Randomized Controlled Trial of Daily Text Messages for Adherence to Pre-Exposure Prophylaxis (PrEP) in Men who have Sex with Men and Transgender Women

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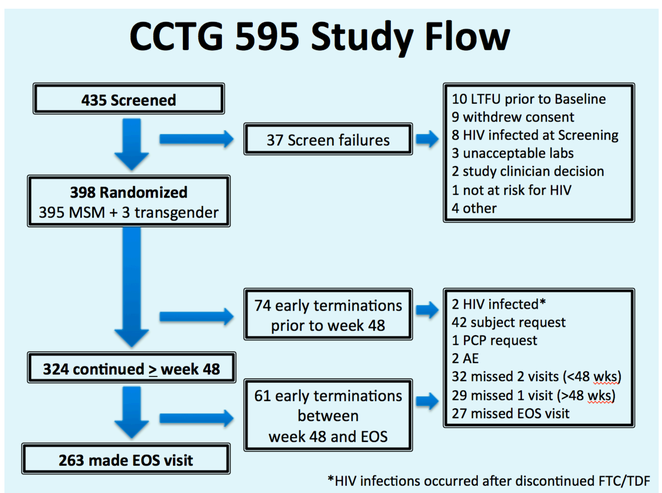
BACKGROUND

The effectiveness of tenofovir/emtricitibine (TDF/FTC) for PrEP depends on maintaining adherence. Previous analyses of efficacy studies suggest that adequate adherence to maintain a dried blood spot (DBS) intracellular tenofovir diphosphate (TFV-DP) level consistent with 4 or more doses per week (>719 fmol/punch) provides 94% protection from HIV. Perfect adherence defined by DBS TFV-DP >1246 fmol/punch provides 99% protection (Castillo-Macilla, 2013). Maintaining adherence to PrEP is therefore critical. Tailored adherence text messages have been developed to help optimize drug adherence.

METHODS

- CCTG 595 was a randomized controlled trial of individualized Texting for Adherence Building (iTAB) versus standard of care (SoC) for adherence to daily TDF/FTC for up to 96 weeks.
- Eligible participants were adult HIV-uninfected men who have sex with men (MSM) and transgender women (TGW) confirmed by Ag/Ab assay or Ab/HIV NAAT.
- Elevated risk of HIV transmission was defined as having: 1) At least one HIV infected sexual partner for ≥4 weeks; 2) Condomless anal intercourse with ≥3 male sex partners who are HIV+ or unknown HIV status in past 3 months ; or 3) Condomless anal intercourse with ≥1 male partner and STI diagnosis in last 3 months.
- Participants were required to have creatinine clearance of at least 60 mL/min; ALT and AST <3x upper limit normal; Hemoglobin>9 g/dL, Absolute neutrophil count >750/mm^3. and platelets >75,000/mm^3. Exclusion criteria included active hepatitis B and urine protein 2+.
- The primary adherence outcome was defined by TFV-DP levels of > 719 fmol/punch at week 12 and last on-drug study visit up until week 48. Subjects who missed week 12 were treated as non-adherent. If their last on-drug visit was week 12 then only week 12 was counted for the adherence outcome.
- The main secondary outcome was the same criteria but with a TFV-DP level of > 1246 fmol/punch.
- Fisher's exact test and logistic regression were used to compare study arms for the primary and secondary outcomes. Multivariable logistic regression models were used to adjust for any confounding related to baseline imbalances in factors that were also potentially associated with the outcome.

Figure 1: STUDY FLOW



RESULTS

- From February 2013 to February 2015, 398 subjects were enrolled (mean age 35 years old; 41% Hispanic or Non-Hispanic Black). Retention on TDF/FTC at week 12 and 48 was 95% and 81%.
- HIV incidence was 0.35/100 person years.
- The composite primary adherence endpoint of >719 fmol/punch was reached by 72.0% in iTAB and 69.2% in SoC with the great majority of subjects exceeding this threshold at week 12 (91.7% vs. 85.6%) and week 48 (83.4% vs. 81.6%), all p's>0.05.
- For the secondary composite endpoint of near-perfect adherence (>1246 fmol/punch), the iTAB arm had higher adherence than SoC (33.5% vs 24.8%) reaching statistical significance after adjusting for age [Odds Ratio=1.56 (95% CI 1.00-2.42 p=0.05)].
- At week 48, those randomized to iTAB vs. SoC had significantly higher near-perfect adherence (51.0% vs 37.4%, p=0.02).

Table 1. BASELINE CHARACTERISTICS

	iTAB arm	Standard of Care	P-value
Gender:			
Male; N(%)	197 (98.5)	198 (100)	0.25
Transgender male to female; N(%)	3 (1.5)	0 (0)	
Age; mean (SD)	35.1 (9.8)	35.4 (8.7)	0.44
Race; N(%):			
Asian	7 (3.6)	5 (2.6)	0.90
Black	26 (13.2)	26 (13.5)	
White	147 (74.6)	148 (76.7)	
Multiple	14 (7.1)	10 (5.2)	
Other	3 (1.5)	4 (2.1)	
Hispanic Ethnicity	61 (30.8)	58 (29.4)	0.83
English Primary Language; N(%)	188 (94)	192 (97)	0.23
Education; N(%):			
<High School	4 (2.0)	0 (0)	0.05
High School	20 (10.0)	11 (5.6)	
Some College	77 (38.5)	72 (36.4)	
Bachelors degree	64 (32.0)	68 (34.3)	
Some Post graduate	5 (2.5)	14 (7.1)	
Advanced Degree	30 (15.0)	33 (16.7)	
Household Income ; N(%):			
< $2000/ month	43 (21.5)	42 (21.2)	0.02
>$2000/ month	115 (57.5)	134 (67.7)	
Refused	42 (21.0)	22 (11.1)	

