A one-pill, once-daily, fixed-dose combination (FDC) of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (EFV/FTC/TDF) regimen is associated with higher unannounced pill count adherence than non-one pill, once-daily

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Background

- Combination antiretroviral therapy requires lifelong adherence to regimens that have significant side effects and/or have complex dosing schedules.
- Active substance abuse, poverty, and lack of access to stable housing are well-established barriers to adherence. The optimal approach to the management of individuals with these risk factors has not been well studied.
- Our group has an established infrastructure for observing treatment outcomes in a large community of marginally housed HIV-infected patients (the REACH cohort). Adherence in this setting is measured by monthly unannounced pill counts. This approach is considered a "gold-standard" method of adherence monitoring and has been validated in this and other populations.
- Once-daily administration of fixed-dose combination efavirenz, emtricitabine and tenofovir DF (FDC EFV/FTC/TDF) has been advocated as a potential preferred regimen in this population given the ease of dosing; however, the CNS side effects and low "genetic barrier" of this regimen may argue against its widespread use.
- In order to determine the effectiveness of fixed-dose once-daily FDC EFV/FTC/TDF in this setting, we prospectively followed a group of at-risk individuals who were prescribed FDC EFV/FTC/TDF in routine clinical care. We compared adherence and viral load outcomes between subjects receiving FDC EFV/FTC/TDF and other regimens using historical data collected in the REACH study.

Methods

- Subjects were identified from an existing cohort of HIV+ homeless and marginally-housed individuals (REACH) and supplemented by recruitment from public health clinics in the Tenderloin and Mission Districts in San Francisco.
- Eligibility:
  - Initiated combination antiretroviral therapy within 6 months of treatment initiation with either (1) FDC EFV/FTC/TDF, (2) ritonavir-boosted protease inhibitor or unboosted protease inhibitor plus two nucleoside reverse transcriptase inhibitors (PI or r-PI) or (3) non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors (NNRTI)
  - Willing to undergo monthly unannounced pill-count visits.
- Adherence over 6 months was compared by regimen type using generalized estimating equations controlling for multiple confounders, including: age, gender, race, education (completed high school), injection drug use, homelessness, Beck Depression Inventory and CD4 nadir.
- Categorical variables were compared with Chi square, continuous variables with analysis of variance, mutivariable analyses with generalized estimating equations. Predictors of HIV RNA suppression <50 copies/mL were analyzed with multivariable logistic regression.

Legend
FDC EFV/FTC/TDF: Efavirenz/Emtricitabine/Tenofovir DF fixed dose combination
PI: protease inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
r-PI: Ritonavir-boosted protease inhibitor
GEE: Generalized estimating equation
BDI: Beck Depression Inventory

Results

Table 1. Characteristics of the Study Population

		r-PI		PI		NNRTI		FDC EFV/FTC/TDF		Total	
Gender	Male	38	66.7	9	81.8	11	78.6	37	78.7	95	73.6
X^2 2.61, p= 0.46	Female	19	33.3	2	18.2	3	21.4	10	21.3	34	26.4
	missing	0		0		0		0		0	
	X^2	1.86	0.17	0.05	1.00	0.0001	1.00				
	p										
Race	White	21	36.8	5	45.5	7	50.0	18	38.3	50	39.1
X^2 7.03 p=0.63	Black	21	36.8	3	27.3	6	42.9	17	36.2	47	36.7
	Hispanic	8	14.0	0	0.0	1	7.1	4	8.5	13	10.2
	Other	7	12.3	3	27.3	0	0.0	8	17.0	18	14.1
	missing	0		0		0		0		0	
	X^2	1.10	0.78	1.75	0.63	2.90					
	p					0.41					
Homeless ever	no	8	14.3	3	27.3	1	7.1	20	42.6	32	25.0
X^2 13.56 p=0.004	yes	48	85.7	8	72.7	13	92.9	27	57.5	96	75.0
	missing	1		0		0		0		1	
	X^2	10.32	0.002	0.87	0.50	5.99					
	p					0.02					
High School	no	20	35.7	3	27.3	3	21.4	13	27.7	39	30.4
X^2 1.50 p=0.68	yes	36	64.3	8	72.7	11	78.6	34	72.3	89	69.5
	missing	1		0		0		0		1	
	X^2	0.76	0.38	0.001	1.00	0.22	0.74				
	p										
Injection Drug Use (ever)	no	16	28.1	3	27.3	6	42.9	22	46.8	47	36.4
X^2 4.55 p=0.21	yes	41	71.9	8	72.7	8	57.1	25	53.2	82	63.6
	missing	0		0		0		0		0	
	X^2	3.90	0.05	1.39	0.32	0.07					
	p					1.00					
Age	Mean Std dev	44.3	7.3	47.5	6.6	43.6	8.6	47.2	8.2	45.6	7.8
F=1.76 p=0.16	Median iqr	45.0	9.0	49.0	14.0	43.5	10.0	47.0	8.0	46.0	9.0
	missing	0		0		0		0		0	
Income	Mean Std dev	730.8	471.7	742.5	429.5	638.5	371.1	821.6	394.9	754.9	430.3
F=0.78 p=0.51	Median iqr	747.0	463.0	765.0	452.0	677.5	411.0	853.0	623.0	764.0	498.0
	missing	0		0		0		0		0	
CD4 current	Mean Std dev	277	195	329	246	292	198	389	219	323	212
F=2.63 p=0.0530	Median iqr	232	228	256	149	270	339	366	317	282	280
	missing	0		0		0		1		1	
Log HIV RNA	Mean Std dev	2.8	1.7	2.2	1.7	2.8	1.8	1.9	1.6	2.5	1.7
F=3.09 p=0..03	Median iqr	2.9	2.6	2.0	2.8	2.8	3.3	1.7	2.7	2.5	2.7
	missing	0		0		0		1		1	
Beck Depression Inventory	Mean Std dev	11.9	10.9	11.5	6.0	17.0	11.5	12.5	10.4	12.6	10.4
F=0.95 p=0.42	Median iqr	9.0	14.0	11.0	8.0	16.0	15.0	12.0	18.0	10.0	15.0
	missing	0		0		0		2		2	

