=60 enrolled:**
  - n=25 on FOTO completed the 24-week randomized part of the study;
    - n=23 continued to week 48
  - n=28 on DAILY completed the 24-week randomized part of the study;
    - n=27 crossed over to FOTO at week 24 with follow up to week 48
  - n=50 with 48-week data
    - n=10 stopped before week 48; all had VL< 50 at discontinuation
    - Reasons: n=5 Loss to follow up; n=4 Withdrew consent; n=1 Pregnancy
    - N=5 on FOTO; n=4 on Control (one dropped before randomization)

Results: Virology Endpoints

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Primary Endpoint : Week 24, % with HIV RNA < 50
As-Treated Analysis

FOTO	DAILY
100% (95% CI 88-100)	86% (95% CI 73-99)

p<0.001 to reject inferiority of FOTO vs. Daily strategy to maintain suppression

Virologic Failure
HIV RNA > 400 Confirmed by Repeat Measurement

No subject on either arm experienced virologic failure during the entire 48-week study

Extension Phase: % HIV RNA < 50
All on FOTO Treatment Schedule

Week 36	90% (95% CI 82-98)
Week 48	90% (95% CI 82-98)

Results: Virologic "Blips"

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Blips: Baseline to Week 24
Randomized

WEEK	DAILY n	DAILY # Pts Blip	DAILY HIV RNA	FOTO n	FOTO # Pts Blip	FOTO HIV RNA
Baseline	30	1	142	29	2	50, 60
4	30	4	52, 57, 68, 80	29	3	77, 130, 146
12	28	1	225	26	3	66, 61, 160
24	28	4	58, 66, 165, 465	25	0	---

Blips: Week 24 to Week 28
Extension Phase

WEEK	ALL SUBJECTS ON FOTO n	# Pts with Blip	HIV RNA
36	50	5	83, 85, 97, 114, 140
48	50	5	71, 88, 128, 160, 200

Results: PK and QOL

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EFV LEVEL (MEC=1000 ng/ml)	FOTO* Mean 60 hours post last dose	DAILY** Mean 12 hours post last dose
> 1000 ng/ml	48%	90%
500-999 ng/ml	37%	1%
< 500 ng/ml	15%	9%

*13 subjects, 92 samples **15 subjects, 74 samples

Quality of Life

0 — 10

I prefer taking HIV medications 7 days per week

I prefer 5 days on and 2 days off HIV medications

- **n=54, Median Response 4 weeks after change from daily to FOTO treatment schedule: 9.5 (IQR 8-10)**

CD4 outcomes and Adverse Events

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- Mean CD4 count increases from baseline to week 24
  - Daily: +9.3 cells/mm^3
  - FOTO: + 1.9 cells/mm^3 P=NS
- Week 24 to 48:
  - Daily to FOTO: +1.1 cells/mm^3
  - FOTO / FOTO: + 29.7 cells/mm^3 P=NS
- AEs judged at least possibly related to study intervention
  - On FOTO strategy: n=5, all mild in severity
  - n=3 with sleep related AEs
    - All resolved with one month (1with additional Rx)
    - 1 night sweats, 1 with "intoxicated feeling" for one day

Adherence to Strategy

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- Self Reported Adherence Summary

	Week 4	Week 12	Week 24
FOTO: # (%) who missed ≥1 day dose in 5-day period	3/29 (10%)	4/26 (15%)	2/25 (8%)
DAILY: # (%) who missed ≥1 day dose in 7-day period	5/30 (17%)	2/28 (7%)	3/28 (11%)
FOTO: # (%) who took 1 *extra* day dose during 2 days off	3/29 (10%)	1/26 (4%)	2/24 (8%)

Note: Median number additional missed days dosing on FOTO and DAILY = 1

FOTO Study: Conclusions

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- The strategy of taking TDF/FTC/EFV five days per week with a two-day interruption successfully maintained virologic suppression in all participants through 48 weeks
  - Adherence data confirms adherence to strategy
  - PK: While nearly half of the trough concentrations were below the MEC for EFV, there was no virologic rebound observed
- Few AEs were noted; all were mild
- The Likert scale demonstrated strong preference for this 5 days on/2 days off schedule
- This strategy has the potential to conserve 28% of the cost of this three-drug regimen

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