Table 2. BASELINE RISK FACTORS

	iTAB arm	Standard of Care	P-value
>=1 HIV+ partner for > 4weeks; N(%)	88 (44.0)	109 (55.1)	0.04
Condomless sex with >=3 HIV+/ unknown partners past 3 months; N(%)	139 (70.2)	137 (69.2)	>0.99
Condomless sex with >= 1 partner and had STI in past 6 months; N(%)	31 (15.5)	35 (17.7)	0.59
Any STI; N(%)	54 (27.0)	50 (25.3)	0.73
Syphilis (TPA+); N(%)	21 (10.5)	12 (6.1)	0.15
Any Methamphetamine Use; N(%)	36 (18.2)	27 (13.8)	0.27
Any Substance Use (not marijuana); N(%)	152 (76.8)	136 (69.4)	0.11
DAST 10 (Substance Use); N(%):			
No or Low	118 (59.6)	131 (66.9)	0.30
Moderate	67 (33.9)	53 (27.0)	
Substantial	13 (6.6)	12 (6.1)	
PHQ9 (Depression); mean (SD)	5.2 (4.9)	4.2 (4.4)	0.03

Figure 2a: RETENTION at 48 Wks

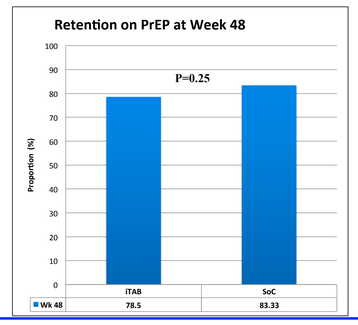


Figure 2b: RETENTION (Whole study)

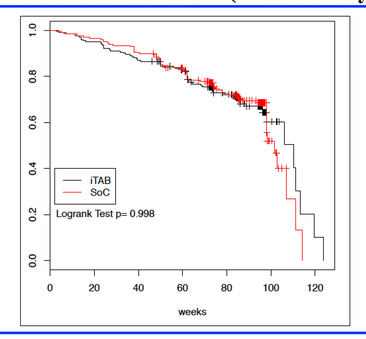


Figure 3a: ADHERENCE Wks 12 and 48 defined by TFV-DP Cutoffs

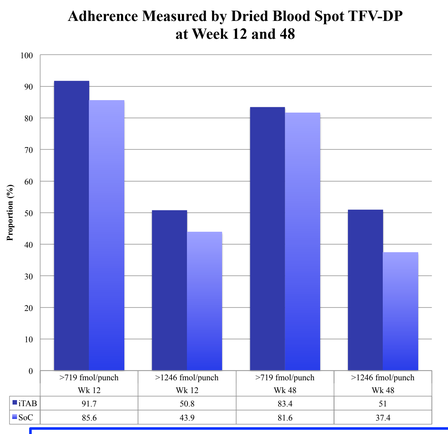


Figure 3b: TFV-DP Distribution within Arms

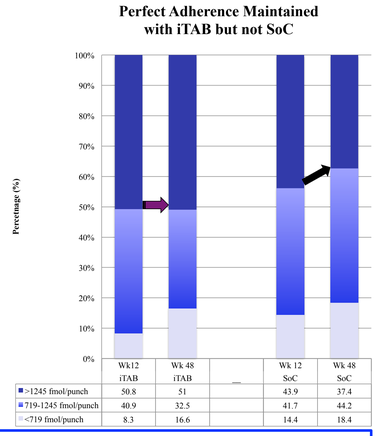


Table 3. PRIMARY OUTCOME (Adequate Adherence)

	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	P
iTAB ARM	1.31	0.83-2.09	0.25
College or greater education	1.94	0.90-4.20	0.09
Monthly Income of $2000 or greater	0.85	0.47-1.57	0.61
Income refused to answer	0.46	0.22-0.95	0.04
White Race	1.60	0.94-2.72	0.08
Primary language other than English	0.41	0.15-1.13	0.08
Ongoing Substance Use	1.79	1.12-2.87	0.015
PHQ9 score	0.96	0.92-1.01	0.12

Multivariable logistic regression includes arm of study in ITT analysis for association with having ≥719 fmol/punch at week 12 and (if there was one) the last study visit up until week 48. Covariates included if they were associated arm at baseline (p<0.1) and with outcome (p<0.15) in univariate analysis.
Ongoing substance use was defined as any substance of abuse (other than marijuana and alcohol) reported in 2 or more of visits

Table 4. SECONDARY OUTCOME (Perfect Adherence)

	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	P
iTAB ARM	1.56	1.00-2.42	0.05
Age	1.03	1.01-1.06	0.01

Multivariable logistic regression includes arm of study in ITT analysis for association with having ≥1246 fmol/punch at week 12 and (if there was one) the last study visit up until week 48. Covariates included if they were associated arm at baseline (p<0.1) and with outcome (p<0.15) in univariate analysis.

CONCLUSIONS

Adherence to PrEP in this study of mainly MSM was high with correspondingly low HIV incidence. All HIV seroconversions were in those that discontinued PrEP. The main effect of iTAB daily texting was to improve durability of perfect adherence. Individualized daily texting for adherence is a low-burden ancillary tool that could be used to maximize long-term PrEP effectiveness by increasing near-perfect adherence.

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FUNDED BY:
CALIFORNIA HIV/AIDS RESEARCH PROGRAM