Table 2. >90% Adherence by Treatment Group

	r-PI		PI		NNRTI		FDC EFV/TDF/FTC		Total	
	n	%	n	%	n	%	n	%	n	%
≤0.9	35	62.5	7	63.6	10	76.9	13	32.5	65	54.2
>0.9	21	37.5	4	36.4	3	23.1	27	67.5	55	45.8

X^2 12.24, p= 0.0066

Table 3. HIV RNA<50c/ml by Treatment Group

	r-PI		PI		NNRTI		FDC EFV/TDF/FTC		Total	
	n	%	n	%	n	%	n	%	n	%
VL>50	30	52.63	5	45.45	8	57.14	12	30	55	45.45
VL≤50	27	47.37	6	54.55	6	42.86	28	70	66	54.55
missing	0		0		0		7		7	

Overall viral suppression was greater in FDC EFV/TDF/FTC than r-PI (p=0.04).
These differences were no longer significant when controlling for adherence and CD4 nadir (r-PI vs EFV/TDF/FDC p=0.47)

Figure 1. Mean Adherence by Regimen and Month

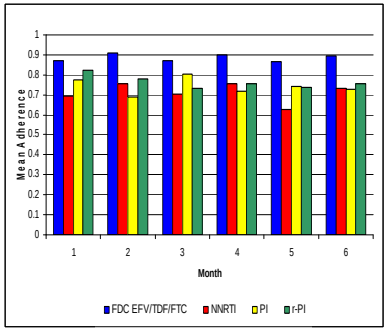
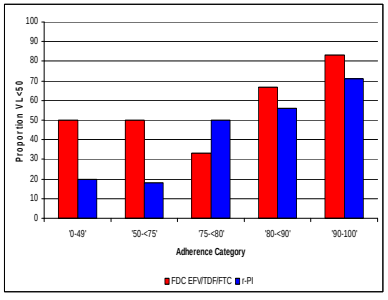


Figure 2. Proportion HIV RNA<50c/ml by Adherence Level



Multivariate Predictors of >90% Adherence

Table 4. GEE Predictors of Adherence: FDC EFV/FTC/TDF vs Everything Else

		z	p
Treatment	FDC EFV/FTC/TDF=1	4.02	<.0001
	Other=0		
Gender	Male=1	0.60	0.546
	Female=0		
Race	White=1	1.99	0.046
	Other=0		
Education	≥High School=1	1.14	0.254
	< High School=0		
Income	Per unit	-1.98	0.047
Homeless ever	yes=1	-0.27	0.786
	no=0		
Injection Drug Use ever	yes=1	0.08	0.939
	no=0		
Nadir CD4	Per unit	3.13	0.002
BDI	Per unit	-0.04	0.971

Table 5. GEE Predictors of Adherence: FDC EFV/FTC/TDF vs r-PI

		z	p
Treatment	FDC EFV/FTC/TDF=1	3.73	0.0002
	r-PI=0		
Gender	Male=1	-0.18	0.855
	Female=0		
Race	White=1	1.64	0.101
	Other=0		
Education	≥High School=1	1.49	0.137
	< High School=0		
Income	Per unit	-1.50	0.134
Homeless ever	yes=1	0.24	0.813
	no=0		
Injection Drug Use ever	yes=1	0.76	0.445
	no=0		
Nadir CD4	Per unit	3.36	0.001
BDI	Per unit	-0.24	0.808

Table 6 GEE Predictors of Adherence: FDC EFV/FTC/TDF vs NNRTI

		z	p
Treatment	FDC EFV/FTC/TDF=1	2.95	0.003
	NNRTI=0		
Gender	Male=1	-0.00	0.997
	Female=0		
Race	White=1	1.28	0.202
	Other=0		
Education	≥High School=1	0.29	0.773
	< High School=0		
Income	Per unit	-1.89	0.059
Homeless ever	yes=1	-0.54	0.591
	no=0		
Injection Drug Use ever	yes=1	-0.57	0.569
	no=0		
Nadir CD4	Per unit	2.80	0.005
BDI	Per unit	0.53	0.594

Conclusions

In a difficult to treat population of patients enriched for substance abuse, psychiatric illnesses and limited access to housing, we found that adherence to FDC EFV/FTC/TDF was higher than that observed in other commonly used regimens. We also observed that this regimen was associated with comparable if not greater virologic efficacy than that observed with historical data. The effectiveness of FDC EFV/FTC/TDF was particularly evident at lower adherence levels, an observation consistent with our prior findings and likely related in part to the pharmacokinetic profile of EFV and perhaps TDF/FTC.

Although these data support the use of the FDC EFV/FTC/TDF in this patient population, several limitations to our study design should be considered. First, treatment regimens were not assigned randomly and unmeasured confounders may have affected our comparisons between various regimens. Second, calendar year and/or treatment era differed among the treatment groups. It is possible that the greater efficacy of FDC EFV/FTC/TDF in our study may have been due in part to its more recent use, when the role of adherence was more widely appreciated. Finally, drug resistance accumulation among those exhibiting incomplete viral suppression was not measured in this study, and was presumably more common in those receiving FDC EFV/FTC/TDF than those receiving boosted PI-based regimens.